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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.

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Original article

Is there any association between plasma lipid profile and severity of COVID-19?

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SUMMARY

Background: COVID-19 is an infectious disease which caused a pandemic with many diseases and fatalities. This new variant of coronavirus called SARS-CoV-2 and is primarily characterized by respiratory symptoms. There are some data indicating that LDL-cholesterol (LDL-C) as well as HDL-cholesterol (HDL-C) levels are inversely correlated to disease severity and could act as a predictor for disease progression and unfavorable prognosis. However, the results of some other studies do not confirm this. This current study aimed to provide an answer to this question.

Methods: This prospective, single-center study analyzed 367 confirmed COVID-19 patients to find whether there are any differences in plasma lipoproteins between survivors and non-survivors patients or between the patients with a "duration of ≤10 days intensive unit care (ICU) stay" and patients with a "duration of >10 days ICU stay".

Results: No association between any lipid/lipoprotein parameter and the severity of COVID-19 could be found but survivors and non-survivors did differ concerning total cholesterol and LDL-C levels.

Conclusion: Multivariate cox regression analysis could not prove any association between lipids/lipoproteins and severe events in COVID-19 patients. Significantly less non-survivors with COVID-19 were taking atorvastatin than survivors which is consistent with the majority of previous findings.

1. Introduction

COronaVIrus Disease 2019 (COVID-19) caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome CoronaVirus 2), a new variant of coronavirus, leading to an infectious disease which was declared a pandemic by the WHO was first originated at Wuhan, in Hubei province, in early December 2019 [1]. The disease is primarily characterized by respiratory symptoms ranging from mild to

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severe respiratory distress syndrome. Until now almost 120 millions of people have got this disease in the world and more than 2.6 millions died.

It is well known that SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as a receptor [2]. However, despite initial concerns about the use of ACE inhibitors and a number of papers discussing this issue [3], European Society of Cardiology (ESC) and American College of Cardiology (ACC) as well as American Heart Association (AHA) and Heart Failure Society of America (HFSA) [4] have recommended not to begin but neither to discontinue ACE inhibitors or angiotensin-II receptor blockers in COVID-19 patients. However, hemodynamic status and clinical findings of patients should be considered to make an optimal decision [5].

It has been shown that SARS-CoV-2 can cause an increased thrombus formation and embolic events either by direct action on platelets leading to endothelial damage or by indirect effects causing inflammation and coagulopathy [6]. Therefore, low-dose aspirin, P2Y purinoceptor ($P2Y_{12}$) inhibitors as well as complement inhibitors and statins might prevent these serious complications of COVID-19.

Concerning plasma lipids and lipoproteins in COVID-19 patients it is indicated that LDL-cholesterol (LDL-C) as well as HDL-cholesterol (HDL-C) levels are inversely correlated to disease severity and could predict disease progression and poor prognosis [7]. This could be partially explained by some older data suggesting that both LDL-C and HDL-C are decreased in critically ill patients because of impairment of lecithin-cholesterol acyltransferase, mainly in sepsis. Thus, regarding that lipid profile may be a predictor of survival, non-survivors have a lower LDL-C and HDL-C level than survivors [8]. It is also well known for many decades that total cholesterol (TC), LDL-C and HDL-C levels are lower in many terminal diseases, such as lung cancers [9]. However, patients with different viral infections such as those with chronic hepatitis B and dengue virus also have decreased TC, LDL-C and HDL-C while patients with human immunodeficiency virus (HIV) infection have decreased HDL-C and increased LDL-C levels [10–12].

Since there is no consistency in published data on association between plasma lipoproteins and severity of COVID-19, particularly concerning survivors and non-survivors, this study was performed.

2. Methods

2.1. Participants and study design

This prospective, single-center study was made in Sina Hospital in Hamadan, Iran. COVID-19 pneumonia patients admitted between May 10, 2020 and October 10, 2020 at hospital because of were included consecutively and prospectively. Included COVID-19 participants were detected in accordance with World Health Organization (WHO) interim guidance [13]. Diagnosis of COVID-19 pneumonia was made according to physical examination, chest computed tomographic (CT) scan confirmed with positive results of reverse-transcriptase–polymerase-chain-reaction (RT-PCR) obtained from nasopharyngeal swab specimens. Incomplete medical records or follow-up data, less than 18 years of age or 80 years above, pregnancy or chronic medical conditions, including fatal acute organ injury (i.e., acute stroke, acute coronary syndrome, and severe acute pancreatitis) were considered as exclusion criteria. All patients were monitored until definite outcomes. These outcomes included: complete recovery and/or discharge, partial recovery (patients who were discharged from the hospital using respiratory aids such as nasal catheters or masks and continued to receive respiratory care at home) or death. Longer stay in the hospital (which is mostly a sign of deterioration in those patients) was another outcome since the length of stay in hospital could be used as an indicator of severity of the disease [14]. The study was approved by the Research Ethics Committee of the Hamadan University of Medical Sciences, Hamadan, Iran, with code (IR.UMSHA.REC.1400.289) and written informed consent of participants was obtained.

2.2. Data collection

Patients demographic characteristic (age, gender, history concerning drug treatment and surgery), comorbidities (diabetes, hypertension, coronary heart disease, chronic renal disease, chronic pulmonary disease, chronic liver disorders, and malignancy), vital signs at the beginning of hospitalization (Apache II score, blood pressure, pulse rate, respiratory rate, temperature and percutaneous oxygen saturation (SPO2)), CT scan findings (consolidation, ground-glass, and bilateral pulmonary) were collected. The patients were treated with antiviral and antibiotic treatment as single drug therapy (antiviral drug lopinavir/ritonavir or hydroxychloroquine), double treatment (an antiviral drug lopinavir/ritonavir or hydroxychloroquine and a cephalosporin or glycopeptide antibiotics such as vancomycin) and triple drug therapy (an antiviral drug such as lopinavir/ritonavir or hydroxychloroquine and two cephalosporins or a cephalosporin and a glycopeptide drug – vancomycin) and some were treated with statins and antihypertensives as well. Laboratory measurements were performed for following parameter: white blood cells count (WBC), lymphocytes count, neutrophil count, platelets count, hemoglobin (HB), erythrocyte sedimentation rate (ESR), creatine phosphokinase (CPK), C-reactive protein (CRP), international normalized ratio (INR), prothrombin time (PT), partial thromboplastin time (PTT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactic acid dehydrogenase (LDH), and lipid profile including total cholesterol (TC), triglycerides (TG), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), and non-HDL-C. Data concerning mortality, length of stay in the intensive care unit (ICU) and in the hospital and treatment procedures including respiratory support (extracorporeal membrane oxygenation (ECMO)), treatment with hyper immune plasma, hemoperfusion and mechanical ventilation (MV) were collected.

2.3. Definitions

In the present study, patients who were admitted to ICU were considered as severe cases. The presence of one of the following criteria was considered for ICU admission: invasive mechanical ventilation due to presence of respiratory distress; cardiovascular shock; acute extrapulmonary organ failure in newly diagnosed patients who required organ support treatment; other critical conditions based on expert specialists' decision for ICU management in accordance with patients' situation.

Cardiovascular disease was defined as experiencing ischemic heart disease, cardiomyopathy, myocardial infarction, serious arrhythmia as well as heart valve disease resulting in myocardial injury and/or cardiac dysfunction. Chronic respiratory disease referred to as respiratory system dysfunction leading to disorder of pulmonary ventilation problems, such as chronic obstructive pulmonary disease (COPD), pulmonary tuberculosis, lung cancer, interstitial lung disease, and bronchial asthma. Acute respiratory distress syndrome (ARDS) was categorized as Berlin definition [15]. Chronic kidney disease was determined as impairment structure or function of kidneys, such as chronic glomerulonephritis, uraemia, interstitial nephritis, polycystic kidney disease, diabetic nephropathy, and hypertensive nephropathy. Acute kidney injury was characterized based on the Kidney Disease Improving Global

Outcomes (KDIGO) definition [16]. Also, chronic liver disease was defined as liver dysfunction, such as chronic viral hepatitis, liver cirrhosis, autoimmune hepatitis, and liver cancer.

TC, TG, HDL-C and LDL-C concentration were assessed at admission in ICU and then every day in the Biochemistry Laboratory of Sina Hospital in Hamedan, Iran. TC, HDL-C, LDL-C and TG concentrations were detected by routine enzymatic assays (CHOL, HDL-C, LDL-C and TRIG methods, Dimension VISTA1 System, Siemens Healthineers™). HDL-C > 1.40 mmol/L; TC < 5.2 mmol/L; and TG < 1.7 mmol/L were considered as reference values. According to the French National Authority for Health (HAS) in 2017 and the ESC/EAS Guidelines for the Management of Dyslipidaemias, LDL-C concentration target values have been recommended as LDL-C <3.0 mmol/L in low to moderate cardiovascular risk patients, and LDL-C <2.6 mmol/L in high risk patients [17].

2.4. Statistical analysis

Mean ± standard deviation (SD) was applied for continuous variables and frequency (percentage) was considered for categorical variables. Since the median of hospitalization was 10 days, we proposed less and more than 10 days as a measure of severity, comparing between non-severe (duration of ≤10 days ICU stay) and severe (duration of >10 days ICU stay) patients. Also and non-survivors vs. survivors were analyzed using Independent sample t-test *or* Mann–Whitney *U*-test (this test was used to analyze all continuous variables because data was not normally distributed). Chi-square test or Fisher exact test (in case of small samples) where used to compare the distribution of categorical data. Finally, univariate and multivariable analyses were performed to check the associations between the laboratory parameters and disease severity. Effects of laboratory variables on the risk of severe events were estimated using the Cox regression model. IBM SPSS version 16 software was used for all statistical analyses. Significance level of 0.05 was used.

3. Results

A total of 367 confirmed COVID-19 patients were recruited in current study. Table 1 shows the demographic and baseline clinical data of patients with COVID-19. No sex and comorbidity differences were identified between the survivors and non-survivor patients neither between the patients with a "duration of ≤10 days ICU stay" nor patients with a "duration of >10 days ICU stay". No vital signs including Apache II score, SPO2, WBC, number of days between symptoms onset and ICU admission and days of hospitalization before ICU admission were significantly associated with severity or mortality. Non-survivor patients were significantly older than-survivors ($p = 0.01$). Atorvastatin was administered in 81 patients (before and during admission) and among them 75 patients (91.5%) received 40 mg while the others were treated with a lower dose. There was a significant negative association between atorvastatin treatment and mortality. Mortality was significantly lower in patients who were treated with atorvastatin ($p = 0.036$). However after adjusting for age and sex as the potential confounders for both treatement with statins and mortality in a logistic regression, no statistical significance between statins and mortality could be proven ($p = 0.213$). Also, 129 patients were treated with antihypertensive drugs (before and during admission). There was no association between antihypertensive drugs and severity of the disease or mortality. A total of 48 patients were treated with captopril as an angiotensin-converting enzyme (ACE) inhibitor, 60 patients used losartan as an angiotensin II receptor blocker (ARB) and 21 patients used other antihypertensive drugs including metoprolol and amilodipine. No association was found between the type of antihypertensive drugs and severity of the disease or mortality (Table 1).

As shown in Table 2, there were no statistically differences in laboratory parameters between patients with a "duration of ≤10 days ICU stay" and patients with a "duration of >10 days ICU stay". Only total cholesterol, LDL-C, TG/HDL-C, and monocytes/HDL-C

Table 1
Demographics and clinical data of patients infected with COVID-19.

Parameter	Total (n = 367)	Severity		p-value	Mortality		p-value
		Duration ≤10 days (n = 160)	Duration >10 days (n = 185)		Survivor (n = 206)	Non-Survivor (n = 161)	
Age, years[a]	66.33 (15.96)	66.54 (16.05)	66.30 (15.89)	0.889	63.37 (16.17)	70.12 (14.91)	**0.001**
Male	205 (56%)	86 (54%)	105 (57%)	0.59	111 (54%)	94 (58%)	0.40
Comorbidity							
Hypertension	161 (44%)	73 (46%)	79 (43%)	0.30	89 (43%)	72 (45%)	0.29
Diabetes	96 (26%)	43 (27%)	47 (25%)	0.81	48 (30%)	48 (30%)	0.15
CVD	98 (27%)	43 (27%)	49 (26%)	1.00	48 (30%)	50 (31%)	0.07
CRD	13 (3.5%)	7 (4.4%)	5 (2.7%)	0.557	7 (3.4%)	6 (3.7%)	0.78
CKD	6 (1/6%)	5 (3.1%)	1 (0.54%)	0.103	3 (1.5%)	3 (1.9%)	0.70
Apache II score[a]	15.47 (2.45)	15.59 (2.42)	15.31 (2.46)	0.29	15.51 (2.28)	15.39 (2.28)	0.66
Oxigen saturation[a]	79.9 (11.54)	78.9 (11.9)	80.9 (10.8)	0.093	80.6 (10.8)	78.9 (12.4)	0.19
White blood cell count[a]	9.98 (8.52)	10.05 (6.42)	9.9 (10.2)	0.092	9.5 (7.15)	10.6 (10.01)	0.24
Days between symptoms onset and ICU admission[b]	6 (2)	6 (2)	6 (2)	0.31	6 (2)	6 (3)	0.27
Days of hospitalization before ICU admission[b]	4 (3)	4 (3)	4 (3)	0.19	4 (3)	4 (3)	0.92
Atorvastatin	81 (22.2%)	36 (22.5%)	41 (22.2%)	0.940	44 (27.3%)	37(18.1%)	0.036
Antihypertensives	129 (35.3%)	64 (40%)	59 (31.9%)	0.117	65 (31.9%)	64(39.8%)	0.118
ACE inhibitor (captopril)	48 (37.2%)	24 (37.5%)	24 (40.7%)	0.935	25 (38.5%)	23 (35.9%)	0.680
ARB (losartan)	60 (46.5%)	30 (46.9%)	26 (44.1%)		28 (43.1%)	32 (50.0%)	
Others	21 (16.3%)	10 (15.6%)	9 (15.3%)		12 (18.5%)	9 (14.1%)	

ACE: Angiotensin-converting enzyme (ACE) inhibitors; ARB: Angiotensin II Receptor Blockers; CRD: Chronic respiratory disease, CVD: Cardiovascular disease, CKD: Chronic kidney disease; ICU: intensive care unit.
Significant p-values are marked in bold.
[a] Mean (sd).
[b] Median (IQR).

Table 2
Baseline laboratory results of patients infected with COVID-19.

Parameter	Severity		p-value	Mortality		p-value
	Duration ≤10 days (n = 160)	Duration >10 days (n = 185)		Survivor (n = 206)	Non-Survivor (n = 161)	
Total cholesterol, mg/dL	126.58 (38.420)	130.21 (36.170)	0.446[a]	128.99 (38.98)	133.26 (127.19)	0.652[a]
Triglycerides, mg/dL	154.20 (89.44)	159.66 (96.04)	0.594[b]	145.16 (72.14)	168.97 (109.38)	0.019[b]
HDL-C, mg/dL	29.21 (13.14)	30.43 (13.63)	0.404[b]	30.85 (12.83)	28.69 (13.79)	0.125[b]
LDL-C, mg/dL	77.39 (35.93)	79.96 (34.36)	0.515[b]	82.09 (31.89)	72.99 (36.99)	**0.017**[b]
Non-HDL-C mg/dL	98.28 (35.97)	98.55 (52.12)	0.594[b]	97.61 (48.4)	97.18 (38.9)	0.927[b]
TG/HDL-C	8.03 (10.91)	7.47 (11.98)	0.660[b]	6.25 (6.19)	9.23 (15.21)	**0.023**[b]
LDL-C/HDL-C	3.23 (2.23)	3.20 (2.05)	0.878[b]	3.19 (1.99)	3.13 (2.21)	0.806[b]
Monocytes/HDL-C	0.13 (0.14)	0.11 (0.12)	0.227[b]	0.11 (0.12)	0.14 (0.14)	**0.041**[b]
Neutrophils/Lymphocytes	6.49 (5.37)	7.11 (7.07)	0.375[b]	6.35 (5.85)	7.53 (7.38)	0.096[b]
Lymphocytes/Monocytes	9.26 (9.20)	9.62 (9.82)	0.738[b]	10.30 (11.23)	9.44 (11.98)	0.491[b]
Platelets/Lymphocytes	17.21 (18.31)	17.71 (20.01)	0.816[b]	17.31 (18.61)	30.30 (154.7)	0.305[b]
MPV, fL	9.21 (3.03)	9.05 (3.91)	0.672[b]	9.28 (3.51)	8.85 (3.55)	0.243[b]
Monocytes, ($\times 10^9$/L)	2.81 (1.78)	2.58 (1.44)	0.185[b]	2.63 (1.63)	2.76 (1.60)	0.453[b]

HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; TG: triglycerides; MPV: Mean platelets volume.
Significant p-values are marked in bold.
[a] Mann–Whitney U test.
[b] Independent samples t test.

showed significant differences between the survivors and non-survivors.

Cox regression analysis was made to analyze the association between the lipids/lipoproteins levels and the "risk of developing severe events" in COVID-19 patients. Table 3 shows multivariate cox regression analysis for severe events in COVID-19 patients. Our results indicated that only mean platelet volume (MPV) and age were associated with lower and higher risk of severe events, respectively (Tables 3 and 4).

4. Discussion

We could find no association between any lipid/lipoprotein parameter and the severity of COVID-19 but there survivors and non-survivors did differ concerning TC and LDL-C concentrations. However, multivariate cox regression analysis could not prove any association between lipids/lipoproteins and severe events in COVID-19 patients.

The results of current study differ from the results of some other studies. Hu et al. were among the first who describe that TC, LDL-C and particularly HDL-C were decreased in COVID-19 patients when compared with the controls and that HDL-C was associated with the severity of COVID-19. They have also noted that in patients with severe disease, in the early stage serum cholesterol level significantly decreased and in the recovery period it tended to be normal [18]. Wang et al. in an observational study showed that HDL-C was lower in COVID-19 patients compared with healthy participants, and that low HDL-C in COVID-19 patients was inversely correlated with developing severe events [19].

Results of some other studies differ from some previously mentioned. Some of them indicated low LDL-C and HDL-C concentrations in ICU admitted patients in severe COVID-19 pneumonia without any association with poor outcomes [20]. Nevertheless, in a retrospective study on 248 patients, severe COVID-19 pneumonia cases ($n = 74$) had higher TG and HDL-C but lower LDL-C levels while TC and LDL-C levels at admission were negatively correlated with length of hospital stay [21]. In Huang et al. recently published cross-sectional retrospective study on 86 severe COVID-19 patients, 132 non-severe COVID-19 patients and 76 healthy individuals. HDL-C was significantly lower in COVID-19 group than in control group and even more significantly lower in severe COVID-19 group than in non-severe COVID-19 group [22]. These results might suggest that HDL-C levels in patients with COVID-19 could reflect the severity of the disease and might have a

Table 3
Multivariate Cox regression analysis for severe events in COVID-19 patients.

Parameter	Hazard ratio	95% CI		p-value
		Lower	Upper	
Age (year)	1.022	1.010	1.035	**0.001**
Gender	0.967	0.670	1.397	0.860
LDL-C, mg/dL	0.995	0.984	1.007	0.439
Triglycerides, mg/dL	1.002	0.999	1.005	0.111
LDL-C/HDL-C ratio	1.080	0.885	1.319	0.448
HDL-C, mg/dL	1.009	0.984	1.034	0.496
Monocyte/HDL-C ratio	1.194	0.046	1.938	0.915
TG/HDL-C	0.998	0.974	1.023	0.880
Total cholesterol, mg/dL	0.995	0.984	1.005	0.306
NonHDL-C mg/dL	1.003	0.994	1.011	0.530
MPV, f	0.943	0.895	0.994	**0.028**
Monocytes ($\times 10^9$/L)	1.027	0.840	1.254	0.797
Neutrophils/Lymphocytes	1.010	0.959	1.063	0.713
Platelets/Lymphocytes	0.999	0.980	1.018	0.913
Lymphocytes/Monocytes	0.983	0.966	1.016	0.455

HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; TG: triglycerides; MPV: Mean platelets volume.
Significant p-values are marked in bold.

Table 4
Univariate Cox regression analysis for severe events in adult COVID-19 patients.

Parameter	Hazard ratio	95% CI		p-value
		Lower	Upper	
Age	1.017	1.006	1.027	**0.002**
Gender	0.912	0.796	1.512	0.572
LDL-C, mg/dL	0.996	0.991	1.001	0.120
Triglycerides, mg/dL	1.001	0.999	1.003	0.109
LDL-C/HDL-C ratio	1.021	0.943	1.105	0.613
HDL-C, mg/dL	0.990	0.978	1.002	0.115
Monocytes/HDL-C ratio	2.119	1.839	2.246	**0.002**
TG/HDL-C	1.012	1.003	1.022	0.008
Total cholesterol, mg/dL	0.997	0.992	1.001	0.158
NonHDL-C, mg/dL	1.000	0.996	1.004	0.942
MPV, fl	0.970	0.892	1.012	0.161
Monocytes, ($\times 10^9$/L)	1.087	0.986	1.199	0.094
Neutrophils/Lymphocytes	1.017	0.995	1.039	0.125
Platelets/Lymphocytes	1.004	0.996	1.013	0.286
Lymphocytes/Monocytes	0.987	0.968	1.007	0.194

HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; TG: triglycerides; MPV: Mean platelets volume.
Significant p-values are marked in bold.

significant impact on the prognosis. The only retrospective study on severe COVID-19 infected patients with confirmed outcomes (survivors or non-survivors) showed an increasing trend of TC, LDL-C and HDL-C in survivors but HDL-C levels were dramatically decreased in non-survivors [23].

In our study survivors were more likely to receive atorvastatin than non-survivors. It is well known that statins are LDL-C lowering drugs with many pleiotropic effects, such as anti-inflammatory activity [24–32]. Although there were some ideas that statins might increase mortality risk in COVID-19 patients, we were among the first groups to suggest using a molecular docking study that statins are potential SARS-CoV-2 main protease inhibitors which can directly affect the virus particle [33]. Afterwards it has been shown that there was an association between antecedent statin use in admitted COVID-19 patients and lower inpatient mortality [34] which may alleviate disease severity leading to a modest reduction in mortality [35]. Several studies have shown that pre-admission statin use was associated with reduced in-hospital mortality in COVID-19 [36]. In two meta-analyses recently published in-hospital use of statins was associated with a lower mortality rate in patients with COVID-19 [37–39]. However, some other authors based upon a study including 7780 patients could not prove that statin therapy might have an effect on hospital mortality of COVID-19 patients although odds of developing COVID-19 were 35% lower in the statin therapy group than in the control group [40]. Another study on 4842 patients with COVID-19 could also not prove any association between recent statin exposure and risk of all-cause mortality or severity of the disease [41]. Therefore, it seems that there are still many open questions concerning the role of statins in COVID-19 patients. However, the results of this study indicating that survivors were more likely to receive atorvastatin than non-survivors are consistent with the most of the published studies.

Concerning the limitations of this study, although the number of participants was not small, a larger number would give a more reliable result. Only one in five of our patients did take a statin, and all of them were treated only with atorvastatin. Therefore, the results concerning the effects of statins on COVID-19 are difficult to interpret. Finally, in the present study lipid/lipoprotein levels were assessed at admission to ICU and not at admission to the hospital. This might be a limitation when comparing the results of this study with some other studies investigating similar issues [20,42–44].

5. Conclusion

There was no association between lipid/lipoprotein parameters and the severity of COVID-19 but there was a significant difference between survivors and non-survivors concerning TC and LDL-C. However, multivariate cox regression analysis could not confirm any association between lipids/lipoproteins and severe events in COVID-19 patients. Non-survivors were less likely to receive atorvastatin than survivors but due to a small number of patients this result has to be reconsidered based upon a much larger number of patients.

Author contribution

Conception: AV, AS; Design: AV, AS, FR; Statistical analysis: MAP; Data collection: LS, ASh, GM; Writing the initial draft: AV, LS, ASh, ZR, MAP, GM; Writing review and editing: FR, TJ, AS; Approval of the final version: all authors.

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Declaration of competing interest

None.

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References

[1] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382:727–33.
[2] Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181:271–80. e8.
[3] Momtazi-Borojeni AA, Banach M, Reiner Ž, Pirro M, Bianconi V, Al-Rasadi K, et al. Interaction between coronavirus S-protein and human ACE2: hints for exploring efficient therapeutic targets to treat COVID-19. Angiology 2021;72:122–30.
[4] Vian J, Pereira C, Chavarria V, Köhler C, Stubbs B, Quevedo J, et al. The renin–angiotensin system: a possible new target for depression. BMC Med 2017;15:144.
[5] Oliveros E, Oni ET, Shahzad A, Kluger AY, Lo KB, Rangaswami J, et al. Benefits and risks of continuing angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, and mineralocorticoid receptor antagonists during hospitalizations for acute heart failure. Cardiorenal Med 2020;10:69–84.
[6] Gu SX, Tyagi T, Jain K, Gu VW, Lee SH, Hwa JM, et al. Thrombocytopathy and endotheliopathy: crucial contributors to COVID-19 thromboinflammation. Nat Rev Cardiol 2021;18:194–209.
[7] Wei X, Zeng W, Su J, Wan H, Yu X, Cao X, et al. Hypolipidemia is associated with the severity of COVID-19. J Clin Lipidol 2020;14:297–304.
[8] Green P, Theilla M, Singer P. Lipid metabolism in critical illness. Curr Opin Clin Nutr Metab Care 2016;19:111–5.
[9] Umeki S. Decreases in serum cholesterol levels in advanced lung cancer. Respiration 1993;60:178–81.
[10] Baker J, Ayenew W, Quick H, Hullsiek KH, Tracy R, Henry K, et al. High-density lipoprotein particles and markers of inflammation and thrombotic activity in patients with untreated HIV infection. J Infect Dis 2010;201:285–92.
[11] Lima WG, Souza NA, Fernandes SOA, Cardoso VN, Godói IP. Serum lipid profile as a predictor of dengue severity: a systematic review and meta-analysis. Rev Med Virol 2019;29:e2056.
[12] Cao WJ, Wang TT, Gao YF, Wang YQ, Bao T, Zou GZ. Serum lipid metabolic derangement is associated with disease progression during chronic HBV infection. Clin Lab 2019;65.
[13] Beierwaltes WH. cGMP stimulates renin secretion in vivo by inhibiting phosphodiesterase-3. Am J Physiol Ren Physiol 2006;290:F1376–81.
[14] Mahboub B, Bataineh MTA, Alshraideh H, Hamoudi R, Salameh L, Shamayleh A. Prediction of COVID-19 hospital length of stay and risk of death using artificial intelligence-based modeling. Front Med 2021;8:592336.
[15] Force* TADT. Acute respiratory distress syndrome: the Berlin definition. JAMA 2012;307:2526–33.
[16] Neubauer B, Machura K, Kettl R, Lopez Maria Luisa SS, Friebe A, Kurtz A. Endothelium-derived nitric oxide supports renin cell recruitment through the nitric oxide–sensitive guanylate cyclase pathway. Hypertension 2013;61:400–7.
[17] Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, et al. 2016 ESC/EAS guidelines for the management of dyslipidaemias. Eur Heart J 2016;37:2999–3058.
[18] Hu X, Chen D, Wu L, He G, Ye W. Declined serum high density lipoprotein cholesterol is associated with the severity of COVID-19 infection. Clin Chim Acta 2020;510:105–10.
[19] Wang G, Zhang Q, Zhao X, Dong H, Wu C, Wu F, 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.
[20] Tanaka S, De Tymowski C, Assadi M, Zappella N, Jean-Baptiste S, Robert T, et al. Lipoprotein concentrations over time in the intensive care unit COVID-19 patients: results from the ApoCOVID study. PLoS One 2020;15:e0239573.
[21] Qin C, Minghan H, Ziwen Z, Yukun L. Alteration of lipid profile and value of lipids in the prediction of the length of hospital stay in COVID-19 pneumonia patients. Food Sci Nutr 2020;8:6144–52.
[22] Huang S, Zhou C, Yuan Z, Xiao H, Wu X. The clinical value of high-density lipoprotein in the evaluation of new coronavirus pneumonia. Adv Clin Exp Med 2021;30:153–6.
[23] Li Y, Zhang Y, Lu R, Dai M, Shen M, Zhang J, et al. Lipid metabolism changes in patients with severe COVID-19. Clin Chim Acta 2021;517:66–73.

[24] Reiner Ž. Statins in the primary prevention of cardiovascular disease. Nat Rev Cardiol 2013;10:453–64.
[25] Bahrami A, Parsamanesh N, Atkin SL, Banach M, Sahebkar A. Effect of statins on toll-like receptors: a new insight to pleiotropic effects. Pharmacol Res 2018;135:230–8.
[26] Ferretti G, Bacchetti T, Sahebkar A. Effect of statin therapy on paraoxonase-1 status: a systematic review and meta-analysis of 25 clinical trials. Prog Lipid Res 2015;60:50–73.
[27] Khalifeh M, Penson PE, Banach M, Sahebkar A. Statins as anti-pyroptotic agents. Arch Med Sci 2021;17:1414–7.
[28] Parizadeh SMR, Azarpazhooh MR, Moohebati M, Nematy M, Ghayour-Mobarhan M, Tavallaie S, et al. Simvastatin therapy reduces prooxidant-antioxidant balance: results of a placebo-controlled cross-over trial. Lipids 2011;46:333–40.
[29] Sahebkar A, Serban C, Mikhailidis DP, Undas A, Lip GYH, Muntner P, et al. Association between statin use and plasma d-dimer levels: a systematic review and meta-analysis of randomised controlled trials. Thromb Haemost 2015;114:546–57.
[30] Shakour N, Ruscica M, Hadizadeh F, Cirtori C, Banach M, Jamialahmadi T, et al. Statins and C-reactive protein: in silico evidence on direct interaction. Arch Med Sci 2020;16:1432–9.
[31] Sohrevardi SM, Nasab FS, Mirjalili MR, Bagherniya M, Tafti AD, Jarrahzadeh MH, et al. Effect of atorvastatin on delirium status of patients in the intensive care unit: a randomized controlled trial. Arch Med Sci 2021;17:1423.
[32] Gorabi AM, Kiaie N, Pirro M, Bianconi V, Jamialahmadi T, Sahebkar A. Effects of statins on the biological features of mesenchymal stem cells and therapeutic implications. Heart Fail Rev 2021;26:1259–72.
[33] Reiner Ž, Hatamipour M, Banach M, Pirro M, Al-Rasadi K, Jamialahmadi T, et al. Statins and the COVID-19 main protease: in silico evidence on direct interaction. Arch Med Sci 2020;16:490–6.
[34] Gupta A, Madhavan MV, Poterucha TJ, DeFilippis EM, Hennessey JA, Redfors B, et al. Association between antecedent statin use and decreased mortality in hospitalized patients with COVID-19. Nat Commun 2021;12:1325.
[35] Marić I, Oskotsky T, Kosti I, Le B, Wong RJ, Shaw GM, et al. Decreased mortality rate among COVID-19 patients prescribed statins: data from electronic health records in the US. Front Med 2021;8:639804.
[36] Chacko SR, DeJoy R, Lo KB, Albano J, Peterson E, Bhargav R, et al. Association of pre-admission statin use with reduced in-hospital mortality in COVID-19. Am J Med Sci 2021;361(6):725–30.
[37] Permana H, Huang I, Purwiga A, Kusumawardhani NY, Sihite TA, Martanto E, et al. In-hospital use of statins is associated with a reduced risk of mortality in coronavirus-2019 (COVID-19): systematic review and meta-analysis. Pharmacol Rep 2021:1–12.
[38] Vahedian-Azimi A, Mohammadi SM, Beni FH, Banach M, Guest PC, Jamialahmadi T, et al. Improved COVID-19 ICU admission and mortality outcomes following treatment with statins: a systematic review and meta-analysis. Arch Med Sci 2021:17.
[39] Vahedian-Azimi A, Mohammadi SM, Banach M, Beni FH, Guest PC, Al-Rasadi K, et al. Improved COVID-19 outcomes following statin therapy: an updated systematic review and meta-analysis. BioMed Res Int 2021:2021.
[40] Oh TK, Song IA, Jeon YT. Statin therapy and the risk of COVID-19: a cohort study of the National Health Insurance Service in South Korea. J Pers Med 2021:11.
[41] Butt JH, Gerds TA, Schou M, Kragholm K, Phelps M, Havers-Borgersen E, et al. Association between statin use and outcomes in patients with coronavirus disease 2019 (COVID-19): a nationwide cohort study. BMJ Open 2020;10:e044421.
[42] Alcantara-Alonso E, Molinar-Ramos F, Gonzalez-Lopez JA, Alcantara-Alonso V, Munoz-Perez MA, Lozano-Nuevo JJ, et al. High triglyceride to HDL-cholesterol ratio as a biochemical marker of severe outcomes in COVID-19 patients. Clin Nutr ESPEN 2021;44:437–44.
[43] Masana L, Correig E, Ibarretxe D, Anoro E, Arroyo JA, Jerico C, et al. Low HDL and high triglycerides predict COVID-19 severity. Sci Rep 2021;11:7217.
[44] Masana L, Correig E, Rodriguez-Borjabad C, Anoro E, Arroyo JA, Jerico C, et al. Effect of statin therapy on SARS-CoV-2 infection-related mortality in hospitalized patients. Eur Heart J Cardiovasc Pharmacother 2020;8(2):157–64. https://doi.org/10.1093/ehjcvp/pvaa128. PMID: 33135047; PMCID: PMC7665420.