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Dyslipidemia is associated with severe coronavirus disease 2019 (COVID-19) infection

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ABSTRACT

Background and aims: The number of positive and death cases from coronavirus disease 2019 (COVID-19) is still increasing. The identification of risk factors for severe outcomes is important. Dyslipidemia has been shown as a long-known risk factor for cardiovascular disease. The aim of this study is to analyze the potential association between dyslipidemia and the severity of COVID-19 infection.
Methods: We systematically searched the PubMed database using specific keywords related to our aims until July 9th, 2020. All articles published on COVID-19 and dyslipidemia were retrieved. Statistical analysis was done using Review Manager 5.4 software.
Results: A total of 7 studies with a total of 6922 patients were included in our analysis. Our meta-analysis showed that dyslipidemia is associated with severe COVID-19 infections [RR 1.39 (95% CI 1.03–1.87), $p = 0.03$, $I^2 = 57\%$, random-effect modelling].
Conclusion: Dyslipidemia increases the risk of the development of severe outcomes from COVID-19 infections. Patients with dyslipidemia should be monitored closely to minimize the risk of COVID-19.

Coronavirus disease 2019 (COVID-19) is a pandemic disease that has been caused a significant burden in all aspects of life, especially health and economics. The number of positive and death cases is still increasing until now. In this meantime, identification of the factors that involve in the development of the severe disease is very important to enable stratification of risk, optimize the reallocation of hospital resources, and guide public health recommendations and interventions. Dyslipidemia has long been established as one of the risk factors for cardiovascular disease. A previous study by Saballs et al. [1] has also shown that one of the components in dyslipidemia, which is high-density lipoprotein (HDL) can predict the presence of respiratory disease and the clinical outcome of community-acquired pneumonia (CAP). However, the association between dyslipidemia and COVID-19 has not yet been established. This study aims to analyze the potential association between dyslipidemia and the severity of COVID-19 infection.

We conducted a systematic search of the literature on PubMed using the keywords “dyslipidemia” OR “hyperlipemia” OR “clinical characteristics” OR “comorbidities” OR “risk factors” AND “coronavirus disease 2019″ OR “COVID-19″, until the present time (July 9th, 2020) with language restricted to English only. The title, abstract, and full text of all articles identified that matched the search criteria were assessed, and those reporting the rate of dyslipidemia in COVID-19 patients with a clinically validated definition of “severe disease” were included in this meta-analysis. The references of all identified studies were also analyzed (forward and backward citation tracking) to identify other potentially eligible articles.

A meta-analysis was performed using Review Manager 5.4 (Cochrane Collaboration) software. Dichotomous variables were calculated using the Mantel-Haenszel formula with random-effects models. We used the I^2 statistic to assess the heterogeneity, value of <25%, 26–50%, and >50% considered as low, moderate, and high degrees of heterogeneity, respectively. The effect estimate was reported as risk ratio (RR) along with its 95% confidence intervals (CIs) for dichotomous variables, respectively. P-value was two-tailed, and the statistical significance set at ≤0.05.

A total of 950 records were obtained through systematic electronic searches and other ways. After screening titles, abstracts, and full texts, 7 studies [2–8] with a total of 6922 COVID-19 patients

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Table 1
Characteristics of included studies.

Study	Sample size	Design	Severe patients		Non-severe patients	
			n (%)	Age (years)	n (%)	Age (years)
Zhang J et al. [2] 2020	140	Retrospective cohort	58 (41.4%)	64 (25–87)	82 (58.6%)	51.5 (26–78)
To W et al. [3] 2020	23	Prospective cohort	10 (43.4%)	66 (39–75)	13 (56.6%)	56 (37–75)
Petrilli C et al. [4] 2020	5279	Prospective cohort	990 (36.2%)	69.5 (19–75)	1739 (63.8%)	59.5 (19–75)
Chang M et al. [5] 2020	211	Retrospective cohort	13 (6.1%)	54 (42–66)	198 (93.9%)	36 (22–50)
Zhang C et al. [6] 2020	1000	Prospective cohort	24 (30%)	64 (50–79)	56 (70%)	45 (30–60)
Simonnet A et al. [7] 2020	124	Retrospective cohort	85 (68.5%)	60 (51–69)	39 (31.5%)	60 (50–72)
Chen Q et al. [8] 2020	145	Retrospective cohort	43 (29.6%)	52 (37–68)	102 (70.4%)	45 (31–58)

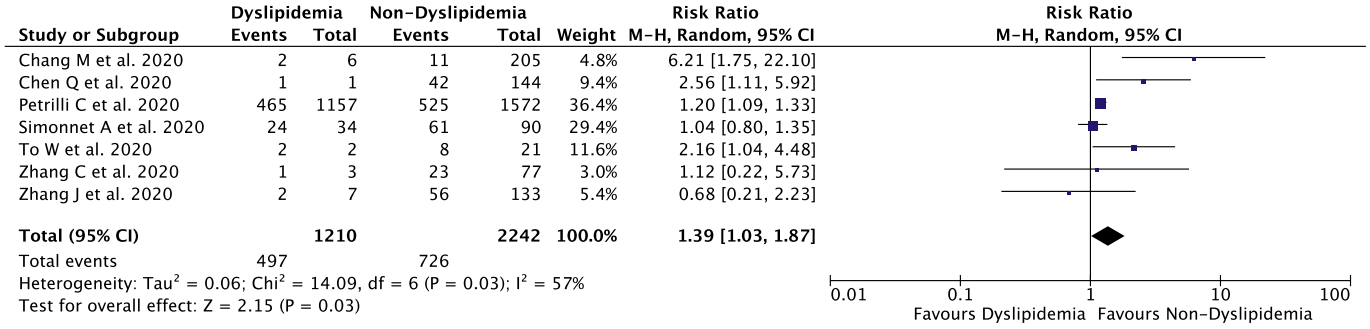

Fig. 1. Forest plot that demonstrates the association of dyslipidemia with severe COVID-19 disease.

were included in the meta-analysis. The essential characteristics of included studies are summarized in Table 1, whilst the individual and pooled RRs for dyslipidemia predicting severe COVID-19 is shown in Fig. 1. Our pooled analysis showed a significant association of dyslipidemia with severe COVID-19, with high heterogeneity [RR 1.39 (95% CI 1.03–1.87), $p = 0.03$, $I^2 = 57\%$, random-effect modelling].

Based on our meta-analysis of available data, dyslipidemia seems to be associated with an enhanced risk of severe COVID-19 infection. Several reasons can be proposed to explain this result. First, patients with dyslipidemia have high levels of low-density lipoprotein (LDL). This LDL can have interaction with macrophages in atherosclerotic plaques that lead to an increase in inflammatory gene expression. Human atherosclerotic plaques express increased levels of cytokines and chemokines that are dependent on MYD88-mediated signaling via various TLRs, especially TLR2, where one of its most important ligands are modified forms of LDL [9]. Moreover, LDL accumulation will give rise to cholesterol crystal formation in macrophages that lead to inflammasome activation. Inflammasome activation will then promote the secretion of the proinflammatory cytokines such as IL-1B and IL-18 [9]. In COVID-19 infections, the presence of high levels of proinflammatory cytokines is associated with severe outcomes via cytokine storm syndrome [10]. Second, besides having high levels of LDL, patients with dyslipidemia also have low levels of high-density lipoprotein (HDL). HDL itself is involved in the regulation of innate immune response. HDL through interaction with ABCA1 or ABCG1 negatively regulates T-cell activation and the expression of inflammatory mediators in macrophages and dendritic cells. Acute phase HDL is also associated with disease activity with a decreased number of small HDL particles is inversely associated with the disease activity score and C-reactive protein (CRP) levels [11]. Therefore, a low amount of HDL will contribute to the dysregulation of the innate immune response, which is the first-line defense mechanism of the body to fight infection, including COVID-19 infection [12]. Finally, in patients with dyslipidemia, the accumulation of LDL and triglycerides will cause endothelial dysfunction [13]. This endothelial dysfunction can be accentuated in COVID-19 infections because the receptor for SARS-CoV-2 which is ACE2 receptor, is also expressed in the endothelial cells [14]. The combination of these will lead to the development of cardiovascular complications that can cause a severe outcome of the patients. Patients with dyslipidemia should hence be advised to take extra precautions to minimize risk exposure to the virus. Physicians should also be engaged in close monitoring of dyslipidemia patients with suspected COVID-19, for timely detecting signs of disease progression. Finally, the presence of dyslipidemia shall be regarded as an important factor in future risk stratification models for COVID-19.

This study has several limitations. First, the presence of confounding factors such as age and nutritional status of patients that can affect the relationship between dyslipidemia and the severity of COVID-19 shall still be considered. Second, no study states the clear cut-off value for dyslipidemia diagnosis, however, we believed that all of these studies must have followed national and/or international guidelines for dyslipidemia diagnosis because these studies have undergone the peer-review process. We hope that this study can still give early insight into further risk stratification for COVID-19 infections.

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Declaration of competing interest

The authors declare no conflict of interest regarding this article.

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References

[1] Saballs M, Parra S, Sahun P, Pellejà J, Feliu M, Vasco C, et al. HDL-c levels predict the presence of pleural effusion and the clinical outcome of community-acquired pneumonia. SpringerPlus 2016;5(1):1491.

[2] Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, Akdis CA, Gao YD. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy 2020;75(7):1730–41.

[3] To KK, Tsang OT, Leung WS, Tam AR, Wu TC, Lung DC, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. Lancet Infect Dis 2020;20(5):565–74.

[4] Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ 2020;369:m1966.

[5] Chang MC, Park YK, Kim BO, Park D. Risk factors for disease progression in COVID-19 patients. BMC Infect Dis 2020;20(1):445.

[6] Zhang C, Qin L, Li K, Wang Q, Zhao Y, Xu B, et al. A novel scoring system for prediction of disease severity in COVID-19. Front Cell Infect Microbiol 2020;10:318.

[7] Simonnet A, Chetboun M, Poissy J, Raverdy V, Noulette J, Duhamel A, et al. LICORN and the lille COVID-19 and obesity study group. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. Obesity 2020;28(7):1195–9.

[8] Chen Q, Zheng Z, Zhang C, Zhang X, Wu H, Wang J, et al. Clinical characteristics of 145 patients with corona virus disease 2019 (COVID-19) in Taizhou, Zhejiang, China. Infection 2020:1–9.

[9] Tall AR, Yvan-Charvet L. Cholesterol, inflammation and innate immunity. Nat Rev Immunol 2015;15(2):104–16.

[10] Soy M, Keser G, Atagunduz P, Tabak F, Atagunduz I, Kayhan S. Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. Clin Rheumatol 2020;39:2085–94.

[11] Kaji H. High-density lipoproteins and the immune system. J Lipids 2013;2013:684903.

[12] McKechnie JL, Blish CA. The innate immune system: fighting on the front lines or fanning the flames of COVID-19? Cell Host Microbe 2020;27(6):863–9.

[13] Kim JA, Montagnani M, Chandrasekran S, Quon MJ. Role of lipotoxicity in endothelial dysfunction. Heart Fail Clin 2012;8(4):589–607.

[14] Froldi G, Dorigo P. Endothelial dysfunction in Coronavirus disease 2019 (COVID-19): gender and age influences. Med Hypotheses 2020;144:110015.