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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).

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 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).

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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 1)**. 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
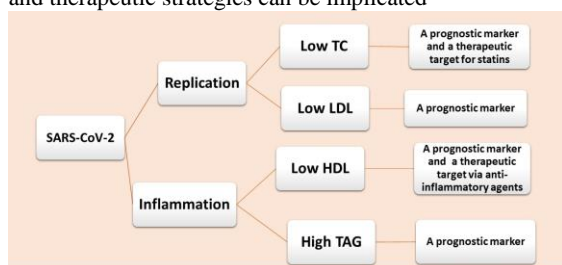

Figure 1: The main hypothesis of the review
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2. Structure of the lipid bilayer of COVID-19:

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.

3. 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 TNFα-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).

4. 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

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colleagues reported that triglyceride levels were higher in non-survivor SARS-CoV-2 patients (31).

5. 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).

6. 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.

7. 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).

8. 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).

9. 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

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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 ± 19.535) and the ICU group (Mean /SD =145.00 ± 28.518) and the outpatient group (Mean /SD = 157.60 ± 92.465)
	LDL-C	There was a statistically significant ($P < 0.001$) difference between the outpatient group (Mean /SD =69.65 ± 28.394) and the ICU group (Mean /SD = 52.16 ± 17.500)
	HDL-C	Mean HDL-C levels were also significantly different between the control group (Mean/SD =39.63 ± 4.531) and both the outpatient group (Mean/SD =34.06 ± 7.332) and the ICU group (37.08 ± 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).

10. 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 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

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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 glycyrrhetinic 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 1 : The main hypothesis of the review

References

1. Suksatan W, Chupradit S, Yumashev AV, Ravali S, Shalaby MN, Mustafa YF, Kurochkin A, Siahmansouri H. Immunotherapy of multisystem inflammatory syndrome in children (MIS-C) following COVID-19 through mesenchymal stem cells. Int Immunopharmacol. 2021 Dec;101(Pt B):108217. doi: 10.1016/j.intimp.2021.108217. Epub 2021 Oct 4. PMID: 34627083; PMCID: PMC8487784.

2. Jasim SA, Mahdi RS, Bokov DO, Najm MAA, Sobirova GN, Bafoyeva ZO, Taifi A, Alkadir OKA, Mustafa YF, Mirzaei R, Karampoor S. The deciphering of the immune cells and marker signature in COVID-19 pathogenesis: An update. J Med Virol. 2022 Nov;94(11):5128-5148. doi: 10.1002/jmv.28000. Epub 2022 Jul 23. PMID: 35835586; PMCID: PMC9350195.

3. Atef, H. (2022). Nutritional fat modulation as a non-pharmacological approach to children infected with COVID-19, a challenge in food biochemistry. *Egyptian Journal of Chemistry*, 65(3), 689-698. doi: 10.21608/ejchem.2021.87893.4234

4. Atef Abdelsattar Ibrahim H, Gamal R, Mohsen M, Amin A A, AbdElSalam Y, et al. Pediatric Dilemma of the Third Wave Pandemic of COVID-19 in A Tertiary Care Hospital for Children. J Compr Ped. 2023;14(3):e136070. https://doi.org/10.5812/compreped-136070.

5. Li GM, Li YG, Yamate M, Li SM, Ikuta K. Lipid rafts play an important role in the early stage of severe acute respiratory syndrome-coronavirus life cycle. Microbes Infect. 2007;9(1):96-102. doi:10.1016/j.micinf.2006.10.015

6. Baglivo M, Baronio M, Natalini G, et al. Natural small molecules as inhibitors of coronavirus lipid-dependent attachment to host cells: A possible strategy for reducing SARS-COV-2 infectivity? Acta Biomed. 2020;91(1):161-164. doi:10.23750/ABM.v91i1.9402

7. Sudhakar, M., Winfred, S.B., Meiyazhagan, G. *et al.* Mechanisms contributing to adverse outcomes of COVID-19 in obesity. *Mol Cell Biochem* (2022).

8. Neha K. Reddy, Vaidehi Kaushal, Alka M. Kanaya, Namratha R. Kandula, Unjali P. Gujral, Nilay S. Shah, Cardiovascular risk factor profiles in North and South Indian and Pakistani Americans: The MASALA Study, American Heart Journal, Volume 244,2022,14-18, ISSN 0002-8703,https://doi.org/10.1016/j.ahj.2021.10.115.

9. Feingold KR. Lipid and lipoprotein levels in patients with COVID-19 infections. Endotext [Internet]. Published online 2020

10. Jin H, He J, Dong C, Li B, Ma Z, Li B, Huang T, Fan J, He G, Zhao X. Altered Lipid Profile Is a Risk Factor for the Poor Progression of COVID-19: From Two Retrospective Cohorts. Front Cell Infect Microbiol. 2021 Sep 30;11:712530. doi: 10.3389/fcimb.2021.712530. PMID: 34660338; PMCID: PMC8515140.

11. Herrera-Moro Huitron, L.; De Jesús-González, L.A.; Martínez-Castillo, M.; Ulloa-Aguilar, J.M.; Cabello-Gutierrez, C.; Helguera-Repetto, C.; Garcia-Cordero, J.; León Juárez, M. Multifaceted Nature of Lipid Droplets in Viral Interactions and Pathogenesis. Microorganisms 2023, 11, 1851. https://doi.org/10.3390/microorganisms11071851

12. Rudiansyah M, Jasim SA, Mohammad Pour ZG, Athar SS, Jeda AS, Doewes RI, Jalil AT, Bokov DO, Mustafa YF, Noroozbeygi M, Karampoor S, Mirzaei R. Coronavirus disease 2019 (COVID-19) update: From metabolic reprogramming to immunometabolism. J Med Virol. 2022 Oct;94(10):4611-4627. doi: 10.1002/jmv.27929. Epub 2022 Jun 20. PMID: 35689351; PMCID: PMC9350347.

13. Roncato R, et al . Lipid rafts as viral entry routes and immune platforms: A double-edged sword in SARS-CoV-2 infection?, Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids, Volume 1867, Issue 6,2022.

14. Abu-Farha M, Thanaraj TA, Qaddoumi MG, Hashem A, Abubaker J, Al-Mulla F. The Role of Lipid Metabolism in COVID-19 Virus Infection and as a Drug Target. Int J Mol Sci. 2020;21(10). doi:10.3390/IJMS21103544

15. E K, T R, D R. Cholesterol, lipoproteins, and COVID-19: Basic concepts and clinical applications. Biochim Biophys Acta Mol cell Biol lipids. 2021;1866(2). doi:10.1016/J.BBALIP.2020.158849

16. Association of pre-pandemic high-density lipoprotein cholesterol with risk of COVID-19 hospitalization and death: the UK Biobank cohort study. Accessed July 5, 2021.

17. AV S, SK K, ZH Y, L F, K K, AT R. COVID-19-Associated dyslipidemia: Implications for the mechanism of impaired resolution and novel therapeutic approaches. FASEB J. 2020;34(8):9843-9853. doi:10.1096/FJ.202001451

18. Bindu G H, Rao VS, Kakkar V V. Friend turns foe: Transformation of anti-inflammatory hdl to proinflammatory HDL during acute-phase response. Cholesterol. 2011;2011. doi:10.1155/2011/274629

19. SK K, LA F, SM G, AT R. The Changing Face of HDL and the Best Way to Measure It. Clin Chem. 2017;63(1):196-210.
doi:10.1373/CLINCHEM.2016.257725

20. CM M, A V, BG N. Low HDL Cholesterol and High Risk of Autoimmune Disease: Two Population-Based Cohort Studies Including 117341 Individuals. Clin Chem. 2019;65(5):644-652. doi:10.1373/CLINCHEM.2018.299636

21. Batty GD, Hamer M. Vascular risk factors, Framingham risk score, and covid-19: Community-

_____

based cohort study. Cardiovasc Res. 2020;116(10):1664-1665. doi:10.1093/cvr/cvaa178

22. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med. 2020;383(2):120-128

23. Begue, F., Tanaka, S., Mouktadi, Z. et al. Altered high-density lipoprotein composition and functions during severe COVID-19. Sci Rep 11, 2291 (2021).

24. Roccaforte V, Daves M, Lippi G, Spreafico M, Bonato C. Altered lipid profile in patients with COVID-19 infection. J Lab Precis Med. 2021;6(3):2-2. doi:10.21037/jlpm-20-98

25. Z Z, Y Y, L F, et al. A Preliminary Study on Blood Lipid Profile in Patients with COVID-19. Published online August 14, 2020. doi:10.21203/RS.3.RS-57301/V1

26. Garg I, Srivastava S, Kumar B. Understanding the Role of HDL during COVID-19 Infection. Coronaviruses. 2020;2(3):289-290. doi:10.2174/2666796701999200918160757

27. Sun JT, Chen Z, Nie P, et al. Lipid Profile Features and Their Associations With Disease Severity and Mortality in Patients With COVID-19. Front Cardiovasc Med. 2020;7(December):1-12. doi:10.3389/fcvm.2020.584987

28. Peng F, Lei S, Zhang Q, Zhong Y, Wu S. Triglyceride/High-Density Lipoprotein Cholesterol Ratio is Associated with the Mortality of COVID-19: A Retrospective Study in China. Int J Gen Med. 2022;15:985-996. Published 2022 Jan 31. doi:10.2147/IJGM.S346690

29. Wendel M, Paul R, Heller AR. Lipoproteins in inflammation and sepsis. II. Clinical aspects. Intensive Care Med. 2007;33(1):25-35.

30. X W, W Z, J S, et al. Hypolipidemia is associated with the severity of COVID-19. J Clin Lipidol. 2020;14(3):297-304. doi:10.1016/J.JACL.2020.04.008

31. Huang W, Li C, Wang Z, et al. Decreased serum albumin level indicates poor prognosis of COVID-19 patients: hepatic injury analysis from 2,623 hospitalized cases. Sci China Life Sci. 2020;63(11):1. doi:10.1007/S11427-020-1733-4

32. Masana, L., Correig, E., Ibarretxe, D., Anoro, E., Arroyo, J. A., Jericó, C., Guerrero, C., Miret, M., Näf, S., Pardo, A., Perea, V., Pérez-Bernalte, R., Plana, N., Ramírez-Montesinos, R., Royuela, M., Soler, C., Urquizu-Padilla, M., Zamora, A., Pedro-Botet, J., & STACOV-XULA research group (2021). Low HDL and high triglycerides predict COVID-19 severity. *Scientific reports*, *11*(1), 7217.

33. FK, W. (2013). How do elevated triglycerides and low HDL cholesterol affect inflammation and atherothrombosis? Current Cardiology Reports, 15(9).

34. Chen, Z., Hu, H., Chen, M., Luo, X., Yao, W., Liang, Q., Yang, F., & Wang, X. (2020). Association of Triglyceride to high-density lipoprotein cholesterol ratio and incident of diabetes mellitus: a secondary retrospective analysis based on a Chinese cohort study. Lipids in Health and Disease, 19(1).

35. Nur Zati Iwani, A. K., Jalaludin, M. Y., Wan Mohd Zin, R. M., Fuziah, M. Z., Hong, J. Y. H., Abqariyah, Y., Mokhtar, A. H., & Wan Mohamud, W. N. (2019).

TG: HDL-C ratio is a good marker to identify children affected by obesity with increased cardiometabolic risk and insulin resistance. International Journal of Endocrinology, 2019.

36. Logette, E., Lorin, C., Favreau, C., Oshurko, E., Coggan, J. S., Casalegno, F., Sy, M. F., Monney, C., Bertschy, M., Delattre, E., Fonta, P. A., Krepl, J., Schmidt, S., Keller, D., Kerrien, S., Scantamburlo, E., Kaufmann, A. K., & Markram, H. (2021). A Machine-Generated View of the Role of Blood Glucose Levels in the Severity of COVID-19. Frontiers in Public Health, 9(July), 1–53.

37. Alcantara-Alonso E, Molinar-Ramos F, Gonzalez-Lopez JA, et al. High triglyceride to HDL cholesterol ratio as a biochemical marker of severe outcomes in COVID-19 patients. Clin Nutr ESPEN. 2021; 15

38. Peng F, Wu S, Lei S, et al. Triglyceride/High-Density Lipoprotein Cholesterol Ratio is associated with the mortality of COVID-19: An Observational Study. Res Sq. 2020;

39. Sampedro-Nuñez, M., Aguirre-Moreno, N., García-Fraile Fraile, L. et al. Finding answers in lipid profile in COVID-19 patients. Endocrine 74, 443–454 (2021).

40. Masana, L., Correig, E., Ibarretxe, D., Anoro, E., Arroyo, J. A., Jericó, C., Guerrero, C., Miret, M. L., Näf, S., Pardo, A., Perea, V., Pérez-Bernalte, R., Plana, N., Ramírez-Montesinos, R., Royuela, M., Soler, C., Urquizu-Padilla, M., Zamora, A., Pedro-Botet, J., Gutierrez, L. (2021). Low HDL and high triglycerides predict COVID-19 severity. Scientific Reports, 11(1), 1–9.

41. Zhang B, Dong C, Li S, Song X, Wei W, Liu L. <p>Triglyceride to High-Density Lipoprotein Cholesterol Ratio is an Important Determinant of Cardiovascular Risk and Poor Prognosis in Coronavirus Disease-19: A Retrospective Case Series Study</p>. Diabetes, Metab Syndr Obes Targets Ther. 2020;13:3925-3936. doi:10.2147/DMSO.S268992

42. Daniel Setiawan Nathan, and Hoo Yumilia. Level of High-density Lipoprotein (HDL) and Triglycerides (TG) Predict Covid-19 Severity: The Systematic Review. International Journal of Medical Science and Health Research Vol. 5, No. 04; 2021 ISSN: 2581-3366

43. Alcántara-Alonso, E., Molinar-Ramos, F., González-López, J. A., Alcántara-Alonso, V., Muñoz-Pérez, M. A., Lozano-Nuevo, J. J., Benítez-Maldonado, D. R., & Mendoza-Portillo, E. (2021). High triglyceride to HDL-cholesterol ratio as a biochemical marker of severe outcomes in COVID-19 patients. Clinical Nutrition ESPEN, 44, 437–444.

44. Wei X, Zeng W, Su J, et al. Hypolipidemia is associated with the severity of COVID-19. J Clin Lipidol. 2020;14(3):297-304. doi:10.1016/j.jacl.2020.04.008

45. Fan J, Wang H, Ye G, et al. Letter to the Editor: Low-density lipoprotein is a potential predictor of poor prognosis in patients with coronavirus disease 2019. Metabolism. 2020;107:154243. doi:10.1016/J.METABOL.2020.154243

46. Moriarty PM, Gorby LK, Stroes ES, Kastelein JP, Davidson M, Tsimikas S. Lipoprotein(a) and Its Potential Association with Thrombosis and

Inflammation in COVID-19: a Testable Hypothesis. Curr Atheroscler Rep. 2020;22(9). doi:10.1007/S11883-020-00867-3

47. Li G, Du L, Cao X, et al. Follow-up study on serum cholesterol profiles and potential sequelae in recovered COVID-19 patients. BMC Infect Dis 2021 211. 2021;21(1):1-10. doi:10.1186/S12879-021-05984-1

48. Uyaroğlu, O. A., Özdede, M., Başaran, N. Ç., Köylü, B., Şahin, T. K., Özışık, L., Tanrıöver, M. D., & Güven, G. S. (2021). Can plasma lipid levels be correlated to severe COVID-19 infection? *Atherosclerosis*, *331*, e138–e139.

49. Zhao Y,et al. Follow-up study on COVID-19 survivors one year after discharge from hospital. International Society for Infectious Diseases. 2021 Nov;112:173-182.

50. Changaripour, S., Sarvazad, H., Barghi, M., Sajadi, E., Sadeghian, M. H., & Roozbahani, N. E. (2022). Lipid profile changes in patients with COVID-19 referred to medical centers in Kermanshah, Iran; a case-control study. *The Journal of International Medical Research*, *50*(2), 3000605221078699.

51. Chien, J-Y, Jerng, J-S, Yu, C-J, et al. Low serum level of high-density lipoprotein cholesterol is a poor prognostic factor for severe sepsis. Crit Care Med 2005; 33: 1688–1693

52. Tanaka, S, Couret, D, Tran-Dinh, A, et al. High-density lipoproteins during sepsis: from bench to bedside. Crit Care 2020; 24: 134.

53. Van Leeuwen, HJ, Heezius, EC, Dallinga, GM, et al. Lipoprotein metabolism in patients with severe sepsis. Crit Care Med 2003; 31: 1359–1366.

54. Mohammedsaeed W, Alahamadey Z, Khan M. Alteration of lipid profile in COVID-19 Saudi patients at Al-Madinah Al-Munawarah. Infection 2020;14:15

55. Masana L, Correig E, Ibarretxe D, Anoro E, Arroyo JA, Jerico C, et al. Low HDL and high triglycerides predict COVID-19 severity. Sci Rep 2021;11:7217.

56. Sorokin, Alexander & Karathanasis, Sotirios & Yang, Zhi-Hong & Freeman, Lita & Kotani, Kazuhiko & Remaley, Alan. (2020). COVID-19-Associated dyslipidemia: Implications for the mechanism of impaired resolution and novel therapeutic approaches. The FASEB Journal. 34. 10.1096/fj.202001451.

57. R L, Y L, X L, L Y, M S, KP L. Network Pharmacology and bioinformatics analyses identify intersection genes of niacin and COVID-19 as potential therapeutic targets. Brief Bioinform. 2021;22(2):1279-1290. doi:10.1093/BIB/BBAA300

58. Pradelli L, Mayer K, Klek S, Omar Alsaleh AJ, Clark RAC, Rosenthal MD, et al.omega-3 fatty-acid enriched parenteral nutrition in hospitalized patients: systematic review with meta-analysis and trial sequential analysis. JPEN J Parenter Enteral.Nutr 2020;44:44–57

59. Langlois PL, D'Aragon F, Hardy G, Manzanares W. Omega-3polyunsaturated fatty acids in critically ill patients with acute respiratory distress syndrome: a systematic review and meta-analysis. Nutrition 2019;61:84–92.

60. Calder PC, Adolph M, Deutz NE, Grau T, Innes JK, Klek S, et al. Lipids in the intensive care unit:

61. recommendations from the ESPEN expert group. Clin Nutr 2018;37:1–18

61. Dushianthan A, Cusack R, Burgess VA, Grocott MP, Calder PC. Immunonutrition for acute respiratory distress syndrome (ARDS) in adults. Cochrane Database Syst Rev 2019;1:CD012041.

62. Calder PC. Omega-3 polyunsaturated fatty acids and inflammatory processes: nutrition or pharmacology? Br J Clin Pharmacol 2013;75(3):645–62.

63. Szabó Z, Marosvölgyi T, Szabó É, Bai P, Figler M, Verzár Z. The Potential Beneficial Effect of EPA and DHA Supplementation Managing Cytokine Storm in Coronavirus Disease. Front Physiol. 2020;0:752. doi:10.3389/FPHYS.2020.00752

64. Edwards IJ, O'Flaherty JT. Omega-3 fatty acids and PPAR γ in cancer. PPAR Res. Published online 2008. doi:10.1155/2008/358052

65. Liu M, Montgomery MK, Fiveash CE, et al. PPARα-independent actions of omega-3 PUFAs contribute to their beneficial effects on adiposity and glucose homeostasis. Sci Reports 2014 41. 2014;4(1):1-9. doi:10.1038/srep05538

66. S K. Peroxisome proliferator-activated receptors and lipoprotein metabolism. PPAR Res. 2008;2008. doi:10.1155/2008/132960

67. Chang R, Ng TB, Sun WZ. Lactoferrin as Potential Preventative and Adjunct Treatment for COVID-19. Int J Antimicrob Agents (2020) 56(3):106118. doi: 10.1016/j.ijantimicag.2020.106118

68. Finzi E. Treatment of SARS-CoV-2 With High Dose Oral Zinc Salts: A Report on Four Patients. *Int J Infect Dis* (2020) 99:307–9. doi: 10.1016/j.ijid.2020.06.006

69. Widjaja G, Doewes RI, Rudiansyah M, Sultan MQ, Ansari MJ, Izzat SE, Al Jaber MS, Kzar HH, Mustafa YF, Hammid AT, Turki Jalil A, Aravindhan S. Effect of tomato consumption on inflammatory markers in health and disease status: A systematic review and meta-analysis of clinical trials. Clin Nutr ESPEN. 2022 Aug;50:93-100. doi: 10.1016/j.clnesp.2022.04.019. Epub 2022 Apr 23. PMID: 35871957.

70. Donma MM, Donma O. The effects of allium sativum on immunity within the scope of COVID-19 infection. Med Hypotheses. 2020 Nov;144:109934. doi: 10.1016/j.mehy.2020.109934. Epub 2020 Jun 2. PMID: 32512493; PMCID: PMC7265825.

71. Diomede L, Beeg M, Gamba A, Fumagalli O, Gobbi M, Salmona M. Can Antiviral Activity of Licorice Help Fight COVID-19 Infection? Biomolecules. 2021 Jun 8;11(6):855. doi: 10.3390/biom11060855. PMID: 34201172; PMCID: PMC8227143.

72. Orlowski S , et al. Coronaviruses, cholesterol, and statins: Involvement and application for Covid-19, Biochimie, Volume 189,2021, Pages 51-64, ISSN 0300-9084,https://doi.org/10.1016/j.biochi.2021.06.005.

73. Surma, Stanisław & Banach, Maciej & Lewek, Joanna. (2021). COVID-19 and lipids. The role of lipid disorders and statin use in the prognosis of patients with SARS-CoV-2 infection. Lipids in Health and Disease. 20. 141. 10.1186/s12944-021-01563-0.

74. Dai J, Wang H, Liao Y, Tan L, Sun Y, Song C, Liu W, Qiu X, and Ding C (2022) Coronavirus Infection

and Cholesterol Metabolism. Front. Immunol. 13:791267. doi: 10.3389/fimmu.2022.791267

75. Abbasi J. The COVID Heart—One Year After SARS-CoV-2 Infection, Patients Have an Array of Increased Cardiovascular Risks. JAMA. 2022;327(12):1113–1114. doi:10.1001/jama.2022.2411

76. Orlowski S , et al. Coronaviruses, cholesterol and statins: Involvement and application for Covid-19, Biochimie, Volume 189,2021, Pages 51-64, ISSN 0300-9084,https://doi.org/10.1016/j.biochi.2021.06.005

77. Barter PJ, Brandrup-Wognsen G, Palmer MK, Nicholls SJ. Effect of statins on HDLC: a complex process unrelated to changes in LDL-C: analysis of the VOYAGER.Database. J Lipid Res 2010;51:1546–53.

78. Permana H, Huang I, Purwiga A, Kusumawardhani NY, Sihite TA, Martanto E, et al.In-hospital use of statins is associated with a reduced risk of mortality in coronavirus-2019 (COVID-19): systematic review and meta-analysis. Pharmacol Rep 2021.

79. Chow R, Im J, Chiu N, Chiu L, Aggarwal R, Lee J, et al. The protective association between statins use and adverse outcomes among COVID-19 patients: a systematic review and meta-analysis. medRxiv. 2021:2021.02.08.21251070.