Retrospective Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
50(2) 1–10

DOI: 10.1177/03000605221078699
journals.sagepub.com/home/imr
SAGE

Lipid profile changes in patients with COVID-19 referred to medical centers in Kermanshah, Iran; a case–control study

Shahab Changaripour[1], Hosna Sarvazad[1], Maryam Barghi[2], Elham Sajadi[3], Mahdi Hashempour Sadeghian[1] and Narges Eskandari Roozbahani[1]

Abstract

Objective: To evaluate blood lipid profiles in patients with coronavirus disease 2019 (COVID-19), and to explore the association with disease severity.

Methods: This case–control study included patients with COVID-19, referred to two medical centers in Kermanshah, Iran (between July 2020 and December 2020), and healthy controls. Lipid profiles were evaluated in patients who were grouped according to severe (intensive care unit [ICU]), or less severe (outpatient), forms of COVID-19, and in healthy controls, and were compared among the three groups.

Results: A total of 132 participants were included, comprising ICU ($n = 49$), outpatient ($n = 48$) and control ($n = 35$) groups. Mean cholesterol levels were lower in the patient groups than in controls; high-density lipoprotein cholesterol (HDL-C) levels were higher in the ICU group versus outpatients, and low-density lipoprotein cholesterol (LDL-C) levels were lower in the ICU group versus outpatients. The frequency of diabetes and hypertension was higher in the ICU group than in the outpatient group. Furthermore, LDL-C level was associated with disease severity (odds ratio 0.966, 95% confidence interval 0.944, 0.989).

[1]Clinical Research Development Center, Imam Reza Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran
[2]Department of Biochemistry, Faculty of Veterinary Medicine, Shiraz University, Shiraz, Iran
[3]Department of Basic Science, Faculty of Veterinary Medicine, Shiraz University, Shiraz, Iran

Corresponding author:
Dr Narges Eskandari Roozbahani, Clinical Research Development Centre, Imam Reza Hospital, Kermanshah University of Medical Sciences, Zakariya Razi Blvd, Kermanshah, Iran. Po. Box: 6714415332
E-mail: neskandari32@gmail.com; narges.Eskandarir@kums.ac.ir

Conclusion: Lipid profiles differ between severe and less severe forms of COVID-19. LDL-C level may be a useful indicator of COVID-19 severity.

Keywords
COVID-19, Dyslipidemias, LDL-C, HDL-C, Odds ratio, SARS-CoV-2

Date received: 19 October 2021; accepted: 18 January 2022

Introduction

Since the onset of the coronavirus disease 2019 (COVID-19) pandemic worldwide in December 2019, various clinical factors including aging,[1] D-dimer and C-reactive protein (CRP) levels,[1,2] albumin depletion,[1] and a history of diabetes,[3] have been reported as risk factors associated with disease severity. A previous study in Iran demonstrated that obesity, higher levels of CRP, blood sugar, D-dimer, and lipid markers are predictive factors of COVID-19-related mortality.[4]

In humans, COVID-19, caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), progresses rapidly to induce acute respiratory distress syndrome (ARDS), leading to the appearance of symptoms.[5] During ARDS due to COVID-19, changes to the host's immunological status occur, including neutropenia, dendritic cell depletion, natural killer cell depletion, decreased T (T CD4+ and CD8+) and B lymphocytes, and increased proinflammatory cytokines. Inflammatory factors attract monocytes, macrophages, and T cells to the site of inflammation, creating a complex called the cytokine storm, which results in host damage to the lungs, increased endothelial and epithelial permeability of the lungs, impaired gas exchange, and severe respiratory failure.[6] Persistent inflammatory response due to cytokine storm, which includes the release of proinflammatory cytokines (tumor necrosis factor-α, interleukin [IL]-6, IL-8, and IL-10),[7] and lymphopenia, are considered part of the main life-threatening complications in patients with SARS-CoV-2 infection. The direct action of released cytokines and chemokines leads to massive cell death that triggers a series of biological reactions, including the production of macrophage-derived eicosanoids that increase inflammation.[8] Increased cytokines may alter the lipid profile of patients with COVID-19.[9] Recent research on disease severity and lipid profile levels shows that low levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) are associated with disease severity and mortality.[10,11] Elevated plasma triglyceride (TG) levels during infection and inflammation are also a known phenomenon.[12,13] COVID-19-induced dyslipidemias are reported to be associated with a notable decrease in HDL levels and an increase in the neutrophil-to-lymphocyte ratio, and this is true even in patients without comorbidity.[14]

High-density lipoprotein cholesterol may play a role in modulating the immune system and controlling infectious diseases; HDL is most likely to bind and neutralize pathogen lipids (e.g., lipopolysaccharide and lipoteichoic acid) that over-activate the immune system in sepsis.[15] HDL-associated apolipoproteins, such as apolipoprotein AI (ApoA-I) and apolipoprotein M (ApoM), interact with receptors

located in lipid rafts within immune cell membranes, such as Toll-like receptors on macrophages,[16] and T-cell receptors,[17] to modulate the immune system. During acute inflammation, LDL and its major apolipoprotein, ApoB, are oxidized, and lipid hydroperoxides, derived from the lipoxygenase pathway, together with hydroxyl-fatty acids, derived from arachidonic acid and linoleic acid, accumulate. They are esterified in oxidized LDLs to induce a cascade of intracellular signaling events that result in the activation of inflammation and dysfunction of endothelial cells. Increased oxidized phospholipids in patients whose lungs are infected with the virus cause the production of macrophage cytokines and pneumonitis.[18]

The induction of dyslipidemias by COVID-19 is well known, yet there remain instances of poor treatment choices for patients with COVID-19. The present study aimed to evaluate the lipid profile status in patients with COVID-19 who were admitted for the first time to either of two medical centers, Imam Reza and Golestan Kermanshah, in Iran, and to explore the association between lipid profile and disease severity.

Patients and methods

Study population and study design

This case–control study included patients with COVID-19 who were admitted to two medical centers: Imam Reza and Golestan Kermanshah, Iran, between July 2020 and December 2020, and who had complete lipid profile data (TG, TC, LDL-C, and HDL-C) in the electronic medical record system at the time of admission, and before any treatment interventions. The confirmed diagnosis of COVID-19 was based on a positive SARS-CoV-2 reverse transcription–polymerase chain reaction result, using specimens derived from sputum, throat swab, or nasopharynx swab. Following enrolment, patients were divided into two categories: intensive care unit (ICU) group and outpatient group, depending on the severity of the disease. Inclusion into the patient groups was not limited by demographic status (age, sex and residency) and/or comorbidities. Patients with a previous history of COVID-19, or who were receiving treatment for COVID-19 prior to study enrolment, were excluded. Age- and sex-matched healthy controls were selected from healthy male and female hospital staff who tested negative for COVID-19. Inclusion criteria for the control group comprised no comorbidities, such as diabetes, autoimmune disorders, hypertension, deep vein thrombosis, cancer, or history of hypercholesterolemia, and no specific medications.

The sample size was based on a previously published study;[19] considering the significance level of 0.05, the test power was 80% and d = 0.2. Using the following formula, the required sample size in each group was calculated to be 48 participants:

$$n = \frac{2 \times \left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 \times S^2}{d^2},$$

$$S^2 = \frac{S_1^2 + S_2^2}{2}$$

Demographic and clinical characteristics, including sex, age, and comorbidities were extracted from the electronic medical record.

Lipid profile testing of patients with COVID-19 was not routine in the two medical centers at the time of the study, and this was recognized as a potential study limitation that may affect the sample size.

The study was approved by the institutional review board and ethics committee of Kermanshah University of Medical Science, Iran (IR.KUMS.REC.1400.008). Written informed consent was obtained from

patients or their families before study inclusion. The reporting of this study conforms to STROBE guidelines.[20]

Lipid profile measuring

Lipid profiles were measured in fasting blood samples obtained from patients at first admission to hospital, and from healthy control participants, using a Mindray BS-420 biochemical auto-analyzer (Mindray, Shenzhen, China) and reagent kits (Biorexfars, Iran), according to the manufacturers' instructions. TC, TG, HDL-C, and LDL-C were measured using the cholesterol oxidase-p-aminophenazone (CHOD-PAP) method; the glycerol phosphate oxidase-p-aminophenazone (GPO-PAP) method; the direct-hydrogen peroxide method; and the direct-surfactant removal method, respectively.

Statistical analyses

The obtained data were statistically analyzed using SPSS statistics software, version 22.0 (IBM, Armonk, NY, USA). Qualitative variables are presented as frequency (percentage) and were compared using χ^2-test and Fisher's exact test. Quantitative variables are presented as mean ± SD. Data with normal distribution were assessed by Kolmogorov–Smirnov test. Student's *t*-test and analysis of variance were used to compare the means of independent groups. The risk factor for disease severity was determined by first performing univariate logistic regression, then entering significant independent variables into a multivariate regression model. In all tests, a *P*-value <0.05 was considered to be statistically significant.

Results

A total of 132 participants, comprising the ICU patient group ($n=49$), the outpatient group ($n=48$), and 35 sex- and age-matched healthy controls, were included in the study (overall mean age, 62.4 ± 13.5 years; 89/132 [67%] male; Table 1).

Frequencies in history of diabetes and hypertension were significantly higher in the ICU group compared with the outpatient group ($P<0.001$). There were no statistically significant between-group differences in the history of cancer, autoimmune disorder, and hypercholesterolemia (with statin treatment). Nonetheless, there was a numerical trend towards higher frequencies in the ICU versus outpatient group (Table 1). A total of 6.1% of the study population had hypercholesterolemia with statin treatment, which included lovastatin, atorvastatin, rosuvastatin, and simvastatin.

Fifty-five of the patients (56.7%) died of COVID-19, of whom, 15 patients (27.3%) belonged to the outpatient group and 40 (72.7%) belonged to the ICU group (Table 1). The survival rate was significantly different between the two patient groups ($P<0.001$).

Analyses of blood lipid profiles revealed that there was no statistically significant difference among the three groups in terms of mean TG ($P=0.208$; Table 2).

There was a statistically significant difference between the control group and both of the patient groups in terms of mean cholesterol ($P=0.013$). The lowest mean cholesterol levels were in the ICU group and the highest values were observed in the control group (Table 2). There was no statistically significant difference in mean cholesterol levels between the ICU and outpatient groups ($P=0.735$).

Mean LDL-C levels were significantly different among the three groups ($P<0.001$), with values decreasing from the outpatient, control, and ICU groups, respectively. There was a statistically significant difference between the outpatient group and the ICU group ($P<0.001$).

Table 1. Demographic and clinical characteristics of patients with confirmed coronavirus disease 2019 (COVID-19), grouped according to less severe disease (outpatient) or severe disease (ICU), and healthy controls.

Variable	Outpatient group ($n = 48$)	ICU group ($n = 49$)	Control group ($n = 35$)	Statistical significance*
Age, years	63 ± 14.3	65.3 ± 14.33	58.03 ± 10.23	NS
Male	38 (79.2%)	32 (65.3%)	19 (54.3%)	NS
Comorbidity				
Diabetes	7 (14.6%)	16 (32.7%)	0	$P < 0.001$
Hypertension	18 (37.5%)	25 (51.0%)	0	$P < 0.001$
Cancer	2 (4.2%)	5 (10.2%)	0	NS
Deep vein thrombosis	2 (4.2%)	2 (4.1%)	0	NS
Autoimmune disorder	4 (8.3%)	9 (18.4%)	0	NS
Hypercholesterolemia (statins)	1 (2.1%)	7 (14.3%)	0	NS
Survival				
Alive	33 (68.8%)	9 (18.4%)	35 (100%)	$P < 0.001$
Dead	15 (31.3%)	40 (81.6%)	0	

Data presented as mean ± SD or *n* (%) prevalence.
ICU, intensive care unit.
*Between patients' groups (χ^2-test).
NS, no statistically significant between-group difference ($P > 0.05$; analysis of variance, χ^2-test, Fisher's exact test).

Table 2. Lipid profiles in patients with confirmed coronavirus disease 2019 (COVID-19), grouped according to less severe disease (outpatient) or severe disease (ICU), and in healthy controls.

Variable	Outpatient group ($n = 48$)	ICU group ($n = 49$)	Control group ($n = 35$)	Statistical significance
TG, mg/dL	157.60 ± 92.465	149.59 ± 63.897	130.31 ± 29.709	NS
Cholesterol, mg/dL	149.85 ± 41.135	145.00 ± 28.518[a]	165.71 ± 19.535	$P = 0.013$
LDL-C, mg/dL	69.65 ± 28.394	52.16 ± 17.500	59.46 ± 6.608	$P < 0.001$
HDL-C, mg/dL	34.06 ± 7.332	37.08 ± 6.757[a]	39.63 ± 4.531	$P = 0.001$

Data presented as mean ± SD.
ICU, intensive care unit; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.
[a]No statistically significant difference versus outpatient group ($P > 0.05$; analysis of variance).
NS, no statistically significant between-group differences ($P > 0.05$; analysis of variance).

Mean HDL-C levels were also significantly different between the control group and both of the patient groups ($P = 0.001$). Although mean HDL-C level in the outpatient group was lower than the control group, there was no statistically significant difference between the two patient groups (Table 2).

To determine the risk factor for severe disease in patients with COVID-19 (ICU patients and outpatients), univariate and multivariate logistic regression methods were applied (Table 3). Based on univariate regression analysis, only LDL-C and HDL-C variables were shown to be significant risk factors for severe COVID-19 (HDL-C: odds ratio [OR] 1.070, 95% confidence interval [CI] 1.001, 1.143, $P = 0.047$; and LDL-C: OR 0.963, 95% CI 0.941, 0.986, $P = 0.002$). In subsequent multivariate

Table 3. Analysis of risk factors for the severity of coronavirus disease 2019 (COVID-19) among lipid profiles of 97 patients with confirmed COVID-19.

	Univariate analysis			Multivariate analysis		
Variable	OR	95% CI	Statistical significance	OR	95% CI	Statistical significance
TG	0.999	0.994, 1.004	NS			
Cholesterol	0.996	0.985, 1.008	NS			
LDL-C	0.963	0.941, 0.986	0.002	0.966	0.944, 0.989	P = 0.004
HDL-C	1.070	1.001, 1.143	0.047			

OR, odds ratio; CI, confidence interval; TG, Triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.
NS, no statistically significant association ($P > 0.05$).

regression analysis, LDL-C remained as a statistically significant risk factor for severe COVID-19 (OR 0.966, 95% CI 0.944, 0.989, $P = 0.004$). These results suggest that for one unit decrease in LDL-C level and one unit increase in HDL-C level, the risk of severe COVID-19 and ICU admission increases.

Discussion

In the present study, blood lipid profiles were investigated in patients with COVID-19, and the associations between blood lipid levels and COVID-19 severity were explored. According to the present results, there was a statistically significant difference between the outpatient group and the ICU group in terms of mean LDL-C levels. In addition, lower LDL-C level was found to be associated with disease severity. On the other hand, although mean HDL-C level in the outpatient group was lower than the control group, there was no statistically significant difference between the two patient groups. Of note, the present study comprised patients whose lipid profiles were obtained prior to treatment for COVID-19, and the results concur with previously published studies that have suggested dyslipidemias are associated with COVID-19 and other viral infections.[19,21–23]

The present findings demonstrated that TC levels were lower in patients with severe and less severe forms of COVID-19 than in healthy controls, but there was no difference in TC levels between the ICU and outpatient groups. There were no differences in TG levels among the groups. Profiles of blood HDL-C and LDL-C levels differed between severe and less severe cases of COVID-19: the HDL-C level was lower in the less severe form of the disease than in the severe form, while the LDL-C level was higher in patients with less severe COVID-19. However, only the LDL-C level was shown to be a risk factor for the severity of the disease. Previously published clinical data show that HDL-C concentration decreases immediately after infection and there is a significant relationship between decreased HDL-C levels and poor prognosis in infectious diseases.[24–26] It is possible that, due to passing the early course of the disease, patients in the present study showed no decrease in HDL-C level in the severe form of the disease. Risk factors of COVID-19 were investigated in a case–control study in northern Iran, and did not find a significant relationship between serum HDL levels and risk of death from COVID-19.[4] Regarding dyslipidemias in patients with COVID-19, some studies have reported a decrease in lipid profiles

as the disease progresses.[11,27] Contrary to the present study, Li et al.[27] and Wang et al.,[28] reported a decrease in HDL-C levels in severe cases of the disease, and HDL-C was shown to be a risk factor for disease severity. However, other studies concur with the present results, and have reported decreased LDL-C levels as a risk factor for disease severity.[29,30]

The relationship between comorbidities and disease severity in the present study population were also examined. Among factors such as diabetes, hypertension, history of hypercholesterolemia, cancer, autoimmune diseases, and deep vein thrombosis, according to the patient's medical records, the frequencies of only diabetes and hypertension were significantly different between severe and less severe COVID-19, but neither was considered to be a risk factor for disease severity. Recently published studies on risk factors associated with disease severity and poor prognosis support the belief that diabetes and hypertension are the most important risk factors for rapid progression and poor prognosis of COVID-19.[2,5,31,32]

In the present study, only 6.1% of the total population had a history of hyperlipidemia treated with statins (including lovastatin, atorvastatin, rosuvastatin, and simvastatin). However, these participants, along with those who had no previous history of hyperlipidemia, developed dyslipidemias following COVID-19. Following the outbreak of COVID-19, research has also been conducted on the effect of existing drugs on the virus, and articles have been published on the role of statins in relieving the symptoms of COVID-19 and other viral infections.[33–35] However, there is a dilemma as to what stage of the disease, and in which group of patients with COVID-19, is statin therapy beneficial, and the type and dose of statin to be given remain unclear.[36] A retrospective study of 4447 patients with COVID-19, at Johns Hopkins Medical Centre, examined the difference in mortality between patients taking statins and those not receiving statins. Evaluation of the average treatment effect of statin use on COVID-19-related mortality showed a risk ratio of 1.00 (95% CI 0.99, 1.01, $P = 0.928$), while the association with severe COVID-19 infection showed a risk ratio of 1.18 (95% CI 1.11, 1.27, $P < 0.001$). Thus, statin use was shown not to be associated with altered mortality, but it was found to be associated with an increased risk of severe COVID-19 infection (by 18%).[37] It is unclear whether hypolipidemia due to statin use may be associated with pneumonia. SARS CoV-2 alters liver function and vascular permeability, reducing LDL biosynthesis and causing leakage of cholesterol and plasma lipids into the alveolar space, thus lowering plasma lipid levels.[30] Possible mechanisms of exacerbation of COVID-19 due to statins include activation of Toll-like receptors, signaling through myeloid differentiation primary response 88 (MyD88) and nuclear factor-κB,[38,39] and increased expression of angiotensin-converting enzyme 2.[40] Therefore, statins may lower a cell's resistance to infection and in turn, increase the odds that the patient will have a more severe case of COVID-19.

The strength of this study is that it was performed in two medical centers dedicated to the admission of patients with COVID-19, and the study population comprised those patients who had not yet received treatment for their disease. Thus, the conclusion regarding the effect of COVID-19 on lipid profile was achieved without the influence of therapeutic intervention. The present results may be limited by the fact that requests for lipid profile testing among patients with COVID-19 are not routine in the present centers; this would have affected the study sample size due to the inclusion criteria, and thus, was a limitation of the study. The proportion of the

present study population with a history of hyperlipidemia treated with statins may not be comparable to recently published studies due to the small sample size. Therefore, to clarify the role of statins in COVID-19, further detailed clinical trials with larger sample sizes are needed.

In general, dyslipidemias in COVID-19 are probably due to cytokine storm, impaired immune function, and impaired lipid metabolism after viral infection. Since dyslipidemias may lead to cardiovascular disease, particularly hypertension, lipid profile changes in patients with COVID-19 should be given increased consideration.

In conclusion, lipid profiles in patients with COVID-19 differ from healthy individuals. In addition, the lipid profile in the severe form of disease differs from the less severe form of COVID-19. LDL-C level may be a useful indicator to determine the severity of COVID-19.

Acknowledgment

The authors are grateful to the Clinical Research Development Centre of Imam Reza Hospital for their kindly assistance and advice.

Author contributions

Study concepts and design: SC and NER; Definition of intellectual content and clinical studies: SC; Data acquisition: SC, HS, MB, ES, MHS, NER; Data/statistical analysis: MHS, NER; Literature search: HS, MB, ES, MHS, NER; Manuscript preparation: HS, MB, ES, MHS, NER; Manuscript review: SC, HS, MB, ES, MHS, NER; Manuscript editing: NER. All authors read and approved the manuscript.

Data accessibility

No additional data are available for this study.

Declaration of conflicting interest

The Authors declare that there is no conflict of interest.

Funding

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

ORCID iD

Narges Eskandari Roozbahani https://orcid.org/0000-0003-2509-9177

References

1. Liu W, Tao Z-W, Wang L, et al. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. *Chin Med J (Engl)* 2020; 133: 1032–1038.
2. 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: 1054–1062.
3. Caramelo F, Ferreira N and Oliveiros B. Estimation of risk factors for COVID-19 mortality-preliminary results. *MedRxiv* 2020; DOI: 10.1101/2020.02.24.20027268 [Preprint].
4. Salari A, Mahdavi-Roshan M, Ghorbani Z, et al. An investigation of risk factors of in-hospital death due to COVID-19: a case-control study in Rasht, Iran. *Ir J Med Sci* 2021; 190: 1321–1333.
5. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020; 180: 934–943.
6. Sun X, Wang T, Cai D, et al. Cytokine storm intervention in the early stages of COVID-19 pneumonia. *Cytokine Growth Factor Rev* 2020; 53: 38–42.
7. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020; 395: 1033–1034.
8. Serhan CN. Pro-resolving lipid mediators are leads for resolution physiology. *Nature* 2014; 510: 92–101.
9. Rajamäki K, Lappalainen J, Öörni K, et al. Cholesterol crystals activate the NLRP3

inflammasome in human macrophages: a novel link between cholesterol metabolism and inflammation. *PloS One* 2010; 5: e11765.
10. Fan J, Wang H, Ye G, et al. Letter to the Editor: Low-density lipoprotein is a potential predictor of poor prognosis in patients with coronavirus disease 2019. *Metabolism* 2020; 107: 154243.
11. Hu X, Chen D, Wu L, et al. Low serum cholesterol level among patients with COVID-19 infection in Wenzhou, China. Preprint 21 February, 2020. Available at SSRN: http://dx.doi.org/10.2139/ssrn.3544826.
12. Khovidhunkit W, Kim M-S, Memon RA, et al. Effects of infection and inflammation on lipid and lipoprotein metabolism: mechanisms and consequences to the host. *J Lipid Res* 2004; 45: 1169–1196.
13. Trinder M, Walley KR, Boyd JH, et al. Causal inference for genetically determined levels of high-density lipoprotein cholesterol and risk of infectious disease. *Arterioscler Thromb Vasc Biol* 2020; 40: 267–278.
14. Kimura LF, Sant'Anna MB, Andrade SA, et al. COVID-19 induces proatherogenic alterations in moderate to severe non-comorbid patients: A single-center observational study. *Blood Cells Mol Dis* 2021; 92: 102604.
15. Karathanasis SK, Freeman LA, Gordon SM, et al. The changing face of HDL and the best way to measure it. *Clin Chem* 2017; 63: 196–210.
16. Suzuki M, Pritchard DK, Becker L, et al. High-density lipoprotein suppresses the type I interferon response, a family of potent antiviral immunoregulators, in macrophages challenged with lipopolysaccharide. *Circulation* 2010; 122: 1919–1927.
17. Kabouridis PS and Jury EC. Lipid rafts and T-lymphocyte function: implications for autoimmunity. *FEBS Lett* 2008; 582: 3711–3718.
18. Sorokin AV, Karathanasis SK, Yang Z-H, et al. COVID-19-associated dyslipidemia: Implications for the mechanism of impaired resolution and novel therapeutic approaches. *FASEB J* 2020; 34: 9843–9853.
19. Yang H, Hou H, Liang X, et al. Lack of significant association between dyslipidemia and COVID-19 mortality. *J Infect* 2021; 82: 276–316.
20. Von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 2007; 147: 573–577.
21. Baker J, Ayenew W, Quick H, et al. High-density lipoprotein particles and markers of inflammation and thrombotic activity in patients with untreated HIV infection. *J Infect Dis* 2010; 201: 285–292.
22. Lee W, Ahn JH, Park HH, et al. COVID-19-activated SREBP2 disturbs cholesterol biosynthesis and leads to cytokine storm. *Signal Transduct Target Ther* 2020; 5: 186.
23. Choi GJ, Kim HM and Kang H. The potential role of dyslipidemia in COVID-19 severity: an umbrella review of systematic reviews. *J Lipid Atheroscler* 2020; 9: 435–448.
24. Chien J-Y, Jerng J-S, Yu C-J, et al. Low serum level of high-density lipoprotein cholesterol is a poor prognostic factor for severe sepsis. *Crit Care Med* 2005; 33: 1688–1693.
25. Tanaka S, Couret D, Tran-Dinh A, et al. High-density lipoproteins during sepsis: from bench to bedside. *Crit Care* 2020; 24: 134.
26. Van Leeuwen HJ, Heezius EC, Dallinga GM, et al. Lipoprotein metabolism in patients with severe sepsis. *Crit Care Med* 2003; 31: 1359–1366.
27. Li Y, Zhang Y, Lu R, et al. Lipid metabolism changes in patients with severe COVID-19. *Clin Chim Acta* 2021; 517: 66–73.
28. Wang G, Zhang Q, Zhao X, et al. Low high-density lipoprotein level is correlated with the severity of COVID-19 patients: an observational study. *Lipids Health Dis* 2020; 19: 204.
29. Osuna-Ramos JF, Rendón-Aguilar H, Jesús-González LAD, et al. Serum lipid profile changes and their clinical diagnostic significance in COVID-19 Mexican patients. *medRxiv* 2020; 2020.08.24.20169789 [Preprint].
30. Wei X, Zeng W, Su J, et al. Hypolipidemia is associated with the severity of COVID-19. *J Clin Lipidol* 2020; 14: 297–304.

31. Abdi A, Jalilian M, Sarbarzeh PA, et al. Diabetes and COVID-19: A systematic review on the current evidences. *Diabetes Res Clin Pract* 2020; 166: 108347.
32. Guo W, Li M, Dong Y, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. *Diabetes Metab Res Rev*. Epub ahead of print 31 March 2020. e3319. DOI: 10.1002/dmrr.3319.
33. Castiglione V, Chiriacò M, Emdin M, et al. Statin therapy in COVID-19 infection. *Eur Heart J Cardiovasc Pharmacother* 2020; 6: 258–259.
34. Grimaldi D, Durand A, Gleeson J, et al. Failure of statins in ARDS: the quest for the Holy Grail continues. *Minerva Anestesiol* 2016; 82: 1230–1234.
35. Rossi R, Talarico M, Coppi F, et al. Protective role of statins in COVID 19 patients: the importance of pharmacokinetic characteristics rather than the intensity of action. *Intern Emerg Med* 2020; 15: 1573–1576.
36. Lee KCH, Sewa DW and Phua GC. Potential role of statins in COVID-19. *Int J Infect Dis* 2020; 96: 615–617.
37. Ayeh SK, Abbey EJ, Khalifa BAA, et al. Statins use and COVID-19 outcomes in hospitalized patients. *PLoS One* 2021; 16: e0256899.
38. Dashti-khavidaki S, Khalili H and Nourian A. Pharmacotherapy considerations in CKD patients with COVID-19, a narrative review. *Iran J Kidney Dis* 2020; 14: 247–255.
39. Totura AL, Whitmore A, Agnihothram S, et al. Toll-like receptor 3 signaling via TRIF contributes to a protective innate immune response to severe acute respiratory syndrome coronavirus infection. *MBio* 2015; 6: e00638–e006315.
40. Shin YH, Min JJ, Lee J-H, et al. The effect of fluvastatin on cardiac fibrosis and angiotensin-converting enzyme-2 expression in glucose-controlled diabetic rat hearts. *Heart Vessels* 2017; 32: 618–627.