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Meta-analysis

Lipid profile as an indicator of COVID-19 severity: A systematic review and meta-analysis

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Article history:
Received 6 June 2021
Accepted 23 July 2021

Keywords:
COVID-19
SARS-CoV-2
Total cholesterol
High-density lipoprotein cholesterol
Low-density lipoprotein cholesterol

SUMMARY

Background: Coronavirus disease-2019 (COVID-19) is a global pandemic. Studies reported dyslipidemia in patients with COVID-19. Herein, we conducted a systematic review and meta-analysis of published articles to evaluate the association of the lipid profile with the severity and mortality in COVID-19 patients.

Methods: PubMed/Medline, Europe PMC, and Google Scholar were searched for studies published between January 1, 2020 and January 13, 2021. Random or Fixed effects models were used to calculate the mean difference (MD) and 95% confidence intervals (CIs). Statistical heterogeneity was assessed using Cochran’s Q test and I² statistics.

Results: This meta-analysis included 19 studies. Of which, 12 studies were categorized by severity, 04 studies by mortality, and 03 studies by both severity and mortality. Our findings revealed significantly decreased levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) in the severe group when compared with the non-severe group in a random effect model. Similarly, random effect model results demonstrated significantly lower levels of HDL-C and LDL-C in the non-survivor group when compared with the survivor group. The level of TC was also found to be decreased in the non-survivor group when compared to the survivor group in a fixed-effect model.

Conclusion: In conclusion, the lipid profile is associated with both the severity and mortality in COVID-19 patients. Hence, the lipid profile may be used for assessing the severity and prognosis of COVID-19.

Prospero registration number: CRD42021216316.

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1. Introduction

Coronavirus Disease-2019 (COVID-19) is an infectious disease, with a ferocious course that has infected many people [1]. This disease is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and was first reported in December 2019 in Wuhan, a city within the Hubei Province of China and rapidly spread throughout China and around the world [2–4]. Given the rapid rise in the number of COVID-19 cases and uncontrolled spread throughout the world, it was declared as a public health emergency of international concern on 30 January, 2020 by World Health Organization (WHO) and further labeled as a pandemic on 11 March 2020, making SARS-CoV-2 the first human coronavirus to cause a pandemic [5,6]. As of 24 May, 2021, the COVID-19 pandemic had over 166 million confirmed cases with 3,459,996 deaths [7]. The rapid emergence of this infectious disease is now the biggest problem affecting public health, social and economic growth [8].

SARS-CoV-2 is a positive-sense single-stranded RNA virus similar to the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome coronavirus (MERS-CoV) and is the newest and seventh member of the coronavirus family that can infect humans [9]. Sequence analysis revealed that SARS-CoV-2 shared 88% sequence identity with two bat-derived severe acute respiratory syndrome (SARS)-like...
coronaviruses, bat-SL-CoVZC45 and bat-SL-CoVZXC21. In addition, SARS-CoV-2 also shared around 79% sequence identity with SARS-CoV and around 50% with MERS-CoV [10]. The SARS-CoV-2 spike (S) protein, composed of S1 and S2 subunits, is responsible for facilitating the entry of the virus into the host cells via surface receptor angiotensin-converting enzyme 2 (ACE2) [10,11]. The entry of SARS-CoV-2 into the target cell is promoted by host protease transmembrane serine protease 2 (TMPRSS2). ACE2 and TMPRSS2 co-express within lung type II pneumocytes, ileal absorptive enterocytes, and nasal goblet secretory cells, which are believed to be host determinants of viral infection at the initial stage [12]. The clinical spectrum of COVID-19 varies from mild to critical illness. While 81% of COVID-19 cases are mild, 14% are severe and 5% are critical. The case fatality rate is 4.5% in critical cases [13]. The risk of poor outcomes increases significantly as patients progress to the severe or critical stage [14]. Therefore, early identification and treatment of patients who are likely to progress to severe or critical cases are crucial.

Lipids form the structural foundations of cellular and viral membranes and hence play an important role in lung biology and the pathophiology of viral disease [15]. Viruses target lipid synthesis and signal modification of host cells in order to generate lipids for their envelopes [16]. For replication of the virus, the involvement of lipids in membrane fusion, envelopment, and transformation is important. The viruses replicate in the host cell; therefore, for entry and release, they must pass through a host cell membrane [15]. Lipids play various roles in the viral invasion, as they may serve as direct and indirect viral receptors, fusion cofactors, and entry cofactors [16]. Furthermore, lipids are also an essential part of the innate and adaptive immune system during infections [17]. Mass spectrometry (MS)-based proteomics analysis revealed that the dysregulation of lipid metabolism may promote the progression of COVID-19 [18,19]. In addition, a study reported that hypolipidemia begins in patients with mild COVID-19 and escalates with the progression and severity of the disease [20].

To the best of our knowledge, no systematic review and meta-analysis has been conducted to date concerning the association of the lipid profile with the severity and mortality in COVID-19. Therefore, we conducted a systematic review and meta-analysis of published articles from January 1, 2020 to January 13, 2021 to evaluate the association of lipid parameters (total cholesterol, HDL-cholesterol, LDL-cholesterol, and triacylglycerols) with the severity and mortality in COVID-19 patients.

2. Methods

2.1. Protocol and registration

This systematic review and meta-analysis was prospectively registered on PROSPERO-The International Prospective Register of Systematic Reviews (Registration No. CRD42021216316) [21] and adheres to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [22].

2.2. Eligibility criteria

Studies that meet the following criteria were included in the meta-analysis: (a) representation for clinical questions (Population: laboratory-confirmed COVID-19 patients; Exposure: severe COVID-19 patients or patients who died due to COVID-19 (non-survivors); Comparator: non-severe COVID-19 patients or COVID-19 patients who survived (survivors); Outcomes: the lipid profile i.e. total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triacylglycerol (TG) levels), (b) observational studies reporting clear extractable data on the lipid profile.

Review articles, conference papers, non-research letters, editorials, commentaries, case reports, research articles with samples below 10, articles not written in English language, and studies that have been conducted exclusively on children or pregnant women were excluded. If two or more studies were conducted at the same place during the same or overlapping period, a study with a larger sample size was included in the present meta-analysis.

2.3. Search strategy and study selection

For the relevant studies, a comprehensive systematic literature search of PubMed/Medline, Europe PMC, and Google Scholar was performed from January 1, 2020 to January 13, 2021 using the following search terms (“COVID-19” OR “2019-nCOV” OR “SARS-CoV-2” OR “novel coronavirus disease” OR “novel coronavirus 2019” OR “coronavirus disease-2019”) AND (“lipid profile” OR “lipid parameters” OR “dyslipidemia”) (Supplement 1). After the initial search, duplicates were removed and two authors (RKM and VR) independently screened titles and abstracts for potentially relevant articles. The full text of relevant articles was reviewed for the eligibility criteria. The reference list of eligible studies and relevant systematic reviews were also reviewed to reduce the literature omissions. We have also included unpublished and preprint articles in our meta-analysis. Disagreements on which studies to include during both title and abstract screen, and the subsequent full-text analysis, were resolved by a third author (NS) and discussed until a consensus was reached.

2.4. Data extraction and quality assessment

Two reviewers (RKM and VR) independently extracted the following data from each included study: first author’s name, country, publication year, hospital, study type, data collection date, gender, age, grouping situation, number of cases in each group, and lipid parameters measured. A third reviewer (NS) checked the article list and extracted data to ensure there were no duplicate articles or duplicate information.

The Newcastle–Ottawa Scale (NOS) was used to evaluate the quality of included studies [23]. For every original study included, the quality assessment was carried out independently by two reviewers (RKM and VR) and the disagreements were resolved through a panel discussion with other reviewers.

2.5. Statistical analysis

The meta-analysis of included studies was performed using Review Manager Version 5.4 and STATA (version 16; Stata Corporation, College Station, TX). When the results of the included studies were present in median and interquartile range (IQR), the mean and standard deviation of lipid parameters were extrapolated from sample size, median and interquartile range (IQR) according to Luo et al. [24] and Wan et al. [25]. Some studies included in our systematic review and meta-analysis reported lipid parameters in mg/dl. In that case, the units were converted to mmol/L to standardize all data. Values in mg/dl were divided by the following conversion factors: 38.67 for total cholesterol, LDL-cholesterol, and HDL-cholesterol; and 88.57 for triacylglycerol [26]. To assess the difference of lipid parameters between severe and non-severe COVID-19 groups or COVID-19 patients who survived (survivor group) and those who died due to COVID-19 (non-survivor group), a pooled mean difference (MD) with 95% confidence interval (CI) was used. To assess statistical heterogeneity among included studies, Cochran’s Q test and I² statistics were...
used. A Cochran's Q value of <0.10 shows significant heterogeneity between studies while $I^2$ statistic was interpreted as 25%, 50%, and 75% representing low, moderate, and high degrees of heterogeneity, respectively. The random-effect model was used if heterogeneity existed; otherwise, the fixed-effect model was used. Sensitivity analysis was carried out by omitting individual studies to assess the stability of the meta-analysis. Funnel plots were constructed for lipid parameters and Egger's test was adopted to statistically assess the potential publication bias (a $p$-value <0.1 indicated significant bias). Except for Egger's test and Cochran's Q test, a $p$-value <0.05 was considered statistically significant.

3. Results

3.1. Outcome of database search

A total of 2681 articles could be initially identified from PubMed/ Medline, Europe PMC, Google Scholar, and other sources. After removing duplicates, 2091 articles remained, of which, 41 articles were selected for full-text assessment after screening the title and abstract. Eventually, 19 studies with a total sample of 5690 confirmed COVID-19 patients were finally selected for qualitative synthesis and meta-analysis after excluding 22 ineligible studies. The PRISMA flow diagram for the study selection process is shown in Fig. 1.

3.2. Characteristics of included studies

All the 19 studies were hospital-based, conducted between January 1, 2020 to January 13, 2021. Of 19 studies, 17 were retrospective and 02 were prospective studies. The majority of the studies were from China [20, 28–32, 34–40, 42–44] and three from other countries including Saudi Arabia [27], Mexico [33], and Spain [41]. A total of 12 studies [20, 28–35, 37, 38, 40] including 3159 COVID-19 patients were categorized by severity; 4 studies [41–44] totaling 1895 COVID-19 patients by mortality, and 3 studies [27, 36, 39] including 636 COVID-19 patients were by both severity and mortality. In 15 severity studies totaling 3795 COVID-19 patients, 1200 were severe COVID-19 patients and 2595 were non-severe COVID-19 patients. Of 3795 COVID-19 patients, 1958 were males and 1837 were females. The severity classification of COVID-19 was based on National Health Commission of China guidelines in 10 studies, WHO guidelines in 01 study, Chinese Center for Disease Control (CDC) guidelines in 01 study, and ICU admission in 02 studies. In addition, 01 study had classified COVID-19 patients into critical and non-critical groups, and in our study; we have included critical COVID-19 patients into severe group and non-critical COVID-19 patients into non-severe group. Furthermore, if COVID-19 patients were classified into four groups i.e. mild, moderate, severe, and critical in included studies then in our meta-analysis, mild and moderate COVID-19 patients were included into non-severe group and severe and critical COVID-19 patients were included into severe group. In 07 mortality studies, totaling 2482 COVID-19 patients, 2118 were survivors and 345 patients had died due to COVID-19 (non-survivors). Of 2482 COVID-19 patients in mortality studies, 1411 were males and 1071 were females. The details regarding the characteristics of the included studies are summarized in Table 1.

![Fig. 1. PRISMA flow chart of the study selection procedure.](image-url)
Table 1
Characteristics of included studies.

### Studies grouped by severity

| Author               | Country Year of publication | Hospitals/Date of data collection | Type of study | Gender (M/F) | Total patients | Non-severe patients | Severe patients | Age, median (IQR) or mean ± SD | Parameters extracted |
|----------------------|----------------------------|----------------------------------|---------------|--------------|-----------------|--------------------|-----------------|-------------------------------|---------------------|
| Alguwaihes AM et al. | Saudi Arabia 2020          | King Saud University Medical City (KSUMC)-King Khaled University Hospital (KRUH) 2020-2021 | Prospective study | 300/139      | 439             | 316                | 123             | 55 (Range:19–101) | HDL-C, LDL-C, TG          |
| Chen C et al.        | China 2020                 | Third People’s Hospital of Shenzhen 2020 | Retrospective study | 198/219      | 417             | 325                | 92              | 47 (34–60)        | TC, TC, HDL-C, LDL-C       |
| Hu X et al.          | China 2020                 | Wenzhou Central Hospital 2020     | Retrospective study | 60/54         | 114             | 87                 | 27              | 48.5 (40.8–57.0) | TC, TC, HDL-C, LDL-C       |
| Li C et al.          | China 2020                 | Jin-yin-tan Hospital 2020         | Retrospective study | 133/109       | 242             | 173                | 69              | 63.0 (53.0–68.3) | TC, HDL-C, LDL-C           |
| Li J et al.          | China 2020                 | Central Hospital of Wuhan 2020    | Retrospective study | 75/59         | 134             | 45                 | 89              | 61.00 (46.75–69.25) | TC, TG                |
| Nie S et al.         | China 2020                 | Renmin Hospital 2020              | Retrospective study | 34/63         | 97              | 72                 | 25              | 39 (30–60)        | TC, TC, HDL-C, LDL-C       |
| Osuna-Ramos JR et al.| Mexico 2020               | three different hospitals from Culiacan, Sinaloa, in northwest Mexico 2019–2020 | Prospective study | 65/37         | 102             | 64                 | 38              | 57 (45.75–64)     | TC, HDL-C, LDL-C           |
| Peng Y et al.        | China 2020                 | TaiKang Tongji Hospital 2020      | Retrospective study | 386/475       | 861             | 579                | 282             | 61.42 ± 14.73    | TC, HDL-C, LDL-C           |
| Ren H et al.         | China 2020                 | Tongji Hospital 2020              | Retrospective study | 78/73         | 151             | 89                 | 62              | 59.5 ± 15.9       | TC, TG                |
| Sun JT et al.        | China 2020                 | Leishenshan Hospital 2020         | Prospective study | 60/39         | 99              | 49                 | 50              | Mild: 52.00 (42.90–62.00); Severe: 70.50 (61.25–80.75) | TC, HDL-C, LDL-C |
| Wang G et al.        | China 2020                 | Public Health Treatment Center of Changsha 2020 | Retrospective study | 115/113       | 228             | 184                | 44              | 45.5 (36.0–60.8) | TC, HDL-C, LDL-C           |
| Wei X et al.         | China 2020                 | Union Hospital 2020                | Retrospective study | 305/292       | 597             | 394                | 203             | 66 (59–72)        | TC, HDL-C, LDL-C           |
| Yang Y et al.        | China 2020                 | HwaMei Hospital, University of Chinese Academy of Sciences-Sino-French Branch of Tongji Hospital 2020 | Retrospective study | 55/87         | 142             | 125                | 17              | 49.10 ± 16.36    | TC, LDL-C, HDL-C           |
| Zhang B et al.       | China 2020                 | Sino-French Branch of Tongji Hospital 2020 | Retrospective study | 58/40         | 98              | 46                 | 52              | 63.9 ± 1.4        | TC, HDL-C, LDL-C           |
| Zhang Q et al.       | China 2020                 | Zhongnan Hospital of Wuhan University in Wuhan, China 2020 | Retrospective study | 36/38         | 74              | 47                 | 27              | 62 (56–72)        | TC, LDL-C, HDL-C           |

### Studies grouped by mortality

| Author               | Country Year of publication | Hospitals/Date of data collection | Type of study | Gender (M/F) | Total patients | Survivors | Non survivors | Age, median (IQR) or mean ± SD | Parameters extracted |
|----------------------|----------------------------|----------------------------------|---------------|--------------|----------------|-----------|---------------|-------------------------------|---------------------|
| Alguwaihes AM et al. | Saudi Arabia 2020          | King Saud University Medical City (KSUMC)-King Khaled University Hospital (KRUH) 2020-2021 | Retrospective study | 300/139      | 439             | 343       | 77            | 55 (Range:19–101) | HDL-C, LDL-C, TG          |

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Table 1 (continued)

| Study | Country | Year | Institution | Design | Dates | Baseline | Follow-up | Sample size | Lipids | Reference |
|-------|---------|------|-------------|--------|-------|----------|-----------|-------------|--------|-----------|
| Aparisi A et al. [41] | Spain | 2020 | Hospital Clinico Universitario de Valladolid | Retrospective study | March 1, 2020 to May 15, 2020 | 376/278 | 654 | 505 | 149 | 70 [58–81] | TC, HDL-C, LDL-C, TG |
| Fan J et al. [42] | China | 2020 | Zhongnan Hospital of Wuhan University | Retrospective study | January 18, 2020 to February 8, 2020 | 11/10 | 21 | 17 | 4 | 62.5 (12.6) | TC, HDL-C, LDL-C |
| Li Y et al. [43] | China | 2020 | West Court of Union Hospital in Wuhan | Retrospective study | February 1, 2020 to March 31, 2020 | 139/77 | 216 | 192 | 24 | 61.3 ± 11.2 | TG, TC, HDL-C, LDL-C |
| Sun JT et al. [36] | China | 2020 | Leishenshan Hospital | Prospective study | February 9, 2020 to April 4, 2020 | 34/16 | 50 | 35 | 15 | 70.50 (61.25–80.75) | TG, TC, HDL-C, LDL-C |
| Yan X et al. [44] | China | 2020 | Wuhan Third Hospital & Tongren Hospital of Wuhan University | Retrospective study | January 11, 2020 to March 3, 2020 | 493/511 | 1004 | 964 | 40 | | |
| Zhang B et al. [39] | Canada | 2020 | Sino-French Branch of Tongji Hospital | Retrospective study | February 6, 2020 to February 28, 2020 | 58/40 | 98 | 62 | 36 | 63.9 ± 1.4 | TC, TG, HDL-C |

IQR: Interquartile range; SD: Standard deviation; NOS: Newcastle-Ottawa Scale; M: Male; F: Female; TC: Total cholesterol; TG: Triacylglycerol; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol.

3.3. Quality assessment

The methodological quality of included studies was assessed by Newcastle–Ottawa Scale (NOS). A score of 0–9 was allocated to each study with higher scores indicating a lower risk of bias. The quality results are shown in Table 1.

3.4. Synthesis of results

For the patients grouped by severity of COVID-19, the analysis of the random effect model (REM) showed that compared with the non-severe group, severe group had significant lower levels of TC (MD = −0.33 mmol/L, 95% CI = [−0.46, −0.20], p < 0.00001; I² = 65%), HDL-C (MD = −0.15 mmol/L, 95% CI = [−0.20, −0.11], p < 0.00001; I² = 86%) and LDL-C (MD = −0.25 mmol/L, 95% CI = [−0.34, −0.16], p < 0.00001; I² = 75%). With reference to TG, we didn’t find any significant difference between severe and non-severe group (MD = 0.03 mmol/L, 95% CI = [−0.19, 0.24], p = 0.80; I² = 97%). Pooled estimates of the lipid profile between severe and non-severe groups are presented in Table 2 and the individual forest plots between severe and non-severe groups for levels of TC, HDL-C, LDL-C, and TG are shown in Fig. 2, Fig. 3, Fig. 4 and Fig. 5 respectively. Similarly, for the patients grouped by mortality, random effect model analysis showed significantly decreased levels of HDL-C (MD = −0.16 mmol/L, 95% CI = [−0.25, −0.07], p = 0.0007; I² = 90%) and LDL-C (MD = −0.49 mmol/L, 95% CI = [−0.63, −0.36], p < 0.00001; I² = 60%) in non-survivor group compared to the survivor group. The level of TC was also found to be decrease in non-survivor group when compared to survivor group in a fixed-effect model (MD = −0.51 mmol/L, 95% CI = [−0.64, −0.39], p < 0.00001; I² = 0%). Though non-survivor group had increased level of TG compared to survivor group in random-effect model, the result was statistically insignificant (MD = 0.27 mmol/L, 95% CI = [−0.13, 0.66], p = 0.19; I² = 97%). Pooled estimates of the lipid profile between survivor and non-survivor groups are presented in Table 3 and the individual forest plots between survivor and non-survivor groups for levels of TC, HDL-C, LDL-C, and TG are shown in Fig. 6, Fig. 7, Fig. 8, and Fig. 9 respectively.

3.5. Sensitivity analysis and publication bias

To evaluate the stability of results, sensitivity analysis was carried out. We found that the combined results did not change significantly after excluding any one specific study in TC, HDL-C, LDL-C, and TG between severe and non-severe groups or survivor and non-survivor groups (Supplement 2 and 3). Funnel plots were constructed for TC, HDL-C, LDL-C, and TG since these parameters were retrieved from >10 studies, and to examine whether there was evidence for statistically significant asymmetry, we had performed Egger’s test. Egger’s test indicated that there was no evidence of substantial publication bias for TC (p = 0.9159), HDL-C (p = 0.8344), LDL-C (p = 0.2082), and TG (p = 0.3491) in studies grouped by severity (Supplement 4). Since less than 10 studies were included in the meta-analysis of the lipid profile in studies grouped by mortality, funnel plots could not be constructed and Egger’s test could not be carried out.

4. Discussion

To the best of author’s knowledge, this is the first systematic review and meta-analysis that investigated the association of the lipid profile with the severity and mortality in COVID-19 patients. The findings of the present meta-analysis revealed significantly decreased levels of TC, HDL-C, and LDL-C are associated with severity and mortality in COVID-19 patients. However, no significant difference was observed in the level of TG between severe and non-severe groups or survivor and non-survivor groups.

Patients may experience dyslipidemia due to chronic inflammation caused by a viral infection, and lipid metabolism plays a key role in the viral life cycle including replication, membrane homeostasis, endocytosis, and exocytosis [45]. In fact, previous experience from SARS-CoV-1 infection showed deranged lipid metabolism following recovery, indicating a biological relationship [46]. Clinical findings showed that patients with acute Epstein-Barr virus (EBV) infection had lower levels of HDL-C, TC and LDL-C compared to their controls [47]. Another study showed that patients with hepatitis B had decreased levels of HDL-C and LDL-C in the cirrhosis phase [48]. In addition, human
immunodeficiency virus (HIV) infected patients had decreased HDL-C and TC and higher TG, compared to HIV-uninfected controls [49]. Similarly, a study revealed that cytomegalovirus infection was linked to lower HDL-C in normal-weight females [50]. Lima et al. conducted a systematic review and meta-analysis of nine studies that evaluated 1953 patients and reported that circulating total cholesterol and LDL-C were inversely and significantly correlated with the severity of dengue fever [51]. The results of the International Monitoring Dialysis Outcomes (MONDO) study also showed that lipid levels were inversely associated with infectious and all-cause mortality [52]. In patients with severe acute respiratory syndrome (SARS), the findings of dyslipidemia are rare. One study showed a lower level of total cholesterol in SARS patients when compared with healthy controls [53]. Another study reported altered lipid metabolism in recovered SARS patients 12 years after infection [46]. These results indicate that patients with coronavirus-related diseases may have dyslipidemia.

However, the underlying mechanism responsible for the reduction in the levels of TC, HDL-C, and LDL-C in severe COVID-19 patients is not clearly understood. Several possible hypotheses have been put forward in this regard. First, the liver plays an important role in lipid metabolism and SARS-CoV-2 may cause damage to the liver and thereby disrupt the uptake and biosynthesis of lipoproteins. A study reported a moderate increase in the levels of liver markers alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP) in about half of all COVID-19 patients, indicating mild or moderate liver injury [20]. Hepatic dysfunction has been seen in 14–53% of COVID-19 patients, particularly in severe and critical patients [54]. This hepatic dysfunction in severe COVID-19 patients would affect the synthesis of lipoproteins. Second, one of the significant features of COVID-19 patients is excessive inflammation, particularly in patients with severe cases or in those who have died [55–58], which causes alteration in lipid metabolism. Proinflammatory cytokines such as IL-6, TNF-α, and IL-1β have been reported to modulate lipid metabolism by altering liver function and decreasing cholesterol efflux and transport in HIV patients [59]. IL-6, TNF-α, and IL-1β may also decrease the synthesis and/or secretion of apolipoproteins in hepatic cell lines in a dose-dependent manner [60]. Moreover, in HIV-1 infection, decreased HDL-C is linked with the impairment of ATP-binding cassette transporter A1-dependent cholesterol efflux from macrophages, and the activation of endothelial lipase and phospholipase A2 by inflammation [61,62]. Inflammation has been found to affect the expression of the hepatic apolipoprotein A-I gene [63] and strengthens the binding of the pro-inflammatory serum amyloid protein A (SAA) which, in turn, displaces and reduces the levels of ApoA-I in HDL [64]. HDL particles loaded with SAA have been shown to clear more rapidly from circulation than normal HDL [17]. During inflammatory setting, reduced plasma levels of lecithin cholesterol acyltransferase (LCAT) can also impair HDL function and further worsen the inflammatory response [65]. Third, the virus-induced inflammatory response could also cause altered vascular permeability resulting in leakage of cholesterol molecule into tissues, such as alveolar spaces to form exudates. Exudates contain high levels of protein and cholesterol [66,67]. Exudates are seen in lung autopsies from SARS patients, in cynomolgus macaques infected with SARS-COV [68–70] as well as in the early phase of COVID-19 lung pathology [71]. Fourth, viral infection causes increased generation of free radicals in host cells [72], which may speed up lipid degradation in COVID-19 patients.

### Table 2

Association of the lipid profile with disease severity in patients of COVID-19.

| Lipid profile | Number of studies | Participants | Statistical method | Heterogeneity | p-value of Egger’s test |
|---------------|------------------|--------------|--------------------|---------------|------------------------|
|               |                  |              | MD [95% CI]         | Model         | p-value                |
|               |                  |              |                    |               |                        |
| TC            | 14               | 3356         | -0.33 [-0.46, -0.20]| REM           | <0.00001               |
| HDL-C         | 13               | 3504         | -0.15 [-0.20, -0.11]| REM           | <0.00001               |
| LDL-C         | 12               | 3404         | -0.25 [-0.34, -0.16]| REM           | <0.00001               |
| TG            | 15               | 3791         | 0.03 [-0.19, 0.24]  | REM           | 0.80                   |

TC: Total cholesterol; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; TG: Triacylglycerol; REM: Random effect model; MD: Mean difference; CI: Confidence interval; P<: p-value of Q-test for heterogeneity.

![Fig. 2](image-url) Forest plot between severe and non-severe groups for total cholesterol (TC).
### Fig. 3. Forest plot between severe and non-severe groups for high density lipoprotein cholesterol (HDL-C).

| Study or Subgroup | Severe Mean | SD | Total | Non-Severe Mean | SD | Total | Mean Difference | IV, Random, 95% CI |
|-------------------|-------------|----|-------|------------------|----|-------|-----------------|-------------------|
| Zhang Q et al. 2020 | 2.21 | 0.55 | 123 | 1.61 | 0.69 | 52 | 0.52 | [-0.34, -0.16] |
| Zhang Q et al. 2020 | 1.61 | 0.58 | 52 | 1.17 | 0.62 | 173 | 0.45 | [-0.38, -0.08] |
| Zhang Q et al. 2020 | 2.41 | 0.65 | 173 | 1.93 | 0.56 | 25 | 0.37 | [-0.36, -0.16] |
| Zhang Q et al. 2020 | 1.89 | 0.82 | 25 | 1.37 | 0.72 | 72 | 0.56 | [-0.38, -0.08] |
| Zhang Q et al. 2020 | 1.17 | 0.56 | 72 | 0.75 | 0.42 | 49 | 0.33 | [-0.38, -0.08] |
| Zhang P et al. 2020 | 2.33 | 0.68 | 49 | 1.88 | 0.53 | 12 | 0.55 | [-0.36, -0.16] |
| Zhang P et al. 2020 | 1.59 | 0.74 | 12 | 1.25 | 0.51 | 6 | 0.34 | [-0.36, -0.16] |
| Zhang P et al. 2020 | 1.93 | 0.71 | 6 | 1.56 | 0.51 | 1 | 0.47 | [-0.36, -0.16] |
| Zhang P et al. 2020 | 1.86 | 0.72 | 1 | 1.48 | 0.51 | 0.1 | 0.47 | [-0.36, -0.16] |

### Fig. 4. Forest plot between severe and non-severe groups for low density lipoprotein cholesterol (LDL-C).

| Study or Subgroup | Severe Mean | SD | Total | Non-Severe Mean | SD | Total | Mean Difference | IV, Random, 95% CI |
|-------------------|-------------|----|-------|------------------|----|-------|-----------------|-------------------|
| Zhang Q et al. 2020 | 2.21 | 0.55 | 123 | 1.61 | 0.69 | 52 | 0.52 | [-0.34, -0.16] |
| Zhang Q et al. 2020 | 1.61 | 0.58 | 52 | 1.17 | 0.62 | 173 | 0.45 | [-0.38, -0.08] |
| Zhang Q et al. 2020 | 2.41 | 0.65 | 173 | 1.93 | 0.56 | 25 | 0.37 | [-0.36, -0.16] |
| Zhang Q et al. 2020 | 1.89 | 0.82 | 25 | 1.37 | 0.72 | 72 | 0.56 | [-0.38, -0.08] |
| Zhang Q et al. 2020 | 2.33 | 0.68 | 72 | 1.88 | 0.53 | 49 | 0.33 | [-0.38, -0.08] |
| Zhang Q et al. 2020 | 1.59 | 0.74 | 49 | 1.25 | 0.51 | 12 | 0.34 | [-0.38, -0.08] |
| Zhang Q et al. 2020 | 1.93 | 0.71 | 12 | 1.48 | 0.51 | 6 | 0.47 | [-0.38, -0.08] |
| Zhang Q et al. 2020 | 1.86 | 0.72 | 6 | 1.56 | 0.51 | 1 | 0.47 | [-0.38, -0.08] |

### Fig. 5. Forest plot between severe and non-severe groups for triacylglycerol (TG).

| Study or Subgroup | Severe Mean | SD | Total | Non-Severe Mean | SD | Total | Mean Difference | IV, Random, 95% CI |
|-------------------|-------------|----|-------|------------------|----|-------|-----------------|-------------------|
| Zhang Q et al. 2020 | 2.21 | 0.55 | 123 | 1.61 | 0.69 | 52 | 0.52 | [-0.34, -0.16] |
| Zhang Q et al. 2020 | 1.61 | 0.58 | 52 | 1.17 | 0.62 | 173 | 0.45 | [-0.38, -0.08] |
| Zhang Q et al. 2020 | 2.41 | 0.65 | 173 | 1.93 | 0.56 | 25 | 0.37 | [-0.38, -0.08] |
| Zhang Q et al. 2020 | 1.89 | 0.82 | 25 | 1.37 | 0.72 | 72 | 0.56 | [-0.38, -0.08] |
| Zhang Q et al. 2020 | 2.33 | 0.68 | 72 | 1.88 | 0.53 | 49 | 0.33 | [-0.38, -0.08] |
| Zhang Q et al. 2020 | 1.59 | 0.74 | 49 | 1.25 | 0.51 | 12 | 0.34 | [-0.38, -0.08] |
| Zhang Q et al. 2020 | 1.93 | 0.71 | 12 | 1.48 | 0.51 | 6 | 0.47 | [-0.38, -0.08] |
| Zhang Q et al. 2020 | 1.86 | 0.72 | 6 | 1.56 | 0.51 | 1 | 0.47 | [-0.38, -0.08] |
Finally, as the uptake following stimulation of LDL receptor expression in hepatocytes by IL-6 released from immunocytes [73].

**Table 3**

| Lipid profile | Number of studies | Participants | Statistical method | Heterogeneity |
|---------------|-------------------|--------------|--------------------|---------------|
| TC            | 6                 | 2043         | MD [95% CI]        |               |
|               |                   |              | Model              | p-value       |
| HDL-C         | 7                 | 2463         | FEM                | <0.00001      |
| LDL-C         | 6                 | 2365         | REM                | 0.0007        |
| TG            | 6                 | 2442         | REM                | <0.00001      |

**Fig. 6.** Forest plot between survivor and non-survivor groups for total cholesterol (TC).

**Fig. 7.** Forest plot between survivor and non-survivor groups for high density lipoprotein cholesterol (HDL-C).

**Fig. 8.** Forest plot between survivor and non-survivor groups for low density lipoprotein cholesterol (LDL-C).

Fifth, the decreased LDL-C levels could also be due to increased LDL uptake following stimulation of LDL receptor expression in hepatocytes by IL-6 released from immunocytes [73]. Finally, as the primary source of cholesterol synthesis is nutrition, the hypocholesterolemia in COVID-19 could also be attributed to malnutrition [74]. A recent study demonstrated deteriorated nutritional states of COVID-19 patients, indicated by continuously decreased levels of albumin in the severe COVID-19 patients [36]. Following recovery from COVID-19, there was a gradual increase in concentrations of HDL-C and LDL-C [29,42,75] which could be due...
to improvement of patient condition. Moreover, in patients who did not survive, TC, HDL-C and LDL-C values were lower at hospital admission and continued to decline until death [42].

This systematic review and meta-analysis has following limitations: First, different guidelines were taken into consideration for the severity classification of COVID-19. Second, most of the studies included in this meta-analysis were retrospective; therefore, the collection of data poses a risk of bias. Third, non-normally distributed data were converted to normally distributed data, which might have induced deviation of the results. Fourth, significant heterogeneity was found in almost all meta-analysis, which tends to weaken our finding’s strength. Fifth, most of the included studies were from China. The inclusion of studies around the world will be required to have a complete picture of the association of the lipid profile with severity and mortality in COVID-19. Despite the above limitation, this systematic review and meta-analysis provides valuable information regarding the association of the lipid profile with severity and mortality in COVID-19.

5. Conclusion

In conclusion, this systematic review and meta-analysis showed decreased levels of TC, HDL-C, and LDL-C in severe COVID-19 patients as compared to non-severe COVID-19. Furthermore, reduced levels of TC, HDL-C, and LDL-C were found in non-survivors compared to survivors, indicating the lipid profile is associated with both the severity and mortality in COVID-19 patients. Hence, the lipid profile may be used for assessing the severity and prognosis of COVID-19. Since the lipid profile is cost-effective and easily accessible in all laboratories, it could help the physician in assessing the severity and prognosis of COVID-19 in resource-limited areas.

Declaration of competing interest

The authors declare that there is no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2021.07.023.

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