



## Lipid Biochemistry as a Mirror Image of SARS-CoV-2 Prognosis



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### Abstract

The Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has resulted in over one hundred million infections and over three million deaths worldwide. Understanding the pathogenesis is critical for the prognostic and therapeutic implications. Viral infections are well-identified to change the lipid profiles and the metabolism of their host cells. Since lipids have various metabolic functions, investigating lipid profile changes in SARS-CoV-2 is an inevitable stage as a trial to attain better strategies for therapy, together with potential prognostic factors in the disease course. Numerous reports have investigated the alterations in lipid profiles that are present during SARS-CoV-2 infection. The most frequently observed alterations are reductions in levels of serum total cholesterol (TC), (low-density lipoproteins) LDL, (high-density lipoproteins) HDL, Apoprotein A1 and elevations of levels of serum Lipoprotein A, triglycerides (TG) and TG/HDL ratio. Viral replications significantly alter the host cell's lipid metabolism program and overuse the cell lipids for their replications. Lower levels of TC, HDL, and LDL are linked to greater severity and mortality rates and higher levels of inflammatory markers. Previous reports proposed that omega-3 derivatives may help modulate the cytokine storm. Besides, statins are shown to be valuable when used after SARS-CoV-2 diagnosis

### Keywords:

Severe acute respiratory syndrome coronavirus 2; Total Cholesterol ;High-density lipoproteins; Low-density lipoproteins; Triglycerides; Statins

### 1. Introduction

SARS-CoV-2 belongs to a large family of enveloped positive-sense RNA viruses. These viruses are known to cause a wide variety of diseases, from the common cold infection to the more severe conditions and pandemics. Examples of these severe conditions are severe acute respiratory syndrome (SARS-COV) and the Middle East Respiratory Syndrome (MERS), which are disease outbreaks that led to worldwide concerns and emergency measures (1-4).

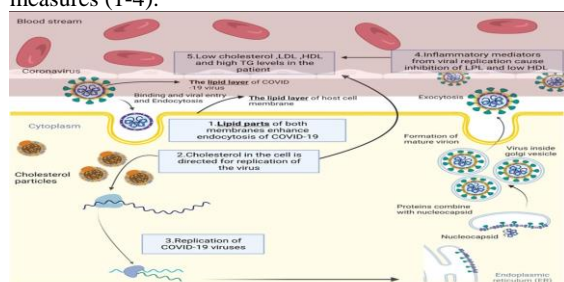


Figure 1 : Graphical Abstract

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Lipids are essential cellular components of SARS-CoV2. In particular, they are necessary for the process of viral invasion and, consequently, the viral pathogenicity, as they are involved in the fusion of the viral membrane to the receptors on the host cell, followed by the viral replication and invasion processes (5). Cholesterol, in particular, and lipid rafts play a prominent fundamental role in the early

stage of viral invasion, eventually leading to cellular infection (6). Early stages of inflammation induced by the infectious process trigger an acute-phase immune response with multiple cellular and cytokine interactions and signaling cascade activation leading to numerous alterations in the lipid and lipoprotein metabolism due to the following events; suppression of fatty acid oxidation, adipose tissue lipolysis and increased de novo hepatic fatty acid synthesis. (7)

Dyslipidemia is associated with multi-organ, and systemic derangement manifested with abnormalities, damage, and malfunction of the immune, cardiorespiratory, endocrinal, and neurological systems, along with accentuated pro-inflammatory condition evidenced by the high pro-inflammatory cytokines levels. It is casually associated with an increased risk of multiple cardiovascular abnormalities, including endothelial dysfunction, dysregulation of the normal vascular remodeling, increased risks of thromboembolic conditions, and pro-coagulant activity due to lowering the threshold for platelet activity (8). Thus, lipid dysregulation may be one of the pathological mechanisms contributing to the high morbidity and mortality resulting from SARS-CoV-2 infection. However, the dynamic changes in lipid profiles in SARS-CoV-2 patients, their value in the prediction of the disease severity and mortality, and their relation to the acute life-threatening event and cytokine storming are still in need of further investigation (9). A former study found that (LDL-C) dyslipidemia before admission was associated with OSTPA (oropharyngeal swab test positive

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again) after discharge for COVID-19 patients and increased mortalities in patients with (TG) dyslipidemia (10). Observations of altered levels of lipids during viral infections may suggest their incorporation in the disease pathophysiology, possibly via the production of the proinflammatory mediators using lipid droplets as substrates (11). Additionally, several studies outlined that deprivation of the cellular cholesterol significantly disturbs SARS-CoV-2 attachment, owing to a redistribution of receptors found in the cholesterol-rich lipids rafts, that would attenuate COVID-19 progress (12). The main hypothesis for this review is that host lipids, especially cholesterol are important for SARS-CoV-2 replication based on the lipid bilayer of the virus as lipids are essential for viral infection; they deliver energy and structural sources to create the membranes for the viral particles (**Figure 2**). Thus, low total cholesterol (TC) and low-density lipoprotein (LDL) levels could be indicative of a severe course, and raising their levels might mean improvement in the SARS-CoV-2 course. In addition, there are inflammatory mediators released in response to SARS-CoV-2 infection. High-density lipoprotein (HDL), being an anti-inflammatory mediator may be consumed. Hence its low level may denote the severity of the condition. Besides, these mediators may disrupt important enzymes such as lipoprotein lipase with subsequent high levels of triglycerides (TG). Therefore, both prognostic and therapeutic strategies can be implicated



Figure 2: The main hypothesis of the review  
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### 1. Structure of the lipid bilayer of COVID-19:

Lipids are essential for multiple cellular components and vital functions of the SARS-CoV-2. For instance, they are involved in the fusion of viral membranes to the host cells and, consequently, the viral replication, which is the primary step in the pathophysiology of the SARS-CoV-2 infection. Cholesterol and lipid particles play an essential role in the early stage of host cell infection (6). Another central role of lipid structures is resembling the structural foundations of viral and cellular membranes. Viruses can affect cellular pathways of lipid synthesis and produce modification signals to the host cells affecting these pathways. Therefore, lipid roles in membrane fusion, envelopment, and transformation are essential for viral replications (13). SARS-CoV-2 replicates within the host cell; so, it is necessary to cross the membrane of the host cell during endocytosis. Lipids have essential functions in this invasion because they can be direct and indirect viral receptors and entry cofactors. (14) In other words, cholesterol-enriched lipid particles represent platforms for entry of SARS-CoV-2 to enter the host cell by endocytosis. Subsequently, higher membrane cholesterol results in higher efficiency of SARS-CoV-2 entry. On the other hand, cholesterol depletion disrupts the viral membrane. (15)

Given the above-mentioned facts, we can conclude that particles that impact lipids such as cholesterol might be targets for hindering viral replications selectively.

### 2. The protective function of HDL and Apoprotein A1 (Apo-I)

HDL components have many features that can contribute to the stimulation of the immune response during various infectious diseases, being a viral scavenger, together with having the ability to change the lipid rafts and cholesterol content in the host cell membrane (16). Its associated apolipoproteins, such as apolipoprotein A-I (ApoA-I) and apolipoprotein M (ApoM), interact with lipids on the cellular membranes receptors, such as the T cell receptors and the toll-like receptors (TLR) on macrophages, thus they can modulate the immune responses (17). In addition, HDL elements have the highest affinity to bind and neutralize pathogen-associated lipids (e.g., lipopolysaccharide, lipoteichoic acid) which have considerable impacts during the excessive immune activation in the course of sepsis. Thus, HDL components could have immunomodulatory, antioxidant, and antithrombotic effects (18-19).

This importance in the immune system can be evidenced by the fact that HDL plasma levels are inversely proportionate to the frequency of multiple autoimmune diseases (20). Consistent with the above-mentioned facts, impaired HDL functions may participate in endothelial dysfunction, together with increased oxidative stress and inflammation, which can aggravate the pathogenic course of SARS-CoV-2 (21). In a previous study, Begue et al. reported a reduction in the inhibitory regulatory effects of HDL on the inflammatory and apoptotic pathways, with a significant increase in the TNF $\alpha$ -induced apoptosis in patients with SARS-CoV-2 (23) and noticed a negative correlation pattern between the preadmission HDL plasma levels and the severity of SARS-CoV-2 infection-related complications, including the cytokine storming and the tissue necrosis, which can be explained by the aggravated inflammatory response, and the increased cell death, respectively. With recovery from SARS-CoV-2 infections, the serum lipid levels return to levels present before infection (24). Therefore, many studies reported that serum ApoA1 might be a good indicator to denote the severity of SARS-CoV-2 (25). Given this strong association of low HDL levels with a higher risk of SARS-CoV-2 infection severity, severely ill SARS-CoV-2 patients highlighted low HDL and apo-1 levels (26). Consequently, low apoA-1 and HDL levels might be promising future biomarkers for severe disease courses and in-hospital mortality in cases of SARS-CoV-2 infection (27).

### 3. How do Triglycerides (TG) reflect the course of SARS-CoV-2?

To date, the relationship between high TG levels and risks of death in patients with SARS-CoV-2 remains controversial. Levels of TG could be affected by many factors such as the general condition of the patient, oxidative stress status, level of pro-inflammatory cytokines, and some medications that are used before or during infection with SARS-CoV-2 (28). Generally, serum TG is high in the sepsis course, and severe inflammation is due to diminished TG hydrolysis. In addition, inflammatory mediators also contribute to suppressing the lipoprotein lipase activity (29). However, serum triglyceride levels might differ in patients with SARS-CoV-2 infections. This is likely due to severe anorexia and

poor dietary intake which commonly occurs in ill patients resulting in low triglyceride levels. It is worth mentioning that high serum TG levels were observed in patients with mild or moderate infections but not in patients with critical illness (30). In contrast, few studies linked the marked elevation of TG during SARS-CoV-2 infection with the worst outcome. Feingold (2020) reported that high levels of TG, together with low levels of lipoprotein cholesterol, could be a biomarker of uncontrolled inflammation and associated with risks of death in patients with SARS-CoV-2 (9). Another study conducted by Huang and his colleagues reported that triglyceride levels were higher in non-survivor SARS-CoV-2 patients (31).

#### 4. How does Triglyceride to High-Density Lipoprotein Ratio reflect the course of SARS-CoV-2?

As previously mentioned, SARS-CoV-2 infection induces dyslipidemia that involves a combination of high triglycerides and low high-density lipoprotein (referred to as triglyceride to high-density lipoprotein (TG/HDL) ratio (32). A low TG/HDL ratio is desirable in adults and children, as elevated TG/HDL ratio is correlated positively to inflammation, insulin resistance, and impaired glucose homeostasis (33-34). The inflammation and insulin resistance are considered key facilitators in the progression of SARS-CoV-2 (35-36). Recent studies showed that the TG/HDL ratio was positively related to leukocyte, neutrophil, interleukin-6, and CRP levels (37-38). In addition, Sampedro-Nuñez and his colleagues found a strong association of elevated TG/HDL ratio with endothelium dysfunction and markers of delayed inflammation and coagulopathy in SARS-CoV-2 patients such as ferritin and D-Dimer. They reported that high inflammatory markers during SARS-CoV-2 infection may inhibit hepatic protein synthesis, including the synthesis of lipoproteins which in turn altered the TG/HDL ratio (39). Elevated TG/HDL ratio (before or during infection with SARS-CoV-2) was associated with a worse prognosis of SARS-CoV-2 severity (40) and this may be explained by the association of severe inflammation with an elevated TG/HDL ratio in those patients (41). Moreover, a high TG/HDL ratio may be also associated with longer hospitalization (42). Zhang and his colleagues demonstrated that the TG/HDL-C ratio was independently associated with the mortality and severity of cardiac diseases in patients with SARS-CoV-2 (41). Thus, the TG/HDL ratio may be a useful, simple, and early predictor marker of SARS-CoV-2's poor prognosis with requirement for the invasive mechanical ventilation (43).

#### 5. TC and LDL course in SARS-CoV-2 infections

LDL levels were inversely correlated with levels of C-reactive protein (CRP). Previous reports have detected a reduction in TC and LDL levels in patients with SARS-CoV-2 infections as compared with normal subjects (9). According to Wei et al, liver dysfunction, altered lipid metabolism brought on by acute inflammation, elevated free radical levels causing lipid degradation, and altered vascular permeability causing leakage of cholesterol molecules into tissues, all may contribute to the decreased LDL biosynthesis in SARS-CoV-2 infections (44). When Fan et al. examined the blood lipid levels of patients who had SARS-CoV-2 infection and compared them with those

who had not, it was found that both LDL and TC levels had significantly decreased at the time of hospital admission and throughout therapy(45). In non-surviving patients, LDL levels showed an irreversible and continuous decrease until death and this study concluded that LDL levels are inversely correlated to the disease severity, which could be a predictor of the disease progress.

#### 6. Lipoprotein A profile in SARS-CoV-2 infections

Reports regards the effect of SARS-CoV-2 infections on lipoprotein(a) (Lp(a)) levels have not yet been described. It is well-recognized that inflammation raises Lp(a) levels, so SARS-CoV-2 infections may also raise Lp(a). It has been hypothesized that an increase in Lp(a) might contribute to some of the clinical abnormalities, such as thrombosis, observed during severe SARS-CoV-2 infections (46).

#### 7. Lipid profiles in recovered SARS-CoV-2 patients

After a wide range of time variation from a few weeks to months, lipid profile after recovery from SARS-CoV-2 tends to return to the previous levels before infection. With the exclusion of individuals taking cholesterol-lowering drugs, both LDL and HDL levels were significantly increased at 3-6 months of follow-up than at admission in severe/critical cases (47). A recent study set a follow-up lipid profile of non-critical SARS-CoV-2 patients after 14-30 days of discharge and compared it to that at the time of admission. It was found that plasma TC, LDL, HDL, and TG levels on follow-up were significantly higher than those levels at admission (48). Normal TG levels in a follow-up study one year after hospitalization were reported (49).

#### 8. Lipid profile changes in patients with SARS-CoV-2 compared to healthy controls (Table 1)

In a previous case-control study that included patients with SARS-CoV-2 and healthy controls, lipid profile levels were assessed in patients who were categorized into severe cases who were admitted to the intensive care unit (ICU), less severe (outpatient) and healthy controls, and the three groups were compared. Levels of mean cholesterol were lower in the diseased groups than in controls; HDL levels were higher in the intensive care unit group versus outpatients, and LDL levels were inferior in the intensive care unit group versus the outpatients. There were pre-existing conditions in the ICU group as diabetes and hypertension. Moreover, LDL levels were linked to the disease severity (50).

**Table 1: Changes in the lipid profiles between healthy individuals and patients with SARS-CoV-2**

Lipid profile	Healthy	Diseased
Cholesterol	Higher	Lower
HDL	Higher	Lower
LDL	Higher	Lower
TG	Lower	Higher

Formerly published reports yielded that HDL concentration diminished immediately once the infection takes place and there is a significant association between reduced HDL levels and the undesirable prognosis in infectious diseases. (51-53). It is probable that, owing to passing the early course of SARS-CoV-2, patients in the above-mentioned study revealed no decrease in HDL

levels in the severe form of SARS-CoV-2. The triglyceride level was higher in the control group and lower in the ICU group. Serum triglyceride levels could be variable in patients with SARS-CoV-2 infections. This is likely due to severe anorexia and poor food intake that commonly occurs in ill patients resulting in low triglyceride levels. In another study (54), it was found that, compared with the healthy controls, the infected patients with SARS-CoV-2 had low levels of serum TC, and LDL and lower levels of HDL-C while TG in these infected patients were higher than in the healthy control. The diseased patients are further sub-classified into asymptomatic, mild to moderate and severe groups. It was detected that the TG levels were significantly higher in the severe infection cases than that in the asymptomatic and mild infection cases respectively. While patients with severe infection had a somewhat lower level of TC than those with asymptomatic and mild infection cases. Furthermore, a significant reduction in the level of HDL was observed in the severe infection cases in contrast to asymptomatic

infection cases. So, the higher TG/HDL-C ratio was found in the severe infection cases, in contrast to the asymptomatic and mild infection groups respectively. Another study found higher TG levels in the severe course of COVID-19 compared to patients with mild severity (55). Thus, it could be stated that the prognostic value of the serum lipid profiles can be guessed via their levels at the disease onset. For example, low levels of TC and LDL can predict the severity. However, this prognostic value can be more dependent on the dynamic changes in the observed levels through the course of SARS-CoV-2 infection, not on a known level at a specific time during the illness. For instance, TC and LDL levels can be prognostic biomarkers when their levels on admission or at the onset of SARS-CoV-2 infection are monitored, either rising or declining over time. Furthermore, this prognostic value would increase if the serum lipid profiles of the patient were correlated with other prognostic markers of inflammation. **Table 2** shows some relevant results of lipids profiles as severity biomarkers.

**Table 2: Some relevant studies showing variations in the severity biomarkers**

Study and author	Severity biomarker	Main Results
Changaripour S, et al. Lipid profile changes in patients with COVID-19 referred to medical centers in Kermanshah, Iran; a case-control study,2022	TC	A statistically significant difference ( $P = 0.013$ ) regards TC between the control group (Mean /SD = $165.71 \pm 19.535$ ) and the ICU group ( Mean /SD = $145.00 \pm 28.518$ ) and the outpatient group (Mean /SD = $157.60 \pm 92.465$ )
	LDL-C	There was a statistically significant ( $P < 0.001$ ) difference between the outpatient group (Mean /SD = $69.65 \pm 28.394$ ) and the ICU group (Mean /SD = $52.16 \pm 17.500$ )
	HDL-C	Mean HDL-C levels were also significantly different between the control group (Mean/SD = $39.63 \pm 4.531$ ) and both the outpatient group (Mean/SD = $34.06 \pm 7.332$ ) and the ICU group ( $37.08 \pm 6.757$ ), ( $P = 0.001$ )
Chien JY, et al. Low serum level of high-density lipoprotein cholesterol is a poor prognostic factor for severe sepsis,2005	Apolipoprotein A-I	A low Apolipoprotein A-I level on day 1 of severe sepsis is significantly associated with an increase in mortality ( 43% in patients with lower Apolipoprotein A-I less than 100 mg/dl in comparison to 19% in patients with levels more than 100 mg/dl )
	HDL Cholesterol	A low high-density lipoprotein levels on day 1 of severe sepsis is significantly associated with an increase in mortality (53% in patients with lower HDL less than 20 mg/dl in comparison to 9 % in patients with levels more than 20 mg/dl) , P value < 0.01
Masana L, et al. Low HDL and high triglycerides predict COVID-19 severity.2021	HDL Cholesterol	The median (IQR) regards HDL levels (in mmol/L) significantly differed (P value = $<0.001$ ) in patients with mild COVID-19, in comparison to patients with severe course ( 0.88(0.72 -1.08) versus 0.73( 0.59 -0.98) respectively.
	TG	The median (IQR) regards TG levels (in mmol/L) significantly differed (P value = $<0.001$ )in patients with mild COVID-19, in comparison to patients with severe course (1.61(1.13 -2.18) versus 1.94( 1.39 -2.88)) respectively.

It is worthwhile to know that some lipid profiles aren't in the same way as the expected prognostic changes. In particular, serum levels of TG couldn't be high in all severe cases. This depends on what is the predominant; the inflammatory mediators that suppress lipoprotein lipase (LPL); causing high TG or the bad general condition of patients that compromises their nutritional intake; causing low TG levels. Also, it could depend on the comorbid condition such as obesity and the previous drugs used (35).

#### 9. Subsequent health hazards that result from SARS-CoV-2-induced dyslipidemia

An earlier investigation concluded that SARS-CoV-2 patients had hypocholesterolemia and

hypertriglyceridemia. Furthermore, it was observed that individuals with severe infections had low levels of high-density lipoprotein cholesterol. Therefore, it might be concluded that individuals who have been severely exposed to SARS-CoV-2 have a significant chance of acquiring cardiovascular illnesses. AIP (Atherogenic Index of Plasma) =  $\log \text{ TG/HDL}$ , which measures atherogenicity in plasma, can expect cardiovascular risk. AIP values between 0.11 to 0.21 indicate intermediate risk, while values below 0.11 indicate minimal risk. AIP values over 0.21 indicate a significant cardiovascular risk. Individuals with severe SARS-CoV-2 infection were shown to have a high risk (AIP=0.66), whereas patients with asymptomatic or moderate illness had a low risk

(AIP=0.081 and AIP=0.11, respectively) (55). Another cross-sectional study of 1411 hospitalized SARS-CoV-2 patients found that low HDL and high TG levels at admission were strong predictors of illness severity and that they were also associated with higher D-dimer and ferritin levels and increased thrombosis risks (56). In other words, a severe SARS-CoV-2 infection might lead to cardiovascular risks that can compromise the prognosis and therapy.

#### 10. Potential nutraceutical and pharmaceutical treatment:

##### 10. 1 Raising HDL through suppression of inflammation

Targeted reduction of the pro-inflammatory cytokines, and increasing the functional HDL-related peptide could improve the clinical course and outcome in these patients (56).

**Niacin** is a water-soluble vitamin with well-known potent anti-inflammatory properties. A recent study evaluates its effect in SARS-CoV-2 patients. Though niacin is well known to increase HDL levels, this study didn't correlate the niacin dose with HDL levels (57).

Administering **PUFAs** (Polyunsaturated fatty acids) in hospitalized SARS-CoV-2 patients diminished the incidence of sepsis (59). It is also associated with shorter ICU and hospital stays and reduced mortality rates (58-62). Szabo et al. have also investigated the effects of the administration of different **PUFAs** such as the eicosapentaenoic acid (EPA) and the docosahexaenoic acid (DHA), both as prophylactic and therapeutic approaches in SARS-CoV-2 infections with encouraging results, especially regarding fatal complications such as the cytokine storming (63). The mechanisms of these effects are still unclear; nevertheless, they are mainly related to the upregulation of the peroxisome proliferator receptor activator (PPAR) gamma(64) and (PPAR) alpha. (65). As being key metabolic receptors with central roles in metabolism in general, and lipid metabolism in particular, such activation eventually leads to a marked increase in the plasma HDL levels as well as a significant reduction in the plasma TG levels (66).

**Lactoferrin** is an extremely conserved, iron-binding 80-kDa glycoprotein that is present in body fluids encompassing bovine and human milk. Lactoferrin appears to be able to improve the host's immune response to infections by enhancing the immune system to counteract the viral invasion and hindering the destructive host immune and inflammatory responses (67).

**Zinc** has anti-viral and immunomodulatory features that could be beneficial in SARS-CoV-2 patients. These impacts are likely due to suppression of viral binding and replication, and this might be relevant to SARS-CoV-2 (68).

**Tomato** :in general, a previous meta-analysis found that tomato consumption has no influence on blood CRP or IL-6 concentrations, but can considerably lower serum TNF-levels.(69)

**Allium sativum**: may be an appropriate preventative approach against COVID-19 infection by boosting immune system cells and suppressing the generation and release of proinflammatory cytokines as well as the proinflammatory adipose tissue derived hormone leptin.(70). It presents in foods such as Garlic

**Licorice**: Glycyrrhiza glabra (licorice) extract's phytotherapeutic effects are mostly attributable to

glycyrrhizin (GR) and glycyrrhetic acid (GA). Among their potential pharmacological activities is the capacity to act against viruses from many families, including the SARS coronavirus.(71)

##### 10. B Reduction of the penetration of SARS-CoV-2 into the host cell

The power of infection related to SARS-CoV-2 relies on cholesterol which exists in the membranes of their target cells. The virus can enter the infected cells either via fusion or through endocytosis encompassing cholesterol-enriched membrane microdomains. These membrane domains could be disorganized by **statins** which hinder cell cholesterol biosynthesis (72). Furthermore, it seems that the usage of statins in patients with SARS-CoV-2 might contribute to the reduction of the risk of dyslipidemia observed in the long-term follow-up of these patients (73).

##### 11. Practical implications:

1. In fact, lipid profiles encompassing cholesterol and lipoproteins can stratify patients regarding their severity, hence it can guide and direct the healthcare workers for the priorities (Table 1). For instance, lower HDL and LDL levels might be associated with increased SARS-CoV-2 disease severity. Besides, increased TG/HDL ratio and low levels of HDL are unfortunately linked to poor prognoses. TG levels may be low in mild to moderate disease courses and high in severe SARS-CoV-2 courses. ApoA-1 and Lp(a) levels can also have prognostic values. To explain, low apoA-1 and high Lp(a) levels are associated with poor outcomes. Furthermore, HDL and LDL levels can detect early recovery from the SARS-CoV-2 course. For example, increased levels compared to low levels at admission may direct the treatment plan from severe to mild cases as the higher levels may indicate improved outcomes and recovery.

2. The baseline dyslipidemia is better to be considered as a risky factor for acquiring SARS-CoV-2 (74). Indeed, higher levels of cholesterol may enhance increased SARS-CoV-2 mediated replication and pathogenicity.

3. Monitoring patients with SARS-CoV-2 for cardiovascular risks is a mandatory step for successful management as the resultant dyslipidemia could increase these risks with subsequent undesirable outcomes (75).

4. It should be worth considering a clinically well-tolerated dose of statin to treat SARS-CoV-2 patients, in the early phase of the infection, to suppress the virus entry into target cells, to control the viral charge, and avoid severe clinical complications (76). It is essential to note that certain statins might have superior HDL-raising capacities than others: Rosuvastatin and Simvastatin being higher than Atorvastatin, the extent of their impact is augmented in a dose-response mean (77). Two systematic reviews have precisely outlined statin effects among patients with SARS-COV2. One systematic review which included 13 RCTs (randomized controlled trials) with a total of 52,122 patients yielded that whereas prehospital use of statins did not have any effect on the rate of mortality, its prescription on hospital admission significantly decreased the risk of death (RR=0.54 (95%CI:0.5-0.58)(75). The result of the other systematic review which included 13 cohorts with over 110,000 patients had consistent findings with a death-hazard ratio of 0.53 (95%CI: 0.26-1.64) among patients that had administered statins after a SARS-COV2



diagnosis (78). Both of these studies provide supportive evidence for the benefit of statins in SARS-COV2.

#### Conclusion:

Following serum lipid profiles and their levels may address the severity of SARS-CoV-2 and modify the treatment strategy. Identifying the baseline values of HDL and LDL levels and tracking their values to recognize patients at higher risks for SARS-CoV-2 severity is recommended, hence stratification of the risks could be addressed. Therefore, these patients are better to be at close monitoring. Still, the prognostic value of patients with SARS-CoV-2 should not be reliant on serum lipid profiles alone. It should be correlated with other inflammatory markers and the clinical condition of the patient.

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#### Figures legend:

**Figure 2 :** The main hypothesis of the review

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