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Δείκτη Βαρύτητας της Νόσου COVID-19;»**

**High-Density Lipoprotein Cholesterol: A Marker of COVID-19 Infection
Severity?**

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Περίληψη

Εισαγωγή και στόχοι: Η συστηματική ανασκόπηση όλων των στοιχείων αναφορικά με τη συσχέτιση μεταξύ της χοληστερόλης των υψηλής πυκνότητας λιποπρωτεϊνών (HDL-C) και της νόσου COVID-19.

Μέθοδοι: Έγινε αναζήτηση στις βάσεις δεδομένων PubMed, PubMed Central και medRxiv (έως τον Μάιο του 2021) για μελέτες σχετικές με την HDL-C και τη νόσο COVID-19. Πραγματοποιήθηκε μια ποιοτική σύνθεση δημοσιευμένων προοπτικών και αναδρομικών μελετών για το ρόλο των χαμηλών επιπέδων της HDL-C στη βαρύτητα της νόσου COVID-19.

Αποτελέσματα: Συμπεριλήφθηκαν συνολικά 33 μελέτες (6 προοπτικές, 27 αναδρομικές) με 11.918 ασθενείς με νόσο COVID-19. Δώδεκα μελέτες σύγκριναν τα επίπεδα της HDL-C κατά την εισαγωγή στο νοσοκομείο μεταξύ ασθενών με COVID-19 και υγιών ατόμων. Σε αυτές τις μελέτες, οι ασθενείς με COVID-19 είχαν σημαντικά χαμηλότερα επίπεδα HDL-C κατά την εισαγωγή σε σύγκριση με την ομάδα των υγιών ατόμων. Επιπρόσθετα, 28 μελέτες σύγκριναν τα επίπεδα της HDL-C μεταξύ ασθενών με COVID-19, διερευνώντας το ρόλο των χαμηλών επιπέδων της HDL-C στην πρόγνωση της νόσου. Από τις παραπάνω μελέτες, 24 έδειξαν συσχέτιση μεταξύ των χαμηλών επιπέδων της HDL-C και της βαρύτητας της νόσου, ενώ μόνο 4 μελέτες δεν έδειξαν συσχέτιση.

Συμπέρασμα: Τα χαμηλά επίπεδα της HDL-C αποτελούν παράγοντα κινδύνου της βαρύτητας της νόσου COVID-19.

Λέξεις-Κλειδιά: χοληστερόλη των υψηλής πυκνότητας λιποπρωτεϊνών, HDL-C, νόσος COVID-19, SARS-COV-2, βαρύτητα της νόσου

Summary

Background and aims: To systematically address all the relevant evidence of the association between high-density lipoprotein cholesterol (HDL-C) and COVID-19 infection.

Methods: We searched PubMed, PubMed Central and medRxiv databases (up to May 2021) for studies related to HDL-C and COVID-19 infection. A qualitative synthesis of published prospective and retrospective studies for the role of low HDL-C levels on COVID-19 infection severity was performed.

Results: Thirty-three studies (6 prospective, 27 retrospective) including 11,918 COVID-19 patients were eligible for the systematic review. Twelve studies compared HDL-C levels on admission in COVID-19 patients with healthy controls. In these 12 studies, COVID-19 patients had significantly lower HDL-C levels on admission compared with that of healthy controls. Twenty-eight studies observed the HDL-C levels among COVID-19 diagnosed patients, to establish the role of low HDL-C values in the prognosis of the infection. Twenty-four studies showed a correlation between low HDL-C levels with disease severity, while only 4 studies showed no association.

Conclusions: Low HDL-C levels should be added in the list of the others well-known risk factors for COVID-19 severity.

Keywords: COVID-19, SARS-COV-2, High-Density Lipoprotein Cholesterol, HDL-C, Severity

1. Introduction

The coronavirus disease 2019 (COVID-19) is caused by a novel strain of coronavirus, named as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [1]. The first case of a patient infected by the SARS-CoV-2, causing viral pneumonia, was presented in December 2019 in the city of Wuhan in China [2]. The World Health Organization (WHO) declared coronavirus disease a global pandemic in March 2020 and an international public health emergency issue. As of May 18th, 2021, there have been 163,312,429 confirmed cases of COVID-19, including 3,386,825 deaths worldwide [World Health Organization, Coronavirus disease (COVID-19) outbreak (<https://covid19.who.int/> accessed 18 May 2021)] [3].

The estimated mortality rate for COVID-19 is about 2.3% [4] among the confirmed cases. Until recently, studies have demonstrated that disease's worse prognosis is associated with patients' older age and comorbidity status [5]. However, studies have brought to the surface that other factors, including patients' laboratory data, can play an additional predictive role in COVID-19 prognosis [5-7]. In particular, low absolute count of lymphocytes, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), D-dimer levels, lactate dehydrogenase (LDH), troponin, ferritin and creatinine phosphokinase (CK) at onset are associated with disease progression and poor outcomes [5, 6].

The majority of patients with mild to moderate disease have a better prognosis, than those who are classified as severe to critical cases, concerning mortality rates [8]. Since the COVID-19 has nowadays become a global threat to public health, an urge has been generated to interpret early patients' laboratory values and to identify those with severe disease and a poorer prognosis, in order to facilitate the appropriate supportive care and improve the recovery rate. As such, cheap and easy to perform biomarkers like lipid levels could be useful in clinical practice, especially in those settings where more sophisticated or expensive biomarkers cannot be performed, like in underdeveloped countries with poor resources. So far, little is known about the association between disease severity and lipid levels. Critical illness is well known to be accompanied by low levels of total cholesterol (TCHOL) and apolipoprotein B [9]. These alterations are attributed to increased production of certain cytokines and may suggest worse prognosis and increased mortality. Low high-density lipoprotein cholesterol (HDL-C) levels may be seen in several infectious diseases [9]. Of note, HDL-C levels can get rapidly decreased in septic conditions [10, 11].

Our aim is to assess the role of HDL-C levels on COVID-19 infection in a systematic way.

2. Materials and Methods

2.1 Literature Search

We searched PubMed, PubMed Central and medRxiv databases up to 18th of May 2021 using the keywords (*HDL-Cholesterol OR high-density lipoprotein cholesterol OR HDL*) AND (*COVID-19 OR SARS-COV-2 OR Coronavirus*).

2.2 Study Design

We performed a qualitative synthesis of published prospective or retrospective studies to evaluate whether low HDL-C levels are associated with COVID-19 infection severity.

2.3 Data Extraction

Studies were independently and thoroughly examined by two investigators and studies' characteristics were extracted. Any discrepancy between the reviewers was resolved by consensus. For the review of our analysis, data extraction was performed with adherence to Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA model, Figure 1) [12]. Original articles are included in the present systematic review. We additionally assessed the references of these articles, as well as reviews on the topic to identify for any missed relevant studies.

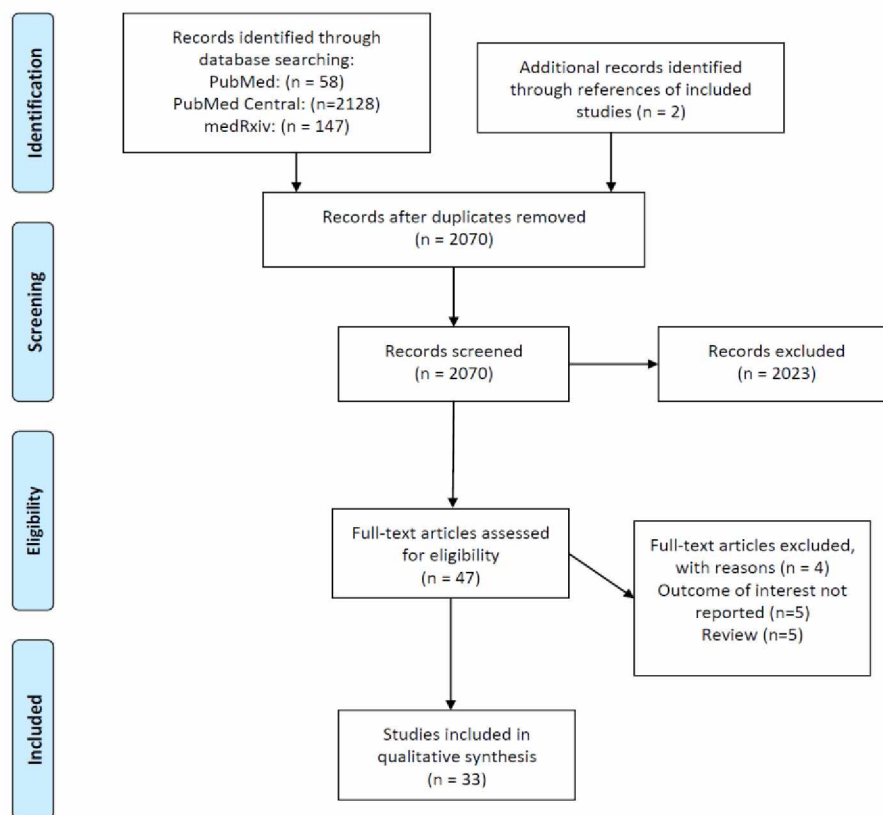


Fig.1. PRISMA flow diagram of articles related to High-Density Lipoprotein Cholesterol and COVID-19 infection

3. Results

Thirty-three studies, with a total of 11,918 COVID-19 patients, were included in our systematic review (Table 1). Twenty-three of them were retrieved from PubMed database, 8 from medRxiv database, 1 from PubMed Central and 1 from Social Science Research Network (SSRN). The studies retrieved from medRxiv and SSRN are preprints and have not been peer-reviewed. Among all 33 studies, 27 were retrospective, while only 6 were conducted prospectively. Twelve studies compared the HDL-C levels on admission in COVID-19 patients with controls (Table 2). In all these 12 studies, COVID-19 patients had significantly lower HDL-C levels on admission compared with that of healthy controls. Twenty-eight studies observed the HDL-C levels among COVID-19 diagnosed patients, to establish any correlation between HDL-C values and prognosis of the disease (Table 3). Among them, 23 studies showed a negative correlation between HDL-C levels and disease severity, while only 1 study showed a positive correlation, and 4 studies showed no association.

3.1 PubMed studies

3.1.1 Prospective:

In an observational cohort study, the association of lipid profile with disease severity and mortality in 99 COVID-19 patients was assessed [13]. The authors found that HDL-C and apoA1 levels were significantly lower in the severe disease group, with mortality cases showing the lowest levels ($p < 0.0001$). Furthermore, HDL-C (OR: 0.643, 95% CI: 0.456–0.906, $p = 0.012$) and apoA1 levels (OR: 0.651, 95% CI: 0.456–0.929, $p = 0.018$) were independently associated with disease severity. Notably, apoA1 and HDL-C levels were negatively correlated with both admission levels and highest concentrations of CRP and interleukin-6, indicating a strong association with the inflammatory status [13].

Tanaka et al. study was conducted among 48 ICU COVID-19 positive patients [14]. Upon admission, HDL-C levels were low [27.1 mg/dL (19.3–34.8)], but throughout disease improvement, HDL-C levels during the 28-study period increased compared with admission ($p = 0.024$). The HDL levels also returned within their normal reference levels in survivors' group. Importantly however, there was no relationship between HDL-C and LDL-C values with mortality (log-rank $p = 0.554$ and $p = 0.083$, respectively). In addition, no differences in HDL-C and LDL-C levels between survivors and non-survivors were observed over time [14].

In a monocentric study conducted in a surgical intensive care unit (ICU) in France, 8 patients admitted for sepsis due to COVID-19 were enrolled [15]. HDL-C levels of these

patients were significantly lower on admission [29.8 mg/dL (18.9-32.1)] compared with that of 16 control healthy subjects [56.5 mg/dL (51.8–65.4)]. Regarding the rest lipid profile, TCHOL, LDL-C and apoA1 levels were lower ($p = 0.0016$, $p = 0.0081$ and $p < 0.0001$, respectively) and triglyceride levels were higher ($p = 0.0152$) in severe COVID-19 ICU patients when compared with controls [15].

3.1.2 Retrospective:

In a population-based study from Hong Kong, among 268 COVID-19 patients, 43 met the primary outcome (composite intensive care unit admission, need for intubation or death) [16]. Those patients had significantly lower HDL-C levels [34.7 mg/dL (27.0-50.2)] compared with that of 225 non-severe cases [42.5 mg/dL (34.7-50.2)], ($p = 0.03$). Similar results regarding LDL-C were observed ($p < 0.0001$) [16].

In a cross-sectional retrospective study, the lipid profile during hospitalization was observed [17]. Among 297 COVID-19 patients, HDL-C levels were significantly higher in 149 patients with mild disease [33.9 mg/dL (27.8-41.7)] compared with that of 148 patients with severe disease [28.2 mg/dL (22.8-37.8)], ($p < 0.001$). On the contrary, triglyceride levels were significantly higher in patients with severe disease [171.5 mg/dL (122.9-254.6)] compared with patients with mild disease [142.3 mg/dL (99.9-192.7)], ($p < 0.001$). The authors concluded that severe outcome was associated with lower HDL-C and higher triglyceride levels [17].

A recent study, using data from the UK Biobank, investigated the relationship between severity of COVID-19 and HDL-C levels [18]. Among included cases, 968 COVID-19 patients had significantly lower HDL-C levels (50 ± 18 mg/dL) compared with that of 3,087 unmatched hospital-based controls C (53 ± 19 mg/dL), ($p < 0.001$). Of importance, a 10 mg/dl increase in serum HDL-C levels was associated with significantly ($p = 0.0004$) reduced risk of SARS-CoV-2 infection [odds ratio (OR), 0.90; 95% CI, 0.85–0.95], identifying HDL-C levels as a clinical risk factor for SARS-CoV-2 infection [18].

A retrospective, single-center, observational study included 424 patients with severe COVID-19 infection (390 survivors, 34 non-survivors) [19]. HDL-C levels were significantly lower on admission in non-survivors [30.9 mg/dL (23.2-34.8)] compared with that of survivors group [34.8 mg/dL (30.9-42.5)], ($p = 0.001$). Similar results were observed regarding apoA1 levels. The authors concluded that low concentrations of HDL-C [AUC: 0.33 (95% CI:0.23–0.43, $p = 0.001$) and apoA1 levels [AUC: 0.28 (95% CI: 0.20–0.36, $p < 0.001$)] at admission were significantly associated with increased disease severity [19].

In a cross-sectional retrospective study, Huang et al. recruited 86 severe COVID-19 patients, 132 non-severe COVID-19 patients and 76 healthy individuals as control group [20]. Serum HDL-C levels in COVID-19 group (39.5 ± 10.8 mg/dL) were significantly lower compared with the control group (58.8 ± 21.3 mg/dL), ($p < 0.05$). Notably, HDL-C levels in patients with severe COVID-19 (32.1 ± 64.6 mg/dL) were significantly lower than that in non-severe COVID-19 patients (44.5 ± 10.5 mg/dL), ($p < 0.05$). The authors concluded that HDL-C represents a poor prognostic factor in COVID-19 disease severity [20].

In another retrospective study conducted in Turkey, the atherogenic index of plasma (AIP), calculated as the base 10 logarithm of the triglyceride to HDL-C ratio, was found to consist an early biomarker to predict pneumonia, intubation and intensive care need in 139 COVID-19 patients [21]. Among them, 26 patients died. The AIP in the deceased group was significantly higher compared with that in the survivor group ($p < 0.001$). Of note, the deceased group had more patients with hypertension ($p = 0.006$), diabetes mellitus ($p = 0.002$), cardiovascular diseases ($p = 0.001$) and chronic renal failure ($p = 0.003$) compared with the survivor group [21]. Regarding lipid profile, TCHOL, HDL-C and LDL-C levels were lower ($p = 0.004$, $p < 0.001$, $p < 0.001$, respectively) and triglyceride levels were higher ($p < 0.001$) in deceased patients when compared with survivors. More specific, HDL-C levels in deceased patients were 28.5 (21.5 - 32.0) mg/dL while in survivors were significantly higher 44.0 (32.5 - 77.0) mg/dL, ($p < 0.001$) [21].

Among 107 COVID-19 inpatients that were included in a retrospective analysis, 82 survived while 25 died [22]. Although no difference was observed in HDL-C levels on admission between survivors and non-survivors (36.7 vs 33.3 mg/dL, $p = 0.323$), on their last tests this difference became profound (41.4 vs 30.6 mg/dL, $p = 0.006$) [22].

A retrospective case-control study conducted in Iran included 250 COVID-19 patients [23]. No significant difference on HDL-C levels was observed between 103 deceased and 147 survived patients. Of note, higher levels of TCHOL [Odds ratio (OR) = 2.55; 95% CI = 1.19–5.45] and LDL (OR = 2.27; 95% CI = 1.07–4.79) as well as elevated triglycerides (OR = 5.14; 95% CI = 2.28–11.56), were identified as independent risk factors of COVID-19 mortality, while no significant association was detected regarding HDL-C [23].

Qin et al., observed the lipid profiles and their alterations in hospitalized patients with COVID-19 pneumonia in 248 patients [24]. In this retrospective study, the authors reported that HDL-C levels were significantly higher in the 74 severe cases (39.8 ± 18.9 mg/dL) compared with 174 common cases on admission (33.3 ± 12.0 mg/dL) ($p < 0.001$). Notably, among 68

severe cases, HDL-C levels were lower in 33 patients who needed hospitalization for more than 29 days compared with the 35 severe cases that needed hospitalization for less than 29 days ($p < 0.05$). Regarding LDL-C, common cases exhibited lower levels (85.1 ± 35.2 mg/dL) compared with that of severe cases (77.0 ± 29.0 mg/dL), ($p = 0.024$). The authors concluded that an increase in LDL-C and HDL-C during hospitalization of severe COVID-19 cases seems to predict disease recovery [24].

Fan et al. study included 21 COVID-19 infected patients [25]. Comparison was made between them and a control group, which included 31 healthy non-COVID-19 individuals. While HDL-C in healthy subjects ranged among normal levels [54.1 mg/dL (38.7-65.8)], COVID-19 subjects' HDL-C levels followed a significant decrease [pre-infection: 54.1 mg/dL (38.7-69.6); on admission: 42.5 mg/dL (30.9-54.1), $p = 0.03$], and remained low during disease's progression [46.4 mg/dL (38.7-54.1) and on discharge [38.7 mg/dL (38.7-54.1)]. Likewise, HDL-C levels among patients who passed away ($n = 4$) decreased steadily until death [on admission: 34.8 mg/dL (30.9-34.8), disease progression: 46.4 mg/dL (34.8-38.7), death: 23.2 mg/dL (19.3-27.1)] [25].

In another study, a total of 98 COVID-19 positive patients were enrolled and divided to ICU/non-ICU and survivors/non-survivors groups [26]. Disease severity was associated with decreased HDL-C levels, since the 46 patients in the non-ICU group had significantly lower HDL-C levels [38.7 (30.9-42.5) mg/dL] compared with the 52 patients in the ICU group [HDL-C = 30.9 (19.3-38.7) mg/dL, $p < 0.05$]. Similarly, disease mortality was associated with decreased HDL-C levels, since the 62 survivors had significantly higher HDL-C levels [34.8 (30.9-42.5) mg/dL] compared with the 36 non-survivors [HDL-C = 27.1 (19.3-38.7) mg/dL, $p < 0.05$]. All in all, the authors concluded that the TG/HDL-C ratio, was independently correlated with myocardial injury, heart failure, disease severity (needing ICU treatment), and mortality in COVID-19 patients [26].

Another study compared the laboratory findings of 50 healthy subjects with those of 597 COVID-19 positive patients, among which, 171 were severe and 32 referred as critical cases on admission [27]. COVID-19 cases presented with significantly decreased HDL values [49 mg/dL (41-58)] on admission compared with the control group [52 mg/dL (40-65), $p < 0.05$]. Notably, HDL-C levels were significantly decreased among critical cases of the COVID-19 cohort on admission [36 mg/dL (29, 43)] compared with the HDL-C levels of the healthy subjects [52 mg/dL (40, 65)], of the mild cases [50 mg/dL (42, 59)] and of the severe ones [HDL-C=50 mg/dL (41, 59). Regarding LDL-C and TCHOL levels, COVID-19 patients had

significantly lower levels on admission when compared with normal subjects ($p < 0.001$). In addition, there were significant and gradual decreases in LDL-C ($p < 0.02$) and TCHOL ($p < 0.05$) levels [mild: 91 mg/dL (76, 104), 173 mg/dL (148, 203), severe: 86 mg/dL (69, 102), 167 mg/dL (138, 197); critical: 69 mg/dL (48, 81), 125 mg/dL (95, 162), respectively, across the three groups. Fatality rate was noted in 2.2% ($n = 13$) (21). The authors concluded that as lipid profile progressively becomes worse, so does the disease severity [27].

Hu et al. collected laboratory values from 114 positive COVID-19 patients on admission and compared them with 80 age-matched healthy controls [28]. Compared with the control group [49.1 mg/dL (46.8–54.5)], infected patients presented with significantly lower HDL-C levels [41.8 mg/dL (36.0–41.8), $p < 0.001$]. Notably, HDL-C levels among severe COVID-19 cases [39.1 mg/dL (34.0–46.4)] were also lower when compared with the mild group [46.8 mg/dL (39.4–57.2), $p < 0.001$]. The authors concluded that decreased serum HDL-C is associated with COVID-19 infection severity [28].

In Huang et al. study, data from 2623 clinically confirmed adult COVID-19 patients was extracted, among which, 2008 (76.6%) were diagnosed as non-critically and 615 (23.4%) as critically ill patients [29]. Median HDL-C levels were remarkably lower among the critically ill group [33.3 mg/dL (0.73–1.05)] compared with the non-critical one [36.7 mg/dL (30.9–44.9), $p < 0.001$], while the death group presented with the lowest HDL values [29.8 mg/dL (21.7–35.6)] [29].

In Wang et al. study, a total of 143 COVID-19 positive patients were enrolled and divided to mild/moderate and severe/critical groups [30]. Disease severity was associated with decreased HDL-C levels ($r = -0.362$, $p = 0.000$), since the 71 patients in the severe/critical group had significantly lower HDL-C levels [34.8 mg/dL (27.1–38.7)] compared with the 72 patients in the mild/moderate group [42.5 mg/dL (34.8–50.3), $p = 0.000$] [30].

Ressaire et al. examined the lipid profile of 31 out of 54 COVID-19 patients admitted to the ICU [31]. On admission, total patients' HDL-C levels were lower than the normal reference [27.8 mg/dL (23.6–40.0)]. Notably, among those, non-survivors ($n = 7$) had lower values of HDL levels [25.9 mg/dL (24.0–42.5)] compared with the 24 patients in the survivor group [32.9 mg/dL (18.2–50.3), $p < 0.28$]. Although no significant difference on HDL-C levels was observed, LDL-C and TCHOL levels were significantly lower in non-survivors compared with survivors ($p = 0.004$ and $p = 0.007$, respectively) [31].

Wang et al. compared HDL-C levels of 1140 healthy individuals with 228 confirmed COVID-19 cases, as well as levels between severe and non-severe COVID-19 patients [32].

Baseline median HDL-C levels upon admission of all COVID-19 patients was significantly lower [30.2 mg/dL (25.5-37.5), $p < 0.001$] in comparison with the control group [53.0 mg/dL (47.2-58.4)]. Of note, severe COVID-19 cases also presented with significantly lower median levels of HDL [26.7 mg/dL (22.8-36.7)], than the non-severe cases [30.6 (26.7-37.5), $p = 0.032$]. Thus, the authors concluded that decreased serum HDL-C were associated with COVID-19 disease severity [32].

Zhang et al. included 74 diabetic patients who were diagnosed with COVID-19 infection. Among those, 47 (63.5%) were characterized as non-severe and 27 (36.5%) as severe cases [33]. While the HDL-C levels of all COVID-19 patients was not among normal values [39.8 mg/dL (32.3–48.3)], mean HDL-C levels of severe cases were statistically lower [HDL-C= 35.6 mg/dL (28.6–46.4)] than that of the non-severe ones [41.8 mg/dL (37.1–49.5), $p < 0.021$] [33].

Xue et al. included 114 patients with positive serology COVID-19 test [34]. Out of these, 58 patients were severe cases (including 5 cases of critically ill patients) and 56 mild to moderate cases. Mean HDL-C levels of COVID-19 patients was low [37.9 mg/dL (30.2–46.0)]. Severe cases and critically ill patients had significantly lower HDL-C levels [34.0 mg/dL (29.0–44.1)] compared with the mild to moderate cases [40.2 mg/dL (30.9–48.0), $p = 0.017$] (29). This study additionally suggested that beyond the lipid profile, novel biomarkers such as high sensitivity C-reactive protein-prealbumin ratio (HsCPAR), high sensitivity C-reactive protein-albumin ratio (HsCAR) and prognostic nutritional index (PNI) may serve as accurate predictors of disease severity [34].

Han et al. collected samples from 52 COVID-19 positive individuals, divided them into symptomatic and asymptomatic groups [35]. Concerning HDL-C levels, while asymptomatic patients had their values among a normal range [48.0 mg/dL (36.7–56.1)], a great decrease was observed among symptomatic ones [32.9 mg/dL (29.4–45.6)], $p = 0.002$. These results, in combination with other biomarkers and panels, suggested that asymptomatic COVID-19 patients presented with normal clinical indicators, whereas the symptomatic ones were not [35].

3.2 Other databases

Similar results were shown in the 8 studies that were retrieved from medRxiv database [36-43], the 1 from PubMed Central [44] and the 1 from Social Science Research Network (SSRN) [45]. The studies retrieved from medRxiv and SSRN are preprints and have not been peer-reviewed. The results of the above studies are summarized in Tables 1, 2 and 3.

First author, Year, (PMID)	Country	Study Design	COVID-19 Patients (n)	Controls (n)	HDL-C levels (mg/dL)				
					Controls	COVID-19	Mild	Severe	Critical
Zhoo et al., 2021 (33833388)	China	Retrospective	268			42.5 (33.5-50.2)	42.5 (34.7-50.2)		34.7 (27.0-50.2)
Masana et al., 2021 (33785815)	Spain	Retrospective	297			30.9 (24.7-40.1)	33.9 (27.8-41.7)	28.2 (22.8-37.8)	
Hilser et al., 2021 (33667465)	USA	Retrospective	968	3087	53 ± 19	50 ± 18			
Li et al., 2021 (33639119)	China	Retrospective	424			34.8 (30.9-42.5)		34.8 (30.9-42.5) Survivors	30.9 (23.2-34.8) Deceased
Huang et al., 2021 (33571404)	China	Retrospective	218	76	58.8 ± 21.3	39.4 ± 10.8	44.5 ± 10.4	32.1 ± 64.6	
Turgay Yildirim et al., 2021 (33524862)	Turkey	Retrospective	139				44.0 (32.5 - 77.0) Survivors		28.5 (21.5 - 32.0) Deceased
Begue et al., 2021 (33504824)	France	Prospective	8	16	56.5 (51.8 - 65.4)	29.8 (19 - 32.1)			
Salari et al., 2021 (33449333)	Iran	Retrospective	250				35.00 ± 13.00 Survivors		35.00 ± 19.00 Deceased
Sun et al., 2021 (33344516)	China	Prospective	99				45.6 (38.7 - 54.9)	36.4 (28.6 - 43.3)	
Ouyang et al., 2020 (33308159)	China	Retrospective	107				41.4 Survivors		27.1 Deceased
Qin et al., 2020 (33282265)	China	Retrospective	248			34.4 ± 14.3	33.3 ± 12	39.8 ± 19	

Zhang et al., 2020 (33122929)	China	Retrospective	98					38.7 (30.9 - 42.5) Non-ICU	30.9 (19.3 - 38.7) ICU
								34.8 (30.9 - 42.5) Survivors	27 (19.3 - 38.7) Deceased
Fan et al., 2020 (32320740)	China	Retrospective	21	31	51.4 (38.7 - 65.7)	42.5 (30.9 - 54.1)	42.5 (30.9 - 54.1)		34.8 (30.9 - 34.8)
Wei et al., 2020 (32430154)	China	Retrospective	597	50	52 (40-65)	49 (41-58)	50 (42-59)	50 (41 - 59)	36 (29 - 43)
Huang et al., 2020 (32567003)	China	Retrospective	2623	-			36.7 (30.9 - 44.9)	33.3 (28.2 - 40.6)	29.8 (21.7 - 35.6) Deceased
Hu et al., 2020 (32653486)	China	Retrospective	114	80	49.1 (46.8 - 54.5)	41.8 (36 - 41.8)	46.8 (39.4 - 57.2)	39 (34 - 46.4)	
Wang et al., 2020 (32677918)	China	Retrospective	143	-		34.8 (30.9 - 46.4)	42.5 (34.8 - 50.2)	34.8 (27 - 38.7)	
Ressaire et al., 2020 (32866665)	France	Retrospective	31	-		27.8 (23.6 - 36)	32.9 (18.2 - 50.3)		25.9 (24 - 42.5)
Wang et al., 2020 (32892746)	China	Retrospective	228	1140	53 (47.2 - 58.4)	30.2 (25.5 - 37.5)	30.6 (26.7 - 37.5)	26.7 (22.8 - 36.7)	
Tanaka et al., 2020 (32970772)	France	Prospective	48	-		27 (19.3 - 34.8)			
Zhang et al., 2020 (32636061)	China	Retrospective	74	-		39.8 (33.3 - 48.3)	41.8 (37.1 - 49.5)	35.6 (28.6 - 46.4)	
Xue et al., 2020 (33045571)	China	Retrospective	114			37.9 (30.2 - 46)	40.2 (30.9 - 48)	34 (28.6 - 44)	
Han et al., 2020 (33028689)	China	Retrospective	52				48 (36.7 - 56)	32.9 (29.4 - 45.6)	

Malik et al., 2021	Pakistan	Prospective	1067	688	47 (36-52)		45 (37-50)	46 (41-50)	40 (37-46)
Peng et. Al, 2020	China	Retrospective	861	1108	58.5 ± 12.4	46.3 ± 12.5	50.7 ± 11.7	43.1 ± 11.6	34.3 ± 9.3
Nie et al., 2020	China	Retrospective	97	-			40.6 (36 - 58)	34 (31.3 - 42.5)	
Aparisi et al., 2020	Spain	Retrospective	654	-		Before admission 51.6 (41.7-62.1)	Survivors 52.6 (43-64)		Non-survivors 47.2 (37.5-60)
						Admission 34 (28 - 43)	34 (28.3-43)		33.5 (27-44)
						7 th day 33 (26.5-41.6)	34 (28-41.8)		27 (19.1-37)
Osuna-Ramos et al., 2020	Mexico	Prospective	102	30	41.43 ± 15.01	29.9 ± 12.19	30 (22-36.5)		26 (16-43)
Rigatti et al., 2020	United States	Retrospective	1520	48505	56.1 (46.2-67.9)	55 (46.2-65.7)			
Zhang et al., 2020	China	Retrospective	43	-			41.8 ± 9.3	42.5 ± 7.7	
Chen et al., 2020	China	Retrospective	291	-		30.2 (25.5 - 37.1)	30.6 (26.7 - 37.5)		25.9 (22.4 - 36.4)
Hu et al., 2020	China	Prospective	71	80	56.8 ± 1.2	45.6 ± 1.2			
Alcántara-Alonso et al., 2021	Mexico	Retrospective	43			29.5 (10.4-76.5)	39.9 (20.1-51.6)	27.6 (19.3-63.5)	22.15(10.4-56.5)

COVID-19: coronavirus disease 2019; HDL-C: High-Density Lipoprotein Cholesterol; ICU: Intensive Care Unit

First author, Year	Country	Study Design	COVID-19 Patients (n)	Controls (n)	HDL-C levels (mg/dL) On admission		Statistical Significance between groups
					Controls	COVID-19	
Hilser et al., 2021	USA	Retrospective	968	3087	53 ± 19	50 ± 18	<i>p</i> < 0.001
Huang et al., 2021	China	Retrospective	218	76	58.8 ± 21.3	39.4 ± 10.8	<i>p</i> < 0.05
Begue et al., 2021	France	Prospective	8	16	56.5 (51.8 - 65.4)	29.8 (19 - 32.1)	<i>p</i> < 0.0001
Fan et al., 2020	China	Retrospective	21	31	51.4 (38.7 - 65.7)	42.5 (30.9 - 54.1)	<i>p</i> < 0.05
Wei et al., 2020	China	Retrospective	597	50	52 (40-65)	49 (41-58)	<i>p</i> < 0.05
Hu et al., 2020	China	Retrospective	114	80	49.1 (46.8 - 54.5)	41.8 (36 - 41.8)	<i>p</i> < 0.001
Malik et al., 2021	Pakistan	Prospective	1067	688	47 (36-52)	NA	<i>p</i> = 0.047
Wang et al., 2020	China	Retrospective	228	1140	53 (47.2 - 58.4)	30.2 (25.5 -37.5)	<i>p</i> < 0.001
Peng et. Al, 2020	China	Retrospective	861	1108	58.5 ± 12.4	46.3 ± 12.5	<i>p</i> < 0.05
Osuna-Ramos et al., 2020	Mexico	Prospective	102	30	41.43 ± 15.01	29.9 ± 12.19	<i>p</i> = 0.0002
Rigatti et al., 2020	United States	Retrospective	1520	48505	56.1 (46.2-67.9)	55 (46.2-65.7)	<i>p</i> = 0.014
Hu et al., 2020	China	Prospective	71	80	56.8 ± 1.2	45.6 ± 1.2	<i>p</i> < 0.001

COVID-19: coronavirus disease 2019; HDL-C: High-Density Lipoprotein Cholesterol; NA: Not Available

First author, Year	Country	Study Design	COVID-19 Patients (n)	HDL-C levels (mg/dL)			COVID-19 Severity Correlation
				Mild	Severe	Critical	
Zhoo et al., 2021	China	Retrospective	268	42.5 (34.7-50.2)		34.7 (27.0-50.2)	<i>p</i> = 0.03
Masana et al., 2021	Spain	Retrospective	297	33.9 (27.8-41.7)	28.2 (22.8-37.8)		<i>p</i> < 0.001
Li et al., 2021	China	Retrospective	424		34.8 (30.9-42.5) Survivors	30.9 (23.2-34.8) Deceased	<i>p</i> = 0.001
Huang et al., 2021	China	Retrospective	218	44.5 ± 10.4	32.1 ± 64.6		<i>p</i> < 0.05
Turgay Yildirim et al., 2021	Turkey	Retrospective	139	44.0 (32.5 - 77.0) Survivors		28.5 (21.5 - 32.0) Deceased	<i>p</i> < 0.001
Salari et al., 2021	Iran	Retrospective	250	35.00 ± 13.00 Survivors		35.00 ± 19.00 Deceased	<i>p</i> = NS
Sun et al., 2021	China	Prospective	99	45.6 (38.7 - 54.9)	36.4 (28.6 - 43.3)		<i>p</i> < 0.001
Ouyang et al., 2020	China	Retrospective	107	41.4 Survivors		27.1 Deceased	<i>P</i> = 0.006
Qin et al., 2020	China	Retrospective	248	33.3 ± 12	39.8 ± 19		<i>p</i> < 0.001
Zhang et al., 2020	China	Retrospective	98		38.7 (30.9 - 42.5) Non-ICU	30.9 (19.3 - 38.7) ICU	<i>p</i> = 0.007
					34.8 (30.9 - 42.5) Survivors	27 (19.3 - 38.7) Deceased	<i>p</i> = 0.001
Fan et al., 2020	China	Retrospective	21	42.5 (30.9 - 54.1)		34.8 (30.9 - 34.8)	<i>p</i> = 0.03
Wei et al., 2020	China	Retrospective	597	50 (42-59)	50 (41-59)	36 (29-43)	<i>p</i> < 0.05
Huang et al., 2020	China	Retrospective	2623	36.7 (30.9 - 44.9)	33.3 (28.2 - 40.6)	29.8 (21.7 -35.6) Deceased	<i>p</i> < 0.001
Zhang et al., 2020	China	Retrospective	74	41.8 (37.1 - 49.5)	35.6 (28.6 - 46.4)		<i>p</i> < 0.05
Xue et al., 2020	China	Retrospective	114	40.2 (30.9 - 48)	34 (28.6 - 44)		<i>p</i> = 0.017

Han et al., 2020	China	Retrospective	52	48 (36.7 - 56)	32.9 (29.4 - 45.6)		$p = 0.002$
Hu et al., 2020	China	Retrospective	114	46.8 (39.4 - 57.2)	39 (34 - 46.4)		$p < 0.001$
Wang et al., 2020	China	Retrospective	143	42.5 (34.8 - 50.2)	34.8 (27 - 38.7)		$p < 0.05$
Ressaire et al., 2020	France	Retrospective	31	32.9 (18.2 - 50.3)		25.9 (24 - 42.5)	$p = \text{NS}$
Wang et al., 2020	China	Retrospective	228	30.6 (26.7 - 37.5)	26.7 (22.8 - 36.7)		$p < 0.001$
Malik et al., 2021	Pakistan	Prospective	1067	45 (37-50)	46 (41-50)	40 (37-46)	$p < 0.01$
Peng et al., 2020	China	Retrospective	861	46.3 ± 12.5	50.7 ± 11.7	43.1 ± 11.6	$p < 0.05$
Nie et al., 2020	China	Retrospective	97	40.6 (36 - 58)	34 (31.3 - 42.5)		$p < 0.05$
Aparisi et al., 2020	Spain	Retrospective	654	34 (28-41.8)		27 (19.1-37)	$p = 0.011$
Zhang et al., 2020	China	Retrospective	43	41.8 ± 9.3	42.5 ± 7.7		$p = \text{NS}$
Chen et al., 2020	China	Retrospective	291	30.6 (26.7 - 37.5)		25.9 (22.4 - 36.4)	$p = 0.009$
Osuna-Ramos et al., 2020	Mexico	Prospective	102	30 (22-36.5)		26 (16-43)	$p = \text{NS}$
Alcántara-Alonso et al., 2021	Mexico	Retrospective	43	39.9 (20.1-51.6)	27.6 (19.3 - 63.5)	22.15 (10.4-56.5)	$p = 0.018$

COVID-19: coronavirus disease 2019; HDL-C: High-Density Lipoprotein Cholesterol; ICU: Intensive Care Unit; NS: non-significant

4. Discussion

This systematic review focuses on the association of HDL-C with COVID-19 infection. Our results suggest that low HDL-C levels consist a poor prognostic factor for COVID-19 severity.

Several well-known poor prognostic factors for COVID-19 infection, such as low absolute lymphocyte count and high levels of C-reactive protein (CRP), D-dimers, troponin, lactate dehydrogenase (LDH), creatine kinase (CK), and ferritin have been previously reported. Additionally, more sophisticated biomarkers such as several interleukin levels are of prognostic value [46]. We now present the evidence regarding HDL-C levels in a systematic way, since it represents a biomarker easy to perform across the universe, is well standardized and is cheap compared to many of the previously reported biomarkers, which are not easy to perform especially in poor resource settings.

A recent analysis that used data of 317,306 (171,466 women) participants from the UK Biobank showed that high HDL-C levels were associated with a lower risk of hospitalisation due to COVID-19 infection [47]. Similarly, data from 9,005 UK Biobank participants (1508 positive for COVID-19 infection) showed that elevated plasma HDL-C, as well as elevated ApoA1 levels, were associated with a reduced odds of testing positive for SARS-CoV-2 (OR = 0.845, 95% CI = 0.788 – 0.907) [48]. Moreover, in another genetic and exposure analysis that included 7,362 subjects from the UK Biobank (1,485 positive for COVID-19 infection) COVID-19 participants had lower HDL-C levels compared with non-COVID-19 participants [49]. In addition, a significant correlation between HDL and genetic factors (single-nucleotide polymorphisms) was observed [49].

Low HDL-C levels may be attributed to inherited disorders or secondary causes [9]. Inherited forms include familial hypoalphalipoproteinemia, Tangier disease or Lecithine:cholesterol acyltransferase (LCAT) deficiency, while secondary causes of low HDL-C levels include cigarette smoking, obesity, low-fat diet, hyperthyroidism, diabetes, chronic kidney disease, malignancies, paraproteinemias, several drugs and infections [9, 50]. Regarding infections, low HDL-C levels may be attributed to several infectious diseases, such as visceral leishmaniasis [51], severe leptospirosis [52], acute brucellosis [53], pulmonary tuberculosis [54], tick-borne encephalitis [55], as wells as chronic hepatitis B and C [56, 57]. Furthermore, HDL-C levels can get rapidly decreased in septic conditions [10, 11].

The mechanisms by which COVID-19 infection reduces HDL-C levels, as well as HDL functionality are not clearly defined. It seems that the “cytokine storm” underlying COVID-19

infection produces immune-mediated inflammatory dyslipoproteinemia, leading to low HDL-C levels [58]. In particular, elevated levels of interleukin-6 and other cytokines in COVID-19 infection may inhibit the apolipoprotein AI synthesis, which results to decreased HDL-C levels. In addition, the “cytokine storm” increases the activity of secretory phospholipase A2 (sPLA2) and endothelial cell lipase, enzymes that metabolize key HDL constituents and eventually leading to decreased HDL-C levels [59]. Furthermore, low HDL-C levels can be partially explained by the increased hepatic production of serum amyloid A (SAA) levels during inflammation [58]. SAA can displace apolipoprotein AI and AII from the HDL surface to produce an SAA-enriched HDL, which is catabolized at a faster rate compared to the normal HDL particle. Moreover, various cytokines during inflammation, decrease the activity of lipoprotein lipase (LPL), thus reducing peripheral clearance of very low density lipoproteins (VLDLs) [59]. This results in elevation of triglycerides and triglyceride-rich lipoproteins (such as VLDLs) leading to an increase of triglyceride content within HDL particles. The triglyceride-rich HDLs are then hydrolysed by the hepatic lipase and the LPL producing small HDLs. Small HDLs lead to increased breakdown of HDL, resulting in decreased HDL-C levels [59]. Of importance, initial COVID-19 data have even indicated that healthy infected individuals display abnormal liver function tests, suggesting a possible direct implication of SARS-CoV-2 in liver damage [30]. As a result, liver dysfunction itself is associated with low to very low HDL-C levels, which, according to recent data, is strongly associated with mortality [60]. The above findings suggest that HDL protein composition and function are altered in COVID-19 patients, implying that not only quantity but also quality of HDL matters [61, 62]. Notably, shotgun proteomics was performed on HDL fractions and their endothelial protective effect was tested on human umbilical vein endothelial cells [15]. Study results showed that HDL particles from ICU severe COVID-19 patients were characterized by quantitative and qualitative abnormalities compared to those isolated from healthy subjects [15]. Those dysfunctional HDL particles were characterized by a loss of protective effect towards endothelial cells in inflammatory conditions [63]. These findings could play a role also in the treatment of the acute phase of COVID-19 infection [64]. Proposed interventions to either improve HDL functionality, such as increasing LCAT activity mentioned above, or replenishment with functional HDL or relevant apolipoproteins, such as ApoA-I mimetic peptides could be beneficial for the management of SARSCoV-2 related complications [58]. Interestingly, a recent study in 115 COVID-19 patients with SARS-COV-2 nucleic acid positive time exceeding 14 days showed that HDL-C reduction was an independent risk factor

of the prolonged nucleic acid turning negative time, suggesting that HDL-C plays a role in virus clearance from the human body [65].

Importantly, HDLs have been shown to be a part of the innate immune system [59]. HDL can buffer toxic materials derived from infection and inflammation by moderating the inflammatory burst. We suggest that this protective mechanism is minimized with the low HDL-C concentrations we find in COVID-19. Hence, low HDL levels are not only a side effect of inflammation and infection, but also contribute to poor disease progression.

Several limitations are present in this systematic review. Most of the studies are of low methodological quality, with the majority being retrospective and a significant percentage of them been reported without peer review process. Small sample sizes, no clear assessing for confounders and heterogeneous reporting further limit the quality of the evidence base. Finally, we were not able to perform a meta-analysis as metrics such as OR were not reported in the vast majority of the studies.

5. Conclusion

After taking the above into consideration, it is clear that HDL-C changes are not only a marker of nutritional status or hypercatabolism but represent a strong and reliable inflammation biomarker and may play a role in the management of COVID-19 infected patients. Large-scale clinical studies are needed to reach more robust conclusions regarding the clinical significance of low HDL-C levels as a predictor of COVID-19 severity. Future studies should consider including lipid profile in COVID-19 infected patients. In addition, these studies should also address if there are common features involved in the pathogenesis of low HDL-C in COVID-19 infection, as little is known in this field. Although promising, there is uncertainty if low HDL-C levels represent a marker of COVID-19 severity based on the existing evidence. However, we strongly suggest that COVID-19 patients may benefit from monitoring more closely their lipid profile.

Highlights

- Patients with COVID-19 have lower HDL-C levels compared with healthy controls.
- Low HDL-C levels consist a poor prognostic factor for COVID-19 severity.
- HDL-C levels represent a cheap, well standardized, and easy to perform, biomarker.
- Improving HDL-C functionality may ameliorate COVID-19 related complications.
- Current evidence is limited by low quality studies.

6. References

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