

Original Research

Elevated triglycerides predict increased mortality in patients with severe COVID-19 - An observational study

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KEYWORDS

COVID-19;
Critical illness;
Intensive care;
Lipoproteins;
Triglycerides;
Mortality

BACKGROUND: Dyslipidemia is common in severe COVID-19, but the prognostic significance of standard lipid parameters remains incompletely defined. Because severe COVID-19 frequently fulfills Sepsis-3 criteria, this setting also provides a relatively homogeneous model of viral sepsis.

OBJECTIVE: To assess the associations of standard serum lipid parameters with mortality in hospitalized patients with severe COVID-19.

METHODS: In this prospective observational cohort study, 191 adults with polymerase chain reaction (PCR)-confirmed COVID-19 admitted to Karolinska University Hospital, Stockholm, Sweden, during March to October 2020 were included. Serum total cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein-cholesterol, triglycerides, apolipoprotein A1 (ApoA1), apolipoprotein B, and lipoprotein(a) were analyzed in samples obtained a median of 5 days after hospital admission. Associations with mortality were evaluated using stepwise Cox regression with adjustment for age, sex, body mass index, time to inclusion, cumulative dexamethasone dose, D-dimer, C-reactive protein, lactate dehydrogenase, creatinine, and sedation status.

RESULTS: Overall, 24 patients (12.6%) died, and 77% fulfilled Sepsis-3 criteria. Nonsurvivors had higher triglycerides than survivors (3.2 vs 2.1 mmol/L; $P = .002$), whereas HDL-cholesterol and ApoA1 were lower. Triglycerides were the strongest independent laboratory predictor of mortality in the fully adjusted model (hazard ratio per 1 mmol/L increase, 1.18; 95% CI, 1.00–1.39; $P = .044$).

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CONCLUSION: Elevated triglycerides were independently associated with mortality in severe COVID-19. These findings support triglycerides as an accessible prognostic biomarker in severe COVID-19 with viral sepsis phenotype, while extrapolation to other forms of sepsis requires further study.
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Introduction

Although COVID-19 is not the same life-threatening pandemic as before, the disease still contains many details that need further investigation. Even if the causative agent is an RNA virus, the clinical condition contains many features that are also found in serious bacterial infections. In a meta-analysis evaluating seriously ill patients with COVID-19, 78% were found to meet the Sepsis-3 criteria for sepsis/septic shock with acute respiratory distress syndrome.¹ Other investigations have confirmed that several features in patients with COVID-19 agree with sepsis, but also point out differences, such as less intensive cytokine storm and another pattern in target plasma proteomics.^{2,3}

In addition to disturbances in a large number of analytic parameters in COVID-19 cases, aberrations in plasma lipids have also been reported. Meta-analyses on lipid parameters (see, eg,⁴⁻⁶) consistently report reductions in total cholesterol, high-density lipoprotein (HDL)-cholesterol, and low-density lipoprotein (LDL)-cholesterol in severe vs nonsevere COVID-19 cases, as well as in nonsurvivors compared to survivors. For triglycerides, statistically significant associations between triglyceride levels and mortality were not obtained. Individual studies, however, have demonstrated stronger links between elevated triglyceride levels and disease severity⁷ or mortality.^{8,9} Similar lipid alterations have previously been reported in cases with bacterial infections with sepsis.^{10,11}

The preceding study investigates serum levels of standard lipid analytes, extended with apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB), and lipoprotein (a) [Lp(a)], in a cohort of hospitalized and severely affected patients with COVID-19 prospectively collected during the initial wave of COVID-19 cases. Our aim was to identify potential associations with clinical characteristics, inflammatory markers, and mortality. Since the majority of these patients fulfilled the criteria for sepsis, they represent an interesting homogenous group with regard to sepsis – 1 microorganism, 1 predominant organ focus. Many studies on lipid aberrations in conjunction with sepsis face difficulties caused by heterogeneities in the patient cohorts and the invading microorganisms.

Methods

Study Cohort and Samples

The Karolinska KI/K Covid-19 Biobank Project is a prospective cohort of patients with SARS-CoV-2, hospitalized

between March and October 2020 at Karolinska University Hospital, located in Stockholm, Sweden, at the departments of infectious diseases, the high dependency unit, and the intensive care unit (ICU). Inclusion criteria were patients with polymerase chain reaction (PCR)-verified COVID-19, with available blood sampling 5 to 24 days after symptom onset and after being admitted to hospital in the acute phase, and capable to consent to study participation. Patients with current malignant disease and/or ongoing immunomodulatory treatment before hospitalization were excluded. Serum samples from a total of 191 patients were utilized to analyze lipid parameters. The patients were between 18 and 91 years of age, and the majority were of male sex (77%) according to medical records. One hundred patients were treated at the ICU, of whom 49 were sedated. The occurrence of sepsis was established by calculation of the Sequential Organ Failure Assessment (SOFA) score. Further patient characteristics are given in Table, grouped by the main outcome of survival.

Blood samples, in addition to the routine care sampling, were collected at enrollment in the study and were biobanked at -80°C for future analysis. Sampling was carried out at a median of 5 days after hospital admittance (IQR 3–11 days). Clinical parameters, such as patient characteristics, level of care, medications, routine laboratory measurements, and outcomes, were compiled in an anonymized dataset by the Karolinska KI/K COVID-19 Study Group.

Measurements of Lipid Parameters

Total cholesterol, HDL-cholesterol, triglycerides, ApoA1, ApoB, and Lp(a) in serum were analyzed with accredited routine analytical methods at the medical unit of Clinical Chemistry at Karolinska University Laboratory, using the Roche Cobas 8000 system (Roche Diagnostics GmbH). Non-HDL-cholesterol was derived by subtracting HDL-cholesterol from total cholesterol. LDL-cholesterol was calculated using the Friedewald formula¹² in samples with triglyceride levels ≤ 4.0 mmol/L, while LDL-cholesterol was not determined in samples with triglycerides > 4 mmol/L ($n = 35$), in accordance with national guidelines in Sweden.¹³ Direct LDL-cholesterol measurements or alternative estimation formulas were not applied.

Statistical Analysis

All statistical analyses were performed using R Studio (Boston, MA, United States) and R (version 4.1.2). *P* values

Table. Clinical characteristics and laboratory parameters of the study participants according to mortality.

	Total (n = 191)	Survivors (n = 167; 87.4%)	Nonsurvivors (n = 24; 12.6%)	P value
Age, y	59.0 (51.0-66.5)	58.0 (50.5-64.0)	66.0 (59.0-70.0)	< .001
Male, n (%)	147 (2,77)	125 (74.9)	22 (7,91)	.116
ICU, n (%)	100 (52.4)	80 (47.9)	203, (83)	.002
Sepsis (SOFA $\geq$ 2), n (%)	147 (77)	123 (74)	24 (100)	.002
Hypertension, n (%)	88 (46.1)	77 (46.1)	11 (45.8)	1.000
Diabetes mellitus, n (%)	54 (28.3)	46 (27.5)	8 (3,33)	.729
Thrombosis, n (%)	20 (10.5)	16 (9.6)	4 (16.7)	.570
Cum. dexamethasone dose (mg)	5.0 (0-25.0)	3.8 (0-17.5)	35.0 (13.7-98.9)	< .001
BMI, kg/m ²	28.5 (25.4-32.0)	28.8 (25.5-32.2)	26.9 (25.3-30.0)	.139
Laboratory parameters				
Total cholesterol (mmol/L)	3.6 (3.1-4.7)	3.7 (3.1-4.6)	3.4 (3.0-5.4)	.717
Non-HDL cholesterol (mmol/L)	2.9 (2.4-4.0)	3.0 (2.4-3.8)	2.9 (2.4-5.0)	.478
Triglycerides (mmol/L)	2.2 (1.5-3.3)	2.1 (1.5-3.1)	3.2 (2.0-4.9)	.002
HDL-C (mmol/L)	0.7 (0.5-0.9)	0.7 (0.5-0.9)	0.5 (0.4-0.7)	.003
LDL-C (mmol/L)	1.8 (1.4-2.4)	1.9 (1.4-2.4)	1.4 (1.0-2.0)	.071
Apolipoprotein B (g/L)	1.0 (0.8-1.2)	1.0 (0.8-1.2)	1.1 (0.7-1.5)	.661
Apolipoprotein A1 (g/L)	0.7 (0.6-0.9)	0.8 (0.6-0.9)	0.6 (0.5-0.7)	.002
Lp(a) (nmol/L)	14 (6-40)	14 (7-42)	10 (4-33)	.193
CRP (mg/L)	105 (59-194)	100 (57-171)	202 (106-278)	.001
Ferritin (μ g/L)	1128 (615-1896)	1094 (590-1891)	1535 (950-1937)	.140
Neutrophil count (10^9 /L)	8.1 (4.7-10.7)	7.8 (4.6-10.0)	11.5 (7.7-13.8)	< .001
D-dimer (mg/L FEU)	1.33 (0.63-3.6)	0.98 (0.58-2.8)	4.4 (2.2-10.4)	< .001
Creatinine (μ mol/L)	71 (55-86)	69 (54-80)	94 (70-152)	< .001
LDH (μ kat/L)	6.4 (5.1-8.5)	6.2 (5.1-7.9)	9.2 (7.5-11.6)	< .001
Thrombocytes (10^9 /L)	277 (217-389)	287 (222-415)	255 (178-281)	.026
IL-6 (ng/L)	51 (16-134)	43 (15-99)	130 (42-507)	.003

Abbreviations: BMI, body mass index; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; ICU, intensive care unit; IL-6, interleukin-6; LDH, lactate dehydrogenase; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); SOFA, Sequential Organ Failure Assessment.

Note: The *P* values for statistical differences were obtained by the Mann-Whitney U-test for skewed variables and by the χ^2 test for categorical variables. Continuous data are expressed as median and IQR.

< .05 were considered statistically significant. All code used for analysis is open-sourced at github.com/tamas875/research-methods. First, baseline characteristics analyses were carried out stratified by mortality. For categorical variables, the numbers per category were obtained with corresponding percentages. *P* values for differences in baseline characteristics were calculated utilizing the Mann-Whitney U-Test for skewed variables and χ^2 test for categorical ones. To investigate the correlation between all baseline variables, Spearman's rank correlation coefficients were calculated, and derived values were used to plot a correlation matrix between continuous variables. Subsequently, Cox regression analysis was performed on triglycerides, and the hazard ratios (HRs) were plotted against triglyceride concentrations. To adjust for potential confounders, several Cox regression models were created in a stepwise manner. Model 1 was a crude analysis. Model 2 was adjusted for age and sex. Model 3 was model 2 + time of hospitalization before inclusion, model 4 was model 3 + cumulative dexamethasone dose, model 5 was model 4 + BMI, model 6 was model 5 + D-dimer, model 7 was model 6 + C-reactive protein (CRP) and LD, model 8 was model 7 + creatinine, and model 9 was model 8 + sedation status. Lastly, the association between triglycerides and

mortality was visualized utilizing cubic splines analysis with 3 knots. The best number of knots (up to 7) was selected by estimating the Akaike information criterion.

Results

The relationships between lipid parameters, clinical characteristics, inflammatory markers, and mortality were explored in 191 hospitalized patients with COVID-19. Initial analyses revealed prevalent lipid aberrations compared to current reference intervals in a large proportion of the cohort, including primarily reduced levels of total cholesterol (96 of 191; 50%), HDL-cholesterol (135 of 191; 71%), and LDL-cholesterol (79 of 156 estimated; 51%), and elevated concentrations of triglycerides (73 of 191; 38%). In total, 165 out of the 191 patients (86%) exhibited at least one of these aberrations.

The Table delineates the characteristics and laboratory parameters of the study cohort, categorized by the main outcome into survivors and nonsurvivors. No statistically significant differences were observed between the groups regarding sex distribution, BMI, prevalence of hypertension or diabetes mellitus, or in the occurrence of thrombosis

during the period of care. However, nonsurvivors (24 individuals; 12.6%) were older with a median age of 66 years, in contrast to 58 years of age in the survivors ($P < .001$). Of the nonsurvivor group, 83% were admitted to the ICU compared to 48% of the survivor group ($P = .002$). One hundred and six patients were treated with corticosteroids at the time of biobank sampling (83% of the nonsurvivors vs 51% of the survivors). The median (IQR) cumulative doses of dexamethasone delivered to those on corticosteroid treatment were 56.3 (26.9-125.6) and 17.4 (7.5-37.5) mg for survivors and nonsurvivors, respectively. According to the SOFA score, 77% of the total patients qualified for sepsis (≥ 2), which included all nonsurvivors. Of the survivors, 74% were classified as having sepsis.

Characterization of the lipid parameters showed that compared to survivors, nonsurvivors had significantly higher triglyceride levels ($P = .002$), along with lower HDL-cholesterol ($P = .003$) and ApoA1 levels ($P = .002$). No significant differences were observed for total cholesterol, non-HDL-cholesterol, LDL-cholesterol, ApoB, or Lp

(a) levels. When comparisons were made regarding sepsis, significant correlations were found between sepsis and elevated levels of triglycerides and reduced concentrations of HDL-cholesterol and apoA1. No correlations reaching significance were obtained for total cholesterol, LDL-cholesterol, ApoB, Lp(a), or non-HDL-cholesterol. Among other routine laboratory analyses obtained within 24 hours from the time of biobank sampling, significantly higher levels of CRP, interleukin-6, D-dimer, creatinine, and lactate dehydrogenase (LDH) were observed in nonsurvivors compared to survivors (see Table for P values). This was also found for neutrophil granulocyte counts in nonsurvivors, while their thrombocyte counts were significantly lower. Serum ferritin levels were generally high but did not differ significantly between the 2 groups.

Correlations between the baseline parameters were expressed in a heat map (Fig 1). As expected, high correlations were seen between total cholesterol and non-HDL-cholesterol, LDL-cholesterol and ApoB, and between HDL-cholesterol and ApoA1, while the lipid parameters showed

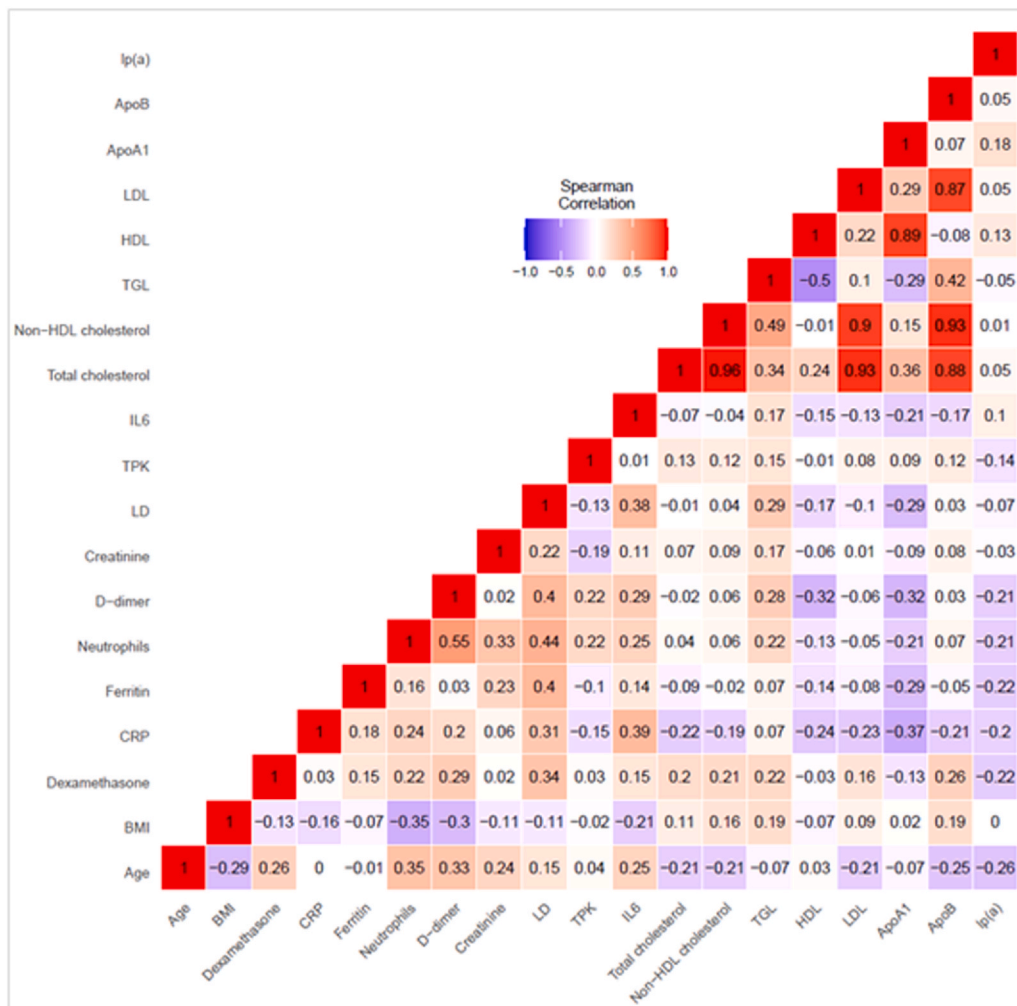


Figure 1. Correlation matrix and heatmap between baseline variables. Correlation coefficients were obtained by Spearman correlation. Abbreviations: ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; BMI, body mass index; CRP, C-reactive protein; HDL, high-density lipoprotein; IL-6, interleukin-6; LD, lactate dehydrogenase; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); TGL, triglycerides; TPK thrombocyte particle count.

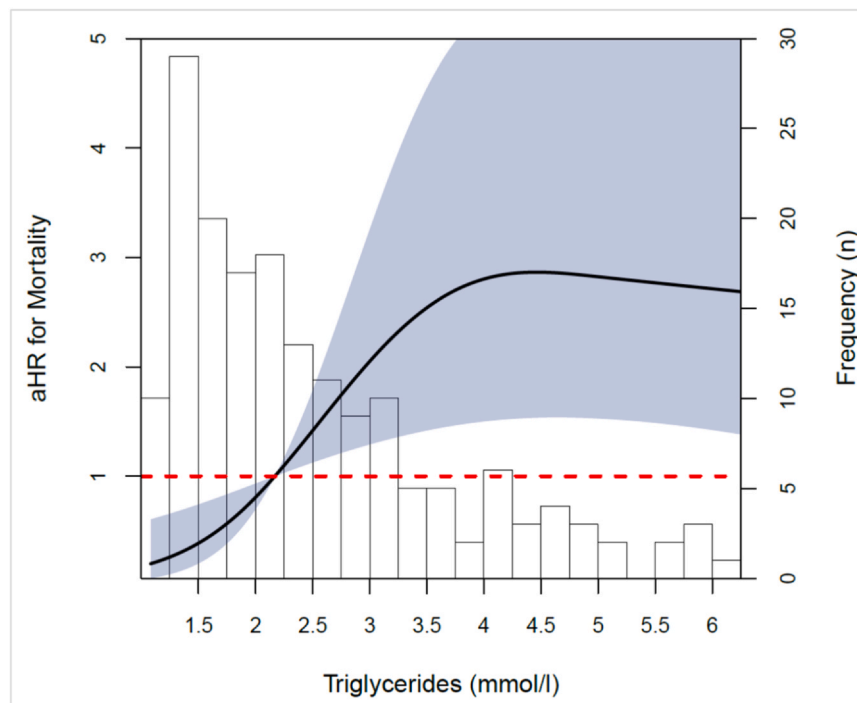


Figure 2. Adjusted hazard ratios (aHR) for mortality at different triglyceride concentrations. The blue area represents the 95% CI of the aHR.

low correlation values with BMI, dexamethasone treatment and the other clinical chemistry parameters. Next, the longitudinal associations of various clinical chemical parameters with mortality were assessed. The results showed the highest concordance indices for serum triglycerides (0.776), followed by HDL-cholesterol (0.745), LDH (0.741), platelet count (0.720), D-dimer (0.714), CRP (0.709), creatinine (0.682), ApoA1 (0.681), neutrophil count (0.627), and IL-6 (0.602).

Since triglycerides showed the strongest association with mortality, this particular lipid parameter was investigated in greater detail using Cox regression analysis. A continuous representation of the HR for mortality at varying triglyceride levels, adjusted HRs for age and sex (aHR), is displayed in Figure 2. Overall, increasing baseline triglyceride levels were associated with higher aHRs for mortality during follow-up. A median triglyceride level of 2.2 mmol/L corresponded to an HR of 1.0. Further Cox regression analyses adjusted for several potential confounders are shown in Figure 3. In the crude analysis (model 1), an increase of 1 mmol/L of triglycerides was associated with a HR of 1.19 (95% CI 1.03-1.36) for mortality. After multivariable adjustment for age, sex, and other potential confounders (models 2-9), the association remained statistically significant in the fully adjusted model 9 (HR 1.18; 95% CI 1.00-1.39, P value .044).

Discussion

The present study of hospitalized patients with COVID-19 demonstrates that elevated triglycerides were the

strongest laboratory parameter associated with fatal outcomes among both lipid and nonlipid parameters. This association was preserved even after adjustment for potential confounders, including treatment with corticosteroids, which was not standard care during the first COVID-19 wave, and propofol, primarily used for sedation in ICU settings. Several nonlipid parameters (eg, LDH, platelet counts, D-dimer, and CRP) also showed a significant association with mortality, but no strong correlations were found between any of these and triglycerides. This indicates that high triglycerides represent an independent risk factor for mortality and that triglyceride levels may be regulated through unique pathways in the context of COVID-19. Furthermore, even if we observed decreased levels of total cholesterol, HDL-cholesterol, and LDL-cholesterol, only HDL-cholesterol reached statistical significance when survivors and nonsurvivors were compared. As expected, ApoA1 levels were also reduced and inversely related to mortality.

Contrary to our results, the meta-analyses by Mahat et al.,⁵ Chidambaram et al.,⁴ and Zinellu et al.,⁶ did not find significant associations between triglycerides and mortality, albeit with notable variability across included studies. For instance, Mahat et al.⁵ found that triglyceride levels were higher in nonsurvivors compared to survivors, but this difference did not reach statistical significance ($P = .19$), and heterogeneity was exceptionally high ($I^2 = 97\%$). In agreement with our findings, several individual studies have demonstrated associations between elevated triglyceride levels and adverse outcomes in patients with COVID-19.^{7-9,14-17} The study by Dai et al.⁸ is the most closely

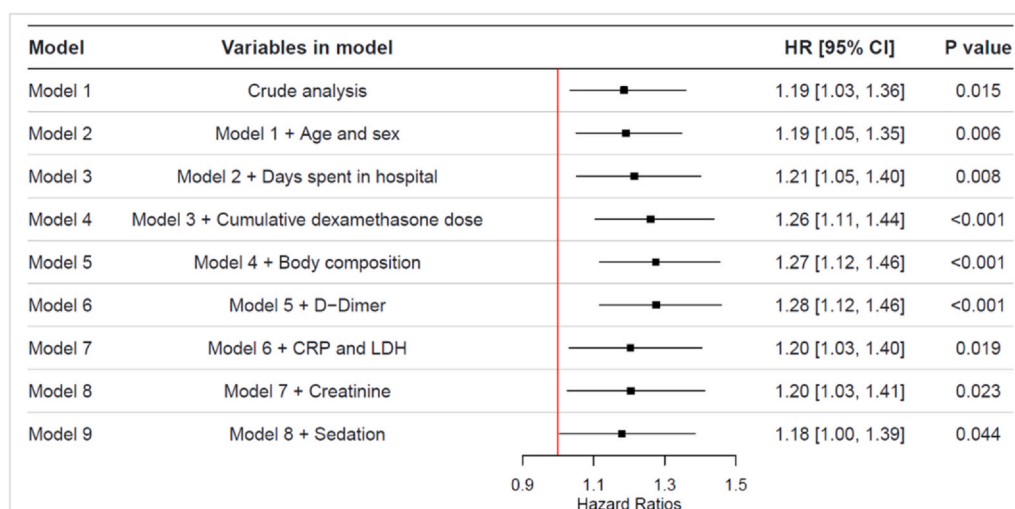


Figure 3. Hazard ratios for mortality per 1 mmol/L increase in triglyceride concentrations. Abbreviations: CRP, C-reactive protein; HR, hazard ratio; LDH, lactate dehydrogenase.

related prior work and demonstrated that hypertriglyceridemia during hospitalization was independently associated with mortality in a large US cohort ($n = 600$). Our findings are consistent with this observation and extend it in some respects. First, we evaluated triglycerides within a broader routinely available lipid panel, with ApoA1, ApoB, and Lp(a) in addition to conventional lipid fractions. Notably, ApoB, non-HDL cholesterol, and Lp(a) did not differ significantly between survivors and nonsurvivors, suggesting that the observed lipid-associated mortality was not primarily explained by total ApoB-containing lipoprotein particle burden, or Lp(a)-related risk. Second, we compared the predictive performance of triglycerides with both lipid and nonlipid laboratory parameters head-to-head using concordance indices. In this analysis, triglycerides had the highest C-index (0.776), exceeding those of CRP, IL-6, neutrophils, platelets, D-dimer, creatinine, and LDH. Third, triglycerides showed no strong correlation with these inflammatory, hemostatic, or tissue injury markers in our cohort, suggesting that triglycerides may provide prognostic information not fully captured by standard acute-phase or organ dysfunction markers. The discrepancies across meta-analyses and individual cohort studies may reflect differences in study populations, comorbidities, and treatment protocols. Notably, the studies included in the relatively early meta-analyses were dominated by Chinese cohorts, whereas individual studies reporting positive associations between triglycerides and adverse outcomes originated from US, European, and Latin American populations. Differences in genetic background and lipid metabolism between populations may contribute to inconsistencies, which highlights the importance of population-specific analyses. eg, Frank et al.¹⁸ reported distinct dyslipidemia patterns between Asian and White populations. A genome-wide analysis by Tanha et al.¹⁹ identified pleiotropic genetic links between triglyceride levels and severe COVID-19, suggesting a potential causal role. Interestingly, the increased

triglycerides do not seem to be confined to the very-LDL fraction since triglyceride-enriched LDL-like particles (lipoprotein Z) were found in patients with COVID-19, indicating potential shifts in lipoprotein composition during severe disease.²⁰

A notable feature of our cohort is that severe COVID-19 frequently fulfilled Sepsis-3 criteria, indicating that the clinical phenotype largely corresponded to viral sepsis. This characterization is consistent with a proteomic analysis from the same biobank cohort, where COVID-19 during 2020 was described as a relatively homogeneous sepsis population—driven by a single pathogen and dominated by respiratory organ dysfunction—and therefore proposed as a model of viral sepsis, showing a neutrophil-driven inflammatory proteomic profile.²¹ Our results also indicated that elevated triglyceride levels correlated well with the sepsis condition, further strengthening the significance of measuring triglycerides in these patients. The homogeneity of the material supports the internal consistency of the findings and generates the hypothesis that similar associations may also be relevant for other forms of sepsis, particularly viral sepsis, warranting further investigation. Thus far, in septic cases in general, elevated concentrations of triglycerides have not been consistently documented. Actually, in 1 study increased levels rather served as predictor of a better prognosis, but the infecting agents were not reported.¹¹

Reduction of HDL- and LDL-cholesterol levels has previously been reported both in cases with bacterial sepsis¹⁰ and viral diseases such as HIV and dengue fever.²² Low levels of HDL-cholesterol are generally considered unfavorable because of the pleiotropic functions associated with HDL, such as anti-inflammatory,²³ antioxidant, and antithrombotic activities. It is not fully understood how lowered LDL-C levels would affect the severity or the outcome of sepsis.

The mechanisms behind the lipid aberrations in patients with COVID-19 are still not satisfactorily explained.

Suggestions have been put forward for hepatic dysfunction, the impact of inflammation, and activation of immune cell subsets, as well as altered expression of lipoprotein receptors. Increased levels of ApoC-III relative to the HDL concentration, detected in patients with COVID-19, may prolong the half-life of triglyceride-rich particles by reducing lipoprotein lipase activity.²⁴ Metabolic involvement and inflammation of the adipose tissue in the body might also occur – patients with overweight and type 1 and 2 diabetes are often more prone to develop severe disease (for a review see²⁵). However, in our patients, no significant differences in BMI or diabetes prevalence between survivors and nonsurvivors were observed. In addition to focusing on distinct biomarkers, there is also an importance to take multidimensional inflammatory profiling into account when aiming to predict outcomes for patients with severe COVID-19. This is an example illustrated by the shown promise of the neutrophil-to-lymphocyte percentage ratio,²⁶ the CRP-to-albumin ratio,²⁷ and more complex clinical scoring systems²⁸ to improve risk prediction in the COVID-19 patient population.

We acknowledge that our study harbors certain limitations to warrant consideration. Primarily, the observational nature of our study might entail inherent biases, and the specificity of the Swedish cohort, consisting of early wave cases, may restrict generalizability. Additionally, measurements of LDL-cholesterol were unavailable in 35 patients (18%) with triglyceride levels >4 mmol/L, which may limit comparisons involving LDL-cholesterol and potentially introduce selection bias since more nonsurvivors had triglyceride values above this level. However, non-HDL cholesterol and ApoB, serving as surrogate measures of atherogenic lipoprotein burden, were available for all patients and did not differ significantly between survivors and nonsurvivors. Furthermore, information on lipid-lowering therapy and parenteral or enteral nutritional support was unavailable. Finally, the number of mortality events was limited relative to the covariates included in the fully adjusted Cox regression model. This raises the potential for some overfitting, and the aHR should be interpreted accordingly. Nevertheless, this is the largest study on serum lipid parameters to our knowledge in Swedish patients with COVID-19. Future investigations could employ more diverse cohorts and possibly multicentric approaches to foster a broader understanding and validation of our findings. Additionally, a deeper exploration into the potential molecular mechanisms underlying the observed lipid aberrations might shed light on potential novel therapeutic avenues.

Taken together, our data suggest that lipid parameters could be an important biochemical marker in severe COVID-19 cases and possibly also in other cases with sepsis, which, however, remains to be tested. Specifically, elevated triglycerides could represent a biomarker for the prediction of an unfavorable outcome. Given that lipid analyses are well established, usually quite accessible, and cost-effective, their incorporation into the routine diagnostics of infectious patients will represent a feasible and valuable strategy.

CRediT authorship contribution statement

Daniel P.O. Eklund: Writing – review & editing, Writing – original draft, Project administration, Funding acquisition, Data curation. **Tamas Szili-Török:** Writing – original draft, Visualization, Formal analysis. **Kristoffer Strålin:** Resources, Data curation. **Claudia Lannsjö:** Formal analysis. **Soo Aleman:** Resources, Data curation. **Mats Eriksson:** Writing – original draft, Resources, Project administration, Conceptualization. **Uwe J.F. Tietge:** Writing – review & editing, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Gösta Eggertsen:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Conceptualization.

Ethics declaration

The authors have NOT obtained informed consent from participants or their legal representatives. The patients provided informed consent before enrollment at the Department of Infectious Diseases and the high-dependency unit. However, the Ethical Review Authority approved that the ICU patients were sampled before consent, although consent was asked for as early as possible. For ICU patients who died before consent, the Ethical Review Authority approved that we assume consent for participation.

This study included organ or tissue donors. This study includes human biological material, and consent was obtained by donors, or their next of kin or legal representatives, for use in this study and for publication of the article. The samples used in this research were not sourced from executed prisoners or prisoners of conscience.

This study was performed in compliance with relevant laws, regulatory frameworks, and guidelines where the research took place. This study was approved by the Swedish Ethical Review Authority. (Approval No. 2020-01558 and Ö47-2021/3.1)

Ethical approval

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Declaration of generative AI and AI-assisted technologies in the writing process

The authors of this manuscript did not use generative AI and AI-assisted technologies in the writing process

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Declaration of competing interest

Dr Aleman received honoraria for lectures/educational events from Gilead, MSD, and Biogen, has participated in advisory boards for Gilead and Ribocure, reports grants from Gilead and AbbVie, all of which are not related to this study. Professor Eriksson has participated in the advisory board of Chinese and Ultragenics and has obtained lecture fees from Sanofi and Novartis. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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