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Serum HDL-c and LDL-c levels as the predictors of COVID-19 severity

Niveles séricos de HDL-c y LDL-c como predictores de la severidad por COVID-19

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SUMMARY

Background: Coronavirus disease 2019 (COVID-19) is a highly contagious disease caused by severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) and comes with various degrees of severity from mild to critical conditions. This study aims to evaluate and clarify the roles of serum HDL-c and LDL-c levels in predicting the COVID-19 severity.
Methods: A systematic search was conducted in four electronic databases, including Scopus, PubMed, SAGE, and CINAHL Plus database in EBSCOhost. The identified articles were screened based on the specified eligibility criteria. The Newcastle-Ottawa Scale (NOS) tool was further used to assess the risk of bias of each included study.
Results: Seven observational studies were included in the qualitative synthesis of this systematic review. In 6 studies (85.71 %), serum HDL-c levels were significantly lower in the severe COVID-19 compared to the non-severe group ($p< 0.05$). One of those 6 studies showed that significantly lower serum HDL-c levels were also found in critical cases of COVID-19 as compared to the severe cases. Serum HDL-c levels were also negatively correlated to the COVID-19 severity ($p= 0.0001$; $r= -0.362$) in one study and had a protective effect towards COVID-19 ($p= 0.001$; age-adjusted OR [95 %CI] = 0.023 [0.002-0.227]) in one other study. However, 5 studies (71.42 %) showed that serum LDL-c levels were not significantly different between severe and non-severe COVID-19 ($p > 0.05$).
Conclusion: Serum HDL-c levels may serve as a better predictor of the disease severity of COVID-19 than serum LDL-c levels.

Keywords: *Cholesterol, COVID-19, HDL, LDL, SARS-CoV-2, severe, systematic review.*

RESUMEN

Antecedentes: *La enfermedad por coronavirus 2019 (COVID-19) es una enfermedad altamente contagiosa causada por el coronavirus del síndrome de dificultad respiratoria aguda grave 2 (SARS-CoV-2) y se presenta con varios grados de gravedad, desde condiciones leves a críticas. Este estudio tiene como objetivo evaluar y aclarar las funciones de los niveles séricos de HDL-c y LDL-c en la predicción de la gravedad de COVID-19.*
Métodos: *Se realizó una búsqueda sistemática en cuatro bases de datos electrónicas, incluyendo la base de datos Scopus, PubMed, SAGE y CINAHL Plus en EBSCOhost. Los artículos identificados se examinaron según los criterios de elegibilidad especificados. La herramienta Newcastle-Ottawa Scale (NOS) se utilizó además para evaluar el riesgo de sesgo de cada estudio incluido.*

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Resultados: *Se incluyeron siete estudios observacionales en la síntesis cualitativa de esta revisión sistemática. En 6 estudios (85,71 %), los niveles séricos de HDL-c fueron significativamente más bajos en el grupo de COVID-19 grave en comparación con el grupo no grave (p< 0,05). Uno de esos 6 estudios mostró que también se encontraron niveles de HDL-c sérico significativamente más bajos en casos críticos de COVID-19 en comparación con los casos graves. Los niveles séricos de HDL-c también se correlacionaron negativamente con la gravedad de COVID-19 (p= 0,0001; r= -0,362) en un estudio y tuvieron un efecto protector frente a COVID-19 (p= 0,001; OR ajustado por edad [IC del 95 %] = 0,023 [0,002-0,227]) en otro estudio. Sin embargo, 5 estudios (71,42 %) mostraron que los niveles séricos de LDL-c no eran significativamente diferentes entre COVID-19 grave y no grave (p> 0,05).*
Conclusión: *Los niveles séricos de HDL-c pueden servir como un mejor predictor de la gravedad de la enfermedad de COVID-19 que los niveles séricos de LDL-c.*

Palabras clave: *Colesterol, COVID-19, HDL, LDL, SARS-CoV-2, grave, revisión sistemática.*

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a highly contagious disease caused by a new recombinant virus, the severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2), and transmitted person-to-person through the droplet from coughs, talks, or sneezes, with a variety of symptoms, including fever, cough, shortness of breath, anosmia, ageusia, chills, headache, muscle soreness, and sore throat. These could persist for 2-14 days (1,2). In the COVID-19 weekly epidemiological update by World Health Organization (WHO), as of 1 November 2020, the number of COVID-19 cases reaches over 46 million cases with 1.2 million deaths globally (3). The general cases were classified into three groups: the confirmed case, the probable case, and the suspected case (4). Moreover, the clinical outcomes were further divided into five groups: asymptomatic cases with a positive result on SARS-CoV-2 nucleic acid test and no sign or symptoms or any radiological findings; mild cases with mild symptoms in the upper respiratory or digestive system, including fever, myalgia, fatigue, diarrhea, or nausea; moderate cases with a lung lesion on chest CT; severe cases with a lung lesion on chest CT and hypoxemia <92 %; and critical cases with the presence of acute respiratory distress syndrome (ARDS) and several complications, including shock, myocardial injury, acute kidney injury, or encephalopathy (5,6).

Although COVID-19 came with various degrees of severity, some mild patients could rapidly progress to severe or even critical states of COVID-19. Early identification of the risk factors of the critical cases could increase our awareness to further facilitate early supportive care and reduce COVID-19 mortality (7). One of them was lipid profiles, as lipids were important in supporting the viral entry (8,9). SARS-CoV-2 was believed to alter the lipid metabolism in the host cells. A decline in serum high-density lipoprotein cholesterol (HDL-c) and low-density lipoprotein cholesterol (LDL-c) levels was observed in the laboratory results of COVID-19 patients (10). It was thought to be caused by the interaction of HDL-c with the spike protein of SARS-CoV-2 and the increased oxidation of LDL-c to oxLDL. Both together could induce further inflammatory processes and increase the severity of COVID-19 (7,11). However, to date, there is no specific study defining and summarizing the actual benefit of HDL-c and LDL-c in predicting the COVID-19 severity due to the lack of evidence. In this systematic review, we will evaluate and clarify the role of HDL-c and LDL-c in determining the degree of COVID-19 severity.

METHODS

Search Strategy

This systematic review was conducted based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement from four electronic medical databases, including Scopus, PubMed, SAGE, and CINAHL Plus database in EBSCOhost. Data search was conducted independently by all authors with inception to 17 October 2020. Keywords used were the combination of Medical Subject Headings (MeSH) terms and other additional terms, and listed as follows: ((“COVID-19”) OR (“COVID19”) OR (“Sars-CoV-2 infection”) OR (“2019-nCoV infection”)

OR ("coronavirus disease 2019")) AND (("HDL") OR ("LDL") OR ("cholesterol") OR ("lipids") OR ("dyslipidemia")) AND (("severe") OR ("severity") OR ("intensive care units")). The search was limited to human participants and restricted to the English language.

Eligibility Criteria

Studies were screened according to the following inclusion criteria: 1) observational study, including case-control study, cross-sectional study, and cohort study; 2) study population covers adult patients (>18 years old) with a confirmed diagnosis of COVID-19 and is classified into some severity groups depending on each study; and 3) the measured outcomes were comparing serum HDL-c and LDL-c levels among the study groups. Whilst, the exclusion criteria were as follows: 1) irrelevant titles and abstracts; 2) irretrievable full-text articles; 3) wrong PICO components; 4) incompatible language; and 5) inappropriate study method.

Data Synthesis and Quality Assessment

Three investigators (AP, SL, and AJ) screened the literature and determined the studies' eligibility independently. Any disagreements were resolved in a consensus involving all authors. The extracted data were author and year of publication, the diagnostic basis of COVID-19 and its severity classification, study location, study design, study population, sample size, age of patients, serum HDL-c levels, serum LDL-c levels, and study outcomes as expressed p-value in each study. Afterward, the quality of included studies was assessed using the Newcastle-Ottawa Scale (NOS) tool to minimize the risk of bias of each study. NOS interpretation in the case-control study was classified into a good-quality study or low risk of bias (score 7-9), moderate-quality study or moderate risk of bias (score 4-6), and poor-quality studies or high risk of bias (score 0-3), while in the cross-sectional study was classified into a very good study or very low risk of bias (score 9-10), good study or low risk of bias (score 7-8), satisfactory study or moderate risk of bias (score 5-6), and unsatisfactory study or high risk of bias (score 0-4). The quality assessment was conducted by three reviewers (AP, SL, and AJ) collaboratively through a group discussion, and the final decision was taken based on all authors' agreement. Moreover, a p-value < 0.05 in each study outcome was considered statistically significant.

RESULTS

Overview of Literature Search

The initial search of this study yielded a total of 420 studies. Of those, we screened 353 titles and abstracts after duplicates removal. Forty-seven studies were further assessed based on the eligibility criteria. Finally, 7 studies were included and analyzed for qualitative synthesis. The process of study selection is provided in Figure 1.

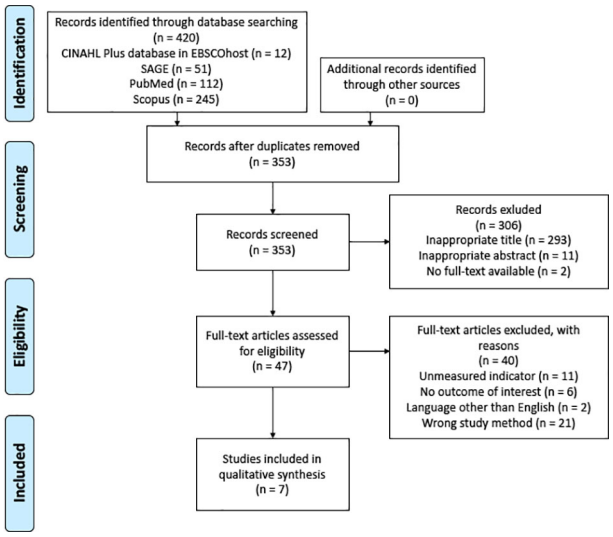

Figure 1. Study Selection Process in PRISMA flowchart.

Characteristics, Results, and Eligibility of the Selected Studies

In this systematic review, three studies were case-control studies (10,12,13) and four studies were cross-sectional studies (7,14–16). All of the eligible studies were published in 2020. Each study's diagnostic basis of COVID-19 and its severity classification was provided in Table 1.

Table 1

Diagnostic basis and severity classification of COVID-19 of the included studies

Author & Year	Diagnostic Basis of COVID-19*	Severity Classification Definition of COVID-19*
Zhang et al. (2020)	Interim guidance for novel coronavirus pneumonia (trial implementation of revised 5th edition) by Chinese National Health Committee	Participants with the diagnosis of COVID-19 were categorized into non-severe and severe groups with the following definitions of severe COVID-19: • Severe COVID-19 was considered if patients had following criteria: (a) respiratory distress with respiratory rate ≥30 breaths/min; (b) resting oxygen saturation ≤93 % on pulse oximeter; and (c) PaO2/FiO2 ≤300 mmHg.
Shu et al. (2020)	A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version)	Participants with the diagnosis of COVID-19 were categorized into mild-moderate and severe-critical groups based on the handbook of COVID-19 prevention and treatment 2020 by Zhejiang University School of Medicine.
D. Wang et al. (2020)	Notice on the novel coronavirus infection diagnosis and treatment plan (trial version 7) by the National Health Commission of the People's Republic of China	Participants with the diagnosis of COVID-19 were categorized into mild-moderate and severe-critical groups with the following definitions: • Mild COVID-19 was considered if patients had minor symptoms and no signs of pneumonia on imaging. • Moderate COVID-19 was considered if patients had fever, respiratory tract symptoms, and positive signs of pneumonia on imaging. • Severe COVID-19 was considered if patients had the following criteria: (a) respiratory distress with respiratory rate ≥30 breaths/min; (b) resting mean oxygen saturation ≤93 %; (c) PaO_2/FiO_2 ≤300 mmHg; (d) pulmonary imaging showed a progression of the lesion >50 % within 28-48h. • Critical COVID-19 was considered if patients had the following criteria: (a) respiratory failure requiring mechanical ventilation; (b) shock; (c) ICU admission due to multiple organ failure.
Hu et al. (2020)	Diagnosis and treatment protocols of the novel coronavirus pneumonia (trial version 7) by National Health Commission of the People's Republic of China	Participants with the diagnosis of COVID-19 were categorized into common and severe groups based on the same guideline.
Wei et al. (2020)	Guidelines of Chinese Thoracic Society and Chinese Medicine Association	Participants with the diagnosis of COVID-19 were categorized into mild, severe, and critical groups with the following definitions: • Mild COVID-19 was considered if patients had fever, cough, fatigue, headache, diarrhea, and with or without mild pneumonia. • Severe COVID-19 was considered if patients had dyspnea, acute respiratory distress, decrease in blood oxygen saturation, lung infiltrates, multiple peripheral ground-glass opacities (GGO) on both lungs. • Critical COVID-19 was considered if patients had respiratory or multiple organ failure and septic shock.

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Author & Year	Diagnostic Basis of COVID-19*	Severity Classification Definition of COVID-19*
Xie et al. (2020)	Diagnosis and treatment protocols for COVID-19 (trial version 7) by National Health Commission of the People's Republic of China	Participants with the diagnosis of COVID-19 were categorized into non-severe (mild-moderate) and severe (severe-critical) groups with the following definitions: • Mild COVID-19 was considered if patients had mild symptoms and no imaging abnormalities. • Moderate COVID-19 was considered if patients had fever, coughing, and signs of pneumonia on imaging. • Severe COVID-19 was considered if patients had respiratory rate ≥30 breaths/min, or resting fingertip oxygen saturation ≤93 %, or PaO_2/FiO_2 ≤300 mmHg. • Critical COVID-19 was considered if patients had respiratory failure requiring mechanical ventilation, or symptoms of shock, or multiple organ dysfunction requiring intensive care.
G. Wang et al. (2020)	Diagnosis and treatment of new coronavirus pneumonia (trial version 6) by the National Health Commission & National Administration of Traditional Chinese Medicine (TCM)	Participants with the diagnosis of COVID-19 were categorized into non-severe and severe groups with the following definitions of severe COVID-19: • Severe COVID-19 was considered if patients had the following criteria: 1) oxygen saturation ≤93 %; 2) PaO_2/FiO_2 ≤300 mmHg; 3) respiratory rate ≥30 breaths/min; 4) receiving mechanical ventilation; 5) pulmonary lesions progressed >50 % in chest CT scan within 28-48h; 6) shock; and 7) ICU admission.

* Provided statements were collected directly from each study without any re-citations in this study
Note. COVID-19 = Coronavirus Disease 2019; CT = Computerized Tomography; FiO_2 = Fraction of Inspired Oxygen; PaO_2 = Partial Pressure of Oxygen.

A total of 2 781 participants were included from 7 studies. Of those, 1 511 participants were diagnosed with COVID-19 in all studies, except a study by Zhang et al. (2020) which included COVID-19 patients with type 2 diabetes mellitus, and 1 270 healthy controls in 3 case-control studies. Neither median nor mean of the patients' age could be summarized due to the difference in data presentation, six studies were using median (IQR) and one study by Shu et al. (2020) was using mean ± SD. One study by Wang et al. (2020) did not present the sample size of each gender and the patients' age in each group of severity.

The qualitative analysis of serum HDL-c and LDL-c levels in the participants are summarized in Table 2 and Table 3, respectively. The key finding of serum HDL-c levels in COVID-19 was 6 of 7 studies (85.71 %) – Zhang et al. (2020), D. Wang et al. (2020), Hu et al. (2020), Wei et al. (2020), Xie et al. (2020), and G. Wang et al. (2020) – generally showed significantly lower serum HDL-c levels in severe COVID-19 patients as compared to non-severe. One of them, a study by Wei et al. (2020), even showed that serum HDL-c levels in critical COVID-19 patients were significantly lower than severe patients. In addition, 2 of 7 studies by D. Wang et al. (2020) and Hu et al. (2020) also stated that serum HDL-c levels were negatively correlated to the COVID-19 severity (p= 0.000; r= -0.362) and had a protective effect towards COVID-19 (p= 0.001; age-adjusted OR [95 %CI] = 0.023 [0.002-0.227]), respectively. Whilst the key finding of serum LDL-c levels was 5 studies (71.42 %) – Zhang et al. (2020), D. Wang et al. (2020), Wei et al. (2020), Xie et al. (2020), and G. Wang et al. (2020) – generally showed

Table 2

Characteristics and Results of HDL-c Findings of the Included Studies

Author & Year	Study Location	Study Design	Population and Classification		Sample Size*	Age of patients	Serum HDL-c Levels**	Summary of HDL-c Findings
Zhang et al. (2020)	Zhongnan Hospital of Wuhan University in Wuhan, China	Cross-sectional study	All COVID-19 patients with type 2 diabetes mellitus	All Severity	74 (36/38)	62 (56, 72)	1.03 (0.86, 1.25) mmol/L	Significantly lower HDL-c levels in severe COVID-19 patients compared to non-severe patients (p = 0.021)
				Non-severe	47 (18/29)	61 (54, 67)	1.08 (0.96, 1.28) mmol/L	
				Severe	27 (18/9)	72 (58, 81)	0.92 (0.74, 1.20) mmol/L	
Shu et al. (2020)	Hubei Provincial Hospital of Traditional Chinese Medicine in Wuhan, China	Cross-sectional study	All confirmed and clinically diagnosis COVID-19 patients	All Severity	293 (135/158)	57.1 ± 15.6	1.1 (0.9, 1.2) mmol/L	No significant difference in HDL-c levels between severe-critical and mild-moderate COVID-19 patients (p= 0.0538)
				Mild-Moderate	207 (79/128)	54.0 ± 15.0	1.1 (0.9, 1.2) mmol/L	
				Severe-Critical	86 (56/30)	64.6 ± 14.5	1.0 (0.9, 1.2) mmol/L	
D. Wang et al. (2020)	Hubei NO.3 People's Hospital of Jianghan University in Wuhan, China	Cross-sectional study	All confirmed COVID-19 patients	All Severity	143 (73/70)	58 (39, 67)	0.9 (0.8, 1.2) mmol/L	Significantly lower HDL-c levels in severe-critical COVID-19 patients compared to mild-moderate patients (p= 0.000)
				Mild-Moderate	72 (29/43)	44 (32, 60)	1.1 (0.9, 1.3) mmol/L	
				Severe-Critical	71 (44/27)	65 (53, 69)	0.9 (0.7, 1.0) mmol/L	
Hu et al. (2020)	Wenzhou Central Hospital in Wenzhou, China	Case-control study	All PCR-confirmed COVID-19 patients and age-matched healthy subjects	Control	80 (42/38)	44.0 (36.0, 57.8)	1.27 (1.21, 1.41) mmol/L	Significantly lower HDL-c levels in all COVID-19 patients compared to controls (p< 0.001)
				All Severity	114 (60/54)	48.5 (40.8, 57.0)	1.08 (0.93, 1.08) mmol/L	

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Author & Year	Study Location	Study Design	Population and Classification		Sample Size*	Age of patients	Serum HDL-c Levels**	Summary of HDL-c Findings
				Common	87 (42/45)	46.0 (36.0, 54.0)	1.21 (1.02, 1.48) mmol/L	Significantly lower HDL-c levels in severe COVID-19 patients compared to common patients (p< 0.001)
				Severe	27 (18/9)	62.0 (53.0, 71.0)	1.01 (0.88, 1.20) mmol/L	
Wei et al. (2020)	Cancer Center, Union Hospital of Tongji Medical College in Wuhan, China	Case-control study	All PCR-confirmed COVID-19 patients and gender- and age-matched normal healthy subjects	Control	50 (27/23)	62 (53, 69)	52 (40, 65) mg/dL	Significantly lower HDL-c levels in all COVID-19 patients compared to controls (p< 0.05)
				All Severity	597 (305/292)	66 (59, 72)	49 (41, 58) mg/dL	
				Mild	394 (189/215)	64 (53, 69)	50 (42, 59) mg/dL	Significantly lower HDL-c levels in critical COVID-19 patients compared to mild and severe patients (p< 0.05)
				Severe	171 (100/71)	69 (64, 77)	50 (41, 59) mg/dL	
				Critical	32 (16/16)	69 (61, 83)	36 (29, 43) mg/dL	Significantly lower HDL-c levels in critical COVID-19 patients compared to severe patients (p< 0.001)
Xie et al. (2020)	Department of Infectious Disease at the Cancer Center, Union Hospital of Tongji Medical College,	Cross-sectional study	All PCR-confirmed COVID-19 patients	All Severity	62 (27/35)	66.0 (53.3, 73.0)	1.2 (1.0, 2.5) mmol/L	Significantly lower HDL-c levels in severe COVID-19 patients compared to non-severe patients (p= 0.042)
				Non-Severe				
				With CVD	16 (4/12)	66.0 (56.3, 73.0)	1.4 (1.2, 1.6) mmol/L	

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Author & Year	Study Location	Study Design	Population and Classification		Sample Size*	Age of patients	Serum HDL-c Levels**	Summary of HDL-c Findings
	Huazhong Science and Technology in Wuhan, China			Without CVD Severe	22 (10/12)	58.0 (42.8, 66.3)	1.3 (1.0, 1.5) mmol/L	Significantly lower HDL-c levels in non-severe COVID-19 patients without CVD compared to non-severe patients with CVD (p= 0.044)
				With CVD	17 (8/9)	73.0 (64.5, 83.0)	1.1 (0.9, 1.3) mmol/L	
				Without CVD	7 (5/2)	69.0 (51.0, 75.0)	1.1 (0.7, 1.7) mmol/L	No significant difference in HDL-c levels between severe COVID-19 patients with and without CVD (p= 0.726)
G. Wang et al. (2020)	Public Health Treatment Center of Changsha, China	Case-control study	All PCR-confirmed COVID-19 patients and gender- and age-matched control patients	Control	1140 (575/565)	45.5 (36.0, 60.8)	1.37 (1.22, 1.51) mmol/L	Significantly lower HDL-c levels in all COVID-19 patients compared to control (p< 0.001)
				All Severity	228 (115/113)	45.5 (36.0, 60.8)	0.78 (0.66, 0.97) mmol/L	
				Non-Severe	184	N/A	0.79 (0.69, 0.97) mmol/L	Significantly lower HDL-c levels in severe COVID-19 patients compared to non-severe patients (p= 0.032)
				Severe	44	N/A	0.69 (0.59, 0.95) mmol/L	

* Sample size are presented in total patients (male/female)
† Age of patients are presented as years in median (interquartile range [IQR]) or mean ± SD
** Serum HDL-c levels are presented in median (interquartile range [IQR])
Note. COVID-19 = Coronavirus Disease 2019; CVD = Cardiovascular Disease; HDL-c = High-Density Lipoprotein Cholesterol; N/A = Not Available; PCR = Polymerase Chain Reaction.

Table 3

Characteristics and Results of LDL-c Findings of the Included Studies

Author & Year	Study Location	Study Design	Population and Classification		Sample Size*	Age of Patients†	Serum LDL-c Levels**	Summary of LDL-c Findings
Zhang et al. (2020)	Zhongnan Hospital of Wuhan University in Wuhan, China	Cross-sectional study	All COVID-19 patients with type 2 diabetes mellitus	All Severity	74 (36/38)	62 (56, 72)	2.60 (1.97, 3.25) mmol/L	No significant difference in LDL-c levels between severe and non-severe COVID-19 patients (p= 0.055)
				Non-severe	47 (18/29)	61 (54, 67)	2.76 (2.16, 3.31) mmol/L	
				Severe	27 (18/9)	72 (58, 81)	2.10 (1.63, 3.13) mmol/L	
Shu et al. (2020)	Hubei Provincial Hospital of Traditional Chinese Medicine in Wuhan, China	Cross-sectional study	All confirmed and clinically diagnosis COVID-19 patients	All Severity	293 (135/158)	57.1 ± 15.6	2.2 (1.8, 2.6) mmol/mL	Significantly lower LDL-c levels in severe-critical COVID-19 patients compared to mild-moderate patients (p= 0.0147)
				Mild-Moderate	207 (79/128)	54.0 ± 15.0	2.3 (1.9, 2.8) mmol/L	
				Severe-Critical	86 (56/30)	64.6 ± 14.5	2.0 (1.7, 2.5) mmol/L	
D. Wang et al. (2020)	Hubei NO.3 People's Hospital of Jianghan University in Wuhan, China	Cross-sectional study	All confirmed COVID-19 patients	All Severity	143 (73/70)	58 (39, 67)	2.6 (2.2, 3.0) mmol/L	No significant difference in LDL-c levels between severe-critical and mild-moderate COVID-19 patients (p= 0.615)
				Mild-Moderate	72 (29/43)	44 (32, 60)	2.6 (2.1, 3.0) mmol/L	
				Severe-Critical	71 (44/27)	65 (53, 69)	2.7 (2.2, 3.0) mmol/L	
Hu et al. (2020)	Wenzhou Central Hospital in Wenzhou,	Case-control study	All PCR-confirmed COVID-19 patients	Control	80 (42/38)	44.0 (36.0, 57.8)	3.06 (2.77, 3.06) mmol/L	Significantly lower LDL-c levels in all COVID-19
					114	48.5	2.19 (0.94,	

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Author & Year	Study Location	Study Design	Population and Classification		Sample Size*	Age of Patients†	Serum LDL-c Levels**	Summary of LDL-c Findings
	China			All Severity	(60/54)	(40.8, 57.0)	2.73) mmol/L	patients compared to controls (p< 0.001)
				Common	87 (42/45)	46.0 (36.0, 54.0)	1.81 (1.52, 2.32) mmol/L	No significant difference in LDL-c levels between severe and common COVID-19 patients (NS)
				Severe	27 (18/9)	62.0 (53.0, 71.0)	1.88 (1.47, 2.28) mmol/L	
Wei et al. (2020)	Cancer Center, Union Hospital of Tongji Medical College in Wuhan, China	Case-control study	All PCR-confirmed COVID-19 patients	Control	50 (27/23)	62 (53, 69)	110 (96, 147) mg/dL	Significantly lower LDL-c levels in all COVID-19 patients compared to control (p< 0.001)
				All Severity	597 (305/292)	66 (59, 72)	88 (74, 102) mg/dL	
				Mild	394 (189/215)	64 (53, 69)	91 (76, 104) mg/dL	Significant decrease of LDL-c levels in COVID 19 patients across all three categories (p< 0.02)
				Severe	171 (100/71)	69 (64, 77)	86 (69, 102) mg/dL	Significantly lower LDL-c levels in mild COVID-19 patients compared to control (p< 0.001)
				Critical	32 (16/16)	69 (61, 83)	69 (48, 81) mg/dL	

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Author & Year	Study Location	Study Design	Population and Classification		Sample Size*	Age of Patients†	Serum LDL-c Levels**	Summary of LDL-c Findings
								Significantly lower LDL-c levels in severe COVID-19 patients compared to mild patients (p< 0.02) Significantly lower LDL-c levels in critical COVID-19 patients compared to severe patients (p< 0.001) Significantly lower LDL-c levels in critical COVID-19 patients compared to severe patients (p< 0.001)
Xie et al. (2020)	Department of Infectious Disease at the Cancer Center, Union Hospital of Tongji Medical College, Huazhong Science and Technology in Wuhan, China	Cross-sectional study	All PCR-confirmed COVID-19 patients	All Severity	62 (27/35)	66.0 (53.3, 73.0)	2.2 (1.9, 2.5) mmol/L	No significant difference in LDL-c levels between severe and non-severe COVID-19 patients with CVD (p= 0.652)
				Non-Severe With CVD	16 (4/12)	66.0 (56.3, 73.0)	2.2 (1.9, 2.6) mmol/L	
				Without CVD	22 (10/12)	58.0 (42.8, 66.3)	2.2 (2.0, 2.3) mmol/L	
				Severe	17	73.0	2.2 (1.8, 3.4)	No significant difference in LDL-c levels

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Author & Year	Study Location	Study Design	Population and Classification		Sample Size*	Age of Patients†	Serum LDL-c Levels**	Summary of LDL-c Findings
				With CVD	(8/9)	(64.5, 83.0)	mmol/L	between non-severe COVID-19 patients with and without CVD (p= 0.636) No significant difference in LDL-c levels between severe COVID-19 patients with and without CVD (p= 0.401)
				Without CVD	7 (5/2)	69.0 (51.0, 75.0)	2.5 (1.9, 3.5) mmol/L	
G. Wang et al. (2020)	Public Health Treatment Center of Changsha, China	Case-control study	All PCR-confirmed COVID-19 patients	Control	1 140 (575/565)	45.5 (36.0, 60.8)	2.83 (2.27, 3.39) mmol/L	Significantly lower LDL-c levels in all COVID-19 patients compared to control (p< 0.001)
				All Severity	228 (115/113)	45.5 (36.0, 60.8)	2.63 (2.21, 3.09) mmol/L	
				Non-Severe	184	N/A	2.65 (2.22, 3.10) mmol/L	No significant difference in LDL-c levels between severe and non-severe COVID-19 patients (p= 0.233)
				Severe	44	N/A	2.60 (2.19, 2.95) mmol/L	

* Sample size are presented in total patients (male/female)
† Age of patients are presented as years in median (interquartile range [IQR]) or mean ± SD
** Serum LDL-c levels are presented in median (interquartile range [IQR])
Note. COVID-19 = Coronavirus Disease 2019; CVD = Cardiovascular Disease; LDL-c = Low-Density Lipoprotein Cholesterol; N/A = Not Available; NS = Not Significant; PCR = Polymerase Chain Reaction.

no significant difference in serum LDL-c levels between severe and non-severe COVID-19 patients. A study by Xie et al. (2020) found that in COVID-19 patients with cardiovascular disease (CVD), serum LDL-c levels were also not significantly different between severe and non-severe groups. The summary of these findings in this study showed that serum HDL-c levels may serve as a better severity predictor in COVID-19 patients than serum LDL-c levels.

The risk of bias using the NOS score was presented in Table 4 and Table 5. All of the included studies were good-quality studies or at low risk of bias.

Table 4

Risk of Bias Assessment of Case-Control Studies Using Newcastle-Ottawa Scale (NOS) Score

NOS Score of Case-Control Study	**Hu et al. (2020)**	**Wei et al. (2020)**	**G. Wang et al. (2020)**
Selection			
Is the case definition adequate?	*	*	*
Representativeness of the cases	*	*	*
Selection of controls	0	0	0
Definition of controls	*	*	0
Comparability			
Study controls for serum HDL-c and LDL-c levels	*	*	*
Study controls for other factors	*	*	*
Exposure			
Ascertainment of exposure	*	*	*
Same method for ascertainment for cases and controls	*	*	*
Non-response rate	*	*	*
Total Score	8	8	7
Interpretation	L	L	L

Note. L = Low risk of bias or good-quality study; NOS = Newcastle-Ottawa Scale.

Table 5

Risk of Bias Assessment of Cross-Sectional Studies Using Newcastle-Ottawa Scale (NOS) Score

NOS Score of Cross-Sectional Study	**Zhang et al. (2020)**	**Shu et al. (2020)**	**D. Wang et al. (2020)**	**Xie et al. (2020)**
Selection				
Representativeness of the sample	*	*	*	*
Sample size	*	*	*	*
Non-respondents	*	*	*	*
Ascertainment of exposure (risk factors)	*	*	*	*
Comparability				
Comparability of subjects in different outcome groups on the basis of design or analysis (data adjustment for confounding factors)	0	0	0	0
Exposure				
Assessment of outcome	**	**	**	**
Statistical test	*	*	*	*
Total Score	7	7	7	7
Interpretation	L	L	L	L

Note. L = Low risk of bias or good study; NOS = Newcastle-Ottawa Scale.

DISCUSSION

We found that low serum HDL-c levels are associated with severe COVID-19 cases, while serum LDL-c levels are not associated with COVID-19 severity. HDL-c is a beneficial lipoprotein in the human body, which consists of triglycerides, cholesterols, and several lipoproteins (Apo-AI, Apo-AII, Apo-AIV, Apo-AV, Apo-C1, Apo-CII, Apo-CIII, and Apo-E) (17). There was a change in the plasma HDL-c levels at the time of viral infections, including human immunodeficiency virus (HIV) and HCV infections. Scavenger receptor class B type I (SR-BI), a protein that took part in the HDL-c life cycle, was known for having a vital role in the HCV infection. Whilst, HIV could modulate the systemic inflammation by decreasing the antioxidant and anti-inflammatory activities due to the transformation of HDL-c to pro-oxidant and pro-inflammatory acute phase HDL-c (18). Although the mechanism of HCV and HIV in decreasing the HDL-c levels have been established, this mechanism remained unclear in SARS-CoV-2 infection. However, several hypotheses stated that the mechanism for the declining of HDL-c levels during COVID-19 was similar to HIV-1 infection. Both shared a similar relationship for the viral infection in the HDL-c and cholesterol pathways. An in vitro investigation of SARS-CoV-2 infection reported that cholesterols were needed in two checkpoints of the SARS-CoV life cycle and took part in the early stage of the viral replication and its binding while penetrating the host cells (12).

HDL-c also has a beneficial function in protecting the host from several diseases, including viral pneumonia. Despite its role as an anti-inflammatory agent, the inflammatory process in infection may alter the HDL-c structure and produce the acute phase serum amyloid A (SAA) protein. SAA could reduce the anti-inflammatory function of HDL-c and further induce the pro-inflammatory condition by activating the macrophages and translocating toll-like receptor 4 (TLR4) into the lipid rafts. As a result, those will decrease the serum HDL-c levels and increase the serum total cholesterol-to-HDL-c (TC/HDL-c) ratio. Those processes were observed in community-acquired pneumonia (CAP) patients, especially viral pneumonia (7,12). Furthermore, a study by G. Wang et al. (2020) also showed that COVID-19 patients with low serum HDL-c levels (<0.65 mmol/L or <25 mg/dL) had significantly higher levels of C-reactive protein ($p<0.001$) compared to high serum HDL-c levels and caused two to three times higher risk of developing severe events in COVID-19 ($p = 0.019$; HR [95 %CI] = 2.827 [1.190-6.714]) (13). Moreover, in COVID-19, HDL-c was bound to the spike protein of SARS-CoV-2. This binding mechanism was inhibited by SR-BI, a receptor that antagonists the activity of HDL-c, through its function on transferring HDL-c back to the liver. However, this protective mechanism was overly active, and instead, it reduced serum HDL-c levels in COVID-19 patients (7). Overall, serum HDL-c levels will drop following the severity of COVID-19. These mechanisms supported our study result: 6 of 7 included studies showed that severe COVID-19 tend to have lower serum levels of HDL-c compared to the non-severe group. Although the levels of HDL-c were correlated with the COVID-19 severity, advanced studies on the role of HDL-c in SARS-CoV-2 infection still needed further investigations.

LDL-c is one of the lipoprotein particles, other than HDL-c, that support the cholesterol distribution in the body. Although LDL-c and HDL-c are formed by similar particles, both have different characteristics. LDL-c was related to the increased risk of atherosclerotic lesion formation, while HDL-c was inversely correlated with this event (19). However, both shared a similar role in combatting infections by neutralizing the bacterial lipopolysaccharides (LPS). Furthermore, some observational studies showed that the LDL-c concentration could decrease up to 30 % during an inflammatory state in sepsis. Low LDL-c concentration could also act as a predictor of sepsis severity (9). Lipids also played an important role in infection, including viral infection. Several types of the virus could use the lipid components as their receptor. *Flaviviridae*, such as HCV and Bovine Viral Diarrheal Virus (BVDV), were known for their involvement in affecting the LDL-c concentration by penetrating the host cells through the LDL receptor (LDL-R) (20). Interaction between low affinity-LDL-Rand HCV was required for an early virion attachment. Dengue virus

also disturbed and altered the patients' lipid profiles, including the total cholesterol (TC) and lipoprotein, especially LDL-c (9,20).

In SARS-CoV-2 infection, the patients' lipid profiles, including HDL-c, LDL-c, and TC, were lower than the healthy controls due to the disturbance in the lipid transfers process. ARDS in COVID-19 could also decrease the lipoprotein levels. While the role of HDL-c in its infection has been hypothesized in the acute phase through the involvement of SAA and SR-BI, the role of LDL-c was still poorly understood (9). The existing hypothesis was explained as follows: LDL-c will be oxidized into oxLDL, which increases the SARS-CoV-2 infection rate by activating the oxLDL-specific scavenger receptor called lectin-like oxLDL receptor (LOX-1). Then, LOX-1 stimulates the intracellular signaling process to produce pro-apoptotic, pro-oxidant, and pro-inflammatory states, resulting in cell dysfunction, atherosclerosis, and CVD. Of this process, the role of LOX-1 was crucial in causing complications in COVID-19 (11). As the consequences, the serum LDL-c levels could fall as shown by Hu et al. (2020), Wei et al. (2020), and G. Wang et al. (2020) in our study, which provided proof of significantly lower LDL-c levels in all COVID-19 patients regardless of the severity, compared to control. However, our study also showed that serum LDL-c levels were not significantly different between severe and non-severe COVID-19 patients in 5 (71.42 %) of the included studies. This contrast finding could be explained by the lower number of COVID-19 patients in each of those studies compared to each of the two other studies stating the opposing result. Finally, based on our study, although the latter role of LDL-c in SARS-CoV-2 infection seemed to be promising in affecting the disease severity, its actual role and mechanism still remained questionable and needed further investigation due to the lower number of evidence as compared to HDL-c (10,12,13).

There are few limitations in this systematic review. First, the majority of the included studies (85.71 %; n= 6) did not provide any odds ratios (ORs) of the analyzed outcomes and were just limited to the p-value. Second, the quantitative analysis was not conducted in this study due to the absence of the mean and standard deviation (SD) data of serum HDL-c and LDL-c levels in all of the included studies. Third, the authors' comprehensions are limited to the English language as stated in the exclusion criteria. Thus, we recommend future studies to evaluate the ORs, mean, and SD to provide future systematic review and meta-analysis in updating the roles of serum HDL-c and LDL-c levels as the potential predictor of the disease severity of COVID-19.

CONCLUSION

We found that low serum HDL-c levels are associated with severe COVID-19 cases, while serum LDL-c levels are not associated with COVID-19 severity. Therefore, serum HDL-c levels may serve as a better predictor of the COVID-19 severity than serum LDL-c levels. We also suggest future studies to further assess, establish, and strengthen the evidence of this potential marker of the disease severity in the COVID-19 era.

Conflict of Interest

All of the authors had no conflict of interest.

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