Lipids in Health and Disease

RESEARCH

Open Access

Lipid profiles, lipid ratios and 28-day mortality risk in non-surgical older patients with critical illnesses: a retrospective cohort study using hospitalization records

Yang Li[1,2†], Jianli Ge[1,2†], Shasha Geng[1,2], Qingqing Li[1,2], Xin Chen[1,2], Yingqian Zhu[1,2], Xiaotong Guo[1,2], Huajie Gu[3*] and Yue Liu[1,2*]

Abstract

Background and aims The relationship between dyslipidemia and mortality varies by age, with an inverse association observed in the oldest age groups. There is limited research examining lipid profiles' correlation with short-term mortality risk in older adults. This study aimed to investigate associations of lipid profiles and lipid ratios with 28-day mortality risk in non-surgical older patients with critical illnesses.

Methods A retrospective cohort study was conducted with non-surgical older patients with critical illness who were admitted to the ICU of Shanghai East Hospital between January 2022 and November 2024. All data were collected via the hospitalization information system. Elastic network models were used to select covariates and Cox proportional hazards models were constructed to examine the association of lipid profiles and lipid ratios with 28-day mortality risk. Restricted cubic splines were used to test for non-linear relationships. Subgroup analyses were performed based on median age and gender.

Results The median age of study's participants was 75 years, 35.91% of whom were female. Those who died within 28 days were more likely to receive dopamine, norepinephrine and mechanical ventilation than survivors. Adjusted models indicated that LDLC (HR = 0.82, 95% CI: 0.69 to 0.97), lbLDLC (HR = 0.79, 95% CI: 0.63 to 0.98), sdLDLC (HR = 0.44, 95% CI: 0.24 to 0.83), LDLC/HDLC (HR = 0.85, 95% CI: 0.73 to 1.00), and sdLDLC/HDLC (HR = 0.63, 95% CI: 0.40 to 1.00) were associated with decreased 28-day mortality risk. However, no non-linear associations were detected. In younger older adults (age < 75 years), TC, non HDLC, remanent C, TC/HDLC and remanent C/HDLC were related to increased short-term mortality risk. In very old adults, TC, LDLC, lbLDLC, sdLDLC, non HDLC, TC/ HDLC, LDLC/HDLC,

†Yang Li and Jianli Ge contributed equally to this work and share first authorship.

*Correspondence:
Huajie Gu
1701375@tongji.edu.cn
Yue Liu
liuyue_5_2009@163.com

Full list of author information is available at the end of the article

lbLDLC/HDLC, and sdLDLC/HDLC were associated with lower 28-day mortality risk. In women, only lower sdLDLC was associated with increased short-term mortality risk.

Conclusion Lower levels of LDLC and its subtypes (lbLDLC, sdLDLC) were associated with increased 28-day mortality risk, particularly in patients aged ≥ 75 years and women. Conversely, elevated residual cholesterol levels correlated with higher mortality in younger older adults (< 75 years). These findings underscore the need for age- and sex-specific lipid management strategies in older patients with critical illnesses.

Keywords Lipid profiles, Mortality risk, Older patients, Critical illness, Hospitalization records

Introduction

The prevalence of age-related health issues has emerged as a pressing global public health concern. Older adults frequently exhibit multiple diseases, a condition known as multimorbidity, and face an elevated risk of mortality with advancing age [1]. Dyslipidemia, a traditional cardiovascular risk factor, has been extensively studied in relation to mortality [2, 3, 4, 5, 6, 7, 8, 9]. However, research has revealed that this association weakens with age, and in very old individuals, it even exhibits an inverse relationship. Observational studies have consistently demonstrated a positive correlation between low levels of total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDLC) with mortality risk [10, 11, 12, 13]. Moreover, studies have shown that lipid ratios provide more precise insights into the relationship between lipids and individual cardiometabolic health compared to single lipid indicators [14, 15, 16, 17]. However, the majority of these studies have focused on the impact of lipids on long-term mortality risk in older adults, with participants either being healthy or having stable disease control. There is a paucity of in-depth research investigating the relationship between lipids and short-term mortality risk in older patients with critical illnesses.

The majority of extant studies have treated lipid profiles and lipid ratios as linear continuous variables or categorized them based on clinical guidelines. This approach has constrained the investigation into their potential non-linear associations with mortality risk. Recently, restricted cubic splines have been widely adopted for dose-response relationship analysis in public health studies. Moreover, emerging evidence suggests sex-specific variations in lipid metabolism and mortality risk, yet prior studies have not thoroughly explored these differences in older patients with critical illnesses. The objective of this retrospective study was twofold: first, to investigate the linear and non-linear associations of lipid profiles and lipid ratios with the 28-day mortality risk in non-surgical older patients with critical illnesses; and second, to examine the impact of gender and age on these associations.

Methods

A retrospective cohort design was employed in this study, and 768 consecutive non-surgical patients admitted to the intensive care unit (ICU) of Shanghai East Hospital between January 1, 2022 and November 30, 2024 were included. After applying further exclusion criteria, including patients younger than 60 years old ($n = 124$), those readmitted to the ICU within 90 days ($n = 11$), and those with missing lipid profiles data ($n = 181$), and those with other missing covariates ($n = 51$), a total of 401 non-surgical older patients with critical illnesses were included in the subsequent analysis (Fig. 1).

This study was conducted in accordance with the Declaration of Helsinki 2024 Edition [18]. Given its nature as a retrospective cohort study, the involvement of patients or the requirement of informed consent was not applicable. Consequently, ethical approval was exempted by the Ethics Committee of Shanghai East Hospital.

Data collection

All data were collected via the hospitalization information system (HIS), encompassing sociodemographic information, resuscitation measures, and disease diagnosis at the time of patient admission. The Charlson comorbidity index (CCI) was subsequently calculated for all patients to assess the severity of comorbidities.

Physiological and laboratory examinations

Data regarding physiological and laboratory examinations were collected during the initial 24 h of ICU admission. These included patient vital signs (heart rate (HR), respiratory rate (RR), oxygen saturation (SaO2), temperature), urine volume, blood pressure (systolic blood pressure (SBP), diastolic blood pressure (DBP)), hematology (white blood cell (WBC), neutrophils, lymphocyte, monocyte, eosinophils, basophilis, red blood cell, hemoglobin, hematocrit, platelet), C-reactive protein, glycated hemoglobin (HbA1c), lipid profiles (triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDLC), high-density lipoprotein cholesterol (HDLC)), liver function (total protein (TP), albumin, alanine transaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AKP), gamma-glutamyltransferase (GGT), total bilirubin (TBIL), direct bilirubin

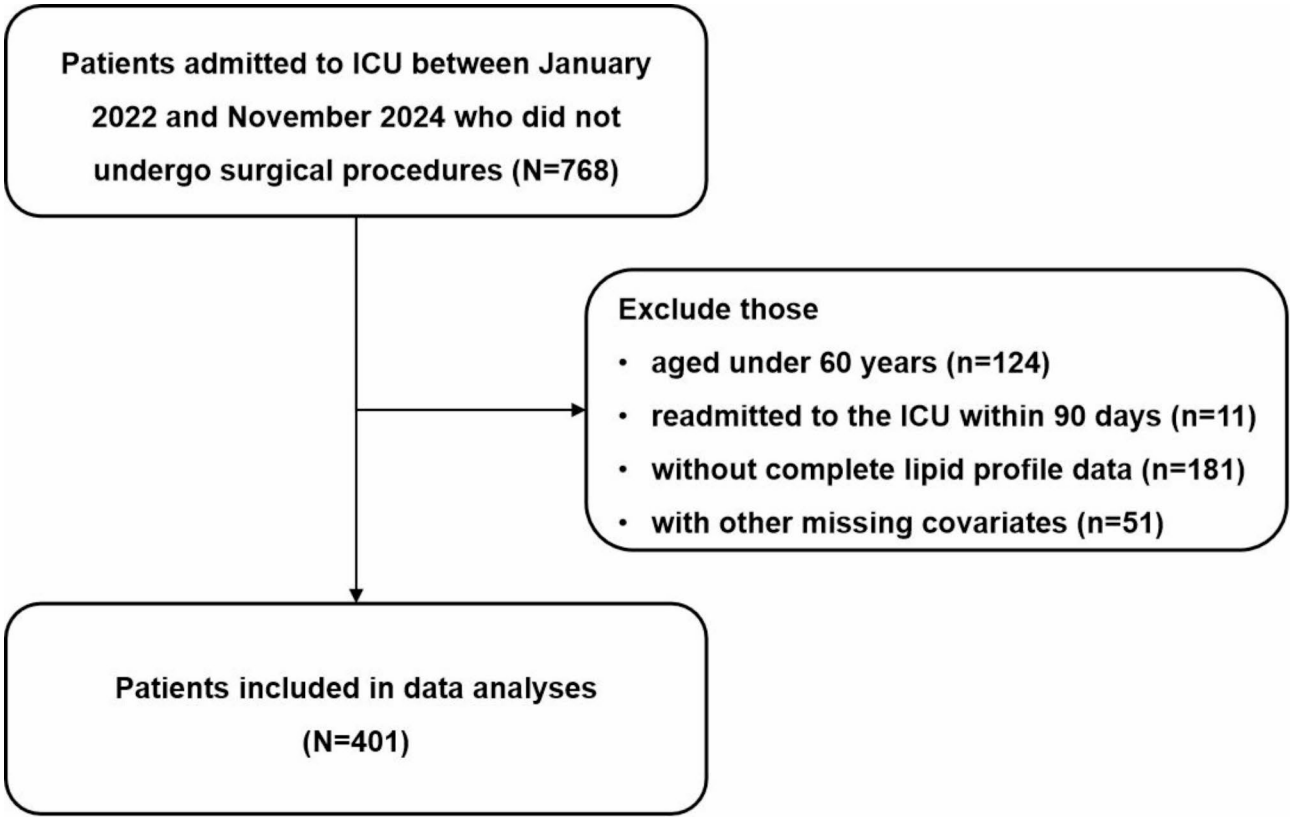

Fig. 1 Flowchart of patient screening and study design

(DBIL), indirect bilirubin (IBIL)), renal function (blood urea nitrogen (BUN), uric acid (UA), serum creatinine (sCr)), electrolytes (sodium (Na), potassium (K), chlorine (Cl), HCO3, calcium (Ca)), and coagulation (international normalized ratio (INR), prothrombin time (PT), activated partial thromboplastin time (APTT)). Researchers referred to other studies for processing possible multiple measurements [19], including taking the worst value, average value, and other ways, as detailed in Table 1. Furthermore, the estimated glomerular filtration rate (eGFR) was calculated based on the Collaboration for Chronic Disease Epidemiology (CKD-EPI) creatinine equation [20].

Lipid profiles and lipid ratios

All patients underwent a standardized lipid test on the first day of their ICU admission, including TG, TC, HDLC and LDLC. An estimation of the two main types of LDLC, large buoyant LDL cholesterol (lbLDLC) and small dense LDL cholesterol (sdLDLC) were calculated using the following equation developed by Maureen et al. [21]:

lbLDLC (mg/dL) = 1.43 × LDLC (mg/dL) − 0.14 × (ln(TG (mg/dL)) × LDLC (mg/dL)) − 8.99.

sdLDLC(mg/dL) = LDLC(mg/dL) - lbLDLC(mg/dL).

Non-high-density lipoprotein cholesterol (non HDLC) and remnant C were also calculated. The following ratios were determined using HDLC as the denominator: TG/HDLC, TC/HDLC, LDLC/HDLC, lbLDLC/HDLC, sdLDLC/HDLC, and remanent C/HDLC.

Outcome

The primary outcome of this investigation was defined as all-cause mortality occurring within 28 days following initial ICU admission. For patients exhibiting less than or equal to 28 days of ICU stay, the occurrence of mortality during this specified period was documented as the actual time of death. Conversely, in instances where mortality did not occur within this time frame, subsequent medical records were systematically reviewed to ascertain survival status within 28 days. For patients with ICU stays longer than 28 days, it was evident that death did not occur.

Statistical analyses

Groups were classified according to the occurrence of a 28-day mortality. Categorical variables were expressed as frequency (percentages), and differences between groups were compared using chi-squared tests or Fisher exact tests. Normality of continuous variables was evaluated using Shapiro-Wilk tests. Due to non-normal

Table 1 Characteristics of the participants at baseline

	Total (*N* = 401)	**Death (*N* = 164)**	**Alive (*N* = 237)**	***P***
Female, n(%)	144(35.91)	57(34.76)	87(36.71)	0.689
Age(year), [M(IOR)]	75(68,83)	75(68,85)	75(69,81)	0.355
Dopamine, n(%)	30(7.48)	20(12.20)	10(4.22)	0.003
Dobutamine, n(%)	15(3.74)	8(4.88)	7(2.95)	0.318
Epinephrine, n(%)	13(3.24)	6(3.66)	7(2.95)	0.695
Norepinephrine, n(%)	143(35.66)	91(55.49)	52(21.94)	< 0.001
Mechanical ventilation, n(%)	177(44.14)	94(57.32)	83(35.02)	< 0.001
Haemodialysis, n(%)	52(12.97)	25(15.24)	27(11.39)	0.259
CCI, [M(IOR)]	2(1,6)	3(1,6)	2(1,5)	0.073
MI, n(%)	23(5.74)	10(6.10)	13(5.49)	0.795
CHF, n(%)	89(22.19)	41(25.00)	48(20.25)	0.261
PVD, n(%)	22(5.49)	6(3.66)	16(6.75)	0.264
CBVA or TIA, n(%)	102(25.44)	42(25.61)	60(25.32)	0.947
Dementia, n(%)	17(4.24)	5(3.05)	12(5.06)	0.325
Chronic pulmonary disease, n(%)	21(5.24)	6(3.66)	15(6.33)	0.238
Connective tissue disease, n(%)	17(4.24)	5(3.05)	12(5.06)	0.325
Peptic ulcer disease, n(%)	7(1.75)	1(0.61)	6(2.53)	0.248
Liver disease, n(%)				0.138
Mild	6(1.50)	2(1.22)	4(1.69)	
Moderate to severe	15(3.74)	10(6.10)	5(2.11)	
Diabetes mellitus, n(%)				0.971
Uncomplicated	64(15.96)	27(16.46)	37(15.61)	
End-organ damage	78(19.45)	32(19.51)	46(19.41)	
Hemiplegia, n(%)	0(0)	0(0)	0(0)	/
Moderate to severe CKD, n(%)	75(18.70)	37(22.56)	38(16.03)	0.099
Localized solid tumor or leukemia or lymphoma, n(%)	83(20.70)	40(24.39)	43(18.14)	0.129
Metastatic solid tumor, n(%)	31(7.73)	16(9.76)	15(6.33)	0.254
AIDS, n(%)	0(0)	0(0)	0(0)	/
HR(bpm), [M(IOR)]	87(76,101)	93(76,109)	84(76,98)	< 0.001
RR(bpm), [M(IOR)]	19(17,20)	19(16,21)	19(17,20)	0.885
SaO_2(%), [M(IOR)]	100(98,100)	99(98,100)	100(98,100)	0.015
Temperature(℃), [M(IOR)]	36.6(36.4,36.9)	36.6(36.4,37.2)	36.5(36.4,36.8)	< 0.001
SBP(mmHg), [M(IOR)]	121(105,135)	118(99,133)	123(108,137)	0.017
DBP(mmHg), [M(IOR)]	67(60,76)	64(56,74)	69(60,77)	0.005
Urine volume(mL), [M(IOR)]	1400(950,1940)	1215(678,1895)	1440(1050,2000)	0.012
WBC(10^9/L), [M(IOR)]	10.62(7.59,15.25)	11.60(8.35,18.63)	9.94(7.25,13.82)	< 0.001
Neutrophils (10^9/L), [M(IOR)]	9.10(5.92,13.29)	10.27(6.92,16.03)	7.93(5.33,11.89)	< 0.001
Lymphocyte (10^9/L), [M(IOR)]	0.85(0.52,1.27)	0.63(0.42,1.06)	0.96(0.63,1.46)	< 0.001
Monocyte(10^9/L), [M(IOR)]	0.60(0.40,0.85)	0.61(0.37,0.86)	0.60(0.42,0.83)	0.789
Eosinophils(10^9/L), [M(IOR)]	0.01(0.00,0.06)	0.00(0.00,0.03)	0.02(0.00,0.09)	< 0.001
Basophilis(10^9/L), [M(IOR)]	0.02(0.01,0.04)	0.02(0.01,0.04)	0.02(0.01,0.04)	0.173
Red blood cell(10^12/L), [M(IOR)]	3.59(2.86,4.15)	3.39(2.79,4.14)	3.70(3.00,4.19)	0.011
Hemoglobin(g/L), [M(IOR)]	105.0(87.0,125.0)	102.0(83.0,124.5)	107.0(91.0,125.0)	0.053
Hematocrit(%), [M(IOR)]	32.2(26.2,38.2)	30.6(25.5,38.4)	33.4(27.7,37.9)	0.042
Platelet(10^9/L), [M(IOR)]	189.0(124.0,249.0)	159.5(96.5,239.0)	201.0(148.0,253.0)	< 0.001
CRP(mg/L), [M(IOR)]	51.22(12.93,105.52)	67.59(28.40,135.64)	34.96(9.46,90.71)	< 0.001
HbA1c(%), [M(IOR)]	6.3(5.8,7.2)	6.3(6.0,7.2)	6.3(5.8,7.2)	0.490
TP(g/L), [M(IOR)]	61.0(53.9,67.7)	57.6(52.7,65.1)	62.6(56.6,68.4)	< 0.001
Albumin(g/L), [M(IOR)]	32.80(29.10,37.70)	31.03(28.12,35.25)	34.30(30.00,38.18)	< 0.001
ALT(U/L), [M(IOR)]	20.0(13.8,42.0)	25.5(14.5,59.5)	18.0(13.0,33.0)	< 0.001
AST(U/L), [M(IOR)]	31.2(21.0,58.8)	41.5(23.4,92.5)	27.9(20.0,49.0)	< 0.001
AKP(U/L), [M(IOR)]	85.0(66.0,110.0)	87.4(73.0,124.6)	81.9(64.1,103.0)	0.013

Table 1 (continued)

	Total (*N* = 401)	Death (*N* = 164)	Alive (*N* = 237)	*P*
GGT(U/L), [M(IOR)]	32.0(18.0,64.0)	37.0(21.7,70.5)	29.0(16.7,57.1)	0.022
TBIL(μmol/L), [M(IOR)]	12.2(8.4,17.9)	12.5(8.5,22.1)	11.9(8.3,16.6)	0.076
DBIL(μmol/L), [M(IOR)]	5.4(3.4,8.7)	6.9(3.9,11.7)	4.9(3.1,7.0)	< 0.001
IBIL(μmol/L), [M(IOR)]	6.0(3.5,9.8)	5.3(3.3,9.7)	6.3(3.7,10.2)	0.200
BUN(mmol/L), [M(IOR)]	8.75(6.00,15.17)	10.58(7.15,17.61)	7.70(5.50,14.30)	< 0.001
UA(μmol/L), [M(IOR)]	316.5(240.1,453.6)	336.5(238.4,489.0)	311.0(244.0,442.0)	0.221
sCr(μmol/L), [M(IOR)]	89.7(66.0,150.5)	102.25(69.45,188.25)	80.0(63.8,128.3)	< 0.001
eGFR(60 ml·min^{-1}·1.73 m^{-2}), [M(IOR)]	66.09(33.88,88.63)	53.17(25.12,83.60)	75.35(41.74,91.00)	< 0.001
Sodium (mmol/L), [M(IOR)]	138.86(135.80,141.57)	138.86(135.04,142.35)	138.86(135.84,141.30)	0.757
Potassium (mmol/L), [M(IOR)]	3.87(3.57,4.23)	3.87(3.56,4.31)	3.87(3.60,4.18)	0.332
Chlorine (mmol/L), [M(IOR)]	104.54(100.70,108.09)	104.54(100.61,109.00)	104.54(101.00,108.00)	0.901
HCO_3(mmol/L), [M(IOR)]	23.9(21.0,26.5)	23.9(19.2,26.3)	23.9(21.8,26.7)	0.010
Calcium (mmol/L), [M(IOR)]	2.03(1.90,2.14)	2.03(1.81,2.11)	2.03(1.95,2.16)	0.014
INR, [M(IOR)]	1.11(1.02,1.28)	1.17(1.07,1.45)	1.07(1.00,1.19)	< 0.001
PT(s), [M(IOR)]	13.0(12.0,14.9)	13.6(12.5,16.8)	12.6(11.8,14.0)	< 0.001
APTT(s), [M(IOR)]	29.4(26.5,33.6)	30.8(27.4,37.1)	28.7(26.1,31.8)	< 0.001
TG(mmol/L), [M(IOR)]	1.13(0.83,1.48)	1.07(0.80,1.41)	1.15(0.84,1.54)	0.164
TC(mmol/L), [M(IOR)]	3.50(2.74,4.44)	3.29(2.55,4.05)	3.77(2.89,4.64)	< 0.001
HDLC(mmol/L), [M(IOR)]	1.05(0.82,1.33)	1.00(0.72,1.33)	1.08(0.87,1.33)	0.047
LDLC(mmol/L), [M(IOR)]	1.93(1.28,2.71)	1.68(1.02,2.26)	2.08(1.42,2.99)	< 0.001
lbLDLC(mmol/L), [M(IOR)]	1.27(0.79,1.92)	1.07(0.53,1.59)	1.38(0.92,2.10)	< 0.001
sdLDLC(mmol/L), [M(IOR)]	0.62(0.47,0.86)	0.56(0.45,0.74)	0.68(0.50,0.91)	< 0.001
Non HDLC(mmol/L), [M(IOR)]	2.38(1.72,3.20)	2.13(1.56,2.95)	2.70(1.88,3.37)	< 0.001
Remanent C(mmol/L), [M(IOR)]	0.44(0.26,0.63)	0.44(0.27,0.65)	0.43(0.25,0.62)	0.580
TG/HDLC, [M(IOR)]	1.07(0.69,1.74)	1.09(0.64,1.95)	1.07(0.73,1.68)	0.883
TC/HDLC, [M(IOR)]	3.41(2.58,4.26)	3.35(2.37,4.20)	3.45(2.81,4.27)	0.102
LDLC/HDLC, [M(IOR)]	1.85(1.23,2.58)	1.61(1.08,2.42)	1.95(1.45,2.79)	0.001
lbLDLC/HDLC, [M(IOR)]	1.20(0.75,1.77)	0.97(0.61,1.62)	1.31(0.87,1.83)	< 0.001
sdLDLC/HDLC, [M(IOR)]	0.65(0.44,0.87)	0.61(0.39,0.86)	0.66(0.47,0.88)	0.093
Remanent C/HDLC, [M(IOR)]	0.41(0.20,0.75)	0.42(0.20,0.87)	0.40(0.20,0.65)	0.292

Abbreviations: CCI, Charlson comorbidity index; MI, myocardial infarction; CHF, congestive heart failure; PVD, peripheral vascular disease; CBVA, cerebrovascular accident; TIA, transient ischemic attack; CKD, chronic kidney disease; AIDS, acquired immunodeficiency syndrome; HR, heart rate; RR, respiratory rate; SaO_2, oxygen saturation; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; CRP, C-reactive protein; Hb1Ac, glycated hemoglobin; TP, Total protein; ALT, alanine transaminase; AST, aspartate aminotransferase; AKP, alkaline phosphatase; GGT, gamma-glutamyltransferase; TBIL, total bilirubin; DBIL, direct bilirubin; IBIL, indirect bilirubin; BUN, blood urea nitrogen; UA, uric acid; sCr, serum creatinine; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; PT, prothrombin time; APTT, activated partial thromboplastin time; TG, triglyceride; TC, total cholesterol; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; lbLDLC, large buoyant LDL cholesterol; sdLDLC, small dense LDL cholesterol

distributions, continuous variables was expressed as medians with interquartile ranges (IQRs) and compared using Wilcoxon rank-sum tests.

Covariates were selected using elastic net regression ($\alpha = 0.5$, $\lambda = 0.058189$) to balance statistical rigor and clinical relevance, with final variables cross-validated against established critical care literature [22]. This resulted in a number of variables of 19, including dopamine, norepinephrine, mechanical ventilation, HR, SaO_2, temperature, WBC, lymphocyte, eosinophils, platelet, CRP, AST, AKP, GGT, BUN, eGFR, HCO_3, INR, and PT. Univariable and multivariable Cox proportional hazards models were constructed using lipid profiles and lipid ratios as independent variables, respectively. To address the potential oversight of clinically significant variables, such as age and gender, which might not reach statistical thresholds in the elastic net, pre-planned subgroup analyses were conducted to explore their roles as effect modifiers. Age stratification was based on the cohort's median age (75 years), with "younger older adults" defined as < 75 years and "very old adults" as ≥ 75 years, aligning with geriatric research classifications.

Non-linear associations were examined using restricted cubic splines (RCS) with three knots positioned at the 10th, 50th, and 90th percentiles of each lipid indicator's distribution. The number and placement of knots were determined to optimize model flexibility while minimizing overfitting, particularly given the cohort's sample size. RCS was selected over polynomial regression due to its ability to capture smooth, non-monotonic trends without requiring prior assumptions about the functional form of the relationship.

All analyses were performed using STATA 18 (StataCorp LLC, Texas, USA) and R 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria), and a two-tailed $P < 0.05$ was considered statistically significant.

Results

Characteristics of the participants at baseline

The median age of the 401 non-surgical older patients with critical illnesses was 75 (68, 83) years, 144 (35.91%) of whom were female. The median CCI was 2 (1, 6). The utilization of vasopressors was observed, with 30 (7.48%) patients receiving dopamine, 15 (3.74%) receiving dobutamine, 13 (3.24%) receiving epinephrine, and 143 (35.66%) receiving norepinephrine. Additionally, 177 (44.14%) patients received mechanical ventilation, and 52% received hemodialysis. As illustrated in Table 1, the proportion of patients who received dopamine and norepinephrine, as well as mechanical ventilation, was higher among those who died within 28 days than among those who survived. In regard to physiological and laboratory indicators at baseline, HR, temperature, WBC, neutrophils, CRP, ALT, AST, AKP, GGT, DBIL, BUN, sCr, INR, PT, and APTT were higher among patients who died within 28 days. Conversely, patients who survived exhibited higher levels of SaO2, SBP, DBP, urine volume, lymphocytes, eosinophils, RBC, hematocrit, platelet, TP, albumin, and eGFR. Furthermore, patients who died within 28 days exhibited lower baseline TC, HDLC, LDLC, lbLDLC, sdLDLC, non HDLC, LDLC/HDLC, and lbLDLC/HDLC. All of the aforementioned differences between groups were statistically significant (all $P < 0.05$).

Associations of lipid profiles and lipid ratios with 28-day mortality

As shown in Fig. 2, the results of the unadjusted Cox proportional hazards models revealed that TC (HR = 0.81, 95% CI: 0.71 to 0.92), LDLC (HR = 0.69, 95% CI: 0.59 to 0.82), lbLDLC (HR = 0.63, 95% CI: 0.51 to 0.78), sdLDLC (HR = 0.28, 95% CI: 0.15 to 0.53), non HDLC (HR = 0.81, 95% CI: 0.70 to 0.93), lbLDLC/HDLC (HR = 0.81, 95% CI: 0.69 to 0.94), and lbLDLC/HDLC (HR = 0.72, 95% CI: 0.58 to 0.89) were all associated with a lower risk of 28-day mortality (all $P < 0.01$). The results of the fully adjusted Cox proportional hazards models suggested that LDLC (HR = 0.82, 95% CI: 0.69 to 0.97), lbLDLC (HR = 0.79, 95% CI: 0.63 to 0.98), sdLDLC (HR = 0.44, 95% CI: 0.24 to 0.83), LDLC/HDLC (HR = 0.85, 95% CI: 0.73 to 1.00), and sdLDLC/HDLC (HR = 0.63, 95% CI: 0.40 to 1.00) were significantly inversely associated with the risk of 28-day mortality (all $P < 0.05$).

However, subsequent replication of the aforementioned multivariable analysis with restricted cubic splines did not demonstrate any non-linear associations between lipid profiles and lipid ratio indices and the 28-day mortality risk (see Fig. 3). This finding indicated that the impact of cholesterol metrics on the 28-day mortality risk in non-surgical older patients with critical illnesses had no substantial dose-response relationship.

Age- and gender-specific associations of lipid profiles and lipid ratios with 28-day mortality

The primary analysis was repeated after stratification by median age (75 years), and the results were displayed in Table 2. Contrary to the findings of the primary

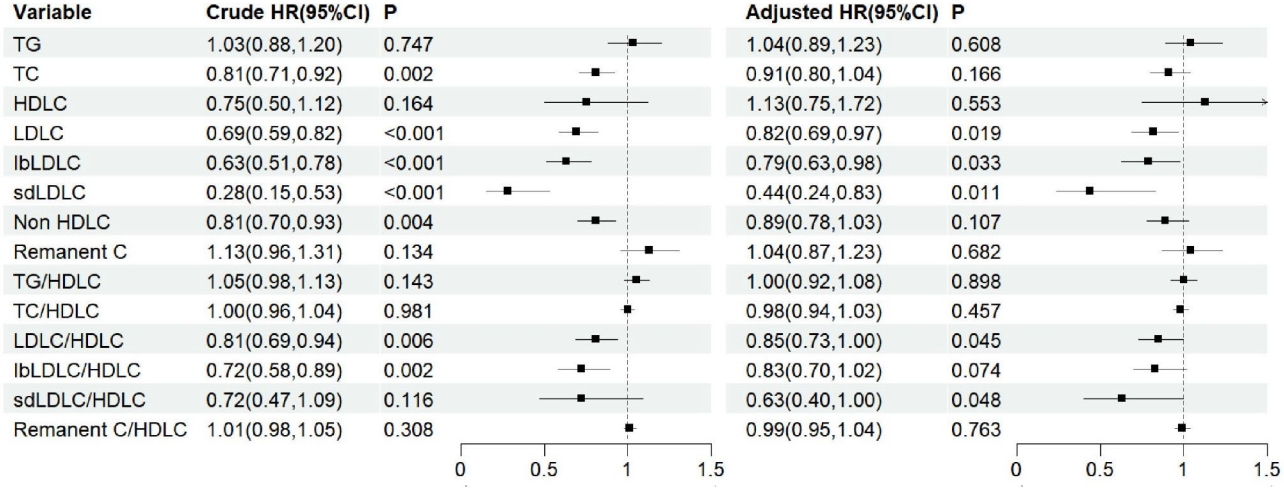

Fig. 2 Associations of lipid profiles and lipid ratios with 28-day mortality using univariable and multivariable analyses with Cox proportional hazards models. Adjusted models were adjusted for dopamine, norepinephrine, mechanical ventilation, heart rate, oxygen saturation, temperature, white blood cell, lymphocyte, eosinophils, platelet, C-reactive protein, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyltransferase, blood urea nitrogen, estimated glomerular filtration rate, HCO3, international normalized ratio and prothrombin time. Abbreviations: HR, hazards ratio; CI, confidence interval; TG, triglyceride; TC, total cholesterol; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; lbLDLC, large buoyant low-density lipoprotein cholesterol; sdLDLC, small dense low-density lipoprotein cholesterol

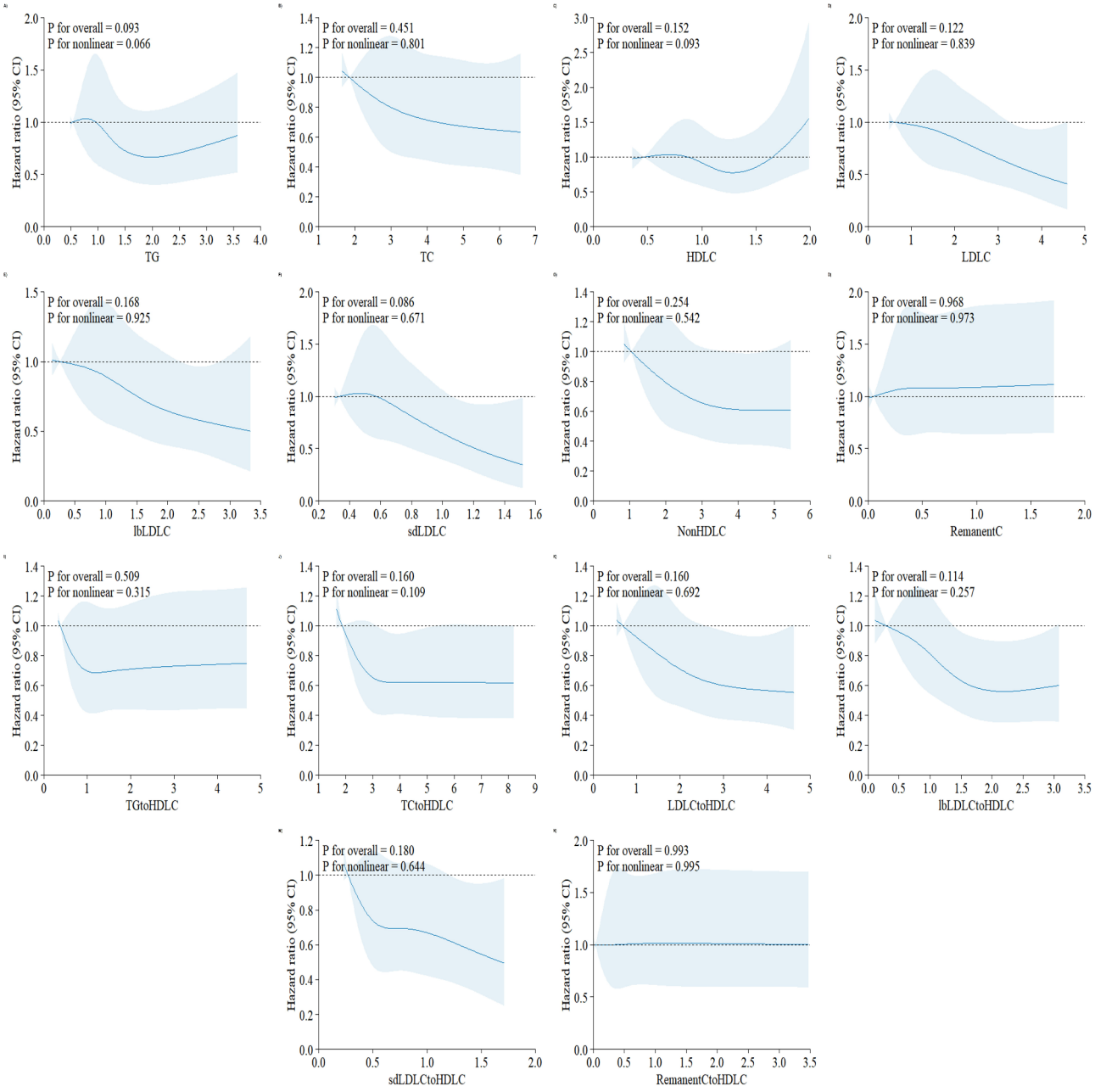

Fig. 3 Non-linear associations of lipid profiles and lipid ratios with 28-day mortality using multivariable Cox proportional hazards models with restricted cubic splines. Adjusted models were adjusted for dopamine, norepinephrine, mechanical ventilation, heart rate, oxygen saturation, temperature, white blood cell, lymphocyte, eosinophils, platelet, C-reactive protein, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyltransferase, blood urea nitrogen, estimated glomerular filtration rate, HCO3, international normalized ratio and prothrombin time. Abbreviations: HR, hazards ratio; CI, confidence interval; TG, triglyceride; TC, total cholesterol; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; lbLDLC, large buoyant low-density lipoprotein cholesterol; sdLDLC, small dense low-density lipoprotein cholesterol

analyses, among younger older adults (Age < 75 years), TC (HR = 1.27, 95% CI: 1.07 to 1.50), non HDLC (HR = 1.27, 95% CI: 1.07 to 1.49), remanent C (HR = 1.35, 95% CI: 1 0.10 to 1.67), TC/HDLC (HR = 1.06, 95% CI: 1.01 to 1.12), and remanent C/HDLC (HR = 1.08, 95% CI: 1.02 to 1.15) were associated with a higher risk of 28-day mortality (all $P < 0.05$). In contrast, in older adults (age ≥ 75 years), consistent with the primary analysis, TC (HR = 0.61, 95% CI: 0.48 to 0.68), LDLC (HR = 0.52, 95% CI: 0.39 to 0.69), lbLDLC (HR = 0.43, 95% CI: 0.30 to 0.62), sdLDLC (HR = 0.13, 95% CI: 0.04 to 0.38), non-HDLC (HR = 0.58, 95% CI: 0.44 to 0.75), TC/HDLC (HR = 0.78, 95% CI: 0.63 to 0.96), LDLC/HDLC (HR = 0.57, 95% CI: 0.42 to 0.76), lbLDLC/HDLC (HR = 0. 42, 95% CI: 0.28 to 0.64), and

Table 2 Age-specific associations of lipid profiles and lipid ratios with 28-day mortality using Cox proportional hazards models

	Age < 75 years		Age ≥ 75 years	
	HR(95%CI)	*P*	HR(95%CI)	*P*
TG	1.11(0.91,1.35)	0.296	1.06(0.85,1.31)	0.622
TC	1.27(1.07,1.50)	**0.005**	0.61(0.48,0.78)	**< 0.001**
HDLC	1.11(0.59,2.09)	0.736	0.91(0.46,1.83)	0.795
LDLC	1.16(0.91,1.49)	0.228	0.52(0.39,0.69)	**< 0.001**
lbLDLC	1.24(0.90,1.71)	0.182	0.43(0.30,0.62)	**< 0.001**
sdLDLC	1.34(0.56,3.21)	0.515	0.13(0.04,0.38)	**< 0.001**
Non HDLC	1.27(1.07,1.49)	**0.005**	0.58(0.44,0.75)	**< 0.001**
Remanent C	1.35(1.10,1.67)	**0.004**	0.89(0.60,1.31)	0.557
TG/HDLC	1.08(0.96,1.21)	0.229	1.00(0.89,1.13)	0.987
TC/HDLC	1.06(1.01,1.12)	**0.013**	0.78(0.63,0.96)	**0.021**
LDLC/HDLC	1.09(0.91,1.31)	0.340	0.57(0.42,0.76)	**< 0.001**
lbLDLC/HDLC	1.12(0.89,1.42)	0.329	0.42(0.28,0.64)	**< 0.001**
sdLDLC/HDLC	1.25(0.67,2.32)	0.482	0.38(0.17,0.84)	**0.017**
Remanent C/HDLC	1.08(1.02,1.15)	**0.009**	0.96(0.86,1.08)	0.487

Adjusted models were adjusted for dopamine, norepinephrine, mechanical ventilation, heart rate, oxygen saturation, temperature, white blood cell, lymphocyte, eosinophils, platelet, C-reactive protein, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyltransferase, blood urea nitrogen, estimated glomerular filtration rate, HCO3, international normalized ratio and prothrombin time. Abbreviations: HR, hazards ratio; CI, confidence interval; TG, triglyceride; TC, total cholesterol; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; lbLDLC, large buoyant low-density lipoprotein cholesterol; sdLDLC, small dense low-density lipoprotein cholesterol

Table 3 Gender-specific associations of lipid profiles and lipid ratios with 28-day mortality using Cox proportional hazards models

	Male		Female	
	HR(95%CI)	*P*	HR(95%CI)	*P*
TG	1.08(0.89,1.30)	0.431	1.04(0.82,1.33)	0.726
TC	0.93(0.78,1.11)	0.450	0.89(0.70,1.13)	0.326
HDLC	1.03(0.60,1.77)	0.905	0.98(0.45,2.14)	0.967
LDLC	0.82(0.65,1.03)	0.087	0.76(0.56,1.02)	0.071
lbLDLC	0.77(0.57,1.04)	0.093	0.73(0.49,1.08)	0.117
sdLDLC	0.53(0.24,1.19)	0.126	0.29(0.09,0.89)	**0.031**
Non HDLC	0.92(0.76,1.12)	0.392	0.88(0.69,1.13)	0.318
Remanent C	1.22(0.91,1.65)	0.186	1.16(0.84,1.61)	0.362
TG/HDLC	1.04(0.93,1.17)	0.498	1.04(0.89,1.21)	0.619
TC/HDLC	0.98(0.88,1.10)	0.784	1.01(0.95,1.08)	0.710
LDLC/HDLC	0.83(0.67,1.02)	0.073	0.93(0.69,1.24)	0.608
lbLDLC/HDLC	0.77(0.58,1.02)	0.071	0.92(0.62,1.36)	0.679
sdLDLC/HDLC	0.65(0.35,1.17)	0.152	0.76(0.32,1.81)	0.535
Remanent C/HDLC	1.06(0.95,1.18)	0.293	1.02(0.95,1.10)	0.557

Adjusted models were adjusted for dopamine, norepinephrine, mechanical ventilation, heart rate, oxygen saturation, temperature, white blood cell, lymphocyte, eosinophils, platelet, C-reactive protein, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyltransferase, blood urea nitrogen, estimated glomerular filtration rate, HCO3, international normalized ratio and prothrombin time. Abbreviations: HR, hazards ratio; CI, confidence interval; TG, triglyceride; TC, total cholesterol; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; lbLDLC, large buoyant low-density lipoprotein cholesterol; sdLDLC, small dense low-density lipoprotein cholesterol

sdLDLC/HDLC (HR = 0.38, 95% CI: 0.17 to 0.84) were all associated with a lower risk of 28-day mortality (all $P < 0.05$).

However, upon stratifying by gender (see Table 3), it was observed that sdLDLC was only associated with a reduced 28-day mortality risk among the female population (HR = 0.29, 95% CI: 0.09 to 0.89; $P = 0.031$).

Discussion

This study investigated that low levels of LDLC, its subtypes (lbLDLC and sdLDLC), and their ratios to HDLC were associated with increased with 28-day mortality risk in non-surgical older patients with critical illnesses. These associations were more significantly in patients aged 75 years or older. Conversely, elevated residual cholesterol levels, including TC, non HDLC, remanent C, TC/HDLC and remanent C/HDLC, were linked to increased mortality risk in younger older adults (< 75 years). Additionally, female patients with lower sdLDLC levels exhibited an increased short-term mortality risk. These findings underscore the importance of age- and sex-specific lipid management strategies for older patients with critical illnesses.

Despite the plethora of studies that have historically centered on the deleterious effects of dyslipidemia, there has been a paucity of research investigating the harms of lower lipid profile or lipid ratio indicators [13], particularly in relation to short-term mortality risk in critical ill patients. A limited number of studies have previously indicated that low lipid levels may increase non-cardiovascular disease deaths in older adults, and that higher cholesterol levels may reduce the risk of death related to cancer, malnutrition, and infections [5, 23, 24, 25, 26]. The present study's findings align with those of a pilot study by Petersen et al. [27], which found that low serum cholesterol levels were associated with increased disease severity in hospitalized patients over 60 years of age. Another study reported that serum cholesterol and lipoprotein concentrations were significantly lower in patients with multiple organ failure, and that mortality was higher in patients with greater decreases [28]. Consequently, lipid profiles or lipid ratio indicators (particularly LDLC and its subtypes) are anticipated to function as predictive tools for short-term mortality risk in older patients with critical illness.

Results from subgroup analyses may be explained by the hypothesis that lower LDLC levels in very old patients are partly a surrogate marker of frailty, as there is evidence that LDLC decreases progressively in the latter decades of life [29]. Maintaining higher LDLC levels in later life implies better overall health and can protect individuals from death. However, large-scale epidemiologic studies, including the Whitehall study and the Framingham study, have associated elevated LDLC with

increased cancer incidence and mortality [30, 31]. One potential mechanism underlying this association involves the role of cholesterol in promoting inflammatory responses. Higher serum cholesterol levels have been observed to enhance toll-like receptor signaling, trigger inflammatory vesicle activation, and stimulate monocyte and neutrophil production in the bone marrow and spleen [32]. The deleterious effects of these pathophysiological mechanisms on the health of younger older adults may obscure the protective role of high LDLC in very old people, ultimately leading to the observed differences in the effects of lipid profiles and lipid ratio indices on short-term mortality risk in different age subgroups in the present study. It is hypothesized that this will provide a framework for the present lipid management strategies employed in hospitalized older patients prior to their transition to ICUs. In contrast to younger older adults, the target values for lipid cholesterol levels in very old or female patients may not be strictly adherent to guideline recommendations. Therefore, it is necessary to improve their nutritional status as much as possible in order to optimize their lipid levels and reduce in-hospital mortality.

Despite the implementation of rigorous and reliable data governance and statistical analysis methodologies in the present study, there are inherent limitations that must be acknowledged. The study methodically explores the correlation between lipid profiles and ratios with the short-term risk of death in non-surgical elderly critical ill patients. The findings of this study propose pragmatic solutions for the early management of lipids in this demographic. Nevertheless, it is imperative to acknowledge the unavoidable limitations that must be taken into consideration. First, the use of lipid-lowering medications may affect baseline lipid levels in older patients. Disease diagnosis and medication use for hyperlipidemia are incomplete in most critical ill patients, and elderly patients in particular may be self-administering lipid-lowering medications that are not documented in their inpatient orders. However, the confounding effect of these medications is limited due to the absence of subsequent lipid-lowering medications during ICU hospitalization, regardless of prior medication use. Secondly, there are still many potential unmeasured confounders, including dietary patterns, body mass index, and environmental exposures, which may also affect the robustness of the results. Thirdly, the study relied on a single measurement of lipids on the first day of ICU admission. Although repeated measurements and biological variability during ICU hospitalization, as well as lipid fluctuations due to other therapeutic measures, may affect association estimates, these factors were not considered in the study. To address these limitations, it is imperative to consider mixed-effects Poisson regression or negative binomial regression to estimate the association between changes in lipid levels during ICU hospitalization and short-term mortality risk. Furthermore, given that this study was based on a post hoc analysis of the data, the sample size was not based on mortality. This limitation resulted in an overemphasis on all-cause deaths, precluding the ability to differentiate between cardiovascular deaths, which are more associated with lipids, and other causes of death. The single-center study design resulted in a sample that was not sufficiently representative, thereby limiting the extrapolation of the conclusions. To further validate the results of the study and guide clinical decision-making, a larger multicenter retrospective cohort design will be adopted.

Conclusion

Lower LDL-C levels and its subtypes (lbLDL-C, sdLDL-C) were associated with increased 28-day mortality risk in older patients with critical illnesses, particularly in patients aged ≥ 75 years and women. Elevated residual cholesterol levels remained a risk factor for younger older adults (< 75 years). These findings suggest that LDL-C control targets may need age- and sex-specific adjustments, balancing cardiovascular risk mitigation with metabolic reserve preservation in older patients with critical illnesses. Large-scale studies are warranted to validate optimal LDL-C thresholds and refine lipid management guidelines for this vulnerable cohort.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12944-025-02545-2.

Supplementary Material 1

Acknowledgements

Not applicable.

Author contributions

Yang Li and Jianli Ge contributed equally to the study design, data analysis and manuscript drafting. Shasha Geng, Qingqing Li, Xin Chen, Yingqian Zhu and Xiaotong Guo contributed to the data management and processing. Huajie Gu and Yue Liu were responsible for project supervision and manuscript revision. All authors approved the final version of the manuscript for publication.

Funding

The authors declare that they received no funding, grants or other support during the preparation of this manuscript.

Data availability

The data that support these findings are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study was conducted via retrospective electronic health records and did not require patient participation or informed consent. The Ethics Committee of Shanghai East Hospital confirmed that no ethical approval was required.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of General Practice, Shanghai East Hospital, Tongji University School of Medicine, Shanghai 200120, China
[2]Department of Geriatrics, Shanghai East Hospital, Tongji University School of Medicine, Shanghai 200120, China
[3]Department of Emergency Intensive Care Unit, Yangpu Hospital, Tongji University School of Medicine, Shanghai 200090, China

Received: 23 February 2025 / Accepted: 21 March 2025
Published online: 27 March 2025

References

1. Ahern F, Sahm LJ, Lynch D, McCarthy S. Determining the frequency and preventability of adverse drug reaction-related admissions to an Irish university hospital: a cross-sectional study. Emerg Med J. 2014;31:24–9.
2. Dong J, Yang S, Zhuang Q, Sun J, Wei P, Zhao X, Chen Y, Chen X, Li M, Wei L et al. The associations of lipid profiles with cardiovascular diseases and death in a 10-Year prospective cohort study. Front Cardiovasc Med 2021;8:745539.
3. Bowe B, Xie Y, Xian H, Balasubramanian S, Zayed MA, Al-Aly Z. High density lipoprotein cholesterol and the risk of All-Cause mortality among U.S. Veterans. Clin J Am Soc Nephrol. 2016;11:1784–93.
4. Wu W, Xiao Z, Liang X, Zhao Q, Luo J, Ding D. Low and High-Density lipoprotein cholesterol and 10-Year mortality in Community-Dwelling older adults: the Shanghai aging study. Front Med 2022;9:783618.
5. Ding M, Wennberg A, Ek S, Santoni G, Gigante B, Walldius G, Hammar N, Modig K. The association of apolipoproteins with later-life all-cause and cardiovascular mortality: a population-based study stratified by age. Sci Rep. 2021;11:24440.
6. Liu L, Han M, Qie R, Li Q, Zhang X, Zhang J, Zhan S, Zhang L, Xu Z, Zhang C, Hong F. A dose–response meta-analysis to evaluate the relationship between high-density lipoprotein cholesterol and all-cause and cardiovascular disease mortality. J Endocrinol Investig. 2022;45:551–62.
7. Kim SH, Son KY. Association between lipoprotein cholesterol and future cardiovascular disease and mortality in older adults: a Korean nationwide longitudinal study. Lipids Health Dis. 2021;20:3.
8. Zhong G-C, Huang S-Q, Peng Y, Wan L, Wu Y-Q-L, Hu T-Y, Hu J-J, Hao F-B. HDL-C is associated with mortality from all causes, cardiovascular disease and cancer in a J-shaped dose-response fashion: a pooled analysis of 37 prospective cohort studies. Eur J Prev Cardiol. 2020;27:1187–203.
9. Liu J, Zeng F-F, Liu Z-M, Zhang C-X, Ling W-h, Chen Y-M. Effects of blood triglycerides on cardiovascular and all-cause mortality: a systematic review and meta-analysis of 61 prospective studies. Lipids Health Dis. 2013;12:159.
10. Weverling-Rijnsburger AWE, Blauw GJ, Lagaay AM, Knock DL, Meinders AE, Westendorp RGJ. Total cholesterol and risk of mortality in the oldest old. Lancet. 1997;350:1119–23.
11. Maihofer AX, Shadyab AH, Wild RA, LaCroix AZ. Associations between serum levels of cholesterol and survival to age 90 in postmenopausal women. J Am Geriatr Soc. 2020;68:288–96.
12. Sittiwet C, Simonen P, Gylling H, Strandberg TE. Mortality and cholesterol metabolism in subjects aged 75 years and older: the Helsinki businessmen study. J Am Geriatr Soc. 2020;68:281–7.
13. Lv Y-B, Yin Z-X, Chei C-L, Qian H-Z, Kraus VB, Zhang J, Brasher MS, Shi X-M, Matchar DB, Zeng Y. Low-density lipoprotein cholesterol was inversely associated with 3-year all-cause mortality among Chinese oldest old: data from the Chinese longitudinal healthy longevity survey. Atherosclerosis. 2015;239:137–42.
14. Byun AR, Lee SW, Lee HS, Shim KW. What is the most appropriate lipid profile ratio predictor for insulin resistance in each sex? A cross-sectional study in Korean populations (The fifth Korea National health and nutrition examination Survey). Diabetol Metab Syndr. 2015;7:59.
15. Kannel WB, Vasan RS, Keyes MJ, Sullivan LM, Robins SJ: Usefulness of the Triglyceride–High-Density Lipoprotein Versus the Cholesterol–High-Density Lipoprotein Ratio for Predicting Insulin Resistance and Cardiometabolic Risk (from the Framingham Offspring Cohort). American Journal of Cardiology 2008;101:497–501.
16. Ridker PM, Rifai N, Cook NR, Bradwin G, Buring JE. Non–HDL cholesterol, apolipoproteins A-I and B100, standard lipid measures, lipid ratios, and CRP as risk factors for cardiovascular disease in women. JAMA. 2005;294:326–33.
17. Shai I, Rimm EB, Hankinson SE, Curhan G, Manson JE, Rifai N, Stampfer MJ, Ma J. Multivariate assessment of lipid parameters as predictors of coronary heart disease among postmenopausal women. Circulation. 2004;110:2824–30.
18. World Medical A. World medical association declaration of Helsinki: ethical principles for medical research involving human participants. JAMA. 2025;333:71–4.
19. Liu X, Hu P, Yeung W, Zhang Z, Ho V, Liu C, Dumontier C, Thoral PJ, Mao Z, Cao D, et al. Illness severity assessment of older adults in critical illness using machine learning (ELDER-ICU): an international multicentre study with subgroup bias evaluation. Lancet Digit Health. 2023;5:e657–67.
20. Group KDIGOKCW. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 2013;2013;3:1-150.
21. Sampson M, Wolska A, Warnick R, Lucero D, Remaley AT. A new equation based on the standard lipid panel for calculating small dense Low-Density Lipoprotein-Cholesterol and its use as a Risk-Enhancer test. Clin Chem. 2021;67:987–97.
22. Helmreich JE. Regression Modeling Strategies with Applications to Linear Models, Logistic and Ordinal Regression and Survival Analysis (2nd Edition). Journal of Statistical Software 2016;70:1–3.
23. Cullen P, Schulte H, Assmann G. The Münster heart study (PROCAM). Circulation. 1997;96:2128–36.
24. Fraunberger P, Nagel D, Walli AK, Seidel D. Serum cholesterol and mortality in patients with multiple organ failure. Crit Care Med. 2000;28:3574–5.
25. Jacobs D, Blackburn H, Higgins M, Reed D, Iso H, McMillan G, Neaton J, Nelson J, Potter J, Rifkind B. Report of the conference on low blood cholesterol: mortality associations. Circulation. 1992;86:1046–60.
26. Weiss A, Beloosesky Y, Schmilovitz-Weiss H, Grossman E, Boaz M. Serum total cholesterol: a mortality predictor in elderly hospitalized patients. Clin Nutr. 2013;32:533–7.
27. Petersen JR, Linde MK, Bissell MG. The possible association of decreased total cholesterol and severity of disease in elderly hospitalized patients. Clin Chim Acta. 2000;290:213–20.
28. Fraunberger P, Nagel D, Walli AK, Seidel D. Serum cholesterol and mortality in patients with multiple organ failure. Crit Care Med. 2000;28(10):3574–5.
29. Tian J, Chen H, Jia F, Yang G, Li S, Li K, Zhang L, Wu J, Liu D. Trends in the Levels of Serum Lipids and Lipoproteins and the Prevalence of Dyslipidemia in Adults with Newly Diagnosed Type 2 Diabetes in the Southwest Chinese Han Population during 2003–2012. Int J Endocrinol 2015;2015:818075.
30. Smith GD, Shipley MJ, Marmot MG, Rose G. Plasma cholesterol concentration and mortality. The Whitehall study. JAMA. 1992;267:70–6.
31. Anderson KM, Castelli WP, Levy D. Cholesterol and mortality. 30 years of follow-up from the Framingham study. JAMA. 1987;257:2176–80.
32. Tall AR, Yvan-Charvet L. Cholesterol, inflammation and innate immunity. Nat Rev Immunol. 2015;15:104–16.

Publisher's note