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Biological Actions, Implications, and Cautions of Statins Therapy in COVID-19

Chengyu Liu[1], *Wanyao Yan*[2], *Jiajian Shi*[3], *Shun Wang*[1], *Anlin Peng*[4], *Yuchen Chen*[3]* *and Kun Huang*[3,5]

[1] Department of Transfusion Medicine, Wuhan Hospital of Traditional Chinese and Western Medicine, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, [2] Department of Pharmacy, Wuhan Fourth Hospital, Wuhan, China, [3] Tongji School of Pharmacy, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, [4] Wuhan Third Hospital, Tongren Hospital of Wuhan University, Wuhan, China, [5] Tongji-Rongcheng Center for Biomedicine, Huazhong University of Science and Technology, Wuhan, China

The Coronavirus Disease 2019 (COVID-19) showed worse prognosis and higher mortality in individuals with obesity. Dyslipidemia is a major link between obesity and COVID-19 severity. Statins as the most common lipid regulating drugs have shown favorable effects in various pathophysiological states. Importantly, accumulating observational studies have suggested that statin use is associated with reduced risk of progressing to severe illness and in-hospital death in COVID-19 patients. Possible explanations underlie these protective impacts include their abilities of reducing cholesterol, suppressing viral entry and replication, anti-inflammation and immunomodulatory effects, as well as anti-thrombosis and anti-oxidative properties. Despite these benefits, statin therapies have side effects that should be considered, such as elevated creatinine kinase, liver enzyme and serum glucose levels, which are already elevated in severe COVID-19. Concerns are also raised whether statins interfere with the efficacy of COVID-19 vaccines. Randomized controlled trials are being conducted worldwide to confirm the values of statin use for COVID-19 treatment. Generally, the results suggest no necessity to discontinue statin use, and no evidence suggesting interference between statins and COVID-19 vaccines. However, concomitant administration of statins and COVID-19 antiviral drug Paxlovid may increase statin exposure and the risk of adverse effects, because most statins are metabolized mainly through CYP3A4 which is potently inhibited by ritonavir, a major component of Paxlovid. Therefore, more clinical/preclinical studies are still warranted to understand the benefits, harms and mechanisms of statin use in the context of COVID-19.

Keywords: SARS-CoV-2, COVID-19, statins, obesity, dyslipidemia, inflammation, immune response, thrombosis

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***Correspondence:**
Yuchen Chen
chenyc93@hust.edu.cn

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INTRODUCTION

Obese individuals are more vulnerable to the SARS-CoV-2 caused Coronavirus Disease 2019 (COVID-19) (1–3). Obese people have ∼46% higher risk for SARS-CoV-2 positive, ∼74% increased odds for intense care unit (ICU) admission and ∼48% increased risk in deaths (4). Severe obesity [body mass index (BMI) ≥35] was significantly associated with the

need for invasive mechanical ventilation (IMV) (5), and was an independent predictor for intubation outcome (6). Moreover, with hyperlipidemia as a major link, obese individuals are prone to cardiovascular disease, hypertension, diabetes, myocardial infarction and stroke, which are among recognized risk factors for adverse COVID-19 outcomes (7–12) (**Figure 1**).

Prevalence of dyslipidemia was 18–39.7% as a comorbid condition in hospitalized COVID-19 patients (13–15). A population-based analysis on 61.4 million adult patients suggested that patients with hyperlipidemic state had 70% increased odds for catching COVID-19 (16). Moreover, COVID-19 patients may develop dyslipidemia that leads to life-threatening metabolic diseases and thrombotic complications (17–19), lipid-regulating agents are thus considered for possible therapeutic effects against COVID-19.

Statins are the most commonly used lipid-regulating drugs, 145.8 million people used statins in 2018 (20). Statins are HMG-CoA reductase inhibitors that can reduce serum total cholesterol, low-density lipoprotein cholesterol (LDL-C) and triglyceride levels, and have other pleiotropic effects such as modulating immune response and alleviating inflammation (21–23). Structurally, statins are classified as lipophilic (atorvastatin, lovastatin, simvastatin, and fluvastatin) and hydrophilic (pravastatin and pitavastatin), while rosuvastatin has an intermediate behavior (24). Statin prescription is majorly under consideration for primary preventions of cardiovascular disease, and other pathologies such as thrombosis (25, 26). Rational use of different types of statins are recommended according to LDL-C lowering need, pre-existing cardiovascular events or related risk factors including dyslipidemia, diabetes, hypertension, and age (25, 26).

Observational studies have suggested protective effects of statins in COVID-19 patients. Statin use was associated with a 55% decreased risk for IMV (27), 22–30% reduced risk of ICU admission (28), and 30–47% lower risk for death (28–33) (**Table 1**). Moreover, statin use prior to admission was associated with 71% reduction in the odds of developing severe COVID-19 (34) and 73% for death (31). High-intensity statin use reduced the risk of death by 49% in COVID-19 patients with coronary artery disease patients (32) (**Table 1**). Possible explanations for these benefits of statins include their recognized cholesterol-reducing, anti-inflammatory and immunomodulatory capacities (21, 23, 49), and also their anti-viral, anti-thrombosis and anti-oxidative abilities (50–53) (**Figure 1**). However, possible side effects of statin should be considered, such as elevated creatine kinase (CK) and serum glucose levels, which are already elevated in severe COVID-19 (19, 54–56). Currently, clinical trials are being conducted worldwide to confirm the safety and benefits of statin use for COVID-19 patients, with criteria including mortality, thrombosis formation, need for ECMO or IMV, viral load etc. (**Table 1**).

Different SARS-CoV-2 variants cause resurges of infections (57–60). Vaccines and antiviral therapies are powerful tools against COVID-19 (61, 62), yet data regarding the responses of obese individuals or statin users to these agents remain limited. It has been hypothesized that vaccines would offer reduced protection in obese individuals, based on evidence of immune cell dysregulation and alterations in inflammatory signaling pathways (4, 63). Given the immunomodulatory effects of statins, concerns have also been raised regarding possible interferences with COVID-19 vaccines. Moreover, cautions should be take that drug interactions between statins and some agents used in COVID-19 treatment, may lead to adverse effects (64–66).

Here, we provide a comprehensive update of the values, possible mechanisms, and noteworthy cautions regarding statin use in COVID-19. This review was conducted by consulting resources from peer-reviewed articles and/or official websites like WHO. Common search terms included "COVID-19 OR SARS-CoV-2" AND "statin OR lipid lowering", etc.

VALUES AND MECHANISMS OF STATINS IN COVID-19

As effective drugs for reducing cholesterol, statins can prevent cardiovascular events which are key risk factors for COVID-19 infection and poor prognosis (9, 67–69). Cholesterol reduction allows statins to affect cell membrane structure and function, particularly lipid rafts that play important roles in viral entry and cellular processes like signal transduction (70–72). Moreover, by

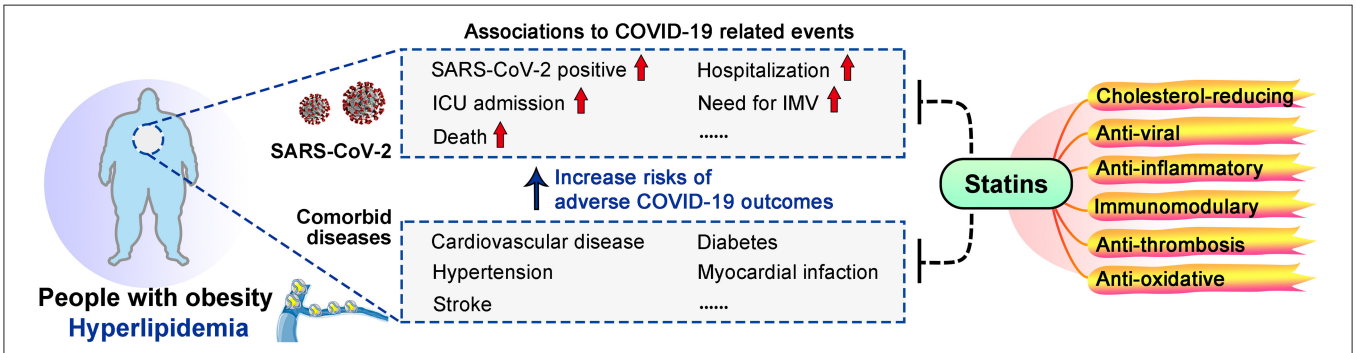

FIGURE 1 | Links between obesity, COVID-19 and statins. Obesity increased the risks of adverse COVID-19 outcomes, and dyslipidemia is a major link between obesity and COVID-19 severity. Statins may benefit COVID-19 patients, especially those with obesity and dyslipidemia, due to their multiple effects.

TABLE 1 | Associations between statins and COVID-19 outcomes, and clinical trials regarding statin use in COVID-19.

References	Type of study	Study cohort	Key findings
Associations between statins and COVID-19 outcomes			
Song et al. (27)	Retrospective study	249 adult patients hospitalized with COVID-19 in Rhode Island, USA	After adjusting for age, sex, race, cardiovascular disease, chronic pulmonary disease, diabetes, and obesity, statin use was significantly associated with decreased risk for IMV [aOR = 0.45, (95% CI: 0.20–0.99)].
Vahedian-Azimi et al. (28)	Meta-analysis	32,715 patients in 24 studies	Statin use is associated with significant reductions in ICU admission (OR = 0.78, 95% CI: 0.58–1.06; $n = 10$; $I^2 = 58.5\%$) and death (OR = 0.70, 95% CI: 0.55–0.88; $n = 21$; $I^2 = 82.5\%$) outcomes, with no significant effect on tracheal intubation (OR = 0.79; 95% CI: 0.57–1.11; $n = 7$; $I^2 = 89.0\%$). Death was reduced further by in-hospital application of stains (OR = 0.40, 95% CI: 0.22–0.73, $n = 3$; $I^2 = 82.5\%$), compared with pre-hospital use (OR = 0.77, 95% CI: 0.60–0.98, $n = 18$; $I^2 = 81.8\%$).
Zhang et al. (29)	Retrospective study	13,981 cases of confirmed COVID-19 admitted in 21 hospitals from Hubei Province, China	The risk for 28-day all-cause mortality was 5.2 and 9.4% in the matched statin and non-statin groups, respectively, with an adjusted HR of 0.58; the use of statins in hospitalized subjects with COVID-19 was associated with a lower risk of all-cause mortality and a favorable recovery profile.
Lee et al. (30)	Nested case-control study	10,448 COVID-19 patients who were hospitalized in Korea	Statins were prescribed in 533 (5.1%) patients. After adjusting for age, sex, and comorbidities, Cox regression showed a significant decrease in hazard ratio associated with the use of statins [aHR, 0.637 (95% CI, 0.425–0.953); $P = 0.0283$]. Statin use is correlated with lower mortality in COVID-19 patients.
Memel et al. (31)	Cohort study	1,179 patients, 676 (57%) were male, 443 (37%) were >65 years old, and 493 (46%) had a BMI ≥30	Inpatient statin use reduced the hazard of death (HR, 0.566; $P = 0.008$). This association held among patients who did and those did not use statins before hospitalization [HR, 0.270 ($P = 0.003$) and 0.493 ($P = 0.04$), respectively]. Statin use was associated with improved time to death for patients aged >65 years but not for those ≤65 years old. Statin use during hospitalization for SARS-CoV-2 infection was associated with reduced 28-day mortality rates.
Choi et al. (32)	Retrospective study	5,375 COVID-19 patients admitted to Mount Sinai Health System hospitals in New York	Compared to non-statin users, both low-to-moderate-intensity (aHR 0.62, 95% CI 0.51–0.76) and high-intensity statin users (aHR 0.53, 95% CI 0.43–0.65) had a reduced risk of death. Subgroup analysis of 723 coronary artery disease patients showed decreased mortality among high-intensity statin users compared to non-users (aHR 0.51, 95% CI 0.36–0.71). Statin use in patients hospitalized with COVID-19 was associated with a reduced in-hospital mortality. The protective effect of statin was greater in those with coronary artery disease.
Rodriguez-Nava et al. (33)	Retrospective cohort study	87 adult patients with COVID-19 admitted to community hospital ICU in Evanston, IL, USA	In the multivariable Cox proportional hazards regression model, atorvastatin non-users had a 73% chance of faster progression to death compared with atorvastatin users (when probability = HR/HR + 1).
Daniels et al. (34)	Retrospective single-center study	170 hospitalized patients with COVID-19 and 5,281 COVID-negative subjects at University of California San Diego Health	Statin use prior to admission was associated with reduced risk of severe COVID-19 (aOR 0.29, 95% CI 0.11–0.71, $P < 0.01$) and faster time to recovery among those without severe disease (aHR for recovery 2.69, 95% CI 1.36–5.33, $P < 0.01$). The association between statin use and severe disease was smaller in the COVID-negative cohort (P for interaction = 0.07).
Rossi et al. (35)	Follow-up study	71 consecutive patients with a pre-existing chronic cardiovascular disease, who become ill from COVID-19	Among 42 statin users, 16/42 (38.1%) took a hydrophilic statin (rosuvastatin in 14 patients and pravastatin in 2), while 26/42 (61.9%) a lipophilic statin (atorvastatin in 22 patients, and simvastatin in 4). The group of lipophilic statins demonstrated a significant reduction in mortality respect both patients who do not take statins, and patients who assumed hydrophilic statins.
Saeed et al. (36)	Observational study	4,252 patients (65 ± 16 years old; 47% female) were admitted with COVID-19, 37% ($n = 1,570$) were Hispanic	Patients with diabetes mellitus on a statin ($n = 983$) reduced cumulative in-hospital mortality (24 vs. 39%; $P < 0.01$) than those not on a statin ($n = 1,283$). Statin use in people with diabetes was associated with a reduced risk of in-hospital mortality during COVID-19. No difference in hospital mortality was noted in patients without diabetes mellitus on or off statin (20 vs. 21%; $P = 0.82$).

(Continued)

TABLE 1 | Continued

References	Type of study	Study cohort	Key findings
De Spiegeleer et al. (37)	Retrospective study	154 COVID-19 diagnosed residents aged 86 ± 7 years in 2 Belgian nursing homes	Statin intake is associated with the absence of symptoms during COVID-19 (OR 2.91; 95% CI 1.27–6.71), which remained statistically significant after adjusting for covariates (aOR 2.65; 95% CI 1.13–6.68). In conclusion, statin intake in older, frail adults could be associated with a considerable beneficial effect on COVID-19 clinical symptoms.
Lala et al. (38)	Retrospective study	2,736 patients with COVID-19 admitted to 1 of 5 Mount Sinai Health System hospitals in New York City	Statins have a protective effect and were associated with improved survival (HR 0.57, 95% CI 0.47–0.69).
Gupta et al. (39)	Retrospective study	2,626 patients admitted with COVID-19, of whom 951 (36.2%) were antecedent statin users.	Among 1,296 patients (648 statin users, 648 non-statin users) identified with 1:1 propensity-score matching, statin use is significantly associated with lower odds of in-hospital mortality within 30 days in the propensity-matched cohort (OR 0.47, 95% CI 0.36–0.62, $P < 0.001$).
Byttebier et al. (40)	Retrospective observational case-control study	959 COVID-19 patients admitted consecutively to four Belgian hospitals	Treatment with statins and ACEIs/ARBs reduced 28-day mortality in hospitalized COVID-19 patients. Moreover, combination treatment with these drugs resulted in a 3-fold reduction in the odds of hospital mortality (OR = 0.33; 95% CI 0.17–0.69). In-hospital treatment with statins, ACEIs/ARBs, and especially their combination saves lives.
Ayeh et al. (41)	Retrospective study	4,447 patients hospitalized at the Johns Hopkins Hospital and affiliated hospitals with COVID-19, 594 (13.4%) were exposed to statins on admission.	The average treatment effect of statin use on COVID-19-related mortality was RR = 1.00 (95% CI: 0.99–1.01, $P = 0.928$), while its effect on severe COVID-19 infection was RR = 1.18 (95% CI: 1.11–1.27, $P < 0.001$).
			Statin use was not associated with altered mortality, but with an 18% increased risk of severe COVID-19 infection.
Kollias et al. (42)	Meta-analysis	41,807 patients, 14% with statin use	Statin therapy was associated with an about 35% decrease in the adjusted risk of mortality in hospitalized COVID-19 patients.
Lee et al. (43)	Two independent population-based nationwide cohort studies	214,207 patients older than 20 years who underwent tests for SARS-CoV-2 infection in South Korea	Statin users were associated with a decreased likelihood of severe clinical outcomes [statin users, 3.98% (32/804); non-users, 5.40% (85/1,573); aRR 0.62; 95% CI 0.41–0.91] and length of hospital stay (statin users, 23.8 days; non-users, 26.3 days; adjusted mean difference −2.87; 95% CI −5.68 to −0.93) than non-users.
			Prior statin use is related to a decreased risk of worsening clinical outcomes of COVID-19 and length of hospital stay but not to that of SARS-CoV-2 infection.
Kow et al. (44)	Meta-analysis	8,990 COVID-19 patients in 4 studies	The pooled analysis revealed a significantly reduced hazard for fatal or severe disease with the use of statins (Pooled HR = 0.70; 95% CI 0.53–0.94) compared to non-use of statins in COVID-19 patients.
Tan et al. (45)	Retrospective study	717 patients admitted to a tertiary center in Singapore for COVID-19 infection.	156 (21.8%) patients had dyslipidaemia and 97% of these were on statins. Logistic treatment models showed a lower chance of ICU admission for statin users when compared to non-statin users (Average treatment effect on statin (ATET): Coeff (risk difference): −0.12 (−0.23, −0.01); $P = 0.028$). Statin use was independently associated with lower ICU admission.

Study Title	Status	Locations	Summary	Key results
COVID-19 related clinical trials of statins				
Intermediate-dose vs. standard prophylactic anticoagulation and statin vs. placebo in ICU patients with COVID-19 (NCT04486508)	Completed	Masih Daneshvari Hospital, Tehran, Iran, Islamic Republic of Iran	This study investigates the safety and efficacy of two pharmacological regimens on outcomes of critically-ill patients (Actual Enrollment: 600 participants) with COVID-19 using a 2 × 2 factorial design.	In adults with COVID-19 admitted to the ICU, atorvastatin was not associated with a significant reduction in the composite of venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or all-cause mortality compared with placebo. The treatment was safe (46)

(Continued)

TABLE 1 | Continued

Study Title	Status	Locations	Summary	Key results
Effectiveness and safety of medical treatment for SARS-CoV-2 (COVID-19) in Colombia (NCT04359095)	Completed	6 hospitals in Colombia including Clinica santa Maria del lago, Clínica Reina Sofía, Fundacion Cardio Infantil, etc.	The study assesses the effectiveness and safety of rosuvastatin plus colchicine, emtricitabine/tenofovir, and their combined use in these patients. Six hundred and forty-nine patients agreed to participate and were enrolled in this study; among them, 633 (97.5%) were included in the analysis. The primary endpoint was 28-day all-cause mortality.	The combined use of emtricitabine with tenofovir disoproxil plus colchicine and rosuvastatin reduces the risk of 28-day mortality and the need for IMV in hospitalized patients with COVID-19 (47).
The impact of statin therapy in the COVID-19 patients (NCT05238402)	Completed	Deniz Demirci Antalya, Turkey	The study is retrospective single-center review of covid-19 patients (actual Enrollment: 707 participants). The study population was divided into patients who received a statin vs. those who did not receive a statin before the hospitalization. The primary outcome was in-hospital mortality during the follow-up period.	No results posted
Statin therapy and COVID-19 infection (NCT04407273)	Completed	Facultat de Medicina i Ciències de la Salut de Reus, Reus, Tarragona, Spain	This is a retrospective observational multicenter study. The SARS-CoV-2 severity of 2,159 COVID-19-infected patients with statin therapy was classified into 9 grades. Primary outcome is the WHO SARS-CoV-2 scale of severity (9 grades) achieved by COVID-19 patients, admitted in the hospital, with and without background statin therapy comparable in age and gender distribution.	No results posted
Randomized, embedded, multifactorial adaptive platform trial for community-acquired pneumonia (NCT02735707)	Recruiting	322 hospitals worldwide	The purpose of this study is to evaluate the effect of about 50 interventions, including statin use, to improve outcome of patients admitted to ICU with community-acquired pneumonia including COVID-19.	No results posted
Colchicine/statins for the prevention of COVID-19 complications (COLSTAT) trial (NCT04472611)	Recruiting	4 hospitals in United States including Bridgeport Hospital, Greenwich Hospital, Yale New Haven Hosptial System, Lawrence and Memorial Hospital	This is a randomized open-label study of the safety and efficacy of the combination of colchicine and Rosuvastatin in addition to standard of care (SOC) compared to SOC alone in hospitalized patients with SARS-CoV-2 (Estimated Enrollment: 466 participants). The primary endpoint is the 30-day composite of progression to severe COVID-19 disease.	No results posted
Managing endothelial dysfunction in critically ill COVID-19 patients at LAUMCRH (NCT04813471)	Recruiting	LAUMCRH Beirut, Lebanon	The study seeks to target endothelial dysfunction in critically ill patients with COVID-19 by giving them an endothelial protocol (L-arginine, Folic Acid, Statin, Nicorandil, Vitamin B complex) and monitor clinical outcome in those patients.	No results posted
Atorvastatin as adjunctive therapy in COVID-19 (NCT04380402)	Recruiting	Mount Auburn Hospital Cambridge, Massachusetts, United States	This study assesses whether adjunctive therapy of COVID-19 with atorvastatin reduces the deterioration in hospitalized patients and improves clinical outcome.	No results posted

(Continued)

TABLE 1 | Continued

Study Title	Status	Locations	Summary	Key results
Helping alleviate the longer-term consequences of COVID-19 (HEAL-COVID) (NCT04801940)	Recruiting	Addenbrookes Hospital, Cambridge, United Kingdom	HEAL-COVID aims to evaluate the impact of treatments on longer-term morbidity, mortality, re-hospitalization, symptom burden and quality of life associated with COVID-19. The first two treatment arms are Apixaban and Atorvastatin.	No results posted
Combination therapies to reduce carriage of SARS-CoV-2 and improve outcome of COVID-19 in ivory coast: a phase randomized IIb trial (NCT04466241)	Recruiting	2 hospitals in Côte D'Ivoire including Service des Maladies Infectieuses et Tropicales, Centre Hospitalier et Universitaire (CHU) and Treichville Abidjan, Côte D'Ivoire Center de Traitement des Maladies Infectieuses (CTMI)	This study proposes to study whether the combination of two drugs (These drugs include the LPV/r already in use in Côte d'Ivoire as well as an antihypertensive drug—telmisartan, and atorvastatin) is more effective than taking a single drug on reducing the viral load in the respiratory tract but also on reducing inflammation.	No results posted
Statin treatment for COVID-19 to optimize neurological recovery (NCT04904536)	Not yet recruiting	The George Institute for Global Health Sydney, New South Wales, Australia	This trial was designed to study whether atorvastatin treatment (40 mg/day) over 18 months can improve neurocognitive function in adults with long COVID neurological symptoms.	No results posted
A study of anticoagulation treatment patterns and outcomes of participants hospitalized with coronavirus disease 2019 (COVID-19) in Japan (NCT04828772)	Active, not recruiting	Medical Data Vision, Tokyo, Japan	This study plans to assess the benefits and harms of anticoagulants (including statins) vs. active comparator, placebo or no intervention in people hospitalized with COVID-19.	Compared with no treatment, anticoagulants may reduce all-cause mortality but the evidence comes from non-randomized studies and is very uncertain (48).
Managing endothelial dysfunction in COVID-19: a randomized controlled trial at LAUMC (NCT04631536)	Active, not recruiting	LAUMCRH Beirut, Lebanon	This trial will examine the potential therapeutic effect of a regiment composed of several medications including atorvastatin as adjunct to mainstream management, to further knowledge in treating COVID-19.	No results posted
Atorvastatin for reduction of 28-day mortality in COVID-19: RCT (NCT04952350)	Active, not recruiting	Mansoura University Hospitals Mansoura, Aldakahlia, Egypt	This randomized placebo-controlled double-blinded clinical trial aims to test the efficacy of administering atorvastatin 40 mg to hospitalized COVID-19 patients for 28 days on the all-cause 28-day mortality.	No results posted
Study of ruxolitinib plus simvastatin in the prevention and treatment of respiratory failure of COVID-19 (NCT04348695)	Unknown	Hospital Universitario Madrid Sanchinarro, Madrid, Spain	This project examines whether the combined use of ruxolitinib with simvastatin show a synergistic effect in the inhibition of viral entry and in the anti-inflammatory effect.	No results posted
Preventing cardiac complication of COVID-19 disease with early acute coronary syndrome therapy: a randomized controlled trial (NCT04333407)	Unknown	Charing Cross Hospital, London, United Kingdom	The trial plans to assess all-cause mortality 30 days after admission in COVID-19 patients (Estimated Enrollment: 3,170 participants) treated with different cardioprotective drugs, including Aspirin 75 mg, Clopidogrel 75 mg, Rivaroxaban 2.5 MG, Atorvastatin 40 mg, Omeprazole 20 mg.	No results posted
Coronavirus response—active support for hospitalized COVID-19 patients (NCT04343001)	Withdrawn	University College Hospital Ibadan, Oyo, Nigeria, and Shifa Tameer-e-Millat University, Rawalpindi, Pakistan	This project aims to evaluate the effect of aspirin (150 mg once daily), losartan (100 mg once daily), and simvastatin (80 mg once daily) in patients with COVID-19 infection.	No results posted

Data was acquired as of April 16, 2022. aHR, adjusted hazard ratio (HR); aOR, adjusted odds ratio (OR); BMI, body mass index; CI, confidence interval; ICU, intense care unit; IMV, invasive mechanical ventilation; I^2, I-squared statistics indicating between-study heterogeneity; RR, risk ratio.

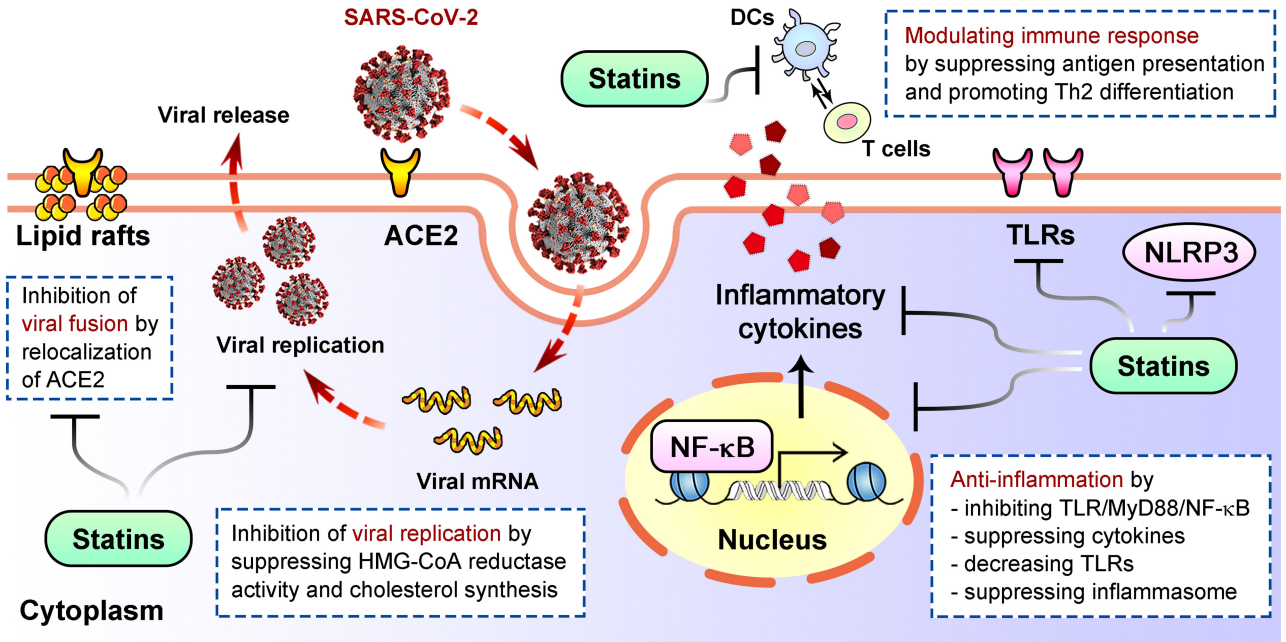

FIGURE 2 | Well established mechanisms of how statins inhibit viral life cycle, alleviate inflammation and modulate immune response after infection. DCs, dendritic cells; TLRs, Toll-like receptors.

reducing intermediate products of cholesterol biosynthesis, statins downregulate protein isoprenylation to regulate numerous signaling pathways including immune responses (73). Hyperactivation of immune responses, elevated systematic inflammation, increased oxidative stress, and thrombosis events have been observed in severe COVID-19, especially among those with obesity or cardiovascular diseases, while statins have shown suppressive effects against these processes (**Figure 1**).

Antiviral Effects

SARS-CoV-2 infection initiates from cell entry by attaching to its receptor ACE2 (70, 71). The cholesterol-rich membrane lipid rafts is crucial for this process. By reducing cholesterol, disrupting lipid raft composition, altering membrane receptor assembly and localization, statins interfere with virus fusion and entry in HIV models (51, 74). Potential mechanism is that statins-mediated blockade of HMG-CoA reductase leads to inhibition of Rho guanosine triphosphatase, a key contributor to clustering of lipid raft-associated receptors (74, 75). Statins may increase ACE2 levels under disease situations with unknown clinical relevance (76), and simvastatin significantly affected SARS-CoV-2 cell entry through displacing ACE2 on lipid rafts (77) (**Figure 2**). Simvastatin can also reduce SARS-CoV-2 replication (77). Viral infection increases HMG-CoA reductase activity and cholesterol synthesis to assist viral replication, which explains the negative impact of statins on viral replication (78, 79) (**Figure 2**). Viral assembly and release following replication can be suppressed by statins through inhibiting mevalonate synthesis and intracellular cholesterol levels (80, 81). Whether statins similarly affect the assembly and release of SARS-CoV-2 remain unknown.

Although multiple statins have showed antiviral effects against different viruses, a study suggested higher efficacy for lipophilic statins against Zika viral replication, possibly because they can enter cells *via* passive transport to reach higher intracellular concentrations (82). Moreover, comparison between the survival curves of patients with a pre-existing chronic cardiovascular disease indicated a significant reduction in mortality in lipophilic statin users vs. hydrophilic group and non-users group (35). Therefore, it will be critical to understand whether and how the type, dose and duration of statin therapy affect antiviral effects and subsequently the outcome of SARS-CoV-2 infection.

Anti-inflammatory and Immunomodulatory Effects

Exacerbated inflammation is a pathological hallmark of COVID-19 (83). During severe COVID-19, a generalized inflammatory state is caused by cytokine storm due to hyperactivation of host immune system, leading to lesions in multiple organs and even death (84). Upon SARS-CoV-2 invasion, antigen-presenting cells recognize the pathogen *via* Toll-like receptors (TLRs) and activates two main downstream pathways, MyD88- and TRIF-dependent pathways, both leading to NF-κB activation (85–88). NF-κB initiates the first stage of inflammasome activation and induces the production of pro-inflammatory factors, including interleukin-6 (IL-6), a key cytokine associated with COVID-19 severity and mortality (89–91). Activation of NLRP3 inflammasome involves in response to infection of

RNA viruses including SARS-CoV-2 (92–95). Patients with a reduced immune fitness and pre-existing systemic inflammatory state, such as obesity or cardiovascular diseases, are prone to demonstrate dysregulated NLRP3 inflammasome activity and pro-inflammatory cytokines expression, resulting in severe COVID-19 (92, 96, 97).

Statins are known for anti-inflammatory and immunomodulatory effects (**Figure 2**). Statins can decrease TLRs expression, suppress MYD88-NF-κB pathway and the levels of pro-inflammatory cytokines like IL-6, IL-8, TNF-α and MCP-1, thereby altering inflammatory pathway to reduce cell damage (21, 98–100). Statins directly regulate NLRP3 inflammasome (101), or suppress TLR4-MyD88-NF-κB pathway to inhibit its activation (102), thus downregulate cytokines including IL-18 and IL-1β (103, 104). Immunomodulatory actions also underlie statins' beneficial effects in pathologic status. For examples, statins block mevalonate generation required for T cell proliferation (105), repress MHC-II molecules that are critical for presenting antigen to T cells (23, 106), and suppress maturation of dendritic cells (107), therefore may alleviate hyperactivation of immune response. Rosuvastatin promotes the differentiation of peripheral blood monocytes into anti-inflammatory M2 macrophages (49, 108); atorvastatin suppresses proliferation of naïve Th0 cells and secretion of Th1 pro-inflammatory cytokines, while enhances secretion of Th2 anti-inflammatory cytokines (109).

Clinical studies indicate that statins decrease serum CRP levels (110), an inflammatory biomarker and risk factor for adverse COVID-19 outcomes (111). Importantly, in-hospital statin use is significantly associated with ameliorated inflammatory responses, as reflected by lower levels of circulating CRP, IL-6 and neutrophil counts in statin users (29). Correspondingly, simvastatin downregulated SARS-CoV-2-infection-triggered inflammation in human neutrophils, peripheral blood monocytes, and lung epithelial Calu-3 cells, showing its anti-inflammatory effect both at the site of viral infection and systemically (77). Statin-mediated CRP reduction can be achieved by lowering LDL-C, suppressing Rac-1 activation and increasing apolipoprotein A-I, all of which alleviate inflammation and subsequent CRP generation (112). Notably, for PCSK9 inhibitors, another class of lipid-lowering drugs that significantly decreases LDL-C but not inflammatory markers like CRP (113, 114), evidence is lacked so far regarding their possible benefits on COVID-19 outcomes, while deeper investigation is needed. Since COVID-19 patients with obesity are prone to immune cell dysregulation and elevated inflammations, further studies are warranted to explore whether and how statins may protect them from COVID-19.

Anti-thrombosis Effects

Thrombosis are among the most frequent complications in COVID-19 patients, especially in critically ill cases (115–117), and elevated D-dimer levels show prognostic significance for poor outcomes (7, 116, 118). Therefore, prevention/alleviation of thrombosis is a key to COVID-19 treatment, especially for obese patients who are prone to ICU admission and thromboembolic events.

Statins can reduce the occurrence of deep vein thrombosis and pulmonary embolism (52, 119–122), common thrombotic events in COVID-19 cases (123, 124). The anti-thrombosis impact of statins not only relates to its cholesterol-lowering effects and to plaque stabilization (125), but also involves lipid-lowering independent inhibitory effect on platelets activation and coagulation cascade, major pathways for thrombosis formation (18, 52, 126). Statins exert antiplatelet effect *via* downregulating prothrombotic factors including platelet thromboxane A2, NOX2 (the catalytic subunit of NADPH oxidase), oxidized low-density lipoprotein (oxLDL) and its receptor CD36 (127–129), and *via* promoting endothelial nitric oxide synthase (eNOS) which improves production of platelet nitric oxide (NO), a potent inhibitor of platelet activation and aggregation (130, 131).

Statins also interfere with clotting system and coagulation cascade. Statins downregulate the expression and activity of tissue factor which initiates the extrinsic pathway of coagulation (132–136), and reduce the serum level of plasminogen activator inhibitor (137); meanwhile, statins upregulate KLF2 that has anticoagulant and atheroprotective effects (138, 139), promote thrombomodulin expression and fibrinolytic activity (140–143). Since a mutual relationship exists between immune activation and thrombus formation (144), the anti-inflammatory actions of statins may also contribute to thrombosis suppression (18).

The anti-thrombosis effect of statins has been widely investigated in patients at risk for cardiovascular disease or those with established atherosclerosis, and varies from different statins (145, 146), but their impacts on COVID-19-related thrombosis remain largely unknown. A clinical trial in ICU admitted COVID-19 patients observed lower rate of thrombosis event in atorvastatin group, although without significant association, suggesting possible anti-thrombosis role of atorvastatin in COVID-19 cases; assessment of outcomes after long-time follow-up is ongoing (46).

Anti-oxidative Effects

Excessive reactive oxygen species (ROS) is associated with high neutrophil to lymphocyte ratio in critically ill COVID-19 (147). In monocytes and macrophages, SARS-CoV-2 infection triggers mitochondrial ROS production, induces HIF1α stabilization and consequently promotes glycolysis which facilitates viral replication (148). Overwhelming oxidative stress also causes local or systemic damages, induces thrombosis, contributing to COVID-19 severity (149).

Statins exerts anti-oxidative effect by attenuating NF-κB activation, reducing circulating oxLDL and their uptake by macrophages, inhibiting oxidant enzymes such as NADPH oxidase and myeloperoxidase, and upregulating the activity of antioxidant enzymes like catalase and paraoxonase (53, 150). Additionally, statins downregulate NOX2-derived oxidative stress, ultimately exerting antiplatelet effects (128, 151–153). Despite these anti-oxidative effects which possibly benefits COVID-19 treatment, statins may induce ROS production, mediate redox imbalance and consequent cellular oxidative damage, especially under excessive or long-term statin use (154).

CLINICAL TRIALS REGARDING STATIN USE AND COVID-19

Currently, among clinical trials regarding statin use and COVID-19, two have published results, while the others remain uncompleted or have not posted results (**Table 1**). In INSPIRATION/INSPIRATION-S study (NCT04486508) conducted in Iran ICU admitted COVID-19 patients, atorvastatin (20 mg/day) was not associated with a significant reduction in the composite of thrombosis, ECMO treatment, or all-cause mortality; however, atorvastatin treatment was safe, and may have clinical importance with lower overall event rates (46). Another study (NCT04359095) was conducted in Colombia (47), emtricitabine with tenofovir disoproxil (200/300 mg/day for 10 days) plus colchicine and rosuvastatin (0.5 mg and 40 mg/day for 14 days) combination reduced the risk of 28-day all-cause mortality by 22%, and lowered the need for IMV (47). These findings indicated safety and potential benefits of statins for COVID-19 treatment, yet the therapeutic effect varies from cohort and medications. More randomized controlled trials are therefore warranted to assess the effect of statin administration alone or in combination with regards of medication dose and duration, and to evaluate the influence of chronic statin use on COVID-19-related in-hospital events or long-term complications.

CAUTIONS ABOUT STATINS USE IN COVID-19

Although statins are generally well-tolerated, for COVID-19 patients especially those with obese or chronic statin use, cautions are required for potential risks of statins-associated muscle symptoms, liver injury, new-onset diabetes, renal injury, and neurological and neurocognitive disorders, which may also result from severe COVID-19 (68, 84, 126, 155, 156) (**Figure 3**).

Statin-associated muscular symptoms (SAMS) are principal cause of poor patient compliance that contribute to adverse outcomes (157, 158). SAMS include fatigue, weakness and pain, possibly accompanied by elevated serum CK levels and activity (54), while similar symptoms also present at early onset of COVID-19 (159). Therefore, for COVID-19 patients who use statins, careful monitoring muscle symptoms and CK levels are necessary; when muscle symptoms occur, assessment and approaches for statin intolerance may be considered (68, 160).

Statins-associated hepatotoxicity may add to COVID-19 related liver injury that potentially caused by psychological stress, systemic inflammation, etc., especially among obese individuals at higher risk of liver dysfunction (161–163). It has been suggested to avoid statin use in the case of severe liver damages, liver failure, and decompensated cirrhosis (24).

COVID-19 may induce or accelerate type 2 diabetes mellitus (T2DM) development as one of its acute and suspected long-term complications (19, 56), while statin may increase incidence of new-onset T2DM, which appears to be more common in obese patients (55, 164, 165). Despite the risk of T2DM, the cardiovascular benefits of statins should not be masked (166). Therefore, statin therapy can be continued in such patients with glucose monitoring, to achieve better glycemic control and avoid developing metabolic disorders after SARS-CoV-2 infection.

Clinicians should also be cautious when treating statin users with COVID-19 who show renal or neurological symptoms and relevant laboratory abnormalities. Renal dysfunction can be caused by SARS-CoV-2 infection and is associated with COVID-19 poor prognosis (167–169); whether statin-associated renal toxicity (170, 171) exacerbates COVID-19-related renal dysfunction remains unclear. There are also concerns regarding whether use of statin (especially lipophilic ones that can cross the blood-brain barrier) may worsen clinical manifestations of nervous system in COVID-19 patients, given their side effects of causing neurological disorders (171, 172).

Caution is also necessary for drug interaction during COVID-19 management. Most statins are predominantly metabolized by CYP450 enzymes, mainly through CYP3A4 (64). Therefore, concomitant administration of CYP3A4 inhibitors, such as some macrolides (clarithromycin/telithromycin/erythromycin) and antiretroviral drugs (lopinavir/ritonavir), with statins can increase the risk of adverse events (68, 173). For severe COVID-19 patients treated with IL-6 receptor blocker tocilizumab, rosuvastatin is recommended (68). Additionally, decreased LDL-C was observed in some severe COVID-19 cases (174, 175). Such finding may due to a more intensive lipid-lowering treatment in patients with high cardiovascular risk who are more vulnerable to COVID-19 (176), and deeper analysis is warranted to better prescribe appropriate intensity statin therapy.

STATINS AND COVID-19 VACCINES

The impact of statins on vaccine efficacy remain controversy. Take influenza vaccine for example, a clinical trial suggested immunosuppressive effect of chronic statin medication may weaken the immune response to vaccine (177), whereas another study indicated that statin did not modify influenza vaccine effectiveness (178). Presently, multiple COVID-19 vaccines have been approved, notably, vaccination participants with BMI $\geq$ 30 had a smaller infection risk reduction than those with BMI $<$ 30 (179), and central obesity (higher waist circumference) is associated with lower neutralizing antibody titers following vaccination (180). Presently, no evidence suggests statin may affect COVID-19 vaccine effectiveness.

STATINS AND COVID-19 ANTIVIRALS

SARS-CoV-2 variants may have substantial immune evasiveness that weakens vaccine protection due to spike protein mutations (57–60). Small molecular antivirals have reduced hospitalization rate and mortality in patients with promising safety (181, 182), among which Paxlovid stands out by reducing the risk of COVID-19-related hospital admission or death by 89% (183, 184). Paxlovid consists of a SARS-CoV-2 main protease inhibitor PF-07321332, and an anti-HIV drug ritonavir that boosts the effectiveness of protease inhibitors (184). However, co-administration of statins and Paxlovid may increase statin

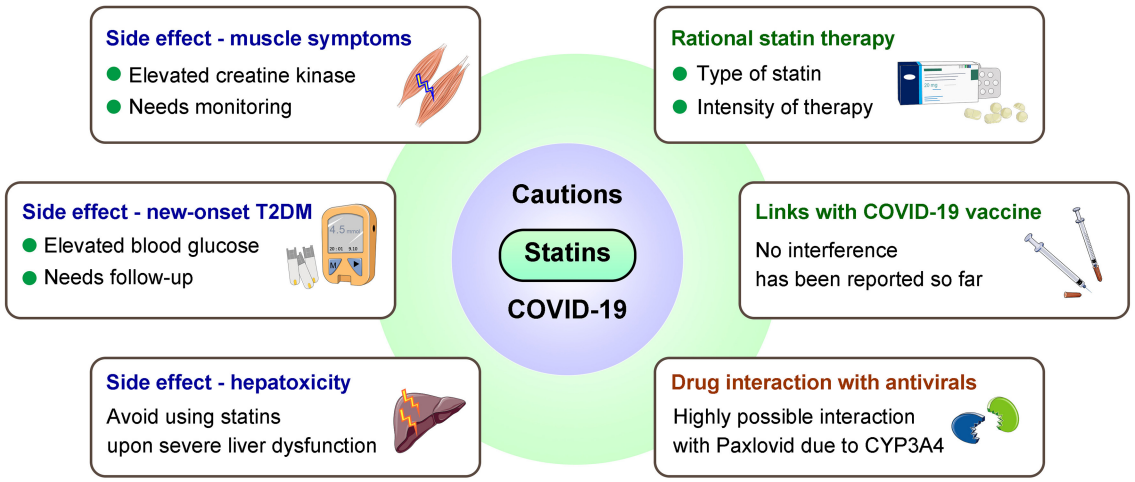

FIGURE 3 | Major cautions for statin use in COVID-19 patients. Considerations are needed from aspects including side effects, interferences with COVID-19 vaccines/antivirals, and proper statin therapy. T2DM, type 2 diabetes mellitus.

exposure and the risk of adverse effects including muscle symptoms and liver toxicity, because ritonavir potently inhibits CYP3A4 through which lipophilic statins are predominantly metabolized (64–66). Therefore, when such concomitant use is needed, it is possible to continue rosuvastatin therapy starting a low dose and titrating up (68, 156). More studies are needed to clarify the possible risks regarding co-administration of statins and antivirals, to find a proper regimen, and to explore whether obesity and dyslipidemia may interfere the efficacy of antivirals.

CONCLUSION AND FUTURE PERSPECTIVES

Current data suggest that statins are safe for COVID-19 patients and may exert therapeutical benefits. Generally, there is no necessity to discontinue statin use, and no evidence suggesting interference between statins and COVID-19 vaccines. However, cautions should be taken to achieve proper medication for statin users with COVID-19, considering possible side effects and drug interaction (**Figure 3**). Two major cautions are: *Proper type of statin.* Compared to hydrophilic statins, lipophilic statins enter cells *via* passive transport to reach higher intracellular concentrations, and have a larger distribution volume, thus may be more protective in respect of anti-viral ability. *Intensity of statin therapy.* Hypolipidemia is harmful. Decreased LDL-C is observed in some COVID-19 patients and associated with COVID-19 severity (174, 175), yet such findings may due to a more intensive lipid-lowering treatment in patients with high cardiovascular risk who are more vulnerable to COVID-19 (176). Low-, moderate-, high-intensity statin therapy should be applied according to specific LDL-C lowering needs. Importantly, careful monitoring of LDL-C, CK, blood glucose and liver function is recommended in context of COVID-19.

Currently known impacts of statins in COVID-19 are mostly based on observational studies and may vary due to heterogenicity in different trials/cohorts. To address the effect of statins in COVID-19 patients, especially in those with obesity or dyslipidemia-related diseases, randomized controlled trials with proper patient stratification are warranted. Moreover, experimental evidence of how different statins act in COVID-19 models are rare, highlighting the importance of related studies.

AUTHOR CONTRIBUTIONS

CL, WY, YC, and KH: conceptualization. CL, WY, YC, and JS: writing—original draft preparation. CL, YC, SW, AP, and KH: writing—review and editing. All authors have read and agreed to the final version of the manuscript.

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