# Lipid Profile and New-Onset Atrial Fibrillation in Patients With Acute ST-Segment Elevation Myocardial Infarction (An Observational Study in Southwest of China)

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**In acute ST-segment elevation myocardial infarction (ASTEMI), new-onset atrial fibrillation (NOAF) was not only associated with worse short-term outcomes but also with higher long-term mortality. This study aimed to evaluate the effect of dyslipidemia on the incidence of NOAF. Among the 985 patients (2014 to 2017) with ASTEMI consecutively enrolled and followed-up for 31 months in this study, 81 patients (8.2%) developed NOAF during hospitalization. Fasting levels of total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were measured using standard procedures. The study population was categorized into 3 groups based on tertiles of lipid profile. Multivariate regression analysis was adjusted for baseline characteristics, laboratory values, angiography findings, and medication. Inverse associations of TC (hazard ratio [HR] 0.54, 95% confidence interval [CI] 0.32 to 0.90) and LDL-C (hazard ratio 0.56, 95% confidence interval 0.31 to 1.00) with NOAF was observed in this study. In contrast, the levels of TG and HDL-C were not associated with NOAF in patients with ASTEMI. Moreover, the all-cause mortality in the NOAF group (19.8%) was apparently higher than that in sinus rhythm goup (6.1%) after a long term follow-up. In conclusion, plasma LDL-C and TC concentrations but neither TG nor HDL-C were inversely correlated to NOAF during hospitalization, which indicated a bad prognosis even after discharge.**  **(Am J Cardiol 2019;124:1512−1517)**

The relation between dyslipidemia and new-onset atrial fibrillation (NOAF) development in the general population remains controversial. Some studies showed that total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) but not high-density lipoprotein cholesterol (HDL-C) or total triglyceride (TG) were inversely correlated with NOAF.[1,2] In contrast, high HDL-C and low TG levels were associated with a reduced risk of NOAF based on the combined analysis of Multi-Ethnic Study of Atherosclerosis and the Framingham Heart Study.[3] Consequently, the association of blood lipids to NOAF remained unclear even in the general population. Thus, the aim of this study was to assess the relation between lipid profile and NOAF in the ST-segment elevation myocardial infarction (STEMI) population.

## Methods

A total of 1,164 consecutive patients admitted to the First Affiliated Hospital of Chongqing Medical University from December 2014 to December 2017 with a diagnosis of STEMI within 12 hours after the symptoms onset were evaluated for this prospective single-center clinical study. The diagnosis of STEMI should meet following criteria in this study: (1) typical chest pain or equivalent syndromes lasting for at least 30 minutes, (2) persistent ST-segment elevation in at least 2 contiguous leads (>0.1 mV in extremity leads or >0.2 mV in precordial leads) or new left bundle-branch block on electrocardiogram, and (3) elevated concentration of troponin I or creatine kinase-MB (CK-MB) more than twice the normal laboratory values.

The exclusion criteria included the following: (1) all previous types of AF (n = 11), (2) patients admitted >24 hours from symptom onset (n = 87), (3) the patients were lost to follow-up in the long term (n = 58), and (4) history of hyperthyroidism and prior pacemaker implantation (n = 23). Thus, the final study population was comprised of 985 patients, and all participants provided a written informed consent.

After admission, patients received medication based on the guideline for treatment for the treatment of STEMI.[4] Clinical evaluation, demographic characteristics, electrocardiogram, 24-hours Holter monitoring (at least once during hospitalization), medical history, angiography treatments, and laboratory data were obtained from hospital records. NOAF was defined as the absence of P-waves, and irregular atrial activity and R-R intervals.[5] Overnight fasting venous blood samples for lipid panel were obtained within 12 to 24 hours from symptom onset. The patients were categorized into 3 groups based on tertiles of lipid profile levels including TC, TG, and LDL-C and HDL-C.

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Long term (median length: 31 months) follow-up data were obtained by telephone interview. The primary outcomes included in-hospitalization AF, cardiogenic shock, and all-cause mortality and long-term (31 months) all-cause mortality. Each patient in this study was contacted once every 3 months by telephone. Moreover, the end time point of follow-up was May 11th, 2019.

The Kolmogorov Smirnov test was used to evaluate the data normality. Continuous variables with normal distribution were presented as mean (standard deviation [SD]) and compared using the unpaired *t* test. Meanwhile continuous variables with skewed distribution were expressed as medians with interquartile ranges (between the 25th and 75th percentile) and compared using the nonparametric test. Categorical variables were presented as frequencies and percentages and compared using the Pearson's chi-squared test. Multivariable logistic regression analysis was performed to evaluate the association of tertiles of lipid profiles and other potential confounders with NOAF development. The odds ratios indicated that relative risk of NOAF in each lipid profile group including TC, TG, HDL-C, and LDL-C compared with the lowest tertiles of those respectively.

The Kaplan Meier plot was used to crudely illustrate the cumulative survival percentage of all-cause mortality based on the presence or absence of NOAF. Additionally, the log-rank test was used to compare the curves of these 2 groups. All statistical tests were 2-tailed, and p value <0.05 was considered as statistically significant. Data analysis was carried out using the IBM SPSS Statistics 23.0 (IBM Corp., Armonk, New York).

## Results

The baseline variables of all patients with STEMI are presented in Table 1. Compared with the patients of sinus rhythm (SR n = 904, 91.5%), the patients in the NOAF group (n = 81, 8.2%) were older, and more likely to be women, and had a faster heart rate, worsen Killip classification, and a higher prevalence of hypertension. The prescription rate of aspirin, clopidogrel, statin, angiotensin converting enzyme inhibitor/angiotensin receptor blocker and anticoagulants were comparable between the 2 groups, whereas the proton pump inhibitor was commonly prescribed in NOAF patients. Nonetheless, However, $\beta$-blocker was less rarely used for NOAF patients may due to the worsen killip class.

Patients' laboratory values and angiography findings were described in Table 2. Interestingly, patients who presented with NOAF had significantly lower LDL-C, TC, TG and the patients with higher cholesterol had a lower NOAF incidence, suggesting that a predictive importance of lipid profile (Figure 1). The creatinine level on admission was numerically higher in the AF group, although no significant difference was noted. High sensitivity C reactive protein, white blood cell, hemoglobin, platelet, troponin, creatine

Table 1
Demographic, clinical and medical therapeutic characteristics of 985 patients with acute ST-segment elevation myocardial infarction according to presence or absence of in-hospital new-onset atrial fibrillation

| Characteristics | Total (n = 985) | Sinus rhythm (n = 904) | NOAF (n = 81) | p Value |
|---|---|---|---|---|
| Age (years) | 63.4 ± 12.6 | 62.9 ± 12.6 | 69.96 ± 10.4 | <0.001 |
| Men | 787 (79.9%) | 729 (80.6%) | 58 (71.6%) | 0.05 |
| Body mass index (Kg/m$^2$) | 24.2 ± 3.7 | 24.2 ± 3.7 | 24.0 ± 3.57 | 0.27 |
| Hypertension | 491 (49.8%) | 440 (48.7%) | 51 (63.0%) | 0.014 |
| Diabetes mellitus | 192 (19.5%) | 172 (19.0%) | 20 (24.7%) | 0.22 |
| Chronic kidney disease | 14 (1.4%) | 12 (1.3%) | 2 (2.5%) | 0.41 |
| Ever smoking | 658 (66.8%) | 605 (66.9%) | 53 (65.4%) | 0.79 |
| Family history for coronary artery disease | 41 (4.2%) | 40 (4.4%) | 1 (1.2%) | 0.37 |
| Previous stroke | 55 (5.6%) | 49 (5.4%) | 6 (7.4%) | 0.46 |
| Previous myocardial infarction | 32 (3.3%) | 29 (3.2%) | 3 (3.7%) | 0.81 |
| Prior percutaneous coronary intervention | 24 (2.3%) | 21 (2.3%) | 3 (3.7%) | 0.44 |
| Prior coronary artery bypass grafting | 3 (0.3%) | 3 (0.3%) | 0 (0.0%) | 0.60 |
| Pulse ( bpm) | 82.7 ± 18.8 | 82.2 ± 18.3 | 87.8 ± 23.5 | 0.01 |
| Systolic blood pressure (mm Hg) | 126.8 ± 26.0 | 126.9 ± 25.8 | 125.1 ± 27.5 | 0.39 |
| Killip class on admission | | | | <0.001 |
| I | 749 (76.0%) | 707 (78.2%) | 42 (51.3%) | |
| II | 119 (12.1%) | 98 (10.8%) | 21 (25.9%) | |
| III | 28 (2.8%) | 23 (2.5%) | 5 (6.2%) | |
| IV | 89 (9.0%) | 76 (8.4%) | 13 (16.0%) | |
| Left ventricular ejection fraction (%) | 55.8 ± 7.3 | 56.0 ± 7.3 | 53.1 ± 8.0 | 0.03 |
| Left ventricular end-diastolic dimension (mm) | 49.5 ± 5.6 | 49.5 ± 5.6 | 50.5 ± 5.5 | 0.17 |
| Medication during hospitalization | | | | |
| Asprin | 919 (93.3%) | 844 (93.4%) | 75 (92.6%) | 0.79 |
| Clopidogrel | 345 (35.0%) | 315 (34.8%) | 30 (37.0%) | 0.69 |
| Statin | 967 (98.2%) | 887 (98.1%) | 80 (100.0%) | 0.98 |
| $\beta$-blockers | 598 (60.7%) | 560 (61.9%) | 38 (46.9%) | 0.008 |
| Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker | 458 (46.5%) | 424 (46.9%) | 34 (42.0%) | 0.39 |
| Anticoagulation drug | 462 (47.0%) | 424 (46.9%) | 38 (46.9%) | 0.93 |
| Proton pump inhibitors | 745 (75.6%) | 672 (74.3%) | 73 (90.1%) | 0.002 |

Table 2
Laboratory test, angiographic characteristics and in-hospitalization outcomes of patients according to presence or absence of in-hospital new-onset atrial fibrillation

| Characteristics | Total (n = 985) | Sinus rhythm (n = 904) | NOAF (n = 81) | p Value |
|---|---|---|---|---|
| Laboratory test | | | | |
| White blood cell ($10^9$/L) | 11.4 ± 3.8 | 11.3 ± 3.8 | 12.0 ± 4.3 | 0.12 |
| Hemoglobin (g/L) | 137.1 ± 21.5 | 137.1 ± 22.0 | 134 ± 21.3 | 0.24 |
| Platelet ($10^9$/L) | 202.5 ± 69.5 | 203.0 ± 69.8 | 196.8 ± 66.2 | 0.44 |
| Creatinine (umol/L) | 84.1 ± 51.2 | 83.1 ± 48.9 | 94.7 ± 71.3 | 0.051 |
| High-sensitivity C-reactive protein (mg/L) | 5.4 (2.3-11.3) | 5.4 (2.2-11.2) | 6.1 (2.7-13.2) | 0.34 |
| Troponin I (ug/L) | 3.12 (0.43-13.82) | 3.12 (0.40-13.78) | 3.10 (0.50-29.55) | 0.49 |
| Creatine kinase-MB (ug/L) | 26.5 (6.6-62.7) | 26.5 (6.5-63.6) | 17.5 (7.6-57.1) | 0.43 |
| $K^+$ (mmol/L) | 4.02 ± 0.46 | 4.04 ± 0.45 | 3.85 ± 0.53 | <0.001 |
| Total cholesterol (mmol/L or mg/dl) | 4.44 ± 1.11 (171.43 ± 42.86) | 4.47 ± 1.11 (172.59 ± 42.86) | 4.10 ± 0.99 (158.26 ± 38.22) | 0.005 |
| Triglycerides (mmol/L or mg/dl) | 1.81 ± 1.62 (160.19 ± 143.37) | 1.85 ± 1.66 (163.73 ± 146.9) | 1.43 ± 0.80 (126.56 ± 70.8) | 0.029 |
| High density lipoprotein cholesterol, (mmol/L or mg/dl) | 1.12 ± 0.32 (43.36 ± 12.39) | 1.11 ± 0.32 (42.97 ± 12.39) | 1.15 ± 0.32 (44.52 ± 12.39) | 0.34 |
| Low density lipoprotein cholesterol, (mmol/L or mg/dl) | 2.87 ± 0.96 (110.96 ± 37.10) | 2.89 ± 0.96 (111.70 ± 37.10) | 2.60 ± 0.86 (100.49 ± 33.24) | 0.01 |
| Angiographic and procedural treatment | | | | |
| Coronary angiography | | | | 0.24 |
| Left main | 6 (0.6%) | 6 (0.7%) | 0 (0.0%) | |
| Left anterior descending | 476 (48.3%) | 439 (48.6%) | 37 (45.7%) | |
| Left circumflex | 80 (8.1%) | 70 (7.7%) | 10 (12.3%) | |
| Right | 372 (37.8%) | 344 (38.1%) | 28 (34.6%) | |
| Multivessel coronary disease (n ≥ 2) | 51 (5.2%) | 45 (5.0%) | 6 (7.4%) | |
| Intra-aortic ballon pump | 20 (2.0%) | 16 (1.8%) | 4 (4.9%) | 0.14 |
| Percutaneous coronary intervention | 851 (86.4%) | 783 (86.6%) | 68 (84.0%) | 0.47 |
| Postprocedural thrombolysis in myocardial infarction flow grade | | | | 0.78 |
| 0 | 49 (5.2%) | 44 (4.9%) | 5 (6.2%) | |
| I | 5 (0.5%) | 5 (0.6%) | 0 (0.0%) | |
| II | 26 (2.7%) | 25 (2.8%) | 1 (1.3%) | |
| III | 897 (91.8%) | 823 (91.8%) | 74 (92.5%) | |
| In-hospitalization outcomes | | | | |
| Temporay pacemaker | 56 (5.7%) | 49 (5.4%) | 7 (8.6%) | 0.23 |
| Cardiogenic shock | 74 (7.5%) | 60 (6.6%) | 14 (17.3%) | <0.001 |
| Hospitalization (days) | 8.5 ± 4.7 | 8.3 ± 4.7 | 10.1 ± 5.3 | 0.002 |
| Death | 32 (3.2%) | 23 (2.5%) | 9 (11.1%) | <0.001 |

kinase-MB and HDL-C values were similar in the NOAF and SR groups. No significant differences in the infarct related artery, prevalence of percutaneous coronary intervention and intra-aortic balloon, and thrombolysis in myocardial infarction flow following percutaneous coronary intervention were found in patients with or without NOAF.

The NOAF group had significantly higher incidences of cardiogenic shock (17.3% vs 6.6%, p <0.001), and all-cause mortality (11.1% vs 2.5%, p <0.001) than the SR group during hospitalization. Furthermore, the NOAF patients had longer hospital stay than the SR patients (10.1 ± 5.3 vs 8.3 ± 4.7 days, p = 0.002).

A multivariable logistic regression analysis was conducted to determine the lipid profiles associated with the incidence of NOAF as shown in Table 3. After adjusting for potential confounders, TC and LDL-C levels were independently inversely associated with the incidence of NOAF in STEMI patients. The odds ratio of NOAF across TC tertiles (<3.91 mmol/L, 3.91 to 4.77 mmol/L, >4.77 mmol/L) were 1 (referent), 0.46 (0.22 to 0.98), and 0.24 (0.1 to 0.58), respectively ($P_{trend}$ = 0.004). Similarly, the odds ratio of NOAF across LDL-C tertiles (<2.42 mmol/L, 2.42 to .41 mmol/L, >3.41 mmol/L) were 1 (referent), 0.23 (0.10 to 0.53), and 0.38 (0.17 to 0.83), respectively ($P_{trend}$ = 0.001). Interestingly, the risk of NOAF in the tertile 2 of LDL-C was significantly lower than that in tertile 3.

During a median follow-up duration of 31 months, the all-cause mortality was 19.8%, and 6.1% in the NOAF and SR group, respectively. The kaplan-Meier analysis indicated that patients with NOAF had significantly higher mortality risk (log-Rank p <0.001, Figure 2).

## Discussion

In our present study, lower LDL-C and TC levels instead of HDL-C or TG levels were independently associated with a higher incidence of NOAF in STEMI patients after multivariable adjustments.

The relation of blood lipids and AF has been studied in several previous publications, which contributed to a controversial result. Two community-based cohorts of Multi-Ethnic Study of Atherosclerosis and Framingham Heart Study indicated that HDL-C and TC were associated with the risk of AF.[3] However, 2 Japanese cohorts and ARIC study

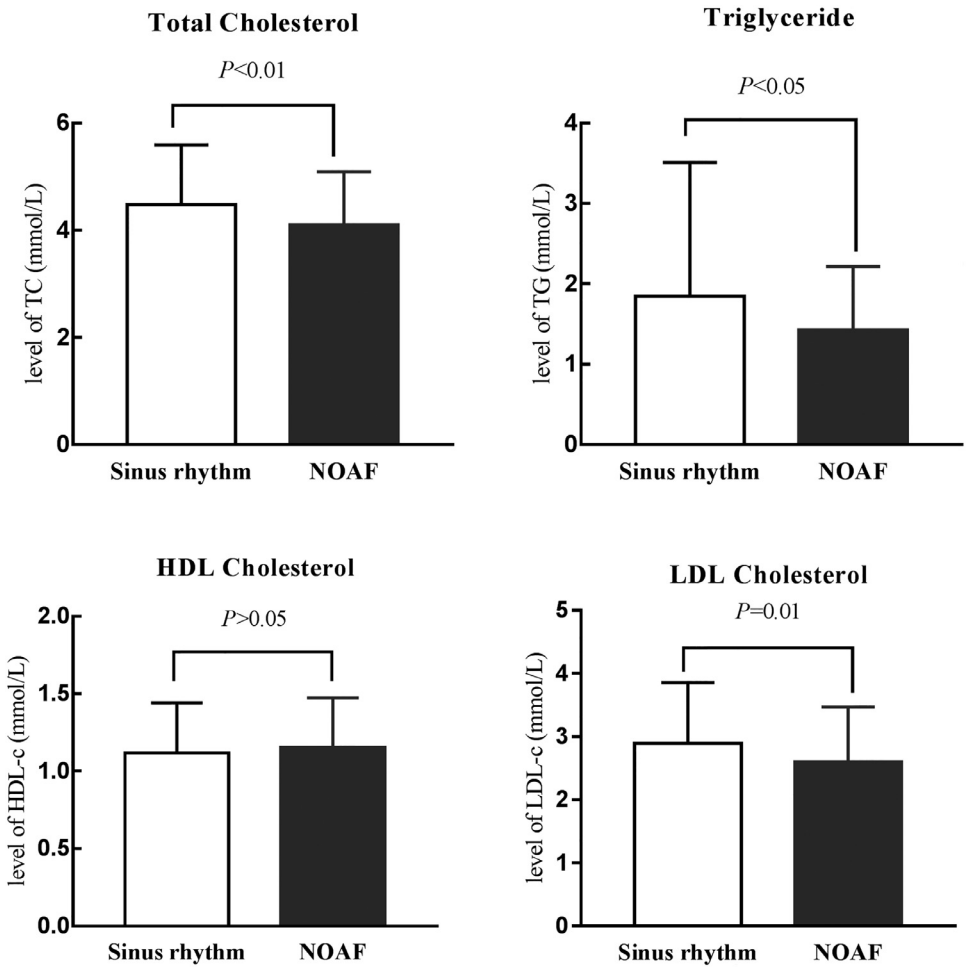


Figure 1. Plasma levels of lipid profile according to presence or absence of in-hospital NOAF.

demonstrated the association of low serum LDL-C and TC, but not TG or HDL-C, with AF.[1,6,7] Furthermore, recent literature provided more evidence that the strong relation of TC and LDL-C or subtypes of LDL-C to AF still existed in both sexes and Chinese population.[2,8,9] Importantly, decreased LDL-C and TC levels were correlated with NOAF during the long-term follow-up of patients with hypertension or chronic heart failure.[10,11] In general, the inverse association of TC and LDL-C with NOAF in this study is consistent with the results of previous prospective studies.[12]

In our cohort, 8.2% (81 of 985) of STEMI patients developed NOAF during hospitalization, which is higher than the AF incidence in the general population due to advanced age, higher prevalence of baseline co-morbidities, inflammatory response, abnormal blood electrolyte levels, and worse cardiac function.[13–17] Thus, age, sex, history of hypertension, history of chronic kidney disease, serum potassium, high sensitivity C-reactive protein, left ventricular ejection fraction, culprit artery were included in this multivariable adjustment model for potential confounders in the previous studies.[18–20] After adjustment in model 3, lower concentrations of TC and LDL-C were risk factors for NOAF while concentrations of HDL-C and TG were less significant factors.

Heusch et al revealed that myocardial ischemia injury of cardiomyocytes predisposed the myocardium for formation of reactive oxygen species.[21] Given the evidence of fragility of cardiomyocytes, several underlying mechanisms might explain the inverse association observed during hospitalization. Firstly, the membrane-stabilizing effect of cholesterol on lipid rafts and caveolae has been confirmed in previous studies, which indirectly determined the localization of ion channels including $K^+$ and $Ca^{2+}$ subunits.[22,23] Secondly, in vitro studies elucidated that cholesterol depletion directly regulated the distribution and activity of Kv1.5 and Kir2.1 channels inducing prolongation of QT interval. Therefore, the cholesterol content may be involved in AF pathogenesis.[24,25] Thirdly, cholesterol reduction triggered the dysfunction of $Ca^{2+}$ channel and increased intracellular $Ca^{2+}$ in cardiomyocyte concentration according to current researches.[26,27] Thus, the lower levels of LDL-C and TC during acute STEMI phase maybe involved in the development of NOAF in hospitalization.

To our knowledge, few studies pertaining to the relation of blood lipids and AF have focused on the acute myocardial infarction population. Hence, this prospective research was the first to report the negative correlation of cholesterol and AF in STEMI patients. Consequently, several limitations need to be addressed. First, this was a single-center study in the southwest of China with a limited sample size (approximately 1000 patients). Second, although many potential interfering covariables were adjusted by our models, we cannot rule out residual confounding. Finally, it was

Table 3
Adjusted logistic regression models for in-hospital new-onset atrial fibrillation according to tertiles of lipid profile

| Tertiles of TC (mmol/L or mg/L) | | Tertile 1 (<3.91 <150.97) reference | Tertile 2 (3.91-4.77 150.97-172.59) Odds Ratio (95% CI) | p Value | Tertile 3 (>4.77 >172.59) Odds Ratio (95% CI) | p Value | $P_{trend}$ |
|---|---|---|---|---|---|---|---|
| | N | 330 | 324 | | 331 | | |
| | NOAF cases | 40 | 27 | | 14 | | |
| | Model 1 | 1 | 0.72 (0.43-1.21) | 0.22 | 0.34 (0.18-0.65) | 0.001 | 0.005 |
| | Model 2 | 1 | 0.74 (0.43-1.26) | 0.27 | 0.35 (0.18-0.67) | 0.002 | 0.008 |
| | Model 3 | 1 | 0.46 (0.22-0.98) | 0.044 | 0.24 (0.1-0.58) | 0.002 | 0.004 |
| Tertiles of TG (mmol/L or mg/L) | | Tertile 1 (<1.11 <98.24) | Tertile 2 (1.11-1.82 98.24-161.08) | | Tertile 3 (>1.82 >161.08) | | |
| | N | 333 | 322 | | 330 | | |
| | NOAF cases | 37 | 29 | | 15 | | |
| | Model 1 | 1 | 0.86 (0.51-1.45) | 0.57 | 0.52 (0.28-0.99) | 0.047 | 0.14 |
| | Model 2 | 1 | 0.82 (0.48-1.40) | 0.47 | 0.50 (0.25-0.98) | 0.040 | 0.13 |
| | Model 3 | 1 | 0.67 (0.31-1.44) | 0.31 | 0.46 (0.19-1.1) | 0.076 | 0.20 |
| Tertiles of LDL-C (mmol/L or mg/L) | | Tertile 1 (<2.42 <93.56) | Tertile 2 (2.42-3.41 93.56-131.29) | | Tertile 3 (>3.41 >131.29) | | |
| | N | 328 | 329 | | 328 | | |
| | NOAF cases | 44 | 18 | | 19 | | |
| | Model 1 | 1 | 0.39 (0.22-0.70) | 0.002 | 0.41 (0.23-0.74) | 0.003 | 0.001 |
| | Model 2 | 1 | 0.40 (0.22-0.72) | 0.002 | 0.43 (0.24-0.78) | 0.006 | 0.002 |
| | Model 3 | 1 | 0.23 (0.10-0.53) | 0.001 | 0.38 (0.17-0.83) | 0.015 | 0.001 |
| Tertiles of HDL-C (mmol/L or mg/L) | | Tertile 1 (<0.97 <37.55) | Tertile 2 (0.97-1.20 37.55-46.46) | | Tertile 3 (>1.20 >46.46) | | |
| | N | 330 | 322 | | 333 | | |
| | NOAF cases | 22 | 25 | | 34 | | |
| | Model 1 | 1 | 1.04 (0.57-1.91) | 0.90 | 1.13 (0.63-2.03) | 0.69 | 0.92 |
| | Model 2 | 1 | 1.05 (0.56-1.96) | 0.88 | 1.25 (0.68-2.30) | 0.47 | 0.74 |
| | Model 3 | 1 | 0.99 (0.44-2.27) | 0.99 | 0.81 (0.36-1.84) | 0.62 | 0.85 |

The associations of TC, TG, LDL-C and HDL-C with new-onset atrial fibrillation were adjusted for models as follows respectively. Moreover, the lowest tertile of TC, TG, LDL-C and HDL-C was referred as the referenced group for the multivariable logistics analysis.

Model 1: Adjusted by age and sex.

Model 2: Adjusted by model 1+ ever smoking, history of hypertension, history of CKD, stroke, history of diabetes, family history for CAD, previous MI, pulse, SBP, killip class on admission.

Model 3: Include age, sex, ever smoking, history of hypertension, history of CKD, stroke, history of diabetes, familiy history for CAD, previous MI, pulse, SBP, killip class on admission, $\beta$-blocker, PPI, white blood cell count, hemoglobin, platelet,creatinine, Troponin I, HsCRP, level of potassium, LVEF (%), culprit artery of LAD, PCI.

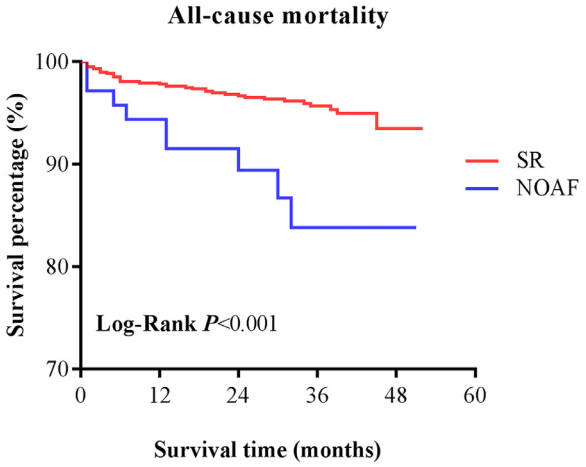


Figure 2. Kaplan-Meier curves for survival percentage by absence or presence of in-hospita. NOAF (all-cause mortality was 19.8% vs 6.1%). SR = sinus rhythm; NOAF = NOAF, new-onset atrial fibrillation.

impossible to define the exact causal relation between cholesterol and NOAF based on the observational data.

In summary, the seemingly paradoxical inverse association of LDL-C and TC with NOAF in the acute STEMI population was confirmed in the present study. Moreover, patients with NOAF during hospitalization had worse prognosis after a relatively long-term follow-up.

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## Disclosures

The authors declare that they have no conflict of interests.

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