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Association between Admission Total Cholesterol and In-Hospital Mortality in Acute Decompensated Heart Failure: A Prospective Cohort Study from Syria

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Research Article

Keywords: acute decompensated heart failure, cholesterol paradox, total cholesterol, LDL-C, in-hospital mortality, prospective cohort, Syria

Posted Date: November 1st, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10883934/v1

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Additional Declarations: No competing interests reported.

Abstract

Background

An apparent inverse relationship between cholesterol levels and mortality — the "cholesterol paradox" — has been described in chronic heart failure, but data from Middle Eastern patients with acute decompensated heart failure (ADHF) are scarce. This study evaluated the association between admission lipid profile and in-hospital mortality in Syrian patients with ADHF.

Methods

A prospective cohort study was conducted at two tertiary university hospitals in Damascus, Syria (Al-Mouassat and Al-Watani) from March 2025 to March 2026, enrolling 166 consecutive adult patients with ADHF (2021 European Society of Cardiology [ESC] criteria). Lipid profiles were measured within 24 hours of admission. Receiver operating characteristic (ROC) curve, bivariate, and multivariate logistic regression analyses were performed; Firth's penalized likelihood regression was used as a sensitivity analysis given the limited number of events.

Results

In-hospital mortality was 15.1% (25/166). Non-survivors had significantly lower total cholesterol (TC) (142.8 ± 38.4 vs. 168.5 ± 42.6 mg/dL, P = 0.005) and low-density lipoprotein cholesterol (LDL-C) (78.4 ± 28.2 vs. 96.6 ± 32.8 mg/dL, P = 0.009). TC showed moderate discrimination (area under the curve [AUC] = 0.712; optimal cutoff ≤ 130 mg/dL); LDL-C showed fair discrimination (AUC = 0.632; optimal cutoff ≤ 88 mg/dL). In multivariate analysis, TC < 150 mg/dL was independently associated with mortality (adjusted odds ratio [AOR] = 2.38, 95% confidence interval [CI]: 1.12–5.06, P = 0.024); LDL-C was significant in bivariate analysis (P = 0.009) but did not retain independent significance after adjustment for TC and other covariates (AOR = 1.89, P = 0.069). Five independent predictors were identified: oxygen saturation < 90%, TC < 150 mg/dL, age ≥ 70 years, New York Heart Association (NYHA) Class IV, and sodium < 135 mEq/L (model AUC = 0.827). Firth's sensitivity analysis yielded consistent estimates.

Conclusions

Lower admission TC is independently associated with higher in-hospital mortality in Syrian ADHF patients, supporting the cholesterol paradox in this previously understudied population. LDL-C was associated with mortality only at the bivariate level. The cutoffs of 130 mg/dL (ROC-derived) and 150 mg/dL (multivariate-derived) should be externally validated in larger multicenter studies that include natriuretic peptides and apply propensity score methods.

Background

Heart failure (HF) is a chronic and progressive clinical syndrome caused by structural and/or functional cardiac abnormalities that result in reduced cardiac output and/or elevated intracardiac pressure [1]. Acute decompensated heart failure (ADHF) refers to previously diagnosed or new-onset HF presenting with rapid worsening of signs and symptoms, and it remains a leading cause of hospitalization and in-hospital death worldwide [2, 3]. Despite advances in pharmacological therapy, in-hospital mortality in ADHF ranges from 4% to 12% in international registries, and identifying simple, routinely available prognostic markers at admission remains a clinical priority [4, 5].

Among the laboratory variables investigated as potential prognostic markers in HF, the lipid profile has attracted particular attention because of an apparent paradox. Elevated total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) are well-established risk factors for atherosclerosis and coronary artery disease in the general population. However, several studies have shown that lower cholesterol levels are associated with worse outcomes in patients with established HF — a phenomenon termed the "cholesterol paradox" [6, 7]. This inverse relationship has been documented across multiple HF populations. Horwich et al. [7] demonstrated in a large US cohort of 17,791 ADHF patients that low TC (< 160 mg/dL) was associated with higher in-hospital mortality. Wang et al. [6] showed that low LDL-C (< 100 mg/dL) was independently associated with higher all-cause mortality in patients with heart failure with reduced ejection fraction (HFrEF) using competing risk analysis. More recently, Brito et al. [8] reported from a Portuguese cohort of 167 ADHF patients that both low TC and low LDL-C were associated with worse in-hospital outcomes, with an LDL-C cutoff of 88 mg/dL identified as the optimal threshold.

However, the cholesterol paradox has not been consistently observed across all populations and study designs. Notably, Yoon et al. [9] examined the relationship between cholesterol and mortality in 2,797 Korean patients with acute HF and found that while low TC was associated with higher mortality in unadjusted analysis, this relationship was no longer significant after propensity score matching, suggesting that the apparent paradox may be driven by confounding rather than a true biological phenomenon. Similarly, He et al. [10] demonstrated that while individual lipid parameters showed inverse associations with mortality in ADHF, the composite biomarker triglyceride-glucose index to high-density lipoprotein cholesterol ratio (TyG/HDL-C) provided superior prognostic discrimination, raising questions about whether individual lipid components are the most informative markers. These conflicting findings highlight the importance of examining the cholesterol paradox in diverse populations and using robust statistical methods to account for potential confounders.

Several mechanisms have been proposed to explain the cholesterol paradox, including the catabolic state of advanced HF (where low cholesterol reflects malnutrition, inflammation, and hepatic dysfunction), the loss of the protective effect of lipoproteins against endotoxemia, and reverse causation (where severe HF causes cholesterol lowering rather than the reverse) [11]. Importantly, the paradox

raises clinical questions about whether conventional lipid-lowering targets are appropriate for patients with advanced HF, particularly in the acute decompensated setting [12, 13].

Despite the growing body of literature on the cholesterol paradox, data from Middle Eastern populations remain scarce, and no prospective study has examined this association in Syrian patients with ADHF. The Syrian healthcare context — characterized by a high burden of ischemic heart disease, evolving patterns of statin utilization, and unique patient demographics — may yield different associations between cholesterol and outcomes than those reported in Western and East Asian cohorts. Moreover, regional reports suggest that admission lipid profiles in Middle Eastern HF populations differ from those in Western registries, yet their prognostic implications have not been systematically evaluated.

We therefore hypothesized that lower admission TC and LDL-C would be independently associated with higher in-hospital mortality in Syrian patients with ADHF. The primary objective of this study was to evaluate the association between admission lipid profile (particularly TC and LDL-C) and in-hospital mortality in patients admitted with ADHF at two university hospitals in Damascus, Syria. The secondary objective was to identify independent clinical and laboratory predictors of in-hospital death in this population.

Methods

Study design and setting

This was a prospective cohort study conducted at Al-Mouassat and Al-Watani University Hospitals in Damascus, Syria, from March 2025 to March 2026. Both hospitals are tertiary-level teaching and referral hospitals affiliated with Damascus University and serve as the principal cardiac referral centers for the greater Damascus area. The study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [14]; a completed STROBE checklist is provided as Supplementary File 1.

Study population

The source population included all adult patients (≥ 18 years) admitted with a primary diagnosis of ADHF, defined according to the 2021 European Society of Cardiology (ESC) Heart Failure Guidelines [2]. Consecutive sampling was used to recruit participants from the emergency department, intensive care unit, and cardiology ward. The inclusion criteria were: (1) age ≥ 18 years; (2) admission with a primary diagnosis of ADHF; (3) availability of a complete lipid profile (TC, LDL-C, HDL-C, triglycerides) measured within 24 hours of admission; and (4) provision of written informed consent.

The exclusion criteria were: (1) absence of a lipid profile within 24 hours of admission; (2) end-stage renal disease (ESRD) on maintenance dialysis; (3) chronic liver disease; (4) active malignancy; (5)

pregnancy or lactation; (6) death or discharge within the first 48 hours of admission; and (7) refusal to participate.

The exclusion of patients who died within 48 hours of admission warrants justification. This criterion was applied to reduce survivorship bias, as patients who die very early may not have had sufficient time for their lipid profile to reflect the metabolic state of established ADHF, and their very early death may be driven by acute catastrophic events (e.g., massive pulmonary embolism, cardiac rupture) rather than the chronic pathophysiological processes underlying the cholesterol paradox. However, this exclusion may also introduce bias by removing the most severely ill patients.

Screening and enrollment

During the study period, a total of 198 patients were screened for eligibility. Of these, 32 were excluded: 8 died or were discharged within 48 hours, 7 lacked a complete lipid profile within 24 hours, 6 had end-stage renal disease on dialysis, 5 had chronic liver disease, 3 had active malignancy, 2 were pregnant, and 1 declined participation. The remaining 166 patients met all eligibility criteria, provided written informed consent, and were enrolled. All 166 patients completed in-hospital follow-up and were included in the final analysis cohort (Fig. 1).

Sample size

The minimum required sample size was calculated a priori using G*Power 3.1.9.7. Based on a two-sided α of 0.05, a power of 80%, an expected in-hospital mortality rate of approximately 10% in ADHF [4, 5], and an effect size (w) of 0.27 (Phi coefficient for chi-square analysis), a minimum of 156 patients was required. To allow for potential missing data and to facilitate multivariate logistic regression analysis, the target sample size was inflated to 166 patients.

With 25 events and 9 candidate predictor variables initially entered into the multivariate model, the events per variable (EPV) ratio during the model-building phase was 2.8:1. Four variables were not retained as independent predictors ($P > 0.05$), yielding a final five-predictor model with an EPV of 5:1. Both EPV values are below the commonly recommended threshold of ≥ 10 [15]. To mitigate the risk of overfitting and unstable estimates, a sensitivity analysis using Firth's penalized likelihood logistic regression was performed [16]. These limitations are acknowledged and their implications discussed below.

Data collection and definitions

Demographic, clinical, echocardiographic, and laboratory data were collected through patient interviews and review of medical records. The collected variables are summarized in Table 1.

ADHF was defined according to the 2021 ESC Heart Failure Guidelines [2]. Venous blood samples were drawn within 24 hours of admission. Given the acute clinical presentation of ADHF, fasting status could not be guaranteed for all patients; however, evidence suggests that non-fasting lipid profiles retain prognostic value and that the magnitude of postprandial lipid change is clinically modest [17, 18]. TC, LDL-C, HDL-C, and triglycerides were measured using standardized enzymatic methods (COBAS c311 analyzer; Roche Diagnostics, Mannheim, Germany) with reagents from the same manufacturer; LDL-C was calculated using the Friedewald equation when triglycerides were < 400 mg/dL and measured directly otherwise. Transthoracic echocardiography was performed for all patients using a GE Healthcare Vivid T8 system, and LVEF was calculated using the modified Simpson's biplane method. Patients were classified into three LVEF categories: HFpEF (LVEF ≥ 50%), HFmrEF (LVEF 40–49%), and HFrEF (LVEF < 40%).

Information on prior statin use was collected as a binary variable (yes/no); however, the type, duration, and dose of statin therapy were not systematically recorded and are acknowledged as a limitation.

The interview was developed by the study team specifically for the purposes of this research; a copy is provided in Supplementary File 2.

Outcomes

The primary outcome was in-hospital mortality (all-cause death during the index hospitalization). Patients were followed daily until discharge or death. Secondary outcomes included the discriminative performance of TC and LDL-C for mortality prediction and the identification of independent predictors of in-hospital death.

Statistical analysis

Data were analyzed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA) and R version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria) for Firth's penalized regression. Continuous variables were normally distributed and expressed as mean ± standard deviation (SD), and compared using the independent samples t-test. Categorical variables were expressed as frequencies and percentages and compared using the chi-square test or Fisher's exact test. Receiver operating characteristic (ROC) curve analysis was used to evaluate the discriminative performance of TC and LDL-C, with area under the curve (AUC), optimal cutoff (Youden's index), sensitivity, specificity, and predictive values reported.

Both bivariate and multivariate logistic regression analyses were used to identify factors associated with in-hospital mortality. Variables with P < 0.10 in bivariate analysis were entered into the multivariate model. Cutoffs for binary transformation of continuous predictors were selected a priori based on ROC-derived thresholds, clinical interpretability, and consistency with prior literature [6, 7, 8]; the higher multivariate cutoff for TC (< 150 mg/dL) versus the ROC-optimal cutoff (≤ 130 mg/dL) reflects a trade-off between statistical optimization and clinical generalizability. The adjusted odds ratio (AOR) with 95%

confidence interval (CI) was reported; model calibration was assessed by the Hosmer–Lemeshow test and discrimination by the model AUC.

Missing data were < 1% for all variables; a complete-case analysis was therefore performed without imputation. Two-tailed P < 0.05 was considered statistically significant.

Bias

Selection bias was minimized by consecutive enrolment of all eligible patients during the study period. Information bias was limited by standardized data collection, central laboratory measurements, and a single echocardiography machine model. Residual confounding by unmeasured variables (e.g., natriuretic peptides, inflammatory markers, nutritional status) is acknowledged as a limitation of the observational design. The exclusion of patients who died within 48 hours may introduce survivorship bias; this is discussed in the Limitations section.

Ethical considerations

Ethical approval

was granted by the Institutional Review Board of the Faculty of Medicine, Damascus University. The study was conducted in accordance with the Declaration of Helsinki (1964) and its later amendments. Written informed consent was obtained from each participant or their legal guardian.

Results

Participant flow

A total of 198 patients were screened during the study period. After applying the exclusion criteria, 166 consecutive patients were enrolled and completed in-hospital follow-up (Fig. 1). There were no losses to follow-up or withdrawals.

Baseline characteristics

The baseline characteristics of the study population stratified by mortality status are presented in Table 1. The mean age of the cohort was 65.4 ± 12.5 years, 62.6% were male, and 53.0% had an ischemic HF etiology. Non-survivors were significantly older than survivors (72.4 ± 10.8 vs. 64.2 ± 12.5 years, P = 0.003) and had significantly lower O_2 saturation (88.4 ± 6.8 vs. 92.6 ± 5.2%, P < 0.001) and lower systolic blood pressure (108.5 ± 18.2 vs. 118.6 ± 22.4 mmHg, P = 0.034). NYHA Class IV was significantly more common among non-survivors (60.0% vs. 27.6%, P = 0.004). There were no significant differences between groups in sex, BMI, HF etiology, most comorbidities, or prior medications.

Table 1
Baseline characteristics of patients with ADHF stratified by in-hospital mortality

Variable	Deaths (n = 25)	Survivors (n = 141)	P-value
Age, years (mean ± SD)	72.4 ± 10.8	64.2 ± 12.5	0.003
Male sex, n (%)	15 (60.0)	89 (63.1)	0.766
BMI, kg/m² (mean ± SD)	24.8 ± 4.2	26.9 ± 5.1	0.053
Ischemic etiology, n (%)	16 (64.0)	72 (51.1)	0.234
Hypertension, n (%)	17 (68.0)	96 (68.1)	0.995
Diabetes mellitus, n (%)	12 (48.0)	58 (41.1)	0.519
Ischemic heart disease, n (%)	16 (64.0)	72 (51.1)	0.234
Prior stroke, n (%)	8 (32.0)	23 (16.3)	0.063
Chronic kidney disease, n (%)	10 (40.0)	34 (24.1)	0.092
COPD, n (%)	5 (20.0)	18 (12.8)	0.498
Prior statins use, n (%)	9 (36.0)	64 (45.4)	0.376
Prior beta-blockers, n (%)	12 (48.0)	82 (58.2)	0.335
Prior ACE inhibitors, n (%)	10 (40.0)	68 (48.2)	0.443
Prior ARBs, n (%)	6 (24.0)	35 (24.8)	0.931
NYHA Class IV, n (%)	15 (60.0)	39 (27.6)	0.004
HFpEF (LVEF ≥ 50%), n (%)	8 (32.0)	54 (38.3)	0.498
HFmrEF (LVEF 40–49%), n (%)	6 (24.0)	42 (29.8)	—
HFrEF (LVEF < 40%), n (%)	11 (44.0)	45 (31.9)	—
Systolic BP (mmHg)	108.5 ± 18.2	118.6 ± 22.4	0.034
Diastolic BP (mmHg)	66.8 ± 12.4	72.3 ± 14.8	0.081
Mean BP (mmHg)	80.8 ± 13.6	86.8 ± 16.2	0.082
Heart rate (bpm)	98.4 ± 18.6	92.2 ± 16.8	0.096
O_2 saturation (%)	88.4 ± 6.8	92.6 ± 5.2	< 0.001

BMI = body mass index; COPD = chronic obstructive pulmonary disease; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; NYHA = New York Heart Association; HFpEF = heart failure with preserved ejection fraction; HFmrEF = heart failure with mildly reduced ejection fraction; HFrEF = heart failure with reduced ejection fraction; BP = blood pressure; SD = standard deviation.

Laboratory findings by mortality status

Non-survivors had significantly lower admission TC, LDL-C, sodium, and hemoglobin, and significantly higher creatinine, compared with survivors (Table 2). HDL-C and triglycerides did not differ significantly between the two groups. Detailed box plots comparing TC and LDL-C between groups are shown in Fig. 2.

Table 2
Laboratory findings at admission stratified by in-hospital mortality

Laboratory variable	Deaths (n = 25)	Survivors (n = 141)	P-value
Sodium (mEq/L)	135.2 ± 5.7	137.6 ± 4.9	0.034
Hemoglobin (g/dL)	10.8 ± 1.6	11.9 ± 1.8	0.004
Creatinine (mg/dL)	1.68 ± 0.92	1.34 ± 0.76	0.046
Total cholesterol (mg/dL)	142.8 ± 38.4	168.5 ± 42.6	0.005
LDL-C (mg/dL)	78.4 ± 28.2	96.6 ± 32.8	0.009
HDL-C (mg/dL)	36.2 ± 10.4	40.8 ± 11.2	0.057
Triglycerides (mg/dL)	118.6 ± 48.2	132.4 ± 56.8	0.254

LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; SD = standard deviation.

Distribution of cholesterol categories

Patients were classified into three TC categories: TC < 150 mg/dL, TC 150–199 mg/dL, and TC ≥ 200 mg/dL. The distribution of these categories differed significantly between non-survivors and survivors (Table 3). Among non-survivors, 64.0% had TC < 150 mg/dL compared with only 39.7% of survivors (P = 0.023). Conversely, only 8.0% of non-survivors had TC ≥ 200 mg/dL compared with 22.7% of survivors.

Table 3
Distribution of total cholesterol categories by mortality status

TC Category	Deaths (n = 25)	Survivors (n = 141)	χ^2	P-value
TC < 150 mg/dL, n (%)	16 (64.0)	56 (39.7)	5.09	0.023
TC 150–199 mg/dL, n (%)	7 (28.0)	58 (41.1)	1.54	0.215
TC ≥ 200 mg/dL, n (%)	2 (8.0)	27 (22.7)	1.83	0.176

Percentages are calculated within each mortality group (row percentages). TC = total cholesterol.

Similarly, patients were classified into three LDL-C categories: LDL-C < 70 mg/dL, LDL-C 70–99 mg/dL, and LDL-C ≥ 100 mg/dL. The distribution of LDL-C categories differed significantly between non-survivors and survivors (Table 4). Among non-survivors, 48.0% had LDL-C < 70 mg/dL compared with 24.8% of survivors (P = 0.018), while only 16.0% of non-survivors had LDL-C ≥ 100 mg/dL compared with 34.8% of survivors.

Table 4
Distribution of LDL-C categories by mortality status

LDL-C Category	Deaths (n = 25)	Survivors (n = 141)	χ^2	P-value
LDL-C < 70 mg/dL, n (%)	12 (48.0)	35 (24.8)	5.62	0.018
LDL-C 70–99 mg/dL, n (%)	9 (36.0)	57 (40.4)	0.16	0.689
LDL-C ≥ 100 mg/dL, n (%)	4 (16.0)	49 (34.8)	3.25	0.072

Percentages are calculated within each mortality group (row percentages). LDL-C = low-density lipoprotein cholesterol.

ROC curve analysis

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the discriminative performance of admission TC and LDL-C for predicting in-hospital mortality (Table 5, Fig. 3). TC showed moderate discrimination with an AUC of 0.712 (95% CI: 0.615–0.809), with an optimal cutoff of ≤ 130 mg/dL yielding a sensitivity of 76.0% and a specificity of 62.4%. LDL-C showed fair discrimination with an AUC of 0.632 (95% CI: 0.534–0.730), with an optimal cutoff of ≤ 88 mg/dL yielding a sensitivity of 64.0% and a specificity of 58.2%. The AUC of TC was numerically higher than that of LDL-C; however, a formal statistical comparison was not performed.

Table 5
ROC curve analysis of TC and LDL-C for predicting in-hospital mortality

Marker	AUC (95% CI)	Optimal cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Total cholesterol	0.712 (0.615–0.809)	≤ 130 mg/dL	76.0	62.4	26.4	93.6
LDL-C	0.632 (0.534–0.730)	≤ 88 mg/dL	64.0	58.2	21.3	90.1

AUC = area under the curve; CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value; TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol. Cutoffs were determined using Youden's index. Lower cholesterol values were treated as positive for mortality prediction (consistent with the cholesterol paradox).

Univariable logistic regression analysis

Of the variables with P < 0.10 on initial bivariate screening (Tables 1 and 2), nine clinically relevant variables were evaluated by univariable logistic regression using a priori cutoffs (Table 6). Oxygen saturation < 90% (OR = 3.24, 95% CI: 1.52–6.92, P = 0.002), NYHA class IV (OR = 2.86, 95% CI: 1.42–5.76, P = 0.003), total cholesterol < 150 mg/dL (OR = 2.68, 95% CI: 1.32–5.44, P = 0.006), serum sodium < 135 mEq/L (OR = 2.52, 95% CI: 1.28–4.96, P = 0.007), age ≥ 70 years (OR = 2.42, 95% CI: 1.28–4.58, P = 0.007), creatinine > 1.5 mg/dL (OR = 2.28, 95% CI: 1.16–4.48, P = 0.017), hemoglobin < 12 g/dL (OR = 2.16, 95% CI: 1.12–4.18, P = 0.022), LDL-C < 88 mg/dL (OR = 2.15, 95% CI: 1.21–3.82, P = 0.009), and systolic blood pressure < 110 mmHg (OR = 1.96, 95% CI: 1.04–3.68, P = 0.038) were all significantly associated with in-hospital death. All nine variables were subsequently entered into the multivariate logistic regression model.

Table 6
Univariable logistic regression analysis of predictors of in-hospital mortality

Variable	OR	95% CI	P-value	Entered MV model
O_2 saturation < 90%	**3.24**	1.52–6.92	0.002	✓
NYHA class IV	**2.86**	1.42–5.76	0.003	✓
Total cholesterol < 150 mg/dL	**2.68**	1.32–5.44	0.006	✓
Serum sodium < 135 mEq/L	**2.52**	1.28–4.96	0.007	✓
Age ≥ 70 years	**2.42**	1.28–4.58	0.007	✓
Creatinine > 1.5 mg/dL	**2.28**	1.16–4.48	0.017	✓
Hemoglobin < 12 g/dL	**2.16**	1.12–4.18	0.022	✓
LDL-C < 88 mg/dL	**2.15**	1.21–3.82	0.009	✓
Systolic BP < 110 mmHg	**1.96**	1.04–3.68	0.038	✓

*OR = odds ratio (unadjusted); CI = confidence interval; MV = multivariate; O_2 = oxygen; NYHA = New York Heart Association; TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; BP = blood pressure. All nine variables with P < 0.10 on initial bivariate screening (*Tables 1 and 2*) were evaluated by univariable logistic regression using a priori clinically meaningful cutoffs and were subsequently entered into the multivariate logistic regression model (*Table 6*). Highly correlated variables (e.g., diastolic and mean blood pressure, collinear with systolic BP) and variables not retained in the multivariate model due to events-per-variable constraints (BMI, prior stroke, chronic kidney disease, HDL-C, heart rate) are not presented in this table but are available in* Tables 1 and 2.

Independent predictors of in-hospital mortality

Multivariate logistic regression analysis (Hosmer–Lemeshow goodness-of-fit: $\chi^2 = 5.30$, df = 7, P = 0.626, indicating adequate calibration; model AUC = 0.827, 95% CI: 0.752–0.902, indicating good discrimination) identified five independent predictors of in-hospital mortality (Table 7, Fig. 4): O_2

saturation < 90% at admission (AOR = 2.68, 95% CI: 1.22–5.88, P = 0.014), TC < 150 mg/dL (AOR = 2.38, 95% CI: 1.12–5.06, P = 0.024), NYHA Class IV (AOR = 2.24, 95% CI: 1.06–4.72, P = 0.035), age ≥ 70 years (AOR = 2.12, 95% CI: 1.08–4.16, P = 0.029), and sodium < 135 mEq/L (AOR = 2.04, 95% CI: 1.02–4.08, P = 0.044).LDL-C (< 88 mg/dL), which was significant in the univariable analysis (OR = 2.15, 95% CI: 1.21–3.82, P = 0.009), did not retain independent significance after adjustment (AOR = 1.89, 95% CI: 0.95–3.76, P = 0.069). The remaining three variables (creatinine > 1.5 mg/dL, hemoglobin < 12 g/dL, and systolic blood pressure < 110 mmHg) were not retained as independent predictors after adjustment (P > 0.05 for all); their adjusted estimates are not presented.

In the sensitivity analysis using Firth's penalized likelihood logistic regression, the direction and magnitude of the associations were consistent with the standard maximum-likelihood estimates, although the confidence intervals remained wide due to the limited number of events (Supplementary Table S1).

Table 7
Multivariate logistic regression analysis of predictors of in-hospital mortality

Variable	AOR	95% CI	P-value
O_2 saturation < 90%	**2.68**	1.22–5.88	0.014
TC < 150 mg/dL	**2.38**	1.12–5.06	0.024
NYHA Class IV	**2.24**	1.06–4.72	0.035
Age ≥ 70 years	**2.12**	1.08–4.16	0.029
Sodium < 135 mEq/L	**2.04**	1.02–4.08	0.044
LDL-C < 88 mg/dL †	**1.89**	0.95–3.76	0.069

AOR = adjusted odds ratio; CI = confidence interval; TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; NYHA = New York Heart Association. † Not retained as independent predictor (P > 0.05). Hosmer–Lemeshow goodness-of-fit: $\chi^2 = 5.30$, df = 7, P = 0.626. Model AUC = 0.827 (95% CI: 0.752–0.902).

Discussion

This prospective cohort study, conducted at two university hospitals in Damascus, Syria, represents one of the first systematic evaluations of the relationship between admission lipid profile and in-hospital mortality in Syrian patients with ADHF. The overall in-hospital mortality rate of 15.1% is consistent with international reports for ADHF (4–12% in most registries, with higher rates in tertiary-care and ICU populations) [4, 5] and closely mirrors the 16.8% rate reported by Brito et al. [8] in a similarly sized Portuguese cohort.

The cholesterol paradox in acute heart failure

The principal finding of this study is that lower admission TC is independently associated with higher in-hospital mortality in ADHF, supporting the existence of the "cholesterol paradox" in this population. This observation is consistent with several prior studies. Horwich et al. [7] demonstrated in a large US cohort of 17,791 ADHF patients that low TC (< 160 mg/dL) was associated with higher in-hospital mortality. Charach et al. [19] similarly reported that baseline low LDL-C was associated with worse outcomes in advanced HF. Wang et al. [6] showed that low LDL-C (< 100 mg/dL) was independently associated with higher all-cause mortality in patients with HFrEF using competing risk analysis. Most recently, Brito et al. [8] reported from a Portuguese cohort of 167 ADHF patients that low TC and low LDL-C were both associated with worse in-hospital outcomes, with an LDL-C cutoff of 88 mg/dL — identical to our finding. This convergence across geographically and ethnically distinct populations (North American, European, Middle Eastern) lends support to the existence of a true biological phenomenon rather than a population-specific artifact, although it does not rule out residual confounding as an alternative explanation.

However, the cholesterol paradox has not been universally replicated. In a study of 2,797 Korean patients with acute HF, Yoon et al. [9] found that while low TC was associated with higher mortality in unadjusted analysis, this relationship disappeared after propensity score matching (PSM). This important finding suggests that the apparent paradox may be driven by confounding — patients with lower cholesterol may have more advanced HF, greater frailty, or more comorbidities — rather than by a true protective effect of higher cholesterol. Our observational design cannot resolve this question, and the absence of PSM in our analysis is an acknowledged limitation. However, PSM may also attenuate genuine prognostic signaling carried by cholesterol as a marker of disease severity, particularly when the matching variables are themselves correlates of disease severity. He et al. [10] further showed that composite biomarkers (TyG/HDL-C) may outperform individual lipid measures, supporting exploration of multidimensional metabolic indices in future research.

Several mechanisms have been proposed to explain the cholesterol paradox. First, low cholesterol may reflect the catabolic state of advanced HF, where cardiac cachexia, malnutrition, and hepatic dysfunction reduce lipoprotein synthesis [12, 20]. Second, lipoproteins have a protective effect against circulating endotoxins (lipopolysaccharides), and low cholesterol may permit higher endotoxin bioactivity, amplifying the inflammatory cascade that characterizes decompensated HF [11]. Third, reverse causation may contribute: severe HF itself may lower cholesterol through hemodynamic and metabolic derangements, rather than low cholesterol directly causing mortality. The cross-sectional nature of our lipid measurement precludes definitive distinction between these mechanisms, but the persistence of the association after multivariate adjustment (including for age, NYHA class, O_2 saturation, and sodium) suggests that low cholesterol is at minimum a marker of physiological vulnerability in ADHF.

LDL-C: bivariate significance without independent association

An important nuance of our findings is that while LDL-C was significantly lower in non-survivors and showed fair discrimination for mortality (AUC = 0.632), it did not retain independent significance in the

multivariate model (P = 0.069). This is in contrast to the findings of Brito et al. [8], who reported that LDL-C remained an independent predictor in their Portuguese cohort. Additionally, with only 25 events, the power to detect an independent effect of LDL-C beyond that of TC is limited. The EPV of 5:1 in the final model (and 2.8:1 during the initial model-building phase with nine candidate variables) is below the recommended threshold of ≥ 10 [15], which increases the risk of both type II error and overfitting. The sensitivity analysis using Firth's penalized likelihood yielded consistent results, providing some reassurance regarding the robustness of our findings. This observation also aligns with the Korean study by Yoon et al. [9], where the association between LDL-C and mortality was attenuated after more rigorous confounding control. It is plausible that LDL-C, while associated with mortality, reflects the same underlying pathophysiological process as TC rather than providing independent prognostic information.

Discriminative performance of TC and LDL-C

The ROC analysis showed that TC provided moderate discrimination for in-hospital mortality (AUC = 0.712), with an optimal cutoff of ≤ 130 mg/dL yielding a sensitivity of 76% and a specificity of 62.4%. LDL-C provided fair discrimination (AUC = 0.632), with a cutoff of ≤ 88 mg/dL. The TC cutoff of ≤ 130 mg/dL in our study is lower than the < 160 mg/dL threshold used by Horwich et al. [7] but is consistent with the increasingly recognized concept that even moderately low cholesterol may signal risk in ADHF. The identical LDL-C cutoff of 88 mg/dL in our study and the Portuguese study by Brito et al. [8] is noteworthy and may represent a reproducible threshold across populations, although external validation is needed.

These AUC values indicate that TC and LDL-C alone are insufficient for individual-level prediction, and they should be interpreted in the context of other clinical and laboratory variables. The five-predictor model (O_2 saturation < 90%, TC < 150 mg/dL, age ≥ 70 years, NYHA Class IV, sodium < 135 mEq/L) achieved an AUC of 0.827, representing good discrimination. This is comparable to established risk scores such as the ADHERE [21] and GWTG-HF [22] models, although direct comparison is limited by differences in study populations and endpoints.

Clinical implications

The findings of this study have several clinical implications. First, the cholesterol paradox should be recognized by clinicians managing ADHF: a low admission cholesterol should not be reassuring, but rather should prompt heightened vigilance. Second, TC ≤ 130 mg/dL may serve as a simple, readily available risk marker that can be incorporated into routine admission assessment. Third, the five-predictor model identified in our multivariate analysis — O_2 saturation < 90%, TC < 150 mg/dL, age ≥ 70 years, NYHA Class IV, and sodium < 135 mEq/L — provides a practical bedside tool for early risk stratification. Patients with two or more of these predictors may warrant closer monitoring, earlier escalation of therapy, and consideration of intensive care admission. However, we emphasize that this model requires external validation before clinical adoption, and its application should be limited to patients with established ADHF; the cholesterol paradox should not be extrapolated to the general

population or to patients with stable chronic HF, in whom conventional lipid-lowering targets remain appropriate.

Importantly, our findings should not be interpreted as evidence against lipid-lowering therapy in HF. The cholesterol paradox reflects an association, not causation, and statin therapy has demonstrated benefits in patients with ischemic HF [13]. The decision to initiate, continue, or discontinue statin therapy in ADHF should be guided by the patient's ischemic risk profile and current guidelines, not by the admission cholesterol level alone.

Limitations

Several limitations should be acknowledged. First, the study was conducted at two tertiary centres in Damascus, limiting generalizability. Second, the observational design precludes causal inference, and the cholesterol paradox may reflect reverse causation or residual confounding by unmeasured variables (natriuretic peptides, C-reactive protein, frailty indices). Third, the absence of propensity score matching — as used by Yoon et al. [9] — is a limitation, although the small sample size would limit its feasibility. Fourth, the exclusion of patients who died within 48 hours may introduce survivorship bias; lipid data for these eight patients were not systematically available, precluding a formal sensitivity analysis. Fifth, a formal screening log was not maintained; screening data were reconstructed retrospectively from hospital admission records. Sixth, with 25 events and 5 predictors in the final model (EPV = 5:1; 2.8:1 during the initial nine-variable model-building phase), below the recommended threshold of ≥ 10 [15], limiting statistical power and increasing the risk of overfitting; Firth's sensitivity analysis partially addressed this concern, but larger studies are needed. Seventh, not all patients were fasting at admission, although non-fasting lipid profiles retain prognostic value [16, 17]. Eighth, the duration and intensity of prior statin therapy were not collected, and lipoprotein(a), apolipoprotein B, and natriuretic peptides were not measured. Ninth, follow-up was limited to the index hospitalization.

Conclusions

In this prospective cohort of 166 Syrian patients with ADHF, lower admission TC was independently associated with higher in-hospital mortality, supporting the cholesterol paradox in this previously understudied Middle Eastern population. LDL-C was associated with mortality only at the bivariate level, likely due to its high correlation with TC and limited statistical power. The five-predictor model (O_2 saturation < 90%, TC < 150 mg/dL, age ≥ 70 years, NYHA Class IV, sodium < 135 mEq/L) provides a practical bedside tool for early risk stratification, although it requires external validation. These findings should not alter current lipid-lowering recommendations but highlight low admission cholesterol as a marker of increased risk in ADHF. Larger multicenter studies with long-term follow-up, natriuretic peptide measurement, propensity score methods, and external validation of this model are needed to confirm these findings and further investigate the mechanisms underlying the cholesterol paradox.

Abbreviations

ACEI
Angiotensin-converting enzyme inhibitor
ADHF
Acute decompensated heart failure
AOR
Adjusted odds ratio
ARB
Angiotensin receptor blocker
AUC
Area under the curve
BMI
Body mass index
BP
Blood pressure
CI
Confidence interval
CKD
Chronic kidney disease
COPD
Chronic obstructive pulmonary disease
ESRD
End-stage renal disease
HF
Heart failure
HFmrEF
Heart failure with mildly reduced ejection fraction
HFpEF
Heart failure with preserved ejection fraction
HFrEF
Heart failure with reduced ejection fraction
HDL-C
High-density lipoprotein cholesterol
ICU
Intensive care unit
IHD
Ischemic heart disease
LDL-C
Low-density lipoprotein cholesterol
LVEF
Left ventricular ejection fraction

NPV
Negative predictive value
NYHA
New York Heart Association
PPV
Positive predictive value
ROC
Receiver operating characteristic
SD
Standard deviation
SPSS
Statistical Package for the Social Sciences
STROBE
Strengthening the Reporting of Observational Studies in Epidemiology
TC
Total cholesterol

Declarations

Ethics approval and consent to participate

Ethical approval was granted by the Institutional Review Board of the Faculty of Medicine, Damascus University. Written informed consent was obtained from each participant or their legal guardian. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Authors' contributions

QD conceptualized the study, collected data, performed the statistical analysis using SPSS version 26, and drafted the manuscript. MAK supervised the study, reviewed the analysis, and critically revised the manuscript. Both authors had full access to the underlying dataset, read and approved the final manuscript, and accept accountability for all aspects of the work.

Acknowledgements

The authors thank the medical and nursing staff at Al-Mouassat and Al-Watani University Hospitals for their cooperation during data collection, and the Department of Internal Medicine, Faculty of Medicine, Damascus University, for institutional support.

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Clinical trial number

Not applicable

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Figures

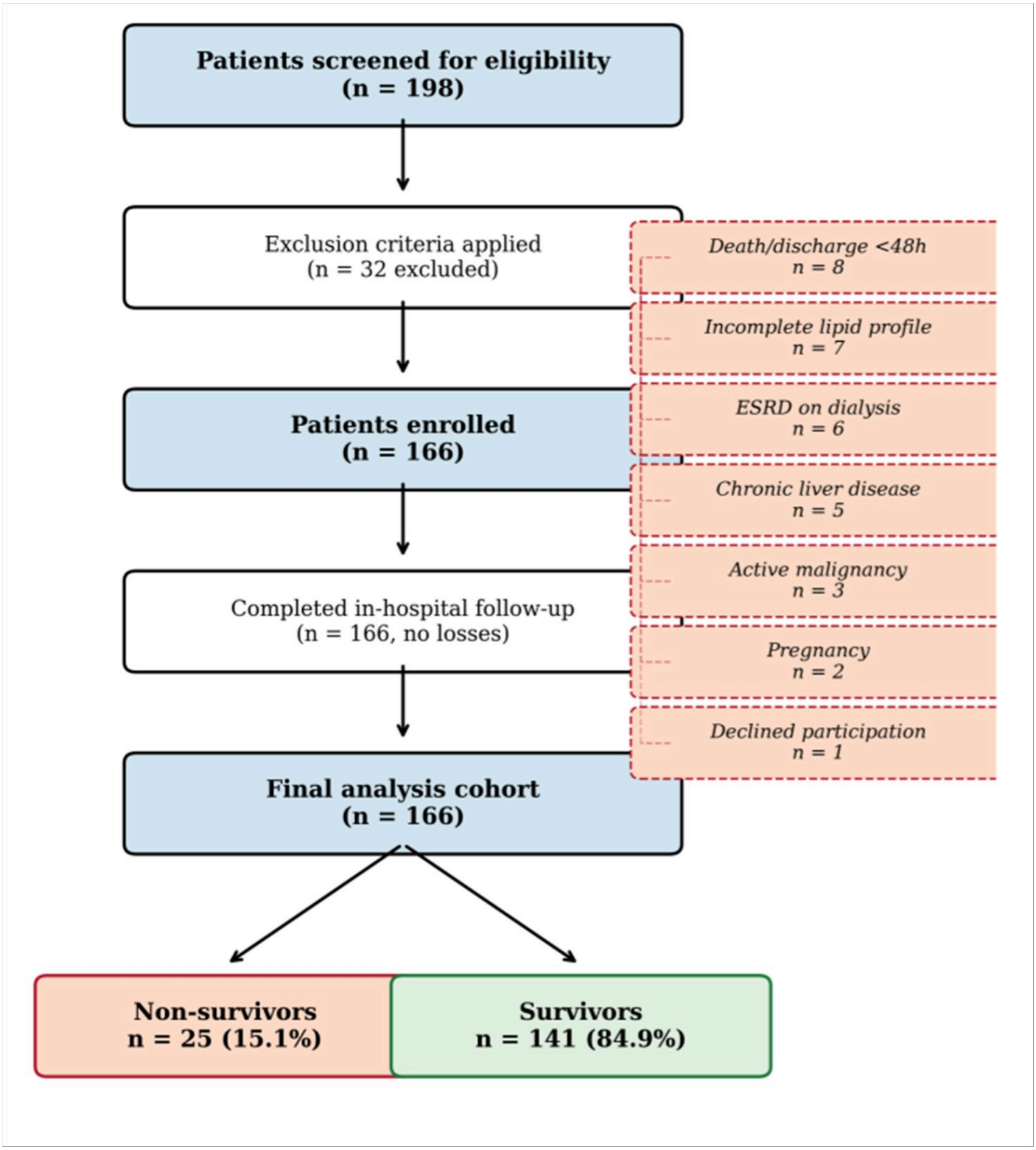


Figure 1

STROBE participant flow diagram. Of 198 screened patients, 32 were excluded (8 died or were discharged within 48 hours, 7 lacked a complete lipid profile within 24 hours, 6 had ESRD on dialysis, 5 had chronic liver disease, 3 had active malignancy, 2 were pregnant, and 1 declined participation). The remaining 166 patients were enrolled and included in the final analysis.

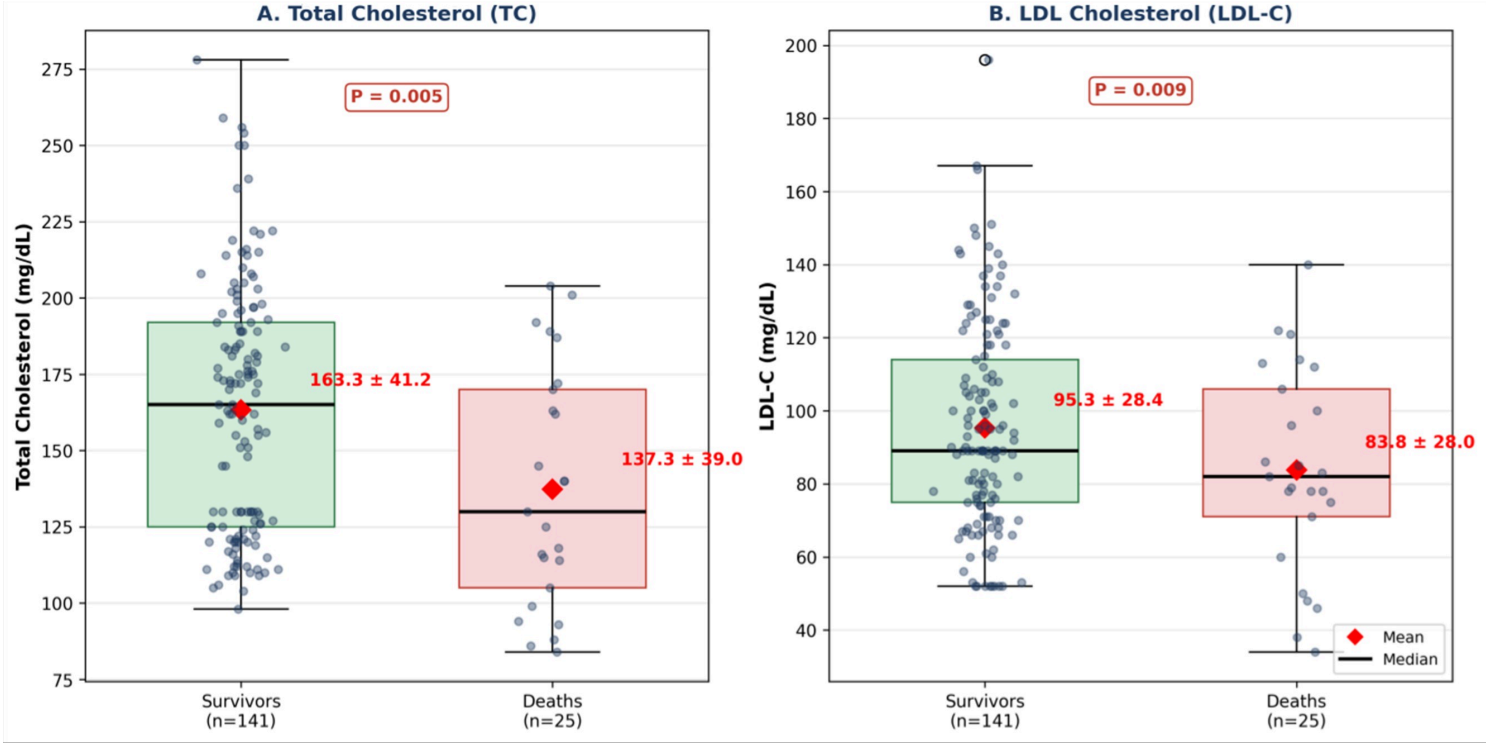


Figure 2

Comparison of admission total cholesterol (TC, panel A) and low-density lipoprotein cholesterol (LDL-C, panel B) between survivors and non-survivors. Box plots show median, interquartile range, and whiskers (1.5xIQR); red diamonds indicate means; individual data points are overlaid. Both TC and LDL-C were significantly lower in non-survivors, consistent with the cholesterol paradox.

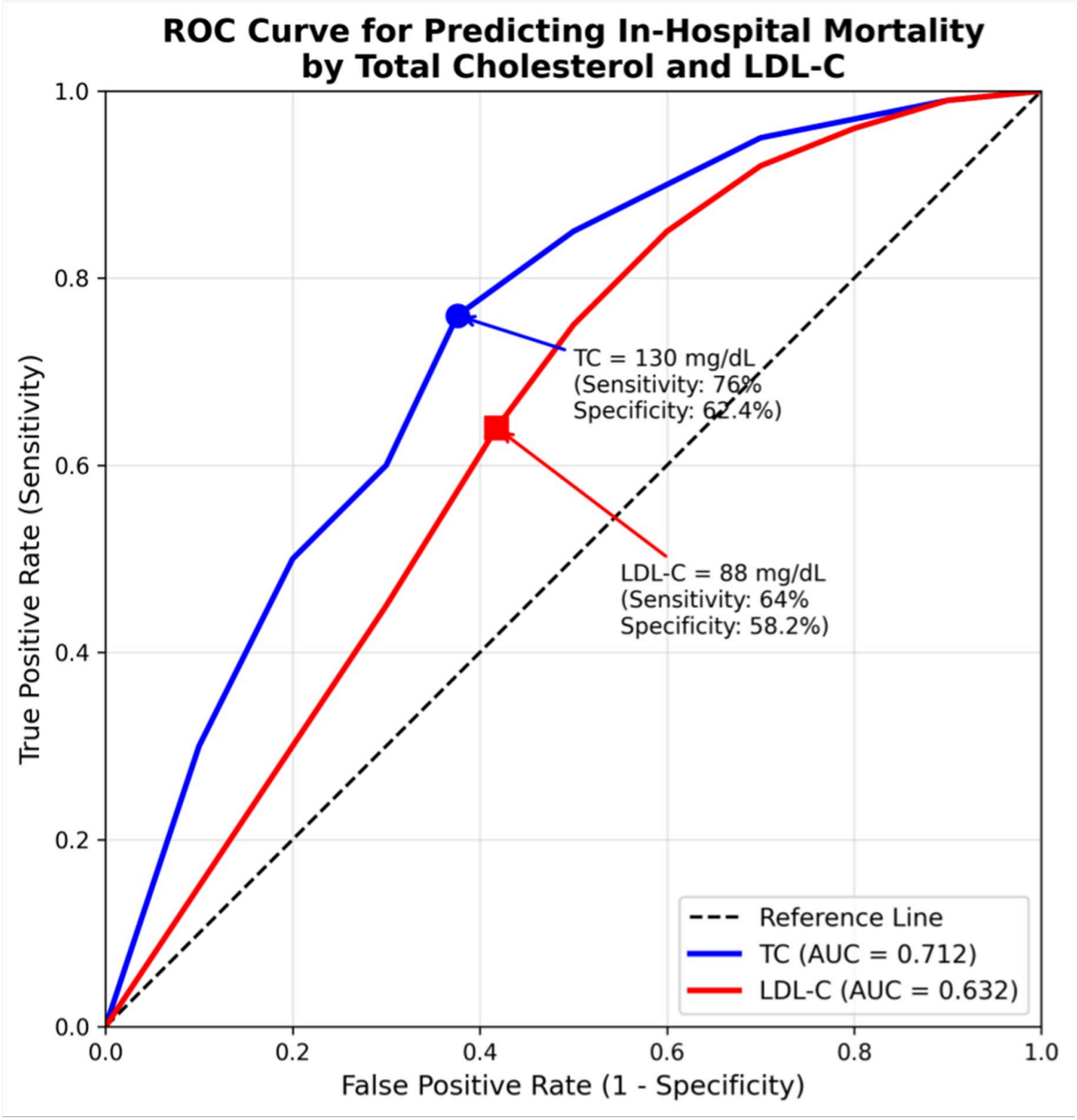


Figure 3

Receiver operating characteristic (ROC) curves for total cholesterol (TC, blue) and low-density lipoprotein cholesterol (LDL-C, red) as predictors of in-hospital mortality. The TC curve shows moderate discrimination (AUC = 0.712), with an optimal cutoff of ≤ 130 mg/dL (sensitivity 76%, specificity 62.4%). The LDL-C curve shows fair discrimination (AUC = 0.632), with an optimal cutoff of ≤ 88 mg/dL (sensitivity 64%, specificity 58.2%). Lower cholesterol values predict in-hospital death (cholesterol paradox).

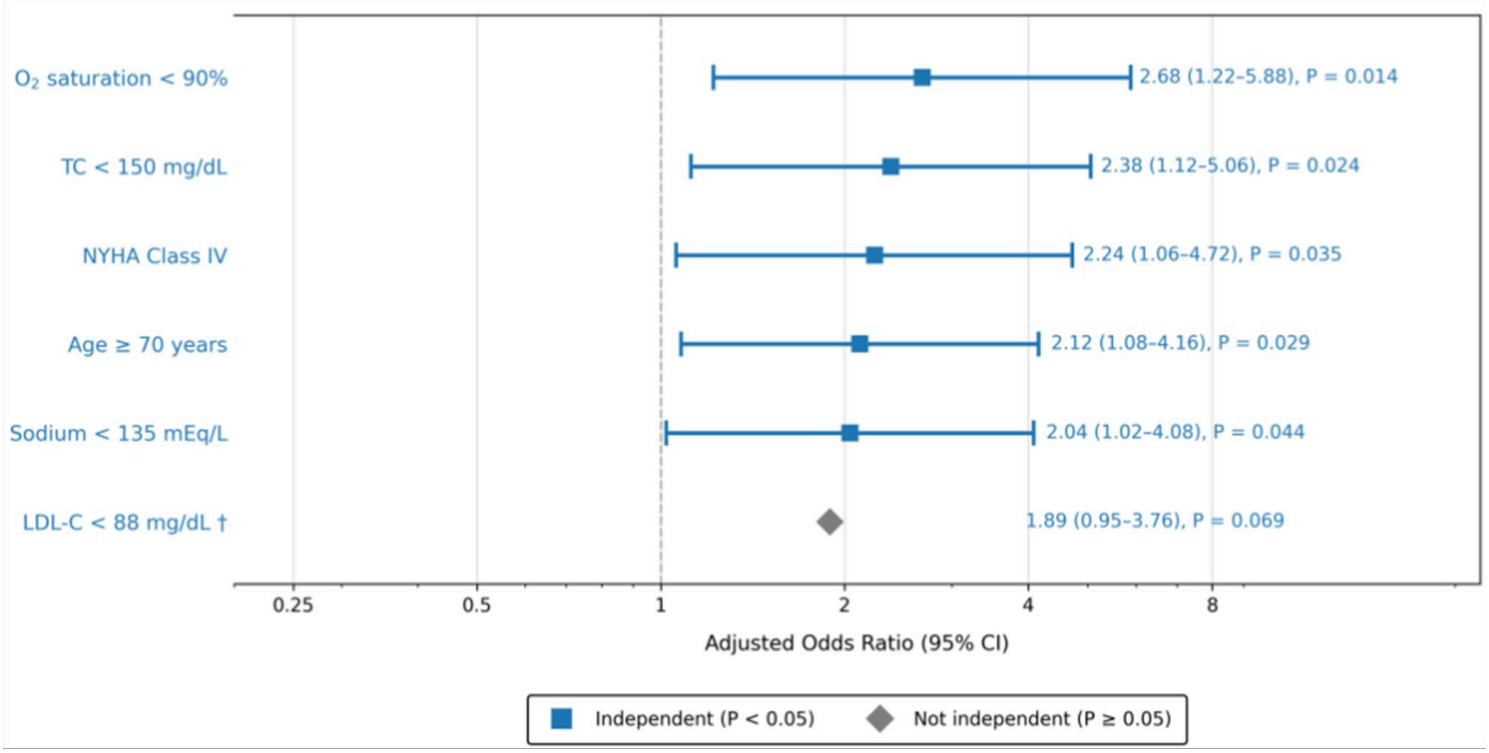


Figure 4

Forest plot of predictors of in-hospital mortality from the multivariate logistic regression model. Blue squares indicate adjusted odds ratios for independent predictors (P < 0.05); the gray diamond indicates LDL-C, which did not reach statistical significance (P = 0.069). Horizontal lines indicate 95% confidence intervals. The dashed vertical line at AOR = 1 indicates no effect.

Supplementary Files

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