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Research Article

# Cardiopulmonary Metabolic Syndrome in Association with COVID-19: A Systematic Review and Meta-Analysis

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## Abstract

A comprehensive search was carried out in mainstream bibliographic databases or Medical Subject Headings, including ScienceDirect, PubMed, Scopus and ISI Web of Science. The search was applied to the articles that were published between January 1999 and July 2022. With strict literature search and screening processes, it yielded 30 articles from 91 articles of initial literature database.

Several previous studies hypothetically reported that the prevalence of diabetes mellitus, hypertension, and dyslipidemia, and obesity in persons older than 60 years were significantly rising. The effects of changes on the immune status and insulin secretion in patients with diabetes are still questionable, whereas several previous studies demonstrated trigger higher stress conditions of the effects of SARS-CoV-2 (COVID-19) contributing to hyperglycemia in patients with diabetes.

Despite the increased risk of adult respiratory distress syndrome (ARDS) and multi-organ dysfunction in early COVID-19 phase or in long COVID-19 phase after diabetes, diabetes alone is not related to an increased risk of respiratory infection, including COVID-19. Diabetes, diabetic traits, and diabetic blood proteins may have the most causal effect on the angiotensin-converting enzyme 2 (ACE 2) expression, particularly, in the lung, thus, diabetes can trigger the risk of COVID-19 infection and increase chance of worst outcome in the long COVID-19 phase and finally, COVID-19 patients with diabetes mellitus will have poor prognosis during long COVID-19 phase.

In conclusion, dyslipidemia, high serum levels of cholesterol, low serum levels of HDL, hypertension and obesity with high expression of ACE 2 in adipose tissue, an epidemic of the last century in conjunction with COVID-19 pandemic, particularly, in the over-60-year-old population are the cardiopulmonary metabolic or cardiometabolic events that could contribute to the COVID-19 disease worsening both in the early and long COVID-19 phases. Treatment type of cardiopulmonary metabolic or cardiometabolic diseases or disorders did not impact the COVID-19 status, but non-treatment of these diseases or disorders could importantly increase COVID-19 incidence. Monitoring of the cardiopulmonary metabolic or cardiometabolic risk factors is urgently needed.

***Keywords:*** *COVID-19; Cardiopulmonary; Cardiometabolic; Diabetes; Dyslipidemia; Human Health; Hypercholesterolemia; Hypertension; Impact; Metabolic; Obesity; Pulmonary; SARS-CoV-2; Statins*

## Abbreviations

ACE 2: Angiotensin-Converting Enzyme 2; ALI: Acute Lung Injury; ARDS: Acute Respiratory Distress Syndrome; BALF: Bronchoalveolar Fluid; BMI: Body-Mass Index; COPD: Chronic Obstructive Pulmonary Disease; CRP: C-Reactive Protein; CVD: Cardiovascular Disease; FEV1: Forced Expiratory Volume in 1 Second; FVC: Forced Vital Capacity; HD: Hemodynamics; HDL: High-Density Lipoprotein; HTN: Hypertension; ICS: Inhaled Corticosteroids; ICU: Intensive Care Unit; IL: Interleukin; IPF: Idiopathic Pulmonary Fibrosis; LDL: Low-Density Lipoprotein; LTB4: Leukotriene B4; NO: Nitric Oxide; PAP: Pulmonary Artery Pressure; PEF: Peak Expiratory Flow; PH: Pulmonary

Hypertension; TIA: Transient Ischemic Attack; TNF: Tumor Necrosis Factor; UK: United Kingdom; US: United States; VFD: Ventilator-Free Days

## Objectives of the Study

The objectives of this study are to identify the better understanding on the mechanisms of interaction between the cardiopulmonary metabolic or cardiometabolic or metabolic changes and SARS-CoV-2 (COVID-19), the scientific opinions change towards the cardiometabolic or metabolic changes-SARS-CoV-2 (COVID-19) associations over time (particularly after 3 months of acute COVID-19 illness phase, namely "long COVID-19" (post-acute COVID-19 illness period)) and place and the changing of the direction and shifting of certainty of research findings of cardiopulmonary metabolic or cardiometabolic or metabolic change-SARS-CoV-2 (COVID-19) studies change or statins treatment benefit in pulmonary diseases or disorders-possibly-related-long-COVID-19 phase.

## Introduction

Several previous studies hypothetically reported that the prevalence of diabetes mellitus, hypertension, and dyslipidemia, and obesity in persons older than 60 years were significantly rising [1]. The effects of changes on the immune status and insulin secretion in patients with diabetes are still questionable [2], whereas several previous studies demonstrated trigger higher stress conditions of the effects of SARS-CoV-2 (COVID-19) contributing to hyperglycemia in patients with diabetes [3]. Increasing serum levels of the high-density lipoprotein (HDL) can suppress the platelet over-activity and the coagulation cascade [4]. The association between hypertension (HTN) and SARS-CoV-2 (COVID-19) is still questionable and is independent from aging or not [5]. Obesity can induce mesenchymal dysfunction and exacerbating the COVID-19-related-cytokine-storm that promoting pulmonary fibrosis [6].

## Methods of the Study

### Search strategy and inclusion criteria

A comprehensive search was carried out in mainstream bibliographic databases or Medical Subject Headings, including ScienceDirect, PubMed, Scopus, and ISI Web of Science. The search was applied to the articles that were published between January 1999 and July 2022. Our first involved performing searches of article abstract/keywords/title using strings of [("COVID-19" or "SARS-CoV-2", "cardiopulmonary", "cardiovascular", "cardiometabolic", "metabolic", "pulmonary" or "lung", "renal" or "nephrological", "endocrinological", "diabetic"," brain", "spinal cord", "nervous system", "esophagogastric" or "gastroesophageal", "gastrointestinal", "musculoskeletal", "bony", and "cartilaginous", "hypertension", "hypertensive", "obese", "obesity", "cholesterol", "hypercholesterolemia", "statins"]. After a first approach of search, published articles focusing on cardiometabolic or metabolic diseases or disorders that related to SARS-CoV-2 or COVID-19 were retained and the information on COVID-19-related cardiometabolic or metabolic type of diseases or disorders was extracted for having a crude knowledge involving their themes. Another round of publication search was conducted for adding the missing published articles that were not identified by the first round.

All keywords combinations from one disease type and climatic variable to bind the population of cases under consideration. Search string for disease groups include ["SARS-CoV-2" or "COVID-19" or "cardiopulmonary" or "cardiovascular" or "cardiometabolic" or "metabolic" or "" or "pulmonary" or "lung" or "endocrinological" or "diabetic" or "renal" or "nephrological" or "nervous system" or "brain" or "spinal cord" or "esophagogastric" or "gastroesophageal" or "musculoskeletal" or "bony" or "cartilaginous" or "hypertension" or "hypertensive" or "obese" or "obesity" or "cholesterol" or "hypercholesterolemia" or "statins"]. The initial literature databases were further manually screened with the following rules: 1) non-SARS-CoV-2 (COVID-19)-related articles were excluded; 2) articles that did not report a human health related to SARS-CoV-2 (COVID-19) were not considered, such as commentary articles, or editorial; 3) non-peer

reviewed articles were not considered to be of a scholarly trustworthy validity; and 4) duplicated and non-English articles were removed. The articles were carefully selected to guarantee the literature quality, which is a trade-off for quantity.

With strict literature search and screening processes, it yielded 30 articles (Table 1 and 2) from 91 articles of initial literature database. Needed article information was extracted from each article by: 1) direct information including journal, title, authors, abstract, full text documents of candidate studies, publishing year; 2) place name of the study area; 3) study period; 4) research method used; 5) type of variables studied; 6) types of COVID-19-realetd cardiometabolic or metabolic diseases or disorders studied; and 7) the conclusions made about the impacts of COVID-19-related cardiometabolic or metabolic diseases or disorders on human health.

## Results

| Year of Publication | Author (s) | Type of the Study | Results of the Study | Reference |
|---|---|---|---|---|
| 2020 | Yang., *et al.* | Single-centered, retrospective, observational | Positive association between diabetes and COVID-19 | [7] |
| 2022 | Shah., *et al.* | Retrospective | Positive association between cardiometabolic diseases/disorders and COVID-19, particularly treatment for diabetes or insulin resistance decreased risk of COVID-19 incidence ($p$ = 0.0187) | [8] |
| 2020 | Guan., *et al.* | Retrospective | Positive association between hypertension and COVID-19 | [9] |
| 2020 | Zekavat., *et al.* | Prospective, population-based epidemiological | Positive association between hypertension and COVID-19 | [10] |
| 2020 | Hariyanto., *et al* | Meta-analysis | Positive association between dyslipidemia and COVID-19 | [11] |
| 2020 | Schmidt., *et al.* | Review | Positive association between hypercholesterolemia, dysregulation of the protective features of surfactant in pulmonary alveolar spaces, and COVID-19 | [12] |
| 2013<br>2015 | Gowdy., *et al.*<br>Tall., *et al.* | Review<br>Review | Positive association between hypercholesterolemia, pulmonary immune responses, and COVID-19 | [13]<br>[14] |
| 2005<br>2014<br>2012 | Park., *et al.*<br>Vieira-Potter., *et al.*<br>Yiu., *et al.* | Cross-sectional<br>Review<br>Prospective phase I clinical trial | Positive association between obese, excess adipose tissue, over-secretion of adipocytes and proinflammatory cytokines (such as C-reactive protein (CRP), interleukin (IL)-6, tumor necrosis factor (TNF)-**α, impaired immune response, cytokine storm, and COVID-19** | [15]<br>[16]<br>[17] |

***Table 1:*** *The results of the studies via the systematic review and meta-analysis.*

| Pulmonary Disease | Study Design | Outcome Associated with Statin Therapy | Reference |
|---|---|---|---|
| *Age-related lung function decline* | Observational study | ↓ decline in FEV1 and FVC | [18] |
| | Retrospective study of current/former smokers | ↓ decline in FEV1 and FVC | [19] |
| *COPD* | Retrospective cohort study | ↓ exacerbations, ↓ intubations | [20] |
| | Retrospective cohort, case control studies | ↓ COPD death | [21] |
| | Population-based analysis | ↓ COPD death | [22] |
| | Nested case control study | ↓ COPD hospitalization, ↓ death | [23] |
| | Retrospective cohort study | ↑survival after exacerbation | [24] |
| *Asthma* | Prospective, randomized, placebo-controlled, crossover trial | ↑ FEV1, ↓ sputum eosinophils and symptoms in patients discontinuing ICS | [25] |
| | Prospective, randomized, placebo-controlled, double-blind crossover trial | ↔ PEF, asthma control<br>↓ sputum macrophage, LTB4 | [26] |
| | Population-based study | ↓ hospitalization for asthma | [27] |
| | Prospective, randomized, placebo-controlled, double-blind trial | ↓ sputum eosinophil percentage in patients co-treated with ICS | [28] |
| | Prospective, randomized, placebo-controlled, double-blind crossover trial | ↔ exhaled NO, lung function, sputum eosinophils | [29] |
| | Retrospective cohort study | ↓ FEV1, ↑ medication requirement, ↑ symptoms compared with asthmatics not started on statins | [30] |
| | Prospective, randomized, placebo-controlled trial | ↔ PEF<br>↑ quality of life score | [31] |
| *ALI* | Retrospective cohort study | ↔ VFD, organ failures, mortality | [32] |
| | Prospective, randomized, placebo-controlled, double-blind trial | ↓ nonpulmonary organ dysfunction<br>↓ BALF interleukin-8<br>↔ ICU mortality | [33] |
| *IPF* | Retrospective cohort study | ↔ survival | [34] |
| *Pulmonary Hypertension* | Prospective observational study | ↑ exercise capacity/improved HD<br>↓ disease progression | [35] |
| | Prospective, randomized, placebo-controlled trial of COPD patients with PH | ↑ exercise capacity<br>↓ dyspnea score, ↓ PAP | [36] |

***Table 2:*** *The results of the studies via the systematic review and meta-analysis. Demonstrating the clinical outcomes of treatment of lung disease with statins that could be related to long-COVID-19 phase.*
*Abbreviations: ALI: Acute Lung Injury; BALF: Bronchoalveolar Fluid; COPD: Chronic Obstructive Pulmonary Disease; FEV1: Forced Expiratory Volume in 1 Second; FVC: Forced Vital Capacity; HD: Hemodynamics; ICS: Inhaled Corticosteroids; ICU: Intensive Care Unit; IPF: Idiopathic Pulmonary Fibrosis; LTB4: Leukotriene B4; NO: Nitric Oxide; PAP: Pulmonary Artery Pressure; PEF: Peak Expiratory Flow; PH: Pulmonary Hypertension VFD: Ventilator-Free Days.*
*(Source: Gowdy KM, Fessler MB. Emerging roles for cholesterol and lipoproteins in lung disease. Pulm Pharmacol Ther 2013; 26 (4): 430-437 [14]).*

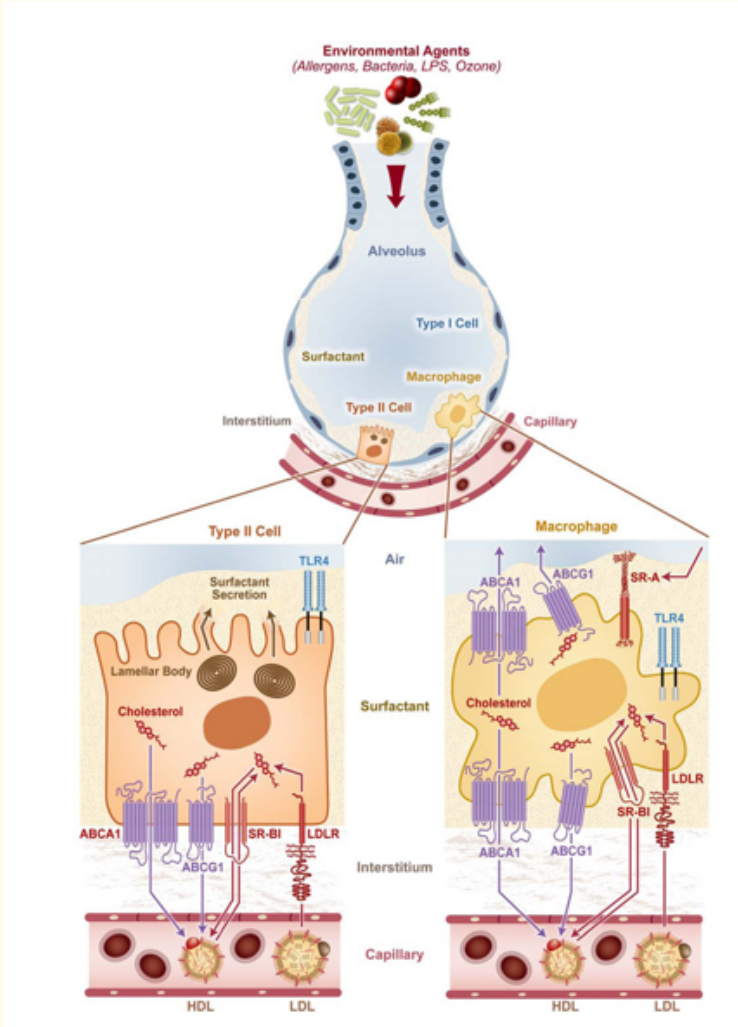


***Figure 1:*** *Demonstrating cholesterol trafficking influences multiple cell types in the lung.*

*Alveolar epithelial type II cells and alveolar macrophages likely receive cholesterol from circulating low density lipoprotein and high density lipoprotein (LDL, HDL) through the LDL receptor (LDLR) and scavenger receptor B type I (SR-BI), respectively. HDL is also the major source of the antioxidant vitamin E for type II cells. Class A scavenger receptors (SR-A) on macrophages play a role in clearance of oxidized alveolar lipids that may otherwise mediate cytotoxic and pro-inflammatory effects. The disposal pathway for cholesterol from type II cells and macrophages involves the cholesterol efflux transporters ATP Binding Cassette (ABC) A1 and ABCG1, and perhaps also SR-BI. ABCA1 also mediates basolateral surfactant efflux from type II cells; deletion of either ABCA1 or ABCG1 leads to severe surfactant proteinosis and lipidosis. Disordered cholesterol/phospholipid trafficking through the lung, such as with ABCG1 deletion, alters immune cell trafficking to the lung as well as the lung's immune responsiveness to a variety of environmental exposures, indicating that there is intimate crosstalk between lipid and immune homeostasis in the lung.*

*(Source: Gowdy KM, Fessler MB. Emerging roles for cholesterol and lipoproteins in lung disease. Pulm Pharmacol Ther 2013; 26 (4): 430-437. DOI: 10.1016/j.pupt.2012.06.002 [14]).*

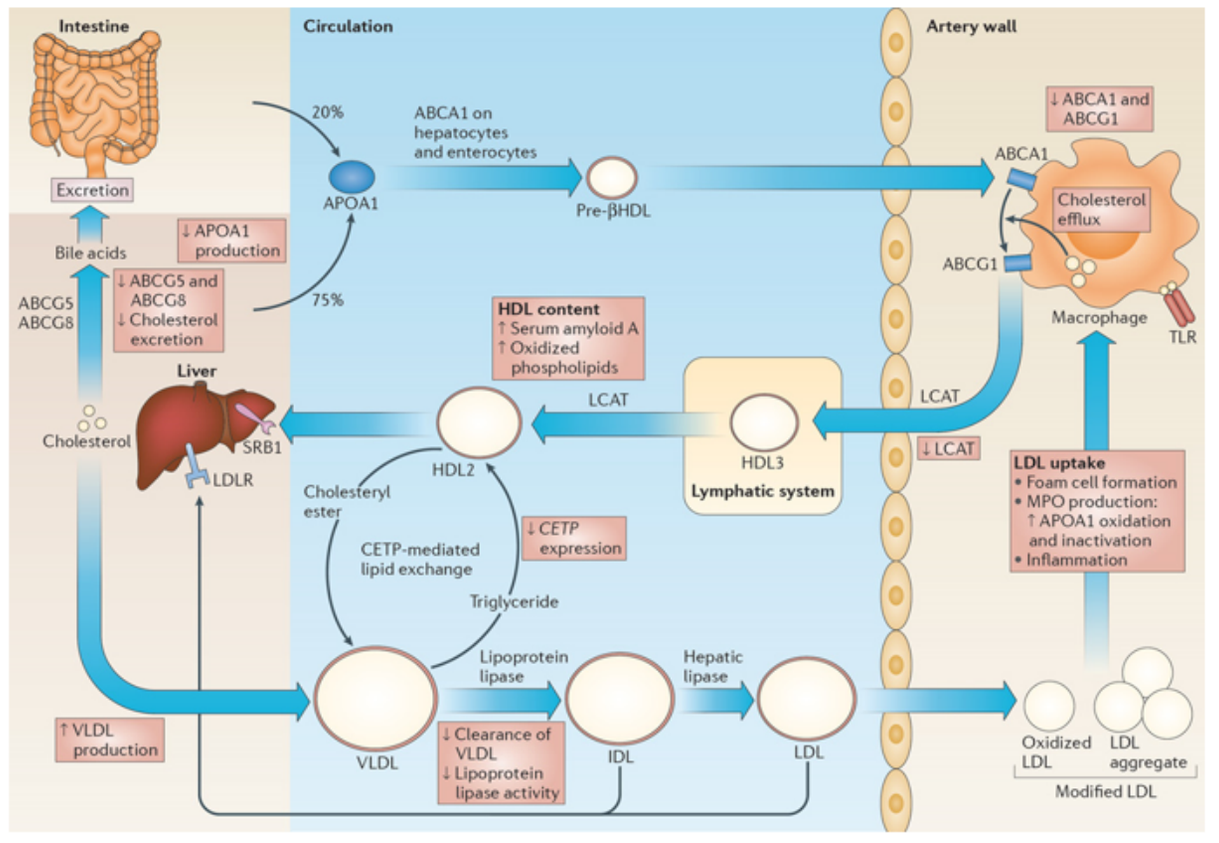


***Figure 2:*** *Demonstrating the RCT and its regulation by innate immune responses.*

*The process of reverse cholesterol transport (RCT) is depicted and how inflammation impairs this process is described in the red boxes. Under physiological conditions, apolipoprotein A1 (APOA1), which is the major protein component of high-density lipoprotein (HDL), is secreted by the liver and the intestines, and is assembled into a pre-βHDL particle as a result of its interaction with the ATP-binding cassette transporter ABC subfamily A member 1 (ABCA1) on hepatocytes and enterocytes. ABCA1 on macrophages promotes cholesterol and phospholipid efflux onto these relatively lipid-poor pre-βHDL particles, initiating the process of RCT. ABCG1 promotes further cholesterol efflux onto HDL particles. Free cholesterol in HDL is esterified by the enzyme lecithin–cholesterol acyltransferase (LCAT), which gives rise to cholesteryl esters. Free cholesterol or cholesteryl esters in HDL may be directly cleared in the liver via scavenger receptor B1 (SRB1), which mediates a process of selective free cholesterol or cholesteryl ester uptake in which the lipid moiety of HDL is mostly removed and the protein portion is recycled into the circulation (not shown). Cholesterol deposited in the liver by RCT can either be recycled in the form of secreted triglyceride-rich, very low-density lipoproteins (VLDLs; the main protein component of which is APOB) or can undergo net excretion into the bile via ABCG5 and ABCG8. In humans, plasma cholesteryl ester transfer protein (CETP) mediates the exchange of cholesteryl esters in HDL with triglyceride in VLDL. A lipolytic cascade mediated by lipoprotein lipase and hepatic lipase causes hydrolysis of triglycerides and results in the formation of cholesterol-rich and cholesteryl ester-rich LDL. Although most LDL is cleared in the liver, LDL may supply cholesterol to peripheral tissues and a small proportion is taken up into the arterial wall, where it is modified by oxidation or aggregation, leading to its uptake by macrophages. Modified LDL in the artery wall promotes Toll-like receptor (TLR) signalling in macrophages and it is taken up by these cells, leading to the formation of macrophage foam cells, the production of myeloperoxidase (MPO) and inflammation. IDL: Intermediate-Density Lipoprotein; LDLR: LDL Receptor.*

*(Source: Tall AR, Yvan-Charvet L. Cholesterol, inflammation and innate immunity. Nat Rev Immunol 2015; 15 (2): 104-116. DOI: 10.1038/nri3793 [15]).*

## Discussion

Results from the authors' systematic review and meta-analysis of 11 published articles (Table 1) [7-11] were all demonstrated positive association between the cardiopulmonary metabolic changes and COVID-19, particularly in the long-COVID-19 phase and demonstrated the benefits from statins therapy in various pulmonary diseases or disorders that could be related to long-COVID-19 phase, except exhaled nitric oxide (NO) levels, peak expiratory flow (PEF), organ failure, ventilator-free days (VFD), intensive-care-unit (ICU) mortality, and the patients' survival (Table 2) [18-36]. Different levels of dyslipidemia (elevated low-density lipoprotein levels, low levels of high-density lipoprotein, cholesterol levels (Figure 1 and 2) [14,15] are strong predictors of lung [14] and cardiovascular diseases (CVD) [37-39] progression that are related to the exacerbation of COPVID-19 via the suppression of the platelet over-activity and the coagulation cascade by the uses of antioxidants and the antithrombotic drugs [4] in the long COVID-19 phase.

Analysis of 107,310 HTN patients in the UK biobank data revealed that around 3% of them developed acute and chronic respiratory diseases, including pneumonia later [11]. Analysis of 1,099 confirmed COVID-19 patients demonstrated that approximately, 15% of the patients with HTN was the single highest risk factor of COVID-19 infection [40]. Approximately, 35.8% of the HTN patients in this study required treatment in the ICU, whereas around 23.7% of the patients had HTN as the most frequent co-morbidity [40].

Despite the increased risk of adult respiratory distress syndrome (ARDS) and multi-organ dysfunction in early COVID-19 phase or in long COVID-19 phase after diabetes, diabetes alone is not related to an increased risk of respiratory infection, including COVID-19 [41]. Diabetes, diabetic traits, and diabetic blood proteins may have the most causal effect on the angiotensin-converting enzyme 2 (ACE 2) expression, particularly, in the lung, thus, diabetes can trigger the risk of COVID-19 infection and increase chance of worst outcome in the long COVID-19 phase [42], and finally, COVID-19 patients with diabetes mellitus will have poor prognosis during long COVID-19 phase [43]. In the United States (US), approximately, three fourth of adults with age more than 20 years meet the criteria for the diagnosis of obese or overweight (body mass index (BMI) of at least 30 $kg/m^2$) [44,45]. Mainly, obesity interfere the physiological process and the functions of immune system that is related to the long COVID-19 phase [46].

Increased serum levels of troponin, a muscle and myocardium enzyme may be related to higher risk of embolic stroke of unknown origin or cardioembolic stroke [47], a cause of high rate of stroke or stroke-related fatalities in both early and long COVID-19 phases [48]. Due to its pro-inflammatory effect, a state of hypercoagulopathy could be induced by SARS-CoV-2 (COVID-19) infection that increases the risk of thromboembolic events, such as pulmonary embolism and transient ischemic attack (TIA) [49,50].

## Conclusion

Dyslipidemia, high serum levels of cholesterol, low serum levels of HDL, hypertension, and obesity with high expression of ACE 2 in adipose tissue, an epidemic of the last century in conjunction with COVID-19 pandemic, particularly, in the over-60-year-old population are the cardiopulmonary metabolic or cardiometabolic events that could contribute to the COVID-19 disease worsening both in the early and long COVID-19 phases. Treatment type of cardiopulmonary metabolic or cardiometabolic diseases or disorders did not impact the COVID-19 status, but non-treatment of these diseases or disorders could importantly increase COVID-19 incidence. Monitoring of the cardiopulmonary metabolic or cardiometabolic risk factors is urgently needed.

## Authors Contributions

Dr. Attapon Cheepsattayakorn conducted the study framework and wrote the manuscript. Associate Professor Dr. Ruangrong Cheepsattayakorn and Professor Dr. Porntep Siriwanarangsun contributed to scientific content and assistance in manuscript writing. All authors read and approved the final version of the manuscript.

## Competing Interests

The authors declare that they have no actual or potential competing financial interests.

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