RESEARCH

Lipids in Health and Disease

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

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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), IbLDLC (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, IbLDLC, sdLDLC, non HDLC, TC/ HDLC, LDLC/HDLC,

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IbLDLC/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 \geq 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 sexspecific 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 indepth 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) = $1.43 \times LDLC$ (mg/dL) $-0.14 \times (\ln(TG (mg/dL)) \times LDLC (mg/dL)) - 8.99.$

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

Iotal Death Aviet P Interline, (%) 144(35.61) 5778-760 6756.71) 0.659 Emmlan, (%) 307.480 27(0.589.81) 0.355 0.059 0.0355 Deparatine, n(%) 15(3.74) 64.680 7(2.99) 0.018 Emmedition, n(%) 13(3.24) 64.680 7(2.99) 0.018 Deparatine, n(%) 13(3.24) 64.680 7(2.99) 0.019 Machanical ventilation, n(%) 13(3.24) 64.680 7(2.99) 0.001 Machanical ventilation, n(%) 12(6.1) 31(6.4 21(1.3) 0.023 Mach(%) 24(2.57) 16(6.1) 13(5.49) 0.025 0.046 VD, n(%) 225.59 63.66 166.73 0.046 VD, n(%) 1742.49 53.05 12.060 0.25 Chen (%) 174.24 53.05 12.060 0.25 Chen (%) 174.24 53.05 12.06 0.23 Chen (%) 174.24 53.05 12.060		T / I		A 1*	
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nachoologies, https://doi.org/10.1001/000000000000000000000000000000		177(44.14) 52(12.07)	94(37.32) 35(15.34)	03(33.02)	< 0.001
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Min, Mix 205, 24) 1000, 100, 100, 100, 100, 100, 100, 100		2(1,0)	3(1,0)	2(1,5)	0.073
Lift, flwb Bir(Z1-19) FL/E.000 FL/E.0000 FL/E.0000 FL/E.0000 FL/E.0000 FL/E.0000 FL/E.0000 FL/E.0000 FL/E.00000 FL/E.000000 FL/E.000000000000000000000000000000000000		23(5.74)	10(6.10)	13(5.49)	0.795
PVD. (pp) (C16.9) (E6.7) (E6.7) (E6.7) (E6.7) CSW or TIA, (Ph) 1225.44) 4225.61) 6025.32 0.947 Dementia, n(%) 125.44) 63.66) 125.06) 0.325 Chronic pulmonary disease, n(%) 174.241 53.05 125.06) 0.325 Connective tissue disease, n(%) 174.241 53.05 125.06) 0.325 Peptic Luber disease, n(%) 174.241 53.05 125.06) 0.325 Mild 61.350 21.22 41.69 1.75 Moderate to severe 0.133 21.91 46.1941 1.75 Incomplicated 64.15.96 27.164.61 37.156.11 1.75 Incomplicated 64.15.96 27.164.61 37.156.11 1.75 Incomplicated to severe CKD, n(%) 75.18.70 37.125.51 38.16.03 0.09 Localized solid turnor or leukernia or lymphoma, n(%) 37.07.10 169.76 156.33.10 2.24 ADS, n(%) 0.07 7.255.51 38.16.03.10 0.001	CHF, n(%)	89(22.19)	41(25.00)	48(20.25)	0.261
CBVA or IVA, IN(%) IO(22.5.44) 42(5.61) 6025.32) 0.384 Dementia, IN(%) IVA(24) 50.05) 125.06) 0.325 Chronic pulmonary disease, n%) IVA(24) 50.05) 125.06) 0.325 Chronic pulmonary disease, n%) IVA(24) 50.05) 125.06) 0.325 Mild 6(1.50) IVA(27) 6(1.50) 6(1.50) 6(1.50) 6(1.50) 122.06)	PVD, n(%)	22(5.49)	6(3.66)	16(6.75)	0.264
Dementa n(%) 1/4/24 5(30) 1/25.06) 0.325 Chronic plumonary disease, n(%) 1/(4.24) 5(305) 1/25.06) 0.238 Connective tissue disease, n(%) 1/(4.24) 5(305) 1/25.06) 0.238 Levr disease, n(%) 1/(4.24) 5(305) 1/25.06) 0.238 Levr disease, n(%) 1/(4.24) 5(0.50) 1/16.00 0.238 Moderate to severe 1/16.01 1/12.20 4/16.90 0.338 Diabetes millitys, n(%) 2/10.40 2/11.00 1/16.00	CBVA or IIA, n(%)	102(25.44)	42(25.61)	60(25.32)	0.947
Chronic pulmonary disease, n(%) 216.24) 61.86) 12(6.33) 0.248 Connective tissues disease, n(%) 7(1.75) 10.61) 6(2.53) 0.248 Liver disease, n(%) 7(1.75) 10.61) 6(2.53) 0.248 Mild 6(1.50) 21.72 4(1.69) 7(1.75) Diabetes mellitus, n(%) 10(6.10) 5(2.11) 7(1.75) Uncomplicated 44(15.96) 27(16.46) 37(15.61) 7(1.75) Indergia n(%) 000 000 000 0.01 7(1.75) Moderate to severe CKD, n(%) 75(18.70) 37(2.56) 38(16.03) 0.029 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) 10(60,70) 90(0) 7(1.72) 84(5.68) <0.001	Dementia, n(%)	1/(4.24)	5(3.05)	12(5.06)	0.325
Connective tissue disease, n(%) 1/(4.24) 5(305) 12(5.06) 0.232 Mild 6(1.50) 1(0.61) 6(2.53) 0.248 Liver disease, n(%) 1 0(5.0) 2(122) 4(1.69) 0.788 Moderate to severe 15(3.74) 10(6.0) 5(2.11) 971 Uncomplicated 64(15.96) 27(16.46) 37(15.61) 7 End-organ damage 64(15.96) 22(19.51) 46(19.41) 1 Hemplegia, n(%) 0(0) 0(0) 0(0) / Moderate to severe (KD, n(%) 75(18.70) 37(22.56) 38(16.03) 0.254 AIDS, n(%) 0(0) 0(0) 0(0) 0(0) 1 1 HR(bpm), (MIOR) 19(7.20) 18(57.610) 93(76.109) 84(76.98) 0.001 SPG(nm(M), (MIOR) 10(098.100) 99(8.100) 1009(8.100, 0) 0.015 Emperature (T), (MIOR) 10(098.100) 100(7.20, 10) 36(56.43.26) 36(50.43.26) 36(0.01, 0) 0.015 100005 0.001 0.00	Chronic pulmonary disease, n(%)	21(5.24)	6(3.66)	15(6.33)	0.238
Peptic ulcer disease, n(%) 71.75 10.611 62.231 0.248 Mid 6(1.50) 2(1.22) 4(1.69) 1 Moderate to severe 0.5374 106(10) 5(2.11) 1 Diabetes mellitus, n(%) 27(16.46) 37(15.61) 1 1 End-organ damage 64(15.96) 27(16.46) 37(15.61) 1 Hemiplegia, n(%) 000 000 000 0 <td>Connective tissue disease, n(%)</td> <td>1/(4.24)</td> <td>5(3.05)</td> <td>12(5.06)</td> <td>0.325</td>	Connective tissue disease, n(%)	1/(4.24)	5(3.05)	12(5.06)	0.325
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) Diabeters mellitus, n(%) 27(16.46) 37(15.61) 97(1 Uncomplicated 64(15.96) 27(16.46) 46(19.41) 1 End-organ damage 78(19.45) 32(10.91) 46(19.41) 1 Localized Solid tumor netwenia or lymphoma, n(%) 82(20.70) 40(24.91) 43(18.14) 0.129 Metastatic solid tumor, n(%) 31(7.73) 16(9.76) 47(5.83) 0.254 ADS, n(%) 0(0) 0(0) 0(0) 0(0) 7 R(bpm), (M(OR)] 19(7.76) (11) 93(76.109) 48(75.83) 0.601 SaO_(%), (MORN] 100(98.100) 99(8.10) 1009.81.00 0.017 Depremerature(°C), (M(OR)] 102(095.1940) 118(99,133) 121(08.137) 0.007 Depremerature(°C), (M(OR)] 106(27.59.15.27) 163(6.43.26) 66(6.37.40) 69(6.07.70 0.001 Vectrophils (10.94/L), (M(OR)] <td< td=""><td>Peptic ulcer disease, n(%)</td><td>7(1.75)</td><td>1(0.61)</td><td>6(2.53)</td><td>0.248</td></td<>	Peptic ulcer disease, n(%)	7(1.75)	1(0.61)	6(2.53)	0.248
Mid 6(1:50) 2(12) 4(169) Moderate to severe 15(3:74) 10(610) 5(2.1) Diabetes mellitus, n(%)	Liver disease, n(%)				0.138
Moderate to severe 15(3.7) 10(6.10) 5(2.11) Diabetes melitus, n(%)	Mild	6(1.50)	2(1.22)	4(1.69)	
Diabetes mellitus, n(%) 0.971 Uncomplicated 64(15.96) 27(16.46) 37(15.61) End-organ damage 0(0) 0.05 56.20,(M(IOR)] 100(7,00) 10(6,21,00) 10(8,10,0) 0.015 56.20,(M(IOR)] 0.016 0.005 0.017 DBR(mmHg), M(IOR)] 0.016 0.005 0.017 0.005 0.017 0.005 0.017 0.005 0.010 0.010 0.010 0.010 0.010 0.010 0.010 0.010	Moderate to severe	15(3.74)	10(6.10)	5(2.11)	
Uncomplicated 64(15.96) 27(16.60) 77(15.61) End-organ damage 78(1945) 32(19.51) 46(19.41) Hemiplegia, n(%) 000 000 000 0.099 Localized solid tumor relukemia or lymphoma, n(%) 82(0.70) 40(24.39) 43(18.14) 0.129 Metastatic solid tumor relukemia or lymphoma, n(%) 81(7.73) 169.76) 156.33 0.254 AlDS, n(%) 000 00 00 / 141.40 0.23 RRbpm, [M(IOR)] 87(76.101 93(76,109) 84(76,98) <0.01	Diabetes mellitus, n(%)				0.971
End-organ damage 78(1945) 32(195,10) 46(1941) Hemiplegia, n(%) 0(0) 0(0 0(0) 0(0) 0(0) 0(0) 0(0) 0.00 0.00 0.00 0.00 0.00 0.01	Uncomplicated	64(15.96)	27(16.46)	37(15.61)	
Hemiplegia. n(%) 0(0) 0(0) 0(0) 0(0) 0(0) Moderate to severe CKD, n(%) 75(18.70) 37(22.56) 38(16.43) 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) 169.76) 15(6.33) 0.254 AIDS, n(%) 0(0) 0(0) 0(0) 0(0) 84(76.98) <0.011	End-organ damage	78(19.45)	32(19.51)	46(19.41)	
Moderate to severe CKD, n(%) 75(18.70) 72(2.56) 38(16.03) 0.099 Localized solid tumor or leukemia or lymphoma, n(%) 31(7.73) 40(24.39) 43(18.14) 0.129 Metastatic solid tumor, n(%) 00 00 15(6.33) 0.254 ADS, n(%) 00 00 00 0 0 RR(bpm), M(IOR) 87(76,101) 93(76,109) 84(76,98) <0.01	Hemiplegia, n(%)	0(0)	0(0)	0(0)	/
Localized solid tumor or leukemia or lymphoma, n(%) 82(0.70) 40(24.39) 43(18.14) 0.129 Metastatic solid tumor, n(%) 15(6.33) 0.254 ADS, n(%) 0(0) 0(0) 0(0) RR(bpm), [M(OR)] 87(76,101) 93(76,109) 84(76,98) <0.001	Moderate to severe CKD, n(%)	75(18.70)	37(22.56)	38(16.03)	0.099
Metastatic solid tumor, n(%) 31(7.3) 16(9.76) 15(6.33) 0.254 AIDS, n(%) 0(0 0(0 0(0 0(0 0 HR(bpn), [M(OR)] 87(7.01) 93(6.109) 84(76.98) <0.018	Localized solid tumor or leukemia or lymphoma, n(%)	83(20.70)	40(24.39)	43(18.14)	0.129
AIDS, n(%) 0(0) 0(0) 0(0) 0(0) 0(0) / HR(bpm, [M(OR)] 87(76,101) 97(76,109) 87(76,109) 87(76,109) 0.001 R(bpm, [M(OR)] 19(17,20) 19(16,21) 19(17,20) 0.85 Sa0 ₂ (%), [M(OR)] 100(98,100) 100(98,100) 0.015 Temperature(°C), [M(OR)] 366(36,436.9) 36.6(36,437.2) 36.5(36,436.8) <0.017	Metastatic solid tumor, n(%)	31(7.73)	16(9.76)	15(6.33)	0.254
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_(M), [M(IOR)] 100(98,100) 90(98,100) 100(98,100) 0.015 Temperature(C), [M(IOR)] 36.6(36.4,36.9) 36.6(36.4,37.2) 36.5(36.4,36.8) <0011	AIDS, n(%)	0(0)	0(0)	0(0)	/
RR(bpm), [M(IOR)] 19(17,20) 19(17,20) 19(17,20) 0.885 SaO ₂ (%), [M(IOR)] 100(98,100) 99(98,100) 100(98,100) 0.015 Temperature('C), [M(IOR)] 36.636.43.69) 36.636.43.72) 36.536.43.6.8) <0.001	HR(bpm), [M(IOR)]	87(76,101)	93(76,109)	84(76,98)	< 0.001
SaO2(%),[M(IOR)]100(98,100)90(98,100)100(98,100)0.015Temperature('C), [M(IOR)]36.6(36.4,36.9)36.6(36.4,37.2)36.5(36.4,36.8)<0.001	RR(bpm), [M(IOR)]	19(17,20)	19(16,21)	19(17,20)	0.885
Temperature(°C), [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)] 100627,59,15.25) 11.60(8.35,18.63) 9.94(7.25,13.82) <0.012	SaO ₂ (%), [M(IOR)]	100(98,100)	99(98,100)	100(98,100)	0.015
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) 94(7.25,13.82) <0.001	Temperature(°C), [M(IOR)]	36.6(36.4,36.9)	36.6(36.4,37.2)	36.5(36.4,36.8)	< 0.001
DBP(mmHg), [M(IOR)]67(60,76)64(56,74)69(60,77)0.005Urine volume(mL), [M(IOR)]1400(950,1940)1215(678,1895)1440(1050,2000)0.012WBC(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	SBP(mmHg), [M(IOR)]	121(105,135)	118(99,133)	123(108,137)	0.017
Urine volume(mL), [M(lOR)] 1400(950,1940) 1215(678,1895) 1440(1050,2000) 0.012 WBC(10^9/L), [M(lOR)] 10.62(7.59,15.25) 11.60(8.35,18.63) 9.94(7.25,13.82) <0.001	DBP(mmHg), [M(IOR)]	67(60,76)	64(56,74)	69(60,77)	0.005
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	Urine volume(mL), [M(IOR)]	1400(950,1940)	1215(678,1895)	1440(1050,2000)	0.012
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	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
Lymphocyte (10^9/L), [M(IOR)]0.85(0.52,1.27)0.63(0.42,1.06)0.96(0.63,1.46)< 0.001Monocyte (10^9/L), [M(IOR)]0.60(0.40,0.85)0.61(0.37,0.86)0.60(0.42,0.83)0.789Eosinophils (10^9/L), [M(IOR)]0.01(0.00,006)0.00(0.00,0.03)0.02(0.01,0.04)0.173Basophilis (10^9/L), [M(IOR)]0.02(0.1,0.04)0.02(0.01,0.04)0.02(0.01,0.04)0.011Hemoglobin (g/L), [M(IOR)]105.0(87.0,125.0)102.0(83.0,124.5)107.0(91.0,125.0)0.053Hematocrit (%), [M(IOR)]32.2(26.2,38.2)30.6(25.5,38.4)33.4(27.7,37.9)0.042Platelet (10^9/L), [M(IOR)]189.0(124.0,249.0)159.5(96.5,239.0)20.10(148.0,253.0)<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
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(0.01,0.04) 0.173 Basophils(10^9/L), [M(IOR)] 0.02(0.01,0.04) 0.02(0.01,0.04) 0.02(0.01,0.04) 0.011 Basophils(10^12/L), [M(IOR)] 3.59(2.86,4.15) 3.39(2.79,4.14) 3.70(3.00,4.19) 0.013 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)] 22.2(26.2,38.2) 30.6(25.5,38.4) 3.4(27.7,37.9) 0.042 Platelet(10^9/L), [M(IOR)] 189.0(124.0,249.0) 159.5(96.5,239.0) 20.10.1(48.0,253.0) <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
Eosinophils(10^9/L), [M(IOR)]0.01(0.00,0.06)0.00(0.00,0.03)0.02(0.00,0.09)<0.01Basophils(10^9/L), [M(IOR)]0.02(0.01,0.04)0.02(0.01,0.04)0.02(0.01,0.04)0.173Red 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)0.011Hemoglobin(g/L), [M(IOR)]105.0(87.0,125.0)102.0(83.0,124.5)107.0(91.0,125.0)0.053Hematocrit(%), [M(IOR)]3.22(26.2,38.2)30.6(25.5,38.4)3.4(27.7,37.9)0.042Platelet(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	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
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	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
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 Hemaglobin(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	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
Hemoglobin(g/L), [M(IOR)]105.0(87.0,125.0)102.0(83.0,124.5)107.0(91.0,125.0)0.053Hematocrit(%), [M(IOR)]32.2(26.2,38.2)30.6(25.5,38.4)33.4(27.7,37.9)0.042Platelet(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	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
Hematocrit(%), [M(IOR)]32.2(26.2,38.2)30.6(25.5,38.4)33.4(27.7,37.9)0.042Platelet(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	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
Platelet(10^9/L), [M(IOR)]189.0(124.0,249.0)159.5(96.5,239.0)201.0(148.0,253.0)<0.001CRP(mg/L), [M(IOR)]51.22(12.93,105.52)67.59(28.40,135.64)34.96(9.46,90.71)<0.001	Hematocrit(%), [M(IOR)]	32.2(26.2,38.2)	30.6(25.5,38.4)	33.4(27.7,37.9)	0.042
CRP(mg/L), [M(IOR)]51.22(12.93,105.52)67.59(28.40,135.64)34.96(9.46,90.71)<0.001HbA1c(%), [M(IOR)]6.3(5.8,7.2)6.3(6.0,7.2)6.3(5.8,7.2)0.490TP(g/L), [M(IOR)]61.0(53.9,67.7)57.6(52.7,65.1)62.6(56.6,84.4)<0.001	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
HbA1c(%), [M(IOR)]6.3(5.8,7.2)6.3(6.0,7.2)6.3(5.8,7.2)0.490TP(g/L), [M(IOR)]61.0(53.9,67.7)57.6(52.7,65.1)62.6(56.6,68.4)<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
TP(g/L), [M(IOR)]61.0(53.9,67.7)57.6(52.7,65.1)62.6(56.6,84.4)< 0.001Albumin(g/L), [M(IOR)]32.80(29.10,37.70)31.03(28.12,35.25)34.30(30.00,38.18)< 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
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	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
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	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
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	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
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	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	Death	Alive	Р
	(N=401)	(N=164)	(N=237)	
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
IbLDLC/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; SaO₂, 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; TBLL, total bilirubin; DBLL, direct bilirubin; BlL, bilirubin; DBL, direct bilirubin; BL, 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; LDLC, large buoyant LDL cholesterol; sdLLC, 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, SaO₂, temperature, WBC, lymphocyte, eosinophils, platelet, CRP, AST, AKP, GGT, BUN, eGFR, HCO₃, 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 \geq 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 (Stata-Corp 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

Variable	Crude HR(95%CI)	Р					Adjusted HR(95%CI)	Р		
TG	1.03(0.88,1.20)	0.747		-			1.04(0.89,1.23)	0.608		
TC	0.81(0.71,0.92)	0.002		-	-		0.91(0.80,1.04)	0.166		
HDLC	0.75(0.50,1.12)	0.164			<u> </u>		1.13(0.75,1.72)	0.553		->
LDLC	0.69(0.59,0.82)	<0.001					0.82(0.69,0.97)	0.019		
IbLDLC	0.63(0.51,0.78)	<0.001					0.79(0.63,0.98)	0.033		
sdLDLC	0.28(0.15,0.53)	< 0.001					0.44(0.24,0.83)	0.011	_ -	
Non HDLC	0.81(0.70,0.93)	0.004			-		0.89(0.78,1.03)	0.107		
Remanent C	1.13(0.96,1.31)	0.134			+		1.04(0.87,1.23)	0.682		
TG/HDLC	1.05(0.98,1.13)	0.143					1.00(0.92,1.08)	0.898	-	
TC/HDLC	1.00(0.96,1.04)	0.981			÷		0.98(0.94,1.03)	0.457	-	
LDLC/HDLC	0.81(0.69,0.94)	0.006			-		0.85(0.73,1.00)	0.045		
IbLDLC/HDLC	0.72(0.58,0.89)	0.002					0.83(0.70,1.02)	0.074		
sdLDLC/HDLC	0.72(0.47,1.09)	0.116					0.63(0.40,1.00)	0.048		
Remanent C/HDLC	1.01(0.98,1.05)	0.308	0	0.5	1	1.5	0.99(0.95,1.04)	0.763 (0 0.5 1	1.5

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 ni-trogen, 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



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; bLDLC, 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)	Р	HR(95%CI)	Р	
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	
IbLDLC	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	
IbLDLC/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; bLDLC, small dense 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)	Р	HR(95%CI)	Р
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
IbLDLC	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
IbLDLC/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; lobLDLC, small dense 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 ageand 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 \geq 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.or g/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.

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

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