Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Chin Med Sci J
March 2021

Vol. 36, No. 1 P. 17-26
doi:10.24920/003866

ORIGINAL ARTICLE

Association Analysis of Hyperlipidemia with the 28-Day All-Cause Mortality of COVID-19 in Hospitalized Patients

Bin Wu[1,2,†], Jianghua Zhou[1,2,†], Wenxin Wang[1,2], Huilin Yang[2,3], Meng Xia[2], Binghong Zhang[4], Zhigang She[1,2], Hongliang Li[1,2,3,5*]

[1]Department of Cardiology, Renmin Hospital of Wuhan University, Wuhan 430071, China
[2]Institute of Model Animal, Wuhan University, Wuhan 430071, China
[3]Basic Medical School, Wuhan University, Wuhan 430071, China
[4]Department of Neonatology, Renmin Hospital of Wuhan University, Wuhan 430072, China
[5]Medical Science Research Center, Zhongnan Hospital of Wuhan University, Wuhan 430071, China

Key words: coronavirus disease 2019 (COVID-19); lipid disorder; mortality; cardiovascular diseases; diabetes

Objective This study aimed to determine the association of hyperlipidemia with clinical endpoints among hospitalized patients with COVID-19, especially those with pre-existing cardiovascular diseases (CVDs) and diabetes.

Methods This multicenter retrospective cohort study included all patients who were hospitalized due to COVID-19 from 21 hospitals in Hubei province, China between December 31, 2019 and April 21, 2020. Patients who were aged < 18 or ⩾ 85 years old, in pregnancy, with acute lethal organ injury (e.g., acute myocardial infarction, severe acute pancreatitis, acute stroke), hypothyroidism, malignant diseases, severe malnutrition, and those with normal lipid profile under lipid-lowering medicines (e.g., statin, niacin, fenofibrate, gemfibrozil, and ezetimibe) were excluded. Propensity score matching (PSM) analysis at 1:1 ratio was performed to minimize baseline differences between patient groups of hyperlipidemia and non-hyperlipidemia. PSM analyses with the same strategies were further conducted for the parameters of hyperlipidemia in patients with increased triglyceride (TG), increased low-density lipoprotein cholesterol (LDL-C), and decreased high-density lipoprotein

Received February 9, 2021; accepted March 5, 2021; published online March 17, 2021.
*Corresponding author Hongliang Li, E-mail: lihl@whu.edu.cn; phone: 86-27-68759302; Fax: 86-27-68759302.
†These authors contributed equally.
This work was supported by grants from National Key R&D Program of China (2016YFF0101500) and the National Natural Science Foundation of China (81970364, 81770053).

cholesterol (HDL-C). Mixed-effect Cox model analysis was performed to investigate the associations of the 28-days all-cause deaths of COVID-19 patients with hyperlipidemia and the abnormalities of lipid parameters. The results were verified in male, female patients, and in patients with pre-existing CVDs and type 2 diabetes.

Results Of 10 945 inpatients confirmed as COVID-19, there were 9 822 inpatients included in the study, comprising 3 513 (35.8%) cases without hyperlipidemia and 6 309 (64.2%) cases with hyperlipidemia. Based on a mixed-effect Cox model after PSM at 1:1 ratio, hyperlipidemia was not associated with increased or decreased 28-day all-cause death [adjusted hazard ratio (*HR*), 1.17 (95% *CI*, 0.95-1.44), P =0.151]. We found that the parameters of hyperlipidemia were not associated with the risk of 28-day all-cause mortality [adjusted *HR*, 1.23 (95% *CI*, 0.98-1.55), P = 0.075 in TG increase group; 0.78 (95% *CI*, 0.57-1.07), P = 0.123 in LDL-C increase group; and 1.12 (95% *CI*, 0.9-1.39), P = 0.299 in HDL-C decrease group, respectively]. Hyperlipidemia was also not significantly associated with the increased mortality of COVID-19 in patients accompanied with CVDs or type 2 diabetes, and in both male and female cohorts.

Conclusion Our study support that the imbalanced lipid profile is not significantly associated with the 28-day all-cause mortality of COVID-19 patients, even in those accompanied with CVDs or diabetes. Similar results were also obtained in subgroup analyses of abnormal lipid parameters. Therefore, hyperlipidemia might be not a major causative factor for poor outcome of COVID-19, which provides guidance for the intervention of inpatients during the epidemic of COVID-19.

CORONAVIRUS disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, has become the major global health concern, with more than 100 million people infected and 2 million deaths in over 220 countries and territories. Cardiovascular diseases (CVDs) and metabolic diseases are common comorbidities among patients with COVID-19 and significantly associated with the occurrence of critical illness and the risk of mortality.[1,2] Effective treatments of these comorbidities are therefore considered important to improve the prognosis of patients with pre-existing CVDs and metabolic diseases in the context of COVID-19.[3,4]

Hyperlipidemia is a well-known risk factor for CVDs and metabolic diseases. It is closely related to the mortality of CVDs and metabolic diseases. A survey conducted in Shenzhen, China found that the prevalence of dyslipidemia in the study population was as high as 34.6%.[5] Notably, 46.2% of patients with COVID-19 also exhibits hyperlipidemia.[6] Considering that lipid metabolism is necessary for membrane fusion between virus and host cell, viral replication, and life cycle of the virus, medicines targeting the lipid metabolism pathways are expected to benefit patients with COVID-19.[7] Indeed, as high-density lipoprotein cholesterol (HDL-C) is an important protective factor for CVDs, decreased level of HDL-C in critically ill patients is significantly associated with severity of the disease.[8] However, there has been no large-sample studies investigating the role of abnormal total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG) and high-density lipoprotein cholesterol(HDL-C) in the outcomes of patients infected by SARS-CoV-2. Therefore, it is urgent to determine the association of increased TG, increased LDL-C, and decreased HDL-C with clinical events among patients with COVID-19.

In the present study, we conducted a multi-centric retrospective cohort study of 9 822 confirmed COVID-19 cases in Hubei Province, China, aiming to determine the association of hyperlipidemia and abnormalities of lipid parameters with 28-day all-cause mortality among patients with COVID-19 using propensity score matching (PSM) analysis and COX regression confounders adjusted analysis. We also verified the results in male and female patients, and in patients with pre-existing CVDs and type 2 diabetes (T2D).

PATIENTS AND METHODS

Study cohort and data collection

This project was reviewed and approved by the institutional ethics committee of each hospital. The exception for the informed consent was granted for collecting electronic medical record data without therapeutic interventions. All patients with confirmed COVID-19 infection from 21 designated hospitals in Hubei Province, China between December 31, 2019 and April 21, 2020 were the candidates of the current multi-centric retrospective cohort study. The COVID-19 infections

were diagnosed by nucleic acid testing through throat-swab specimen or Chest computed tomography (CT) on readmission, which was in accordance with WHO interim guidance and the Novel Coronavirus Pneumonia Prevention and Control Guideline (the 5th edition) issued by the National Health Commission of China.[9,10] The exclusion criteria included age < 18 or ⩾ 85 years old, in pregnancy, with acute lethal organ injury (e.g., acute myocardial infarction, severe acute pancreatitis, or acute stroke), hypothyroidism, malignant diseases, severe malnutrition, normal lipid profile under lipid-lowering drugs therapy (e.g., statin, niacin, fenofibrate, gemfibrozil, and ezetimibe). The comorbidities of COVID-19 patients were determined through medical history and diagnosis at admission.

The medical records were reviewed by a multidisciplinary team, including data expert, statisticians and physicians. Before data extraction, the identity information of patients was removed through anonymization processes, and replaced with specific coding system. The information we collected from electronic medical records included patients' age, gender, clinical symptoms, clinical features, medical histories, laboratory examinations, imaging examinations, therapeutic interventions, and clinical outcomes. The laboratory examinations we collected included routine blood test, serum liver and renal function test, serum cardiac injury markers, D-dimer, lipid profiles, inflammatory markers. Medical histories comprised cancer, chronic obstructive pulmonary disease, coronary heart disease, T2D, coronary heart disease, cerebrovascular diseases, chronic liver disease, and chronic renal disease. For the imaging examinations, we recorded whether or not the disease involved bilateral lungs on chest CT. Medication information included statins, niacin, fibrate, ezetimibe, insulin, oral hypoglycemic drugs, antihypertensive drugs, antiplatelet drugs, and anticoagulation drugs. Physicians double-checked all collected data to ensure the accuracy.

Definition

Hyperlipidemia was defined when the patient's serum lipid test met any of the following criteria: TG ⩾1.7 mmol/L; TC ⩾5.2 mmol/L; LDL-C ⩾3 mmol/L; HDL-C <1.0 mmol/L, non-HDL-C ⩾4.1 mmol/L, according to the *2016 Chinese Guideline for the Management of Dyslipidemia in Adults*[11] and *2019 European Society of Cardiology/ European Atherosclerosis Society (ESC/EAS) Guidelines for the management of dyslipidaemia.*[12] T2D was identified based on the patient's medical history and the guideline for prevention and control of diabetes in primary care released in 2018.[13] Cardiovascular disease in our study included hypertension, coronary heart disease, myocardial infarction, stroke, cerebrovascular disease.[14] Hypertension was identified when systolic blood pressure ⩾140 mmHg and/or diastolic blood pressure ⩾90 mmHg. The endpoint was defined as 28-day all-cause death from admission, and the death information was obtained from the death record in the hospitalized patient's course records.

Statistical analysis

In order to address the potential confounding variables associated with exposure to hyperlipidemia, and reduce the effects of the potential confounders, we conducted propensity score matching (PSM) analysis to balance hyperlipidemia related variables, such as comorbidities, heart rate, respiratory rate, SpO2, chest CT lesion, estimated glomerular filtration rate (eGFR), alanine aminotransferase (ALT), cardiac troponin I (cTnI), neutrophil count, lymphocyte count, C-reactive protein (CRP), procalcitonin (PCT), and medications. For missing data of the laboratory variables, we applied non-parametric missing value imputation through the missForest procedure of the R Programming Language. The analysis of random forest based on the rest variables of the dataset was used to predict the missing values and to estimate the internal cross-validated errors. PSM was used to calculate standardized difference (SD). In order to further analyze the effects of hyperlipidemia on mortality in COVID-19 patients in subgroups of different lipid parameters features, and the pre-existing type 2 diabetes and CVDs, we conducted PSM analysis at 1:1 ratio on patients with increased TG (TG increase group), patients with increased LDL-C (LDL-C increase group), and patients with decreased HDL-C (HDL-C decrease group), as well as patients groups of pre-existing CVDs and T2D. The variables in the two groups were balanced successfully when the absolute value of SD after proportioning was less than 0.1. In the final analysis, patients with normal lipid were paired with patients of different categories of hyperlipidemia at a ratio of 1:1.

Data were presented as median and interquartile range (IQR) for continuous variables, or percentage and frequency for categorical variables. After PSM analysis, the Cox proportional hazard models were used to calculate hazard ratio (HR) for comparing the

risks of 28-day all-cause mortality between the two groups. In order to validate the effect of hyperlipidemia among patients with COVID-19, we performed the PSD analysis and Cox proportional hazard models in patients of different gender and patients with pre-existing CVDs and T2D. A two-sided $P < 0.05$ was considered statistical significance. Data analyses were performed using R Foundation for Statistical Computing (version 3.6.3, Vienna, Austria) and SPSS Statistics (version 23.0, IBM, Armonk, NY, USA).

RESULTS

Baseline characteristics of the participants before and after PSM analyses

Of the initial 10 945 patients with confirmed COVID-19 infection, 1123 patients were excluded according to the enrollment criteria, and 9822 patients were included for the analysis, comprising 3513 (35.8%) cases without hyperlipidemia [median age, 59 (IQR 45-68) years old; 41.28% men] and 6309 (64.2%) cases with hyperlipidemia [median age, 59 (IQR 48-68) years old; 53.69% men] (**Fig. 1**).

Compared to the normal lipid group, patients with hyperlipidemia had higher percentage of T2D [17.36% *vs.* 11.61%; *SD*=0.164], coronary heart disease (9.56% *vs.* 5.55%; *SD*=0.152) on admission. Furthermore, patients with hyperlipidemia had a higher percentage of increased leukocyte count (11.08% *vs.* 7.71%; *SD*=0.116), increased neutrophil count (16.89% *vs.* 11.77%; *SD*=0.146), elevated CRP (52.65% *vs.* 46.1%; *SD*=0.131), and elevated PCT (45.06% *vs.* 34.95%; *SD*=0.207) than patients without hyperlipidemia. For in-hospital treatments, more COVID-19 patients with hyperlipidemia were on medications of antidiabetic drugs, antihypertensive drugs, or antiplatelet.

By 1:1 matching, 3506 patients in the hyperlipidemia group [median age, 58 (IQR 47-67) years old; 45.55% men] were matched at 1:1 ratio to 3506 patients in the controls group [median age, 59 (IQR 45-68) years old; 41.36% men]. After PSM analyses, the baseline differences between the two groups were well balanced except for CRP. The details of baseline characteristics of enrolled patients before and after

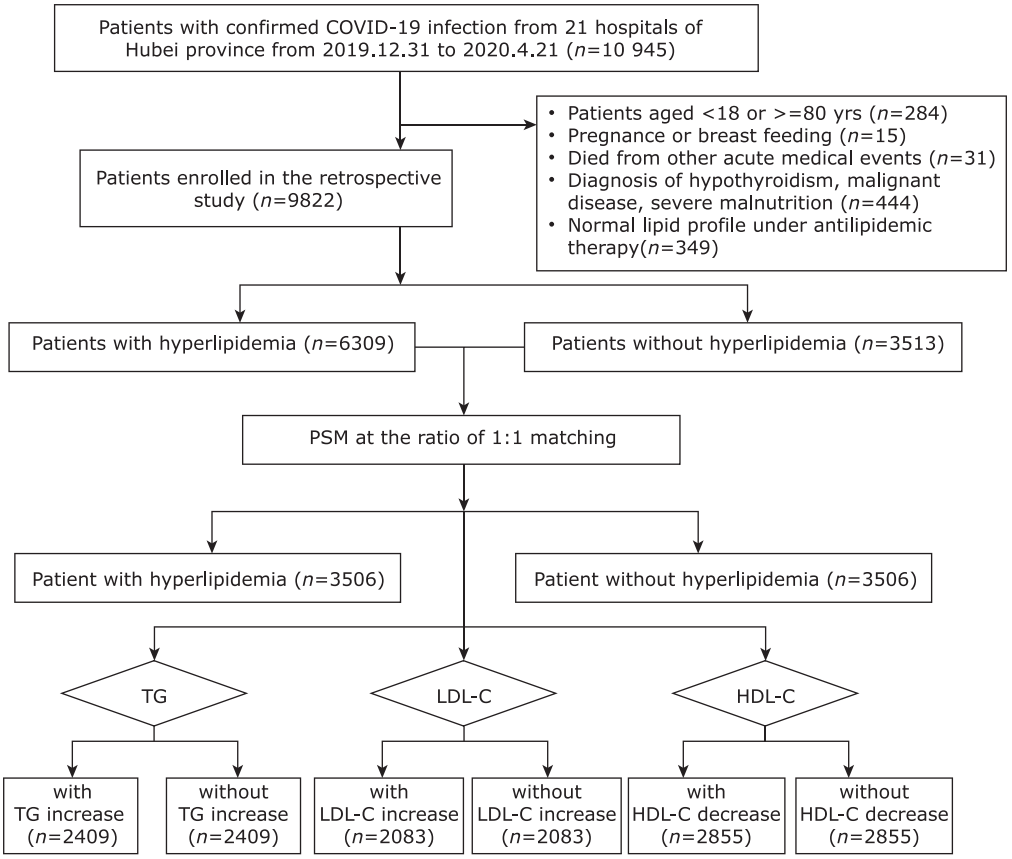

Figure 1. The flowchart showing the strategy of patient enrollment and grouping for analyses. PSM, propensity score matching; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol.

PSM were shown in **Table 1**. There were 2 484 patients (1 242 patients with hyperlipidemia and 1 242 without hyperlipidemia) in the CVDs group, and 946 patients (473 patients with hyperlipidemia and 473 without hyperlipidemia) in the type 2 diabetes group for further analysis, respectively.

Hyperlipidemia was not associated with risks of 24-day all-cause mortality

Following mixed-effect Cox model analysis, after adjusting for age, gender and CRP, hyperlipidemia was not associated with increased or decreased 28-day all-cause death risk [adjusted HR, 1.17 (95% *CI*, 0.95-1.44), *P* =0.151]. The characteristics of participants after matching were shown in **Table S1** of the supplements. After adjusting confounding factors, we found the parameters of hyperlipidemia were not associated with the risk of 28-day all-cause death in TG increase group [adjusted *HR*, 1.23 (95% *CI*, 0.98-1.55), *P* = 0.075] , LDL-C increase group [adjusted *HR*, 0.78 (95% *CI*, 0.57-1.07), *P* = 0.123] , and in HDL-C decrease group [adjusted *HR*, 1.12 (95% CI, 0.9-1.39), *P* = 0.299], respectively (**Table 2**).

Hyperlipidemia was not associated with risks of all-cause mortality in different gender groups

The PSM analysis on different genders and the association of hyperlipidemia with the risk of all-cause mortality in male or female patients with COVID-19 was presented in **Table 2**. The characteristics of patients after matching were shown in **Table S2, S3** of the supplements. In male patients with COVID-19, we found hyperlipidemia was not associated with 28-day all-cause mortality compared to patients without hyperlipidemia, with adjusted *HR* of 1.24 (95% *CI*, 0.91-1.70), *P* = 0.176 after adjusting age, CRP increase and PCT level. The result in the female group was consistent, with adjusted *HR* of 0.91(95% *CI*, 0.66-1.25), *P* = 0.547 after adjusting age, blood glucose level, D-dimer increase, and red blood cells decrease. For parameters of hyperlipidemia, the increases of TG and LDL-C, and the decrease of HDL-C were not significantly associated with the mortality risk in both gender groups.

Hyperlipidemia was not associated with increased risks of all-cause mortality in patients with CVDs and T2D

The characteristics of patients with CVDs and T2D after matching were shown in **Table S4, S5** of the supplements. Among COVID-19 patients with pre-existing CVDs, hyperlipidemia were not associated with the increased risk of 28-day all-cause mortality, with the adjust *HR* of 0.96 (95% *CI*, 0.73-1.26), *P* = 0.765 after adjusting age, sex, blood glucose level, and CRP increase. When stratified by parameters of hyperlipidemia, the adjusted *HR* was 1.19 (95% *CI*, 0.88-1.60), *P* = 0.253 for TG increase, 0.78 (95% *CI*, 0.52-1.17), *P* = 0.235 for LDL-C increase, and 1.00 (95% *CI*, 0.75-1.33), *P* = 0.991 for HDL-C decrease (**Table 3**). The results of patients with T2D were similar. After adjusting age, sex, blood glucose level, CRP increase and ALT increase, hyperlipidemia was not associated with the risk of 28-day all-cause death, with the adjusted *HR* of 0.74 (95% *CI*, 0.49-1.13), *P* = 0.164 for any abnormal serum lipid parameter, 1.07 (95% *CI*, 0.70-1.64), *P* = 0.752 for TG increase, 0.72 (95% *CI*, 0.40-1.30), *P* = 0.279 for LDL-C increase, and 1.17 (95% *CI*, 0.76-1.81), *P* = 0.468 for HDL-C decrease.

DISCUSSIONS

In the present study, we retrospectively enrolled 10 945 patients infected by SARS-CoV-2 to investigate the relationship between hyperlipidemia and adverse clinical outcomes. The results indicated that hyperlipidemia at baseline was not associated with 28-day all-cause death. Further analyses demonstrated that no significant association existed between abnormality in lipid parameters (elevated LDL-C and TG, decreased HDL-C) and 28-day all-cause death. These findings demonstrated hyperlipidemia may not be an important prognostic factor for COVID-19 patients. This result is consistent with a study from New York with 200 patients infected by SARS-CoV-2, in which hyperlipidemia was not associated with in-hospital mortality using an univariate logistic regression model.[6]

COVID-19 is an acute infectious disease characterized by the increase of inflammatory cytokines and the dysfunction of immune system, which leads to multi-organ damages and mortality.[15–17] According to previous studies, the time period from symptom onset to death of COVID-19 might be short,[18,19] while the development from hyperlipidemia to clinical adverse events is a chronic and long-term process.[20–22] Therefore, we hardly observed the direct clinical outcomes of hyperlipidemia during the following period of 28 days. Additionally, according to previous studies, the main specific causes of non-survivors

Table 1. Baseline characteristics of the study cohort before and after matching

Characteristics	Study cohort			Cohort after matching (1:1)[b]		
	Hyperlipidemia [a] (*n*=6309)	Normal (*n*=3513)	*SD*	Hyperlipidemia [a] (*n*=3506)	Normal (*n*=3506)	*SD*
Age [years, median (IQR)]	59(48-68)	59(45-68)	0.083	58(47-67)	59(45-68)	−0.001
Gender-male [*n* (%)]	3387(53.69)	1450(41.28)	0.250	1597(45.55)	1450(41.36)	0.085
Heart rate [bpm, median (IQR)]	85(78-97)	84(78-96)	0.049	85(78-96)	84(78-96)	0.005
Respiratory [bpm, median(IQR)]	20(19-21)	20(19-21)	0.104	20(19-21)	20(19-21)	−0.018
SBP [mmHg, median (IQR)]	129(120-141)	128(118-139)	0.087	128(119-140)	128(118-139)	0.025
DBP [mmHg, median (IQR)]	80(72-88)	79(72-86)	0.101	79(72-87)	79(72-86)	0.038
SpO_2 [%, median(IQR)]	97(95-98)	97(96-98)	−0.06	98(96-98)	97(96-98)	0.024
Comorbidities on admission [*n* (%)]						
Chronic obstructive pulmonary disease	67(1.06)	47(1.34)	−0.025	45(1.28)	45(1.28)	0.000
Diabetes	1095(17.36)	408(11.61)	0.164	386(11.01)	408(11.64)	−0.020
Heart failure	40(0.63)	23(0.65)	−0.003	20(0.57)	23(0.66)	−0.011
Coronary heart disease	603(9.56)	195(5.55)	0.152	204(5.82)	195(5.56)	0.011
Cerebrovascular diseases	196(3.11)	81(2.31)	0.049	89(2.54)	81(2.31)	0.015
Chronic liver disease	151(2.39)	76(2.16)	0.015	75(2.14)	76(2.17)	−0.002
Chronic renal diseases	266(4.22)	103(2.93)	0.002	112(3.19)	103(2.94)	0.015
Medications [*n* (%)]						
Insulin	975(15.45)	320(9.11)	0.194	332(9.47)	320(9.13)	0.012
Oral hypoglycemic drugs	1352(21.43)	456(12.98)	0.225	474(13.52)	456(13.01)	0.015
non-ACEI/ARB antihypertensive drug	1907(30.23)	873(24.85)	0.121	814(23.22)	872(24.87)	−0.039
ACEI/ARB	628(9.95)	233(6.63)	0.121	215(6.13)	233(6.65)	−0.021
Antiplatelet	533(8.45)	110(3.13)	0.229	89(2.54)	110(3.14)	−0.036
Chest CT on admission [*n* (%)]						
Bilateral lesions	5154(87.05)	2808(83.60)	0.098	2718(83.35)	2807(83.74)	−0.011
Lab tests on admission [*n* (%), or median(IQR)]						
Leukocyte count > 9.5×10^9/L	697(11.08)	270(7.71)	0.116	313(8.98)	270(7.73)	0.045
Neutrophil count > 6.3×10^9/L	1062(16.89)	412(11.77)	0.146	455(13.05)	412(11.80)	0.038
Lymphocyte< 1.1×10^9/L	2595(41.26)	1400(40.00)	0.026	1405(40.28)	1394(39.91)	0.008
RBC < 3.5×10^{12}/L (female) or 4.0×10^{12}/L (male)	2568(40.83)	1579(45.14)	−0.087	1441(41.32)	1574(45.09)	−0.076
CRP > ULN [c]	2103(52.65)	821(46.10)	0.131	1257(51.52)	819(46.11)	0.108
PCT > ULN [c]	2479(45.06)	1021(34.95)	0.207	954(31.39)	1020(34.99)	−0.076
ALT > 40 U/L	1679(26.63)	640(18.23)	0.202	611(17.45)	640(18.27)	−0.021
eGFR value (mL/min)	103.57 (87.61-120.50)	105.30 (89.21-122.61)	−0.073	107.34 (91.14-125.22)	105.29 (89.21-122.55)	0.043
D-dimer > ULN [c]	3024(52.06)	1351(42.26)	0.197	1479(46.88)	1351(42.32)	0.092
cTnI > ULN [c]	446(10.96)	160(7.35)	0.125	153(7.65)	160(7.36)	0.013

IQR, interquartile range; SD, standardized difference; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotension II receptor blocker; RBC, red blood cells; CRP, C-reactive protein; PCT, procalcitonin; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; cTnI, cardiac troponin I; ULN, upper limit of normal. 1 mmHg=0.133 Kpa

[a] Patients were defined as hyperlipidemia if meeting any of the following criteria: TG ⩾ 1.7 mmol/L; TC ⩾ 5.2 mmol/L; LDL-C ⩾ 3 mmol/L; HDL-C < 1.0 mmol/L, non-HDL-C ⩾ 4.1 mmol/L.

[b] The propensity score matching model included age, gender, respiratory rate, DBP, comorbidities (chronic obstructive pulmonary disease, cerebrovascular diseases, hypertension, heart failure, coronary heart disease, diabetes, chronic liver disease, chronic renal diseases), medication, incidences of abnormal laboratory variables including leukocyte count, neutrophil count, PCT, ALT, D-dimer.

[c] ULN was defined according to criteria of each hospital.

Table 2. The association of hyperlipidemia with risk of 28-day all-cause mortality in total, male, and female patients with COVID-19 after propensity score matching at 1:1 ratio

Categories	Number of patients (*n*)	Deaths (*n*)	Adjusted *HR* (95% *CI*)	*P* value [a]
All patients of matched cohort [b]				
Hyperlipidemia group *vs*. non-hyperlipidemia group	3506 *vs*. 3506	231 *vs*. 193	1.17 (0.95, 1.44)	0.151
TG ⩾1.7 mmol/L group *vs*. TG<1.7 mmol/L group	2409 *vs*. 2409	180 *vs*. 137	1.23 (0.98, 1.55)	0.075
LDL-C ⩾3 mmol/L group *vs*. LDL-C<3 mmol/L group	2083 *vs*. 2083	67 *vs*. 95	0.78 (0.57, 1.07)	0.123
HDL-C <1.0 mmol/L group *vs*. HDL-C ⩾1.0 mmol/L group	2855 *vs*. 2855	213 *vs*. 157	1.12 (0.90, 1.39)	0.299
Male patients in matched cohort [c]				
Hyperlipidemia group *vs*. non-hyperlipidemia group	1449 *vs*. 1449	135 *vs*. 112	1.24 (0.91, 1.70)	0.176
TG ⩾1.7 mmol/L group *vs*. TG<1.7 mmol/L group	1145 *vs*. 1145	114 *vs*. 81	1.23 (0.92, 1.66)	0.170
LDL-C ⩾3 mmol/L group *vs*. LDL-C<3 mmol/L group	988 *vs*. 988	43 *vs*. 46	1.00 (0.65, 1.52)	0.983
HDL-C <1.0 mmol/L group *vs*. HDL-C ⩾1.0 mmol/L group	1499 *vs*. 1499	131 *vs*. 86	1.27 (0.94, 1.72)	0.113
Female patients in matched cohort [d]				
Hyperlipidemia group *vs*. non-hyperlipidemia group	2014 *vs*. 2014	92 *vs*. 81	0.91 (0.66, 1.25)	0.547
TG ⩾1.7 mmol/L group *vs*. TG<1.7 mmol/L group	1233 *vs*. 1233	62 *vs*. 50	1.14 (0.78, 1.66)	0.509
LDL-C ⩾3 mmol/L group *vs*. LDL-C<3 mmol/L group	1099 *vs*. 1099	24 *vs*. 33	0.82 (0.48, 1.39)	0.456
HDL-C <1.0 mmol/L group *vs*. HDL-C ⩾1.0 mmol/L group	1326 *vs*. 1326	79 *vs*. 66	1.00 (0.71, 1.40)	0.993

TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; HR, hazard ratio; CI, confidence interval.

[a] *P* values were calculated based on Cox model analysis.

[b] Cox model adjusted age, gender, CRP, and hospital site was treated as a random effect.

[C] Cox model adjusted age, CRP increase, PCT level increase, and hospital site was treated as a random effect.

[d] Cox model adjusted age, blood glucose level, D-dimer increase, blood red cells decrease, and hospital site was treated as a random effect.

Table 3. The association of hyperlipidemia with risk of 28-day all-cause mortality among COVID-19 patients with CVDs and type 2 diabetes after propensity score matching at ratio of 1:1.

Categories	Number of Patients (*n*)	Deaths (*n*)	Adjusted *HR* (95% *CI*)	*P* value [a]
Cardiovascular diseases [b]				
Hyperlipidemia group *vs*. non-hyperlipidemia group	1242 *vs*. 1242	128 *vs*. 114	0.96 (0.73,1.26)	0.765
TG ⩾1.7 mmol/L group *vs*. TG<1.7 mmol/L group	1004 *vs*. 1004	115 *vs*. 81	1.19 (0.88,1.60)	0.253
LDL-C ⩾3 mmol/L group *vs*. LDL-C<3 mmol/L group	814 *vs*. 814	42 *vs*. 59	0.78 (0.52,1.17)	0.235
HDL-C <1.0 mmol/L group *vs*. HDL-C ⩾1.0 mmol/L group	1131 *vs*. 1131	124 *vs*. 90	1.00 (0.75,1.33)	0.991
Type 2 diabetes [c]				
Hyperlipidemia group *vs*. non-hyperlipidemia group	473 *vs*. 473	52 *vs*. 54	0.74 (0.49,1.13)	0.164
TG ⩾1.7 mmol/L group *vs*. TG<1.7 mmol/L group	515 *vs*. 515	56 *vs*. 40	1.07 (0.70,1.64)	0.752
LDL-C ⩾3 mmol/L group *vs*. LDL-C<3 mmol/L group	364 *vs*. 364	20 *vs*. 29	0.72 (0.40,1.30)	0.279
HDL-C <1.0 mmol/L group *vs*. HDL-C ⩾1.0 mmol/L group	492 *vs*. 492	56 *vs*. 43	1.17 (0.76,1.81)	0.468

[a] *P* values were calculated based on Cox model analysis.

[b] Cox model adjusted age, sex, blood glucose level, CRP increase, and hospital site was treated as a random effect.

[c] Cox model adjusted age, sex, blood glucose level, CRP increase, ALT increase, and hospital site was treated as a random effect.

among patients with COVID-19 were acute respiratory distress syndrome (ARDS) and respiratory failure.[23,24] Although there were no studies investigating the association of ARDS and hyperlipidemia with respiratory failure, lipid-lowing treatments were found not helpful for improving the prognosis of patients with moderate-to-severe COPD or sepsis-associated acute respiratory distress syndrome.[25,26]

Our recent study suggested that statin significantly decreased the risk of 28-day all-cause mortality versus non-statin (5.2% *vs.* 9.4%) in the matched groups of patients with COVID-19. The potential mechanism was that the anti-inflammatory and immunomodulatory associations of statins with decreased levels of CRP, interleukin 6 (IL-6), and neutrophil counts in COVID-9 patients on statin therapy.[27] On the other hand, the level of lipid fluctuates during the course of COVID-19.[26] Patients with COVID-19 are likely to have poor nutritional status during hospitalization,[28] which may increase serum level of TG and decrease the levels of TC, LDL-C and HDL-C. Meanwhile, the progression of disease affects the level of lipid, with the result that non-survivors of COVID-19 were reported to have significant decrease in serum lipids during the period from pre-infection to death.[29] Therefore, the fluctuation of lipids may be more meaningful for predicting the clinical events among patients with COVID-19 than lipid level at baseline. Well-designed prospective studies are needed to further investigate the effect of lipid profile change on the prognosis of patients with COVID-19.

In terms of the lipid parameters, the increases of LDL-C and oxidized LDL-C could contribute to the expression of AT1R on vascular smooth muscle cell and human coronary artery endothelial cells, which enhances the responses to angiotensin Ⅱ (Ang Ⅱ) and the effects of angiotensin-converting enzyme/angiotensin Ⅱ/angiotensin type 1 receptor (ACE/AngⅡ/AT1R) axis.[30–32] On the other hand, LDL-C is a critical indicator for antilipidemic drugs in patients with CVDs and diabetes. Results from a meta-analysis including 28 trials and 186 854 patients found that per 1.0 mmol/L reduction in LDL-C could reduce 24% of major cardiovascular related events.[33] Although some studies advocated drugs targeting lipid metabolism may be a potentially effective therapy for COVID-19,[7] direct clinical evidence investigating associations between the increase of LDL-C level and COVID-19 outcomes is still missing. Here, our results demonstrated that the increase of LDL-C at baseline was not associated with 28-day all-cause death after PSM analysis and adjusting relative confounders. The subgroup analysis in males and females showed consistent results. These evidences imply that lowering the lipid level may not improve the prognosis of patients infected by SARS-CoV-2.

On the other hand, HDL-C is a well-known protective factor for CVDs and exerts anti-inflammatory capacity in chronic diseases.[34,35] A recent study reported that the level of HDL-C was low in critically ill patients, which was significantly associated with disease severity.[36] Meanwhile, decreased level of HDL-C was found in patients with sepsis, which increased the risk of acute multiple organ failure and mortality in these patients.[37,38] However, HDL-C decrease was not associated with increased risk of mortality in the present study. The inconsistency could be explained by the differences in the characteristics of included patients, the sample size, and follow up period between the two studies. Of note, in different genders and in patients with CVDs or diabetes, the HDL-C decrease in our study was also not associated with risk of 28-day all-cause death as well.

There are several limitations in current study. First, this is a retrospective study, the past illness history may not be fully reported in some patients. Therefore, prospective cohort studies with geographical diversity are needed to further investigate the effect of hyperlipidemia on COVID-19 outcomes. Second, some important lipid parameters, such as apolipoprotein A1, apolipoprotein B and free fatty acid that have been demonstrated closely related to the development and adverse clinical outcomes of cardiovascular and metabolic diseases were not investigated for their associations with COVID-19 in this study due to data missing. Third, we did not investigate the association between changes of lipid profiles and the disease progression because we lacked the longitudinal monitoring data of lipid profiles in patients with COVID-19. Fourth, examinations of lipid were carried out at different time points during hospitalization, which may induce bias when Cox proportional hazard models were conducted.

In conclusion, hyperlipidemia on admission, including abnormalities in different lipid parameters, was not associated with 28-day all-cause mortality among patients with COVID-19. This result was consistent with that obtained in patients with CVD and T2D. Our study provides a certain reference for the management of patients with COVID-19 during hospitalization. Well-designed prospective cohort studies are needed in future to determine the association between hyperlipidemia and outcomes in clinical context of COVID-19.

Supplementary materials

Table S1-S5 are available online at http://cmsj.cams.cn/EN/10.24920/003866.

Conflict of interests

None.

REFERENCES

1. Zhang P, Zhu L, Cai J, et al. Association of inpatient use of angiotensin-converting enzyme inhibitors and angiotensin Ⅱ receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. Circ Res 2020; 126(12):1671-81. doi:10.1161/CIRCRESAHA.120.317134.
2. Zhu L, She ZG, Cheng X, et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. Cell Metab 2020; 31(6):1068-77.e3. doi: 10.1016/j.cmet.2020.04.021.
3. Guo T, Fan Y, Chen M, et al.Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). JAMA Cardiol 2020; 5(7):811-8. doi:10.1001/jamacardio.2020.1017.
4. Bornstein SR, Rubino F, Khunti K, et al. Practical recommendations for the management of diabetes in patients with COVID-19. Lancet Diabetes Endocrinol 2020; 8(6):546-50. doi: 10.1016/S2213-8587(20)30152-2.
5. Ni WQ, Liu XL, Zhuo ZP, et al.Serum lipids and associated factors of dyslipidemia in the adult population in Shenzhen. Lipids Health Dis 2015; 14(1):1-11. doi: 10.1186/s12944-015-0073-7.
6. Palaiodimos L, Kokkinidis DG, Li W, et al. Severe obesity is associated with higher in-hospital mortality in a cohort of patients with COVID-19 in the Bronx, New York. Metabolism 2020; 108:154262. doi: 10.1016/j.metabol.2020.154262.
7. Abu-Farha M, Thanaraj TA, Qaddoumi MG, et al. The role of lipid metabolism in COVID-19 virus infection and as a drug target. Int J Mol Sci 2020; 21(10):3544. doi: 10.3390/ijms21103544.
8. Tanaka S, Labreuche J, Drumez E, et al. Low HDL levels in sepsis versus trauma patients in intensive care unit. Ann Intensive Care 2017; 7(1):4-11. doi: 10.1186/s13613-017-0284-3.
9. Peñarrubia L, Ruiz M, Porco R, et al. Multiple assays in a real-time RT-PCR SARS-CoV-2 panel can mitigate the risk of loss of sensitivity by new genomic variants during the COVID-19 outbreak. Int J Infect Dis 2020; 97:225-9. doi: 10.1016/j.ijid.2020.06.027.
10. Official website of the National Health Commission of People's Republic of China. The prevention and control guideline for novel coronavirus pneumonia (5th edition). http://www.nhc.gov.cn/xcs/zhengcwj/202002/a5d6f7b8c48c451c87dba14889b30147.shtml. Released February 21, 2020; accessed February 21, 2020.
11. Joint committee issued Chinese guideline for the management of dyslipidemia. 2016 Chinese guideline for the management of dyslipidemia in adults. Zhonghua Xin Xue Guan Bing Za Zhi 2016; 44(10):833-53. Chinese. doi:10.3760/cma.j.issn.0253-3758.2016.10.005.
12. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. Atherosclerosis 2019; 290:140–205. doi: 10.1016/j.atherosclerosis.2019.08.014.
13. Chinese Diabetes Society; National Office for Primary Diabetes Care. National guidelines for the prevention and control of diabetes in primary care(2018). Zhonghua nei ke za zhi 2018; 57(12):885-93. Chinese. doi: 10.3760/cma.j.issn.0578-1426.2018.12.003.
14. Jakubowski KP, Cundiff JM, Matthews KA. Cumulative childhood adversity and adult cardiometabolic disease: A meta-analysis. Heal Psychol 2018; 37(8):701-15. doi: 10.1037/hea0000637.
15. Tay MZ, Poh CM, Rénia L, et al. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol 2020; 20(6):363–74. doi: 10.1038/s41577-020-0311-8.
16. Cao X. COVID-19: immunopathology and its implications for therapy. Nat Rev Immunol 2020; 20(5):269-70. doi: 10.1038/s41577-020-0308-3.
17. Touyz RM, Li H, Delles C. ACE2 the Janus-faced protein-from cardiovascular protection to severe acute respiratory syndrome-coronavirus and COVID-19. Clin Sci 2020; 134(7):747-50. doi: 10.1042/CS20200363.
18. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: Retrospective study. BMJ 2020; 368(m1091):1-14. doi: 10.1136/bmj.m1091.
19. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York city area. JAMA 2020; 323(20):2052-9. doi: 10.1001/jama.2020.6775.
20. Shao B, Heinecke JW. HDL, lipid peroxidation, and atherosclerosis. J Lipid Res 2009; 50(4):599-601. doi: 10.1194/jlr.E900001-JLR200.
21. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 2005; 352(16): 1685-95. doi: 10.1056/NEJMra043430.
22. Steinberg D. An interpretive history of the cholesterol

controversy, part III: Mechanistically defining the role of hyperlipidemia. J Lipid Res 2005; 46(10):2037-51. doi: 10.1194/jlr.R500010-JLR200.

23. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395(10229):1054–62. doi: 10.1016/S0140-6736(20)30566-3.
24. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020; 8(5):475-81. doi:10.1016/S2213-2600(20)30079-5.
25. Criner GJ, Connett JE, Aaron SD, et al. Simvastatin for the prevention of exacerbations in moderate-to-severe COPD. N Engl J Med 2014; 370(23):2201-10. doi: 10.1056/nejmoa1403086.
26. Truwit JD, Bernard GR, Steingrub J, et al. Rosuvastatin for sepsis-associated acute respiratory distress syndrome. N Engl J Med 2014; 370(23):2191-200. doi: 10.1056/NEJMoa1401520.
27. Zhang XJ, Qin JJ, Cheng X, et al. In-hospital use of statins is associated with a reduced risk of mortality among individuals with COVID-19. Cell Metab 2020; 32(2):176-87.e4. doi: 10.1016/j.cmet.2020.06.015.
28. Liu G, Zhang S, Mao Z, et al. Clinical significance of nutritional risk screening for older adult patients with COVID-19. Eur J Clin Nutr 2020; 74(6):876-83. doi: 10.1038/s41430-020-0659-7.
29. Deniz O, Gumus S, Yaman H, et al. Serum total cholesterol, HDL-C and LDL-C concentrations significantly correlate with the radiological extent of disease and the degree of smear positivity in patients with pulmonary tuberculosis. Clin Biochem 2007; 40(3-4):162-6. doi: 10.1016/j.clinbiochem.2006.10.015.
30. Ishiyama Y, Gallagher PE, Averill DB, et al. Upregulation of angiotensin-converting enzyme 2 after myocardial infarction by blockade of angiotensin Ⅱ receptors. Hypertension 2004; 43(5):970-6. doi: 10.1161/01.HYP.0000124667.34652.1a.
31. Dijkman R, Jebbink MF, Deijs M, et al. Replication-dependent downregulation of cellular angiotensin-converting enzyme 2 protein expression by human coronavirus NL63. J Gen Virol 2012; 93(Pt 9):1924-9. doi: 10.1099/vir.0.043919-0.
32. Putnam K, Shoemaker R, Yiannikouris F, et al. The renin-angiotensin system: A target of and contributor to dyslipidemias, altered glucose homeostasis, and hypertension of the metabolic syndrome. Am J Physiol Hear Circ Physiol 2012; 302(6): H1219-30. doi: 10.1152/ajpheart.00796.2011.
33. Cholesterol Treatment Trialists' Collaboration. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. *Lancet* 2019; 393(10170):407–15. doi: 10.1016/S0140-6736(18)31942-1.
34. Lemmers RFH, van Hoek M, Lieverse AG, et al. The anti-inflammatory function of high-density lipoprotein in type II diabetes: A systematic review. J Clin Lipidol 2017; 11(3):712-24. doi: 10.1016/j.jacl.2017.03.013.
35. Hui N, Barter PJ, Ong KL, et al. Altered HDL metabolism in metabolic disorders: Insights into the therapeutic potential of HDL. Clin Sci 2019; 133(21):2221-35. doi: 10.1042/CS20190873.
36. Wei X, Zeng W, Su J, et al. Hypolipidemia is associated with the severity of COVID-19. J Clin Lipidol 2020; 14(3):297-304. doi: 10.1016/j.jacl.2020.04.008.
37. Guirgis FW, Donnelly JP, Dodani S, et al. Cholesterol levels and long-term rates of community-acquired sepsis. Crit Care 2016; 20(1):1-12. doi: 10.1186/s13054-016-1579-8.
38. Cirstea M, Walley KR, Russell JA, et al. Decreased high-density lipoprotein cholesterol level is an early prognostic marker for organ dysfunction and death in patients with suspected sepsis. J Crit Care 2017; 38:289-94. doi: 10.1016/j.jcrc.2016.11.041.