International Journal of General Medicine

Dovepress
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ORIGINAL RESEARCH

Association Between High-Density Lipoprotein Cholesterol and Length of Hospital Stay in Acute Pancreatitis: A Retrospective Cohort Study

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Background: Acute pancreatitis (AP) is a complex inflammatory disorder with varying degrees of severity, impacting patient recovery and healthcare resource utilization. The length of hospital stay (LOS) is a pivotal indicator of recovery, and identifying factors influencing LOS can offer insights into AP management. High-density lipoprotein cholesterol (HDL-C), known for its cardioprotective properties, has been posited to influence AP outcomes; however, its relationship with LOS remains unclear.

Objective: This study aimed to investigate the potential correlation between HDL-C levels and LOS in patients with AP, considering the effects of demographic factors, comorbidities, and other clinical parameters.

Methods: A retrospective cohort study was conducted. Data collection adhered to the STROBE guidelines, and baseline clinical and laboratory variables were analyzed. Statistical analysis comprised univariate and multivariate regression models, Generalized Additive Models (GAM), and stratified linear regression models to assess the relationship between HDL-C and LOS, while accounting for confounding factors.

Results: After adjusting for key confounders, including age, sex, BMI, WBC, HB, PLT, CRP, ALT, AMY, TB, GLU, LDL-C, SCR, BUN, ALB, Ca2+, and the presence of comorbidities such as hypertension, gallstones, diabetes mellitus, liver dysfunction, renal insufficiency, smoking and alcohol consumption, the study revealed a nonlinear relationship between HDL-C levels and LOS, with an inflection point at 1.5 mmol/L. Below this threshold, HDL-C was significantly and inversely correlated with LOS, whereas above this threshold, HDL-C was positively correlated with LOS. Subgroup analyses emphasized that in non-diabetic, non-alcoholic and non-hyperlipidemic pancreatitis patients, there is a negative correlation between HDL-C levels and LOS.

Conclusion: HDL-C exhibits a U-shaped relationship with LOS in patients with AP, suggesting that both low and high levels of HDL-C may influence hospital stay duration. These findings underscore the importance of considering HDL-C levels in the clinical management of AP. Especially in patients who are non-diabetic, non-hyperlipidemic, and non-alcoholic, the management of HDL-C may significantly reduce hospital stay.

Keywords: acute pancreatitis, length of hospital stay, high-density lipoprotein cholesterol, non-linear relationship, retrospective cohort study, personalized treatment

Introduction

Acute pancreatitis (AP) is an inflammatory condition with a spectrum of severity ranging from mild to life-threatening, often necessitating hospitalization and close monitoring.[1] In 2019, the global incidence of AP was estimated to be approximately 196.8 thousand deaths, which is a substantial increase compared to previous years, indicating a growing concern regarding this condition.[2] The burden of AP is further illustrated by the associated disability-adjusted life years (DALYs), which reached around 9.0 million globally, marking a 3.88-fold increase since 1990. These figures highlight healthcare systems' ongoing challenges in managing AP.[2] The length of hospital stay (LOS) is a critical metric in evaluating patient recovery and healthcare resource allocation.[3] Identifying factors that influence LOS can provide

Received: 28 August 2024
Accepted: 14 December 2024
Published: 30 December 2024

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insights into the management and prognosis of AP.[4] Among the various clinical and biochemical parameters, high-density lipoprotein cholesterol (HDL-C) has garnered attention due to its potential role in modulating inflammatory responses.[5] HDL-C, reputed as the "good cholesterol", is integral to reverse cholesterol transport and possesses anti-inflammatory and antioxidant properties.[6] Studies have shown that low levels of HDL-C are associated with an increased risk of cardiovascular and non-cardiovascular mortality.[7] Physicians can tailor treatments for patients based on HDL-C levels, and for those with extremely low HDL-C levels, they may consider adjusting the treatment plan. For instance, medications such as Cholesteryl Ester Transfer Protein (CETP) inhibitors could be used to elevate HDL-C levels.[8] Research has found that HDL-C levels significantly decreased during hospitalization in patients with COVID-19, which may correlate with the severity of the disease. Lower HDL-C levels are considered an adverse prognostic factor for the severity of COVID-19, hence, the variation in HDL-C levels can serve as one of the important clinical indicators when the medical team assesses the timing for hospital discharge.[9] Its significance extends beyond cardiovascular health, with emerging evidence suggesting a link between HDL-C levels and outcomes in inflammatory diseases, including AP.[10] However, the relationship between HDL-C and AP outcomes is not straightforward and may be modulated by multiple confounding factors such as age, sex, comorbidities, and nutritional status.[11,12] Previous studies have reported mixed findings on the association between HDL-C levels and AP outcomes, with some suggesting a protective role of HDL-C in reducing LOS.[13–15] In a retrospective cohort study involving patients with acute pancreatitis, it was found that lower HDL-C levels were significantly associated with poorer clinical outcomes, including extended hospital stays.[16] Additionally, another study emphasized that reduced HDL-C levels were identified as an independent risk factor for persistent organ failure, pancreatic necrosis, and in-hospital mortality in patients with acute pancreatitis. The findings suggest that lower HDL-C levels may indicate a more severe inflammatory response, which could lead to a longer hospital stay.[17] Neither of the studies above further investigated the non-linear relationship between HDL-C and LOS.

This study aims to investigate the correlation between HDL-C levels and LOS in patients with AP, taking into account a comprehensive set of potential confounders. We hypothesize that HDL-C may exhibit a U-shaped relationship with LOS, identifying threshold values that could have significant implications for the management and recovery trajectories of patients with AP. Furthermore, we aim to explore the modifying effects of demographic factors and comorbidities on the HDL-C and LOS relationship, providing a more nuanced understanding of HDL-C's role in the context of AP.

Methods

Data Source

The independent variables and confounders were baseline levels collected within 24 hours after admission, including clinical data such as age, sex, and comorbidities (including hypertension, diabetes, common bile duct stones, liver dysfunction, smoking (including former smokers), alcohol consumption (including former drinkers) and renal insufficiency), as well as laboratory test results at admission (including white blood cells (WBC), triglycerides (TG), hemoglobin (HB), platelets (PLT), C-reactive protein (CRP), alanine aminotransferase (ALT), amylase (AMY), total bilirubin (TB), glucose (GLU), serum creatinine (SCR), blood urea nitrogen (BUN), albumin (ALB), calcium ions (Ca2+), high-density lipoprotein-cholesterol (HDL-C), and low-density lipoprotein-cholesterol (LDL-C)). Our research strictly adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[18] The determination of covariates is based on previously published literature as well as our clinical experience.[15,19]

Study Population

This is a retrospective cohort study with data derived from the hospital's electronic medical record system. Patients diagnosed with acute pancreatitis (AP) admitted to the Department of Gastroenterology at Ningbo Second Hospital from July 2020 to June 2023 were included. The diagnosis of AP requires two of the following three characteristics: (1) epigastric pain; (2) serum lipase or amylase activity more than three times the upper limit of normal; (3) characteristic findings of AP on computed tomography (CT) or magnetic resonance imaging (MRI). Patients with serum total triglycerides (TG) >11.3 mmol/L (1000 mg/dL), or serum TG levels between 5.65–11.3 mmol/L accompanied by lipemic serum, and without other risk factors for AP, can be diagnosed with hypertriglyceridemic

pancreatitis (HTGP).[15] The exclusion criteria were as follows: (1) age less than 18 years; (2) poor quality of abdominal CT imaging; (3) absence of necessary covariate data. This study was conducted with approval from the Ethics Committee of Ningbo Second Hospital. The data were collected from the electronic medical record system of our hospital. All data were anonymized and did not contain any information that could identify the participants. As this study involved retrospective analysis, informed consent from the subjects was not required. As the study is retrospective and the data are fully anonymized, informed consent is waived. The research has been approved by the Ethics Committee of Ningbo No.2 hospital.

Statistical Analysis

The entire statistical analysis process was divided into five stages. Initially, we analyzed the baseline characteristics of the participants according to the principles of HDL-C categorized by quartiles (Q1: <1.0; Q2: 1.0 to < 1.2 mmol/L; Q3: 1.2 to < 1.4 mmol/L; Q4:1.4 to < 3.1 mmol/L): (1) continuous variables were presented as means ± standard deviations (for normally distributed data) or medians (interquartile ranges) (for skewed distributions), and categorical variables were expressed as frequencies or percentages; (2) one-way analysis of variance (for normally distributed data), Kruskal–Wallis *H*-test (for skewed distributions), and chi-square tests (for categorical variables) were utilized to determine if there were significant differences in means and proportions among groups. Secondly, we employed univariate linear regression models to assess the relationship between HDL-C and LOS. Thirdly, under the STROBE statement recommendations,[20] we presented results for unadjusted, minimally adjusted, and fully adjusted analyses. Covariates were adjusted in the model if the odds ratio changed by at least 10% upon their inclusion.[21] Fourthly, given that HDL-C is a continuous variable, a Generalized Additive Model (GAM) was used to identify non-linear relationships. In the presence of non-linear associations, a two-piece linear regression model was applied to calculate the threshold effects of HDL-C on LOS based on the smooth curve plot. Recursive methods automatically calculated the inflection point by taking the maximum likelihood value when a clear ratio between HDL-C and LOS was evident in the smooth curve.[22] Fifthly, subgroup analyses were conducted using stratified linear regression models. Likelihood ratio tests were applied to examine effect modification and interaction between subgroups.

Results

Baseline Characteristics of Participants

The average age of the participants was 57.6 ± 17.7 years old, and about 57.9% of them were male. Baseline characteristics were listed in Table 1. The table delineates the baseline characteristics of the participants, categorized

Table 1 Baseline Characteristics of Participants

HDL-C (quartile, mmol/L)	Q1 < 1.0	Q2 1.0 to < 1.2	Q3 1.2 to < 1.4	Q4 1.4 to < 3.1	P-value
N (cases)	176	171	186	184	
Age (years, mean ± sd)	57.9 ± 17.7	58.1 ± 17.9	55.7 ± 18.5	58.8 ± 16.7	0.411
BMI (kg/m2, mean ± sd)	24.1 ± 4.2	24.9 ± 3.6	24.5 ± 4.1	23.2 ± 3.9	<0.001
WBC (*10^9/L)	9.5 ± 4.7	9.2 ± 4.3	9.3 ± 4.5	8.9 ± 4.0	0.905
HB (*10^12/l)	126.2 ± 23.6	128.5 ± 25.2	131.7 ± 25.1	133.2 ± 20.1	0.008
PLT (*10^9/L)	191.3 ± 82.0	195.6 ± 73.6	202.2 ± 68.4	196.2 ± 58.7	0.229
CRP (mg/L)	109.0 ± 104.7	87.4 ± 100.6	73.8 ± 99.9	63.5 ± 90.6	<0.001
ALT (U/L)	124.1 ± 314.6	95.2 ± 151.1	113.5 ± 168.8	150.0 ± 201.2	0.412
AMY (U/L)	314.4 ± 565.6	325.2 ± 411.3	551.0 ± 1907.9	344.5 ± 426.7	0.162
TB (μmol/L)	39.2 ± 50.7	31.1 ± 50.3	27.9 ± 35.2	28.9 ± 29.0	0.126
GLU (mmol/L)	7.9 ± 4.3	7.7 ± 3.3	7.3 ± 3.3	7.9 ± 3.8	0.436
SCR (μmol/L)	80.6 ± 58.2	77.6 ± 71.9	67.7 ± 30.6	65.3 ± 26.0	0.021
BUN (mmol/L)	6.1 ± 4.2	5.4 ± 3.8	5.4 ± 3.0	5.2 ± 2.4	0.201

(*Continued*)

Table 1 (Continued).

HDL-C (quartile, mmol/L)	Q1 < 1.0	Q2 1.0 to < 1.2	Q3 1.2 to < 1.4	Q4 1.4 to < 3.1	P-value
ALB (g/L)	34.2 ± 6.9	37.1 ± 4.7	38.5 ± 5.3	39.2 ± 4.7	<0.001
Ca2+ (mmol/L)	2.1 ± 0.2	2.2 ± 0.2	2.2 ± 0.2	2.2 ± 0.2	<0.001
TG (mmol/L)	2.9 ± 5.9	3.5 ± 5.4	3.2 ± 8.9	5.0 ± 13.3	<0.001
LDL-C (mmol/L)	2.2 ± 0.8	2.7 ± 1.0	2.8 ± 0.9	3.2 ± 1.4	<0.001
Hospital stay (days)	10.0 (6.0–15.0)	9.9 ± 6.2	9.6 ± 5.7	9.3 ± 6.8	0.019
Sex					<0.001
Male	115 (65.3%)	110 (64.3%)	104 (55.9%)	86 (46.7%)	
Female	61 (34.7%)	61 (35.7%)	82 (44.1%)	98 (53.3%)	
Hypertension					0.195
No	111 (63.1%)	116 (67.8%)	137 (73.7%)	125 (67.9%)	
Yes	65 (36.9%)	55 (32.2%)	49 (26.3%)	59 (32.1%)	
Gallstone					0.584
No	124 (70.5%)	124 (72.5%)	131 (70.4%)	140 (76.1%)	
Yes	52 (29.5%)	47 (27.5%)	55 (29.6%)	44 (23.9%)	
Diabetes Mellitus					0.726
No	136 (77.3%)	133 (77.8%)	152 (81.7%)	146 (79.3%)	
Yes	40 (22.7%)	38 (22.2%)	34 (18.3%)	38 (20.7%)	
Hypohepatia					0.079
No	106 (60.2%)	118 (69.0%)	133 (71.5%)	115 (62.5%)	
Yes	70 (39.8%)	53 (31.0%)	53 (28.5%)	69 (37.5%)	
Renal insufficiency					0.032
No	159 (90.3%)	162 (94.7%)	180 (96.8%)	177 (96.2%)	
Yes	17 (9.7%)	9 (5.3%)	6 (3.2%)	7 (3.8%)	
Smoking					0.016
No	123 (69.9%)	125 (73.1%)	139 (74.7%)	154 (83.7%)	
Yes	53 (30.1%)	46 (26.9%)	47 (25.3%)	30 (16.3%)	
Alcohol consumption					0.358
No	139 (79.0%)	129 (75.4%)	147 (79.0%)	153 (83.2%)	
Yes	37 (21.0%)	42 (24.6%)	39 (21.0%)	31 (16.8%)	

Abbreviations: WBC, White blood cells; TG: Triglyceride; HB, hemoglobin; PLT, platelets; CRP, C-reactive protein; ALT, Alanine aminotransferase; AMY, Amylase; TB, Total bilirubin; GLU, Glucose; SCR, Serum creatinine; BUN, Blood urea nitrogen; ALB, Albumin; Ca2+, Calcium ions; BMI, Body mass index; HDL-C, High-density lipoprotein-cholesterol; LDL-C, Low-density lipoprotein-cholesterol; Q1, First Quartile; Q2, Second Quartile; Q3, Third Quartile; Q4, Fourth Quartile.

into quartiles (Q1 to Q4) of HDL-C levels. WBC counts were relatively consistent across quartiles, with no significant differences ($P > 0.05$). HB levels showed a significant increase from Q1 to Q4 ($P = 0.008$). PLT counts did not differ significantly across the quartiles ($P > 0.05$). CRP levels, a marker of inflammation, significantly decreased from Q1 to Q4, indicating a negative correlation with HDL-C levels ($P < 0.001$). ALT levels showed no significant trend across quartiles ($P > 0.05$). TB levels were significantly lower in Q3 compared to Q1 ($P = 0.047$). GLU levels did not exhibit a significant trend across the quartiles ($P > 0.05$). SCR levels were significantly lower in Q3 and Q4 compared to Q1 and Q2 ($P < 0.05$). BUN levels also showed a decreasing trend from Q1 to Q4 ($P < 0.05$). ALB levels increased significantly from Q1 to Q4, indicating a positive correlation with HDL-C levels ($P < 0.001$). Ca2+ levels were consistent across all quartiles, with a significant difference observed ($P < 0.001$). LDL-C levels increased significantly from Q1 to Q4 ($P < 0.001$). The average hospital stay was significantly shorter for participants in Q4 compared to Q1 ($P < 0.05$). The sex distribution showed a significant difference across quartiles, with a higher proportion of females in Q4 and a higher proportion of males in Q1 ($P < 0.001$). Smoking prevalence shows a significant decrease from Q1 to Q4, indicating that higher HDL-C levels may be associated with a lower prevalence of smoking. Regarding comorbidities, there were no significant differences in the prevalence of hypertension, gallstone, diabetes mellitus, hypohepatia and alcohol

consumption across the quartiles (P > 0.05). However, renal insufficiency was significantly more prevalent in Q1 compared to the other quartiles (P = 0.032).

Univariate Analysis

The results of the univariate analysis are shown in Table 2. The univariate analysis reveals that various factors are significantly associated with the Length of Hospital Stay. Specifically, increasing age, BMI, white blood cell count, and fasting glucose levels are linked to a longer hospital stay. Additionally, elevated levels of CRP, ALT, AMY, TB, SCR, and BUN, which are indicators of inflammation or liver and kidney function, also contribute to a longer stay. On the other

Table 2 The Results of the Univariate Analysis

	Statistics	Effect Size (β)	P value
Sex			
Male	415 (57.9%)	0	
Female	302 (42.1%)	−0.0 (−1.0, 0.9)	0.958
Age (years)	57.6 ± 17.7	0.0 (0.0, 0.1)	0.027
BMI (kg/m2)	24.1 ± 4.0	0.1 (0.0, 0.3)	0.018
WBC (*10^9/L)	9.2 ± 4.4	0.3 (0.2, 0.4)	<0.001
HB (*10^12/l)	130.0 ± 23.7	−0.0 (−0.0, 0.0)	0.257
PLT (*10^9/L)	196.4 ± 71.0	−0.0 (−0.0, 0.0)	0.342
CRP (mg/L)	83.0 ± 100.2	0.0 (0.0, 0.0)	<0.001
ALT (U/L)	121.1 ± 218.4	0.0 (0.0, 0.0)	0.001
AMY (U/L)	386.1 ± 1056.0	0.0 (0.0, 0.0)	0.003
TB (μmol/L)	31.7 ± 42.2	0.0 (0.0, 0.0)	<0.001
GLU (mmol/L)	7.7 ± 3.7	0.4 (0.2, 0.5)	<0.001
LDL-C (mmol/L)	2.7 ± 1.1	0.2 (−0.3, 0.6)	0.431
SCR (μmol/L)	72.6 ± 50.1	0.0 (0.0, 0.0)	<0.001
BUN (mmol/L)	5.5 ± 3.4	0.4 (0.3, 0.6)	<0.001
ALB (g/L)	37.3 ± 5.8	−0.3 (−0.3, −0.2)	<0.001
Ca2+ (mmol/L)	2.2 ± 0.2	−7.3 (−9.6, −4.9)	<0.001
Hypertension			
No	489 (68.2%)	0	
Yes	228 (31.8%)	1.4 (0.4, 2.4)	0.007
Gallstone			
No	519 (72.4%)	0	
Yes	198 (27.6%)	2.3 (1.3, 3.4)	<0.001
Diabetes Mellitus			
No	567 (79.1%)	0	
Yes	150 (20.9%)	2.1 (1.0, 3.3)	<0.001
Hypohepatia			
No	472 (65.8%)	0	
Yes	245 (34.2%)	2.5 (1.5, 3.5)	<0.001
Renal insufficiency			
No	678 (94.6%)	0	
Yes	39 (5.4%)	3.2 (1.1, 5.3)	0.003
Smoking			
No	541 (75.5%)	0	
Yes	176 (24.5%)	−0.3 (−1.4, 0.9)	0.657
Alcohol consumption			
No	568 (79.2%)	0	
Yes	149 (20.8%)	0.7 (−0.5, 1.9)	0.240
HDL-C (mmol/L)	1.2 ± 0.4	−1.4 (−2.6, −0.2)	0.025

hand, higher albumin and calcium levels seem to be protective, correlating with shorter stays. Furthermore, comorbidities such as hypertension, gallstone, diabetes, liver dysfunction, and renal insufficiency are associated with increased hospital stays, but higher HDL-C levels are related to decreased stays.

The Results of the Relationship Between HDL-C and LOS

This study analyzed the relationship between HDL-C levels and the duration of hospital stay across various regression models presented in Table 3. The crude model evidenced a significant negative association between HDL-C levels and hospital stay length (β = −1.4, 95% CI: −2.6 to −0.2, P = 0.025), suggesting that for each increase in HDL-C level, there was a corresponding decrease in hospital stay duration. This association was robust to adjustments for age and sex in the first adjusted model, yielding effect sizes and significance that closely mirrored the crude analysis (β = −1.4, 95% CI: −2.6 to −0.2, P = 0.024). However, upon refinement within the fully adjusted model, which incorporated a range of influential variables including BMI, WBC, HB, PLT, CRP, ALT, AMY, TB, GLU, LDL-C, SCR, BUN, ALB, Ca2+, as well as prevalent comorbidities such as hypertension, gallstone disease, diabetes mellitus, hypohepatia, renal insufficiency, smoking and alcohol consumption, the initial association was attenuated and rendered non-significant (β = −0.6, 95% CI: −1.9 to 0.7, P = 0.372). Analysis per standard deviation of HDL-C corroborated this trend, showing significance following minimal adjustment but not after full adjustment. Further stratification of HDL-C into quartiles revealed a progressively heightened negative association with hospital stay in the unadjusted and minimally adjusted models, which attenuated and lost significance in the fully adjusted model, as indicated by P-values of 0.338, 0.172, and 0.111 for quartiles 2, 3, and 4, respectively. The trend analysis corroborated the crude models with a significant P-value of 0.003, which, however, did not withstand the comprehensive adjustment, yielding a non-significant P-value of 0.173.

The Analyses of Non-Linear Relationship

In our investigation, we discerned a significant non-linear relationship between HDL-C levels and the length of hospital stay, as depicted in Figure 1. The two-piecewise linear regression model, detailed in Table 4, was employed to dissect this complex association after adjusting for a myriad of factors including sex, age, BMI, WBC, HB, PLT, CRP, ALT, AMY, TB, GLU, LDL-C, SCR, BUN, ALB, Ca2+, and the presence of comorbidities such as hypertension, gallstone, diabetes mellitus, hypohepatia, renal insufficiency, smoking and alcohol consumption. The inflection point of HDL-C, determined by our analysis, was identified at 1.5 mmol/L. For HDL-C levels below this threshold, the effect size was −2.6 with a 95% confidence interval ranging from −4.5 to −0.7, which was statistically significant (P = 0.006). This suggests that for each decrement in HDL-C level below 1.5 mmol/L, there was a significant increase in the length of hospital stay. Conversely, for HDL-C levels above the inflection point of 1.5 mmol/L, the effect size was positive, indicating a decrease in the length of hospital stay. The 95% confidence interval for this effect was from 0.5 to 5.8 and it also reached statistical

Table 3 Relationship Between HDL-C and the Length of Hospital Stay in Different Models

Variable	Crude (β, 95% CI, P)	Adjust I (β, 95% CI, P)	Adjust II (β, 95% CI, P)
HDL-C	−1.4 (−2.6, −0.2) 0.025	−1.4 (−2.6, −0.2) 0.024	−0.6 (−1.9, 0.7) 0.372
HDL-C per SD	−0.5 (−1.0, −0.1) 0.025	−0.6 (−1.0, −0.1) 0.024	−0.2 (−0.7, 0.3) 0.372
HDL-C (quartile)			
Q1	Ref	Ref	Ref
Q2	−1.4 (−2.8, −0.1) 0.039	−1.4 (−2.8, −0.1) 0.038	−0.6 (−1.9, 0.6) 0.338
Q3	−1.8 (−3.1, −0.4) 0.009	−1.7 (−3.1, −0.4) 0.012	−0.9 (−2.1, 0.4) 0.172
Q4	−2.1 (−3.4, −0.7) 0.003	−2.1 (−3.4, −0.7) 0.003	−1.1 (−2.5, 0.3) 0.111
P trend	0.003	0.003	0.173

Notes: Crude model: we did not adjust other covariants. Adjusted I model: we adjusted age and sex. Fully adjusted model II: we adjusted sex, age, BMI, WBC, HB, PLT, CRP, ALT, AMY, TB, GLU, LDL-C, SCR, BUN, ALB, Ca2+, hypertension, gallstone, diabetes mellitus, hypohepatia, renal insufficiency, smoking, alcohol consumption.
Abbreviations: CI, confidence interval; Ref, reference.

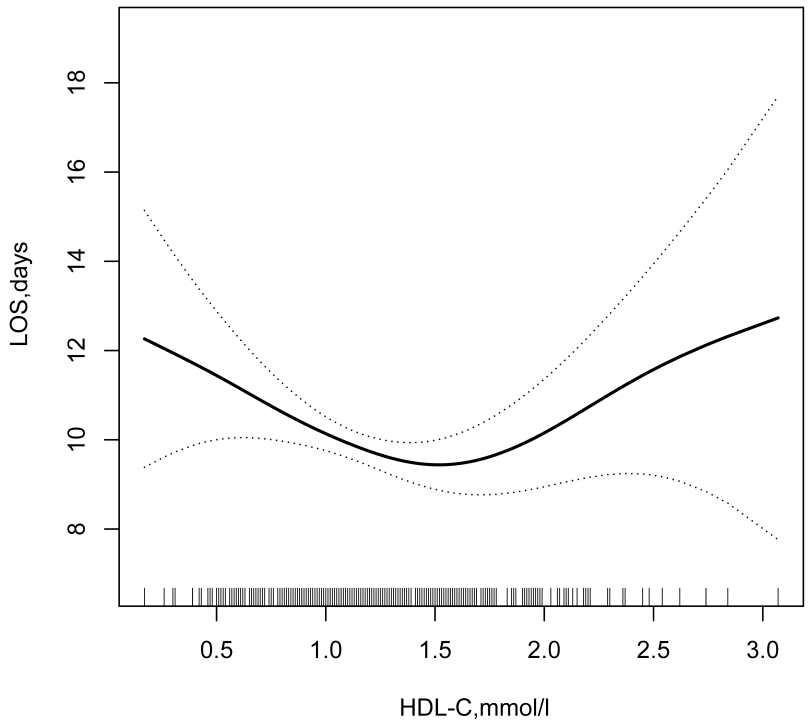

Figure 1 The relationship between HDL-C and LOS. A nonlinear relationship between them was detected after adjusting for sex, age, BMI, WBC, HB, PLT, CRP, ALT, AMY, TB, GLU, LDL-C, SCR, BUN, ALB, Ca2+, hypertension, gallstone, diabetes mellitus, hypohepatia, renal insufficiency, smoking and alcohol consumption..

significance (P = 0.019). This implies that higher HDL-C levels, beyond the inflection point, are associated with longer hospital stays.

The Results of Subgroup Analyses

As delineated in Table 5, significant interaction effects were observed for several subgroups when assessing the impact of HDL-C levels on hospital LOS. Notably, the interaction for sex demonstrated a not statistically significant difference (P = 0.148), with females showing a robust negative effect size (β = −2.6, 95% CI: −4.3 to −0.9, P = 0.003), in contrast to males whose effect was not statistically significant (β = −0.3, 95% CI: −2.0 to 1.4, P = 0.716). Age also presented an unnotable interaction, with a P-value of 0.088. Participants aged 60 and above exhibited a significant negative effect size (β = −2.6, 95% CI: −4.3 to −0.9, P = 0.004), whereas those below 60 showed an effect that did not reach statistical significance (β = −0.5, 95% CI: −2.1 to 1.2, P = 0.570). BMI subgroups revealed a lack of statistically significant interaction (P = 0.466). Albumin levels emerged as a non-significant modifier, with the interaction P-value at 0.070. Patients with low albumin levels (<40 g/L) had a significant negative effect size (β = −2.1, 95% CI: −3.6 to −0.6, P = 0.006), while those with higher albumin levels did not (β = 1.8, 95% CI: −0.5 to 4.0, P = 0.121). Diabetes mellitus, hyperlipidemic pancreatitis and alcohol consumption all exhibit significant interactions with high-density lipoprotein

Table 4 The Results of the Two-Piecewise Linear Regression Model

The inflection point of HDL-C (mmol/l)	Effect size (β)	95% CI	P value
< 1.5	−2.6	(−4.5, −0.7)	0.006
≥1.5	3.1	(0.5, 5.8)	0.019

Notes: Effect: LOS Cause: HDL-C. Adjusted: sex; age; BMI; WBC; HB; PLT; CRP; ALT; AMY; TB; GLU; LDL-C; SCR; BUN; ALB; Ca2+; hypertension; gallstone; diabetes mellitus; hypohepatia; renal insufficiency; smoking; alcohol consumption.

https://doi.org/10.2147/IJGM.S487993

Table 5 Effect Size of HDL-C on LOS in Prespecified and Exploratory Subgroups

Characteristic	No of participants	Effect size (95% CI)	P value	P for interaction
Sex				0.148
Male	415	−0.3 (−2.0, 1.4)	0.716	
Female	302	−2.6 (−4.3, −0.9)	0.003	
Age(years)				0.088
>60	329	−2.6 (−4.3, −0.9)	0.004	
<=60	388	−0.5 (−2.1, 1.2)	0.570	
BMI (kg/m2)				0.466
<18.5	46	−2.9 (−6.6, 0.8)	0.128	
≥18.5, <23	257	−1.3 (−2.6, 0.0)	0.057	
≥23	414	−0.7 (−2.8, 1.4)	0.514	
ALB (g/L)				0.070
<40	485	−2.1 (−3.6, −0.6)	0.006	
≥40	232	1.8 (−0.5, 4.0)	0.121	
GLU (mmol/L)				0.140
<6.1	309	−2.8 (−4.3, −1.3)	<0.001	
≥6.1	408	−0.5 (−2.2, 1.2)	0.564	
TB (μmol/L)				0.140
<20.5	413	−1.7 (−3.2, −0.3)	0.019	
≥20.5	304	−0.9 (−2.9, 1.1)	0.391	
Diabetes Mellitus				0.014
No	567	−2.0 (−3.2, −0.8)	<0.001	
Yes	150	1.2 (−2.3, 4.6)	0.502	
Hypertension				0.093
No	489	−1.6 (−3.0, −0.3)	0.016	
Yes	228	−0.7 (−3.2, 1.9)	0.609	
Renal insufficiency				0.818
No	678	−1.1 (−2.4, 0.1)	0.076	
Yes	39	−2.0 (−7.3, 3.3)	0.468	
Hypohepatia				0.866
No	472	−0.8 (−2.3, 0.6)	0.257	
Yes	245	−2.1 (−4.2, −0.0)	0.050	
Hyperlipidemic pancreatitis				0.035
No	558	−2.5 (−3.8, −1.3)	<0.001	
Yes	159	2.4 (−0.7, 5.5)	0.129	
Gallstone				0.101
No	519	−0.6 (−2.1, 0.8)	0.409	
Yes	198	−3.3 (−5.4, −1.3)	0.002	
Smoking				0.941
No	541	−1.5 (−2.9, 0.0)	0.052	
Yes	176	−1.4 (−3.4, 0.7)	0.190	
Alcohol consumption				
No	568	−2.7 (−4.0, −1.4)	< 0.001	< 0.001
Yes	149	3.0 (0.1, 5.9)	0.047	

Notes: Adjusted: sex; age; BMI; WBC; HB; PLT; CRP; ALT; AMY; TB; GLU; LDL-C; SCR; BUN; ALB; Ca2+; hypertension; gallstone; diabetes mellitus; hypohepatia; renal insufficiency; smoking; alcohol consumption.

cholesterol (HDL-C) levels, with P-values of 0.014, 0.035, and less than 0.001, respectively. Those without diabetes showed a significant negative effect (β = −2.0, 95% CI: −3.2 to −0.8, P = 0.001), whereas those with diabetes mellitus did not display a significant association (β = 1.2, 95% CI: −2.3 to 4.6, P = 0.502). Similarly, the absence of hyperlipidemic pancreatitis was linked to a significant negative effect (β = −2.5, 95% CI: −3.8 to −1.3, P < 0.001), while its presence led to a non-significant positive effect (β = 2.4, 95% CI: −0.7 to 5.5, P = 0.129). Patients who do not consume alcohol exhibit

a negative correlation between HDL-C and Length of Stay (LOS) (β = −2.7, 95% CI: −4.0 to −1.4, P < 0.001); in contrast, patients who consume alcohol show a positive correlation between HDL-C and LOS (β = 3.0, 95% CI: 0.1 to 5.9, P = 0.047). This is an interesting discovery.

Discussion

The purpose of this study was to investigate the correlation between HDL-C and LOS. After comprehensive model analysis, including sensitivity analysis, no significant association was found between HDL-C and LOS. However, the study also revealed a nonlinear relationship between HDL-C and LOS. Particularly, the impact of HDL-C on LOS showed different patterns of correlation on either side of the inflection point of HDL-C (1.5). Specifically, on the left side of the inflection point, HDL-C measured at baseline showed a negative correlation with LOS; however, on the right side of the inflection point, HDL-C measured at baseline showed a positive correlation with LOS. For this type of U-shaped relationship, we speculate that HDL-C has antioxidant effects and can alleviate oxidative stress in patients with acute pancreatitis. Oxidative stress is one of the important pathological mechanisms of acute pancreatitis, and HDL-C mitigates this damage by scavenging free radicals.[16] Therefore, in patients with acute pancreatitis, HDL-C levels are usually significantly reduced, which is associated with the weakening of its anti-inflammatory function.[23] In the inflammatory state, cytokines promote the activity of endothelial lipase, leading to a decrease in HDL-C.[24] The reduction of HDL-C may further lead to an increase in free fatty acid (FFA) levels, thereby exacerbating the acidic environment of the pancreas and promoting inflammatory responses.[16] Thus, the lower the HDL-C, the longer the hospital stay. However, we also observed a peculiar increase in LOS for the high HDL-C group. We speculate that this may be related to the dysfunction of some HDL particles in the inflammatory response.[25,26] Due to the limitations of a retrospective study, we were unable to further investigate the functionality of HDL-C in our research. Future studies are needed to elucidate this issue. Furthermore, a significant discovery was that alcohol consumption is a crucial confounding factor. Patients who do not consume alcohol demonstrated a negative correlation between HDL-C and LOS, while patients who consume alcohol showed a positive correlation between HDL-C and LOS. In response to this discovery, we have the following hypothesis: Previous studies have confirmed a positive dose-response relationship between alcohol intake and HDL-C concentrations.[27] Heavy drinkers typically exhibit more complex lipid profiles, which may include extremely high levels of HDL-C.[28,29] Increased alcohol consumption among the drinking population may raise HDL-C concentrations above 1.5 mmol/L, thus making HDL-C positively correlated with LOS. Additionally, an interesting finding in the study was that among participants without diabetes and hyperlipidemia, HDL-C showed a negative correlation with LOS. Previous studies have confirmed that HDL-C is independently associated with the hospital stay duration in patients with hypertriglyceridemia-induced pancreatitis and serves as an independent predictive factor. The conclusion remains valid even after adjusting for sex ratio and age.[15] In this study, when adjusting for sex and age only, we also observed an independent correlation between HDL-C and LOS, which is consistent with previous research. However, after including a sufficient number of confounding factors, the correlation between HDL-C and LOS became insignificant. Therefore, we speculate that there may be a specific confounding factor that is strongly related to both HDL-C and LOS. For this reason, we conducted further stratified analyses and interaction tests. In the stratified analysis, we found that in the non-diabetic population, an increase in HDL-C levels was associated with a reduction in hospital stay, while in the diabetic population, there was no significant correlation between HDL-C and hospital stay duration. This suggests that diabetes is associated with lipid metabolism and hospital stay duration.[30–33] Furthermore, in the population without hyperlipidemic pancreatitis, an increase in HDL-C levels is associated with a decrease in hospital stay; however, in hyperlipidemic pancreatitis, there is no significant correlation between HDL-C and hospital length of stay (LOS). Relevant research also confirms the association between HDL-C and LOS.[34,35]

The observed correlations between HDL-C levels and various health parameters, such as BMI, ALB and CRP, are consistent with previous findings that suggest HDL-C may play a role in inflammation and overall health.[36–38] The lack of significant trends in ALT and GLU levels across HDL-C quartiles contrasts with some studies but aligns with others, indicating that the relationship between these parameters and HDL-C may be more complex and context-dependent.[39,40] The protective effect of higher albumin levels is supported by studies that have linked nutritional status with hospital outcomes.[41,42] In our subgroup analysis, we observed a positive correlation between HDL-C levels and hospital stay

duration in female and elderly populations (>60 years old). These findings are consistent with research that has reported sex-specific differences in lipid metabolism and their impact on health. Although the interaction effects did not show statistically significant differences, they emphasize the importance of considering demographic factors when studying the relationship between HDL-C and health outcomes.[43] Our study has numerous strengths. Firstly, we utilized the Generalized Additive Model (GAM) to identify non-linear relationships and illustrated the U-shaped relationship between HDL-C and LOS with smooth curve graphs. The use of GAM will aid in better uncovering the true relationship between exposure and outcome. Secondly, as this study is observational, there are inevitable potential confounding factors; hence, we employed rigorous statistical corrections to minimize residual confounding. We confirmed the previously reported inverse relationship between HDL-C and LOS. Thirdly, our novel finding is the existence of a U-shaped relationship between HDL-C and LOS. We calculated the inflection point (1.5) using recursive algorithms and discovered the saturation effect of HDL-C and LOS with piecewise linear regression.

In prior publications within the same field, a scarcity of studies has been observed to implement sub-group analyses. Our study has several limitations. First, as this is a single-center study, the study population may be influenced by patient demographics, healthcare standards, and economic conditions. The lack of external validation means that the results should be interpreted with some caution until they can be replicated in other settings. Second, the omission of medical insurance, economic conditions, and the severity of acute pancreatitis as confounding factors implies that the duration of hospital stay could be influenced by a patient's economic background and the extent of their illness. Third, the serum concentration of HDL-C is influenced by a multitude of factors, such as various medications. However, due to the nature of retrospective studies, it is impossible to fully capture these circumstances. In future studies, we will conduct prospective studies or multicenter trials to validate our findings, include a broader range of independent variables, and further explore the function of HDL-C in the context of acute pancreatitis, providing a deeper understanding of the underlying mechanisms. This approach will not only strengthen the evidence base for clinical decision-making but also aid in the development of personalized treatment strategies for patients with acute pancreatitis.

Conclusion

In conclusion, this study contributes to the understanding of HDL-C's role in health and recovery, emphasizing the need for a nuanced approach to lipid metabolism in clinical practice. HDL-C exhibits a U-shaped relationship with LOS. The inflection point is at 1.5 mmol/l; when HDL-C levels exceed 1.5 mmol/l, there is a positive correlation with LOS, whereas when HDL-C levels are below 1.5 mmol/l, there is an inverse correlation with LOS. Based on these findings, future research could conduct multicenter studies or trials to validate these results and explore the function and mechanisms of HDL-C in varying severities of pancreatitis and its relationship with LOS.

Abbreviations

WBC, White blood cells; CI, Confidence interval; SD, Standard deviation; TG, Triglyceride; HB, hemoglobin; PLT, platelets; CRP, C-reactive protein; ALT, Alanine aminotransferase; AMY, Amylase; TB, Total bilirubin; GLU, Glucose; SCR, Serum creatinine; BUN, Blood urea nitrogen; ALB, Albumin; Ca2+, Calcium ions; BMI, Body mass index; HDL-C, High-density lipoprotein-cholesterol; LDL-C, Low-density lipoprotein-cholesterol.

Data Sharing Statement

The dataset for this study is available upon request from the corresponding author.

Ethics Approval and Informed Consent

This is a retrospective study with all data anonymized. The research protocol has been approved by the local Ethics Committee of Ningbo Second Hospital. All research was conducted in accordance with the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

There is no funding to report.

Disclosure

The authors declare that they have no competing interests.

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