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Research Article

# Triglyceride Levels and COVID-19 Severity: A Systematic Review and Meta-Analysis

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## Abstract

**Introduction:** The severity of Coronavirus Disease 2019 (COVID-19) has been linked to lower levels of lipid profile, including total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol. However, the relationship between triglycerides and COVID-19 severity is still controversial. Thus, this study aimed to evaluate the association between triglyceride concentration and COVID-19 severity.

**Methods:** The systematic review adhered to the PRISMA guidelines. Heterogeneity was assessed using Thompson's $I^2$ and $Tau^2$ statistics, and the Standardized Mean Difference (SMD) and 95% confidence intervals (CIs) in triglyceride levels were calculated using random-effects models. Publication bias was evaluated using Egger's test.

**Results:** Our meta-analysis included 12 observational studies with a total of 5,369 confirmed COVID-19 patients. Of these, 3,956 (46% males) had non-severe COVID-19, and 1,513 (59% males) had severe COVID-19 during follow-up. The SMD in triglyceride levels was 0.110 (95% CI=[0.004, 0.217], P=0.042), indicating a significant difference between the non-severe and severe groups. The studies exhibited moderate heterogeneity in the triglyceride levels ($I^2$=50.7%). A meta-regression analysis showed that the SMD of triglyceride was significantly associated with the risk ratio of hyperlipidemia (coefficient=-1.40, P=0.007). No publication bias was detected in the studies according to Egger's test.

**Conclusion:** Our systematic review and meta-analysis revealed that lower serum triglyceride concentrations were associated with severe COVID-19 in patients. Further investigation is needed to determine whether lower triglyceride levels increase COVID-19 severity in larger populations.

**Keywords:** COVID-19; Lipids; Prognosis; Severity; Triglycerides

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## Abbreviations

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

COVID-19: coronavirus disease 2019

TC: total cholesterol

LDL-C: low-density lipoprotein cholesterol

HDL-C: high-density lipoprotein cholesterol

TG: triglycerides

SMD: standardized mean difference

Cis: confidence intervals

RT-PCR: real-time reverse transcriptase-polymerase chain reaction

RR: respiration rate

ICU: intensive care unit

BMI: body mass index

NOS: Newcastle-Ottawa quality assessment scale

IQR: interquartile range

SD: standard deviations

RR: risk ratio

TRL: TG-rich lipoprotein

VLDL: very low-density lipoproteins

## Introduction

The COVID-19 pandemic has inflicted unprecedented global morbidity and mortality, with devastating consequences for public health, social and economic wellbeing [1]. In response to the pandemic, the scientific community has launched an intensive investigation into the multifactorial determinants of COVID-19 severity and outcomes, including comorbidities, age, sex, genetics, and environmental

factors [2]. In recent years, increasing attention has been focused on the role of lipids, including triglycerides, as critical mediators of systemic inflammation and immune response [3]. Although the exact mechanisms linking lipid metabolism and COVID-19 pathogenesis remain elusive, numerous studies have explored the potential association between serum triglyceride levels and COVID-19 severity, with conflicting results. Despite the clinical relevance of this issue, there is currently no consensus on the impact of serum triglyceride levels on COVID-19 outcomes. Some studies have suggested that elevated serum triglyceride levels are associated with a higher risk of severe disease and mortality, while others have found no significant association [4,5]. Therefore, the objective of this systematic review and meta-analysis is to provide a comprehensive assessment of the current evidence regarding the relationship between serum triglyceride levels and COVID-19 severity. Our study aims to synthesize the existing literature, identify knowledge gaps and inconsistencies, and suggest avenues for future research. By doing so, we hope to contribute to a more nuanced understanding of the complex interplay between lipid metabolism and COVID-19 pathogenesis, which could inform the development of more effective prevention and treatment strategies.

## Methods

This systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [6], as described in a PRISMA checklist (Table 1). The protocol for the systematic review was pre-registered in the PROSPERO database (registration number: CRD42022317185). All studies included in the meta-analysis were approved by the institutional review board of the corresponding institutions, and all patients provided informed consent for their data to be used for research purposes.

### Systematic Literature Search

A comprehensive search of electronic databases, including PubMed, Embase, and MEDLINE, was conducted to identify relevant studies investigating the association between serum triglyceride levels and the severity of COVID-19. The search was limited to studies published up until March 31, 2022. The following medical subject heading (MeSH) terms were used in the search: “COVID-19”, “SARS-CoV-2”, “triglycerides”, “lipid profile”, “severity”, “mortality”, “prognosis”, and “retrospective studies”. The reference lists of all relevant articles were also manually screened to identify additional studies.

### Eligibility Criteria

Eligible studies were required to meet the following inclusion criteria: (1) observational studies, including case-control and retrospective cohort designs, investigating the association between serum triglyceride levels reported upon admission and COVID-19 severity; (2) COVID-19 patients confirmed by a positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR) result for SARS-CoV-2 in respiratory specimens and hospitalized, aged more than 18 years old; (3) COVID-19 patients classified into two groups based on clearly defined patient symptoms, including non-severe and severe case groups; (4) studies reporting numbers for patients in the non-severe and severe case groups and raw values for triglyceride levels reported upon admission.

COVID-19 severity was diagnosed in accordance with the Novel Coronavirus Pneumonia Diagnosis and Treatment Intern Guidance [7]. In this meta-analysis, severe cases of COVID-19 were defined as meeting at least one of the following criteria: (1) shortness of breath and a respiration rate (RR) $\geq$ 30 breaths per minute; (2) oxygen saturation $\leq$ 93%; (3) PaO2/ FiO2 $\leq$ 300 mmHg; (4) progression of pulmonary lesions greater than 50% on chest CT within 24 to 48 hours; (5) receipt of mechanical ventilation; (6) shock; or (7) admission to an intensive care unit (ICU) or death. Non-severe cases were defined as confirmed COVID-19 patients not meeting these criteria.

### Study Screening and Data Extraction

Two reviewers (LJS and ZML) independently screened all retrieved literature by titles and abstracts and filtered out letters, comments, editorials, reviews, meta-analyses, practice guidelines, case reports, or research articles. If two or more study participants overlapped, the study with the largest sample size was included. Duplicate publications were eliminated and essential information was extracted from the literature using Zotero 6.0 (Corporation for Digital Scholarship, Vienna, VA, USA). Two independent reviewers (LJS and YRQ) extracted the following data from each eligible study: first author name, year of publication, country of centers, study location, study design, patient profile (total number of patients, age, body mass index (BMI), and sample size in the non-severe cases, severe cases), and triglyceride levels. Any disagreements between the investigators were resolved through consensus or referred to a third reviewer (YSK) for resolution.

### Quality Assessment

The quality of each eligible study was assessed using the Newcastle-Ottawa Scale (NOS) for observational studies by two reviewers (HZY and DHB). The NOS evaluates the quality of non-randomized studies by considering the selection of study groups, the comparability of groups, and the ascertainment of the exposure or outcome of interest. A score of 7 or higher was considered to indicate a high-quality study [8]. Any disagreements related to the quality assessment were settled by another author (ZYL or ZF).

### Data Synthesis and Analysis

The meta-analysis was performed using the meta package in Stata software (Stata SE 16, TX, US). The standardized mean difference (SMD) and 95% confidence interval (CI) were calculated for the difference in triglyceride levels between COVID-19 patients with different severity categories. When variables were presented as median and interquartile range (IQR), they were converted into means and standard deviations (SD) using Wan et al.’s method [9].

Heterogeneity between studies was assessed using Cochran’s Q statistic, Thompson’s $I^2$, and $Tau^2$ statistics, with an $I^2$ value of 50% or higher indicating significant heterogeneity. A continuous variable meta-analysis of pooled SMD with 95% CI was performed using the common-effect inverse-variance model. The robustness of the meta-analysis was assessed using Jackknife sensitivity analyses by omitting each included study. Potential publication bias was assessed using Egger’s test and a funnel plot. Meta-regression analysis was performed to examine potential sources of heterogeneity in the association between serum triglyceride levels and COVID-19 severity, including the year of publication, country, mean age, gender distribution, BMI, hypertension, diabetes mellitus, and coronary artery disease cases. The significance of meta-regression coefficients was assessed using a *Z*-test.

## Results

A total of 12 studies were included in this systematic review and meta-analysis after applying the inclusion and exclusion criteria through full-text screening. The PRISMA flow diagram, shown in figure 1, describes the study selection process.

### Study Characteristics

All 12 studies were retrospective cohort hospital-based studies published between January 2020 and December 2021. Ten studies were from China [10-19] and two were from Turkey [19,20]. The study sample consisted of 5369 COVID-19 patients, of which 3956 (46% male) had non-severe disease and 1513 (59% male) had severe disease at follow-up. According to the National Health Commission of China guidelines, COVID-19 patients were classified into mild, moderate, severe, and critical. Nine studies followed these guidelines, while the remaining three studies used different diagnostic criteria but met the eligibility criteria. In this meta-analysis, severe and critical COVID-19 patients were classified as severe cases, and mild and moderate COVID-19 patients were classified as non-severe cases. Four studies classified patients as non-severe or severe, with critical cases being classified as severe. The unit of triglyceride concentrations in three studies was measured in mg/dL, and all triglyceride concentrations were within the reference range for triglyceride (0.45-1.69 mmol/L or <150 mg/dL) in China, except for the two non-severe groups in the included studies. Table 1 summarizes the detailed characteristics of the included studies.

### Quality Assessment

The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS). Two studies scored 9 points, seven studies scored 8 points, and three studies scored 7 points, indicating high-quality studies with low risk of bias. The results of the quality assessment are shown in table 2.

### Results of Synthesis

The meta-analysis was conducted to determine the difference in triglyceride levels between COVID-19 patients with different disease severity. The standardized mean difference (SMD) and 95% CI were calculated and found to be 0.110 (95% CI=[0.004, 0.217]), indicating a significant difference in triglyceride levels between COVID-19 patients with different disease severity ($P$<0.05). Heterogeneity was assessed using the Cochran's Q statistic, Thompson's $I^2$, and $Tau^2$ statistics, and was found to be moderately significant ($I^2$=50.7%). The forest plot of the meta-analysis is shown in figure 2.

### Publication Bias and Meta-Regression

Publication bias was assessed using Egger's test and a funnel plot and was found to be non-significant (P=0.136). The funnel plot is shown in figure 3. The results of the Jackknife sensitivity analysis indicated that the meta-analysis was robust, with no significant changes in the results after omitting any one study (Figure 4). Meta-regression analysis was conducted to examine potential sources of heterogeneity, including the year of publication, country of origin, mean difference in age and BMI, and odds-ratios of male gender and the presence of hypertension, diabetes mellitus, hyperlipidemia, and coronary artery disease. The results of the meta-regression analysis indicated that hyperlipidemia was significantly associated with heterogeneity (coefficient=-1.40, P=0.007). The detailed results of the meta-regression are shown in table 2.

Meta-regression analysis to assess the impact of the covariates on the mean difference of triglyceride levels (mmol/L) between patients with non-severe and severe COVID-19.

## Discussion

In this systematic review and meta-analysis, we sought to explore the potential association between triglyceride levels and the severity of COVID-19. Our analysis revealed a significant difference in triglyceride levels between patients with severe and non-severe COVID-19. Notably, patients with severe COVID-19 had lower triglyceride levels compared to those with non-severe COVID-19, with a clinically relevant effect size (SMD value of 0.11) [21,22].

### Comparisons with other studies

Previous studies have implicated dyslipidemia and lipid profile as possible risk factors for COVID-19 [23], yet the relationship between triglyceride levels and COVID-19 severity remains unclear. In our study, we found an unexpected inverse relationship between serum triglyceride levels and COVID-19 severity, which differs from some previous studies that have reported positive associations between triglyceride levels and COVID-19 severity. For example, a study conducted by Kenes MT et al., [24] found that elevated triglyceride levels were associated with increased risk of severe COVID-19 in an American population. Another study by Zhong P et al., [25] reported similar findings in a Chinese population. While our results are consistent with Wei X et al., [16] that elevated triglyceride levels in COVID-19 patients with non-severe cases. Several meta-analyses of lipid profiles in COVID-19 patients found that lower levels of total cholesterol, LDL-C, and HDL-C were associated with severity and mortality in COVID-19 patients. However, these meta-analyses found no significant association between triglyceride levels and COVID-19 severity [26-28]. This discrepancy may be attributed to variations in the inclusion and exclusion criteria, inconsistent severity stratification, or missing information on the timing of blood collection for laboratory measurements.

### Implications for clinical practice

Specifically, we observed that patients with severe COVID-19 had significantly lower triglyceride levels compared to those with non-severe disease. Although the exact mechanism underlying this inverse association is not fully understood, it is possible that decreased triglyceride levels reflect a dysregulated lipid metabolism and compromised immune function in severely COVID-19 patients [29]. Alternatively, COVID-19 treatment may need to be individualized based on the patient's triglyceride levels, it could be that triglyceride-lowering treatments, such as fibrates, which are commonly used in patients with hypertriglyceridemia [30], might confer protective effects against severe COVID-19. Furthermore, future research could investigate the predictive role of triglyceride levels in COVID-19 prognosis, which could help clinicians better anticipate disease progression and take appropriate therapeutic measures.

### Potential mechanisms between triglyceride levels and COVID-19 severity

Several possible mechanisms may explain the observed association between serum triglyceride levels and COVID-19 severity. These

| First author name | Year | Country | Data sources | Non-severe cases of COVID-19 | | | | Severe cases of COVID-19 | | | | NOS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Number of patients (Male) | Age, median (IQR) or mean ± SD | BMI (kg/m2) | Triglyceride (mmol /L or mg/dL), median (IQR) or mean ± SD | Number of patients (Male) | Age, median (IQR) or mean ± SD | BMI (kg/m2) | Triglyceride (mmol /L or mg/dL), median (IQR) or mean ± SD | |
| Ali Barman | 2021 | Turkey | Okmeydani Training and Research Hospital | 185 (113) | 53.12±18.5 | NR | 156.6±71.9 | 139 (84) | 65.4±15.5 | NR | 133.7±59.2 | 9 |
| Chuming Chen | 2020 | China | Third People's Hospital of Shenzhen, Shenzhen | 325 (139) | 41 (31–56) | 22.68 (20.43-24.97) | 0.91 (0.70–1.37) | 92 (59) | 61 (52–65) | 24.52 (22.84-26.68) | 1.02 (0.83–1.24) | 8 |
| Guohui Xue | 2020 | China | The Jinyintan Hospital, Wuhan | 56 (30) | 60.50 (52.25–68.75) | NR | 1.45 (1.12–1.88) | 58 (34) | 64.00 (49.75–73.00) | NR | 1.23 (1.00–1.70) | 8 |
| Guyi Wang | 2020 | China | Public Health Treatment Center of Changsha, Changsha | 184 | NR | NR | 1.09 (0.79–1.47) | 44 | NR | NR | 1.08 (0.76–1.36) | 7 |
| Jia Teng Sun | 2020 | China | Leishenshan Hospital, Wuhan | 49 (26) | 52 (42–62) | NR | 1.21 (0.81–1.80) | 50 (34) | 70.50 (61.25–80.75) | NR | 0.96 (0.70–1.62) | 8 |
| Müge Bilge | 2021 | Turkey | Bakirköy Dr. Sadi Konuk Training and Research Hospital | 347 (207) | 53.89±16.34 | NR | 145.83±75.65 | 470 (301) | 59.38±14.84 | NR | 144.22±77.30 | 8 |
| Qianhui Zhang | 2020 | China | Zhongnan Hospital of Wuhan University, Wuhan | 47 (18) | 61 (54–67) | 24.66 (21.72–27.69) | 1.50 (0.93–2.31) | 27 (18) | 72 (58–81) | 24.54 (22.64–26.99) | 1.18 (0.89–1.77) | 7 |
| Wei Huang | 2020 | China | Tongji Hospital, Wuhan | 2008 (943) | 61(49-69 | 23.53 (21.48, 25.48) | 1.25 (0.96-1.77) | 383 (219) | 65 (53-73) | 24.09 (22.04,-25.83) | 1.30 (0.99-1.71) | 7 |
| Xingzhong Hu | 2020 | China | Wenzhou Central Hospital, Wenzhou | 87 (42) | 46 (36–54) | NR | 1.13 (0.93–1.74) | 27 (18) | 62.0 (53.0–71.0) | NR | 1.32 (1.06–1.63) | 8 |
| Xiuqi Wei | 2020 | China | Union Hospital of Tongji Medical College, Wuhan | 394 (189) | 64 (53-69) | NR | 150 (124-213) | 171 (100) | 69 (64-77) | NR | 142 (89-189) | 9 |
| Zhe Zhu | 2021 | China | HwaMei Hospital, Ningbo | 125 (47) | 48.04±16.66 | 23.50±3.42 | 1.44 (0.98-2.00) | 17 (8) | 56.88±11.61 | 26.13±5.47 | 1.22 (0.83-2.29) | 8 |
| Zhihua Lv | 2020 | China | Renmin Hospital of Wuhan University, Wuhan | 49 (24) | 63.0±12.5 | NR | 1.18 (0.99-1.58) | 35 (18) | 62.1±15.5 | NR | 1.33 (0.98-1.67) | 8 |

**Table 1:** Study Characteristics.

Extracted characteristics of the patients with COVID-19 from included studies Abbreviations: IQR: Interquartile range; SD: Standard deviation; BMI: body mass index; NR: not reported; NOS: Newcastle-Ottawa scale.

| Confounding variable | Number of studies Meta-regression | Co-efficient [95%CI] | P-value |
|---|---|---|---|
| Year of publication | 12 | 0.04 [-0.25,0.33] | 0.755 |
| Country | 12 | 0.07 [-0.20,0.33] | 0.636 |
| Age(year) | 12 | -0.07 [-0.41,0.26] | 0.667 |
| Sex male(%)* | 11 | 0.25 [-0.57,1.07] | 0.551 |
| BMI(kg/m2)# | 4 | 0.21 [-0.28,0.71] | 0.399 |
| Hypertension | 8 | 0.12 [-0.17,0.42] | 0.417 |
| Diabetes mellitus(%)* | 7 | 0.10 [-0.55,0.26] | 0.202 |

| | | | |
|---|---|---|---|
| Hyperlipidemia(%)* | 3 | -1.40 [-2.43,-0.38] | 0.007 |
| Coronary artery disease(%)* | 6 | 0.03 [-0.10,0.15] | 0.672 |

**Table 2:** Meta-regression analysis.

#Mean difference of the variable between patients with severe and non-severe COVID-19.

*Difference in proportion of the variable between patients with severe and non-severe COVID-19 disease. CI, Confidence interval.

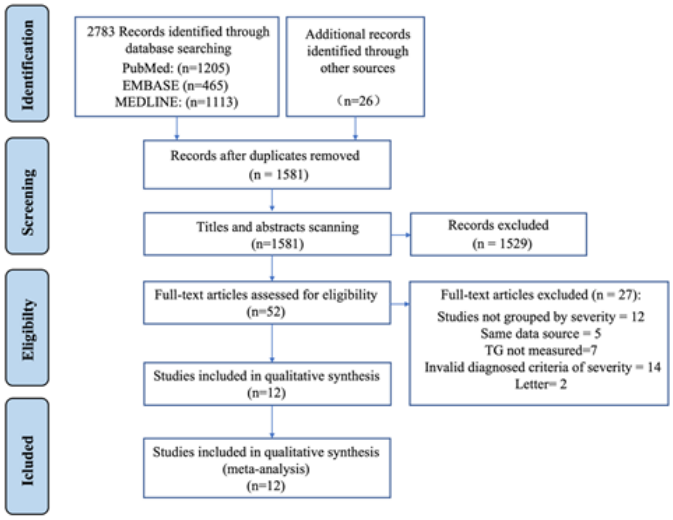


**Figure 1:** PRISMA flow chart of the study selection process.

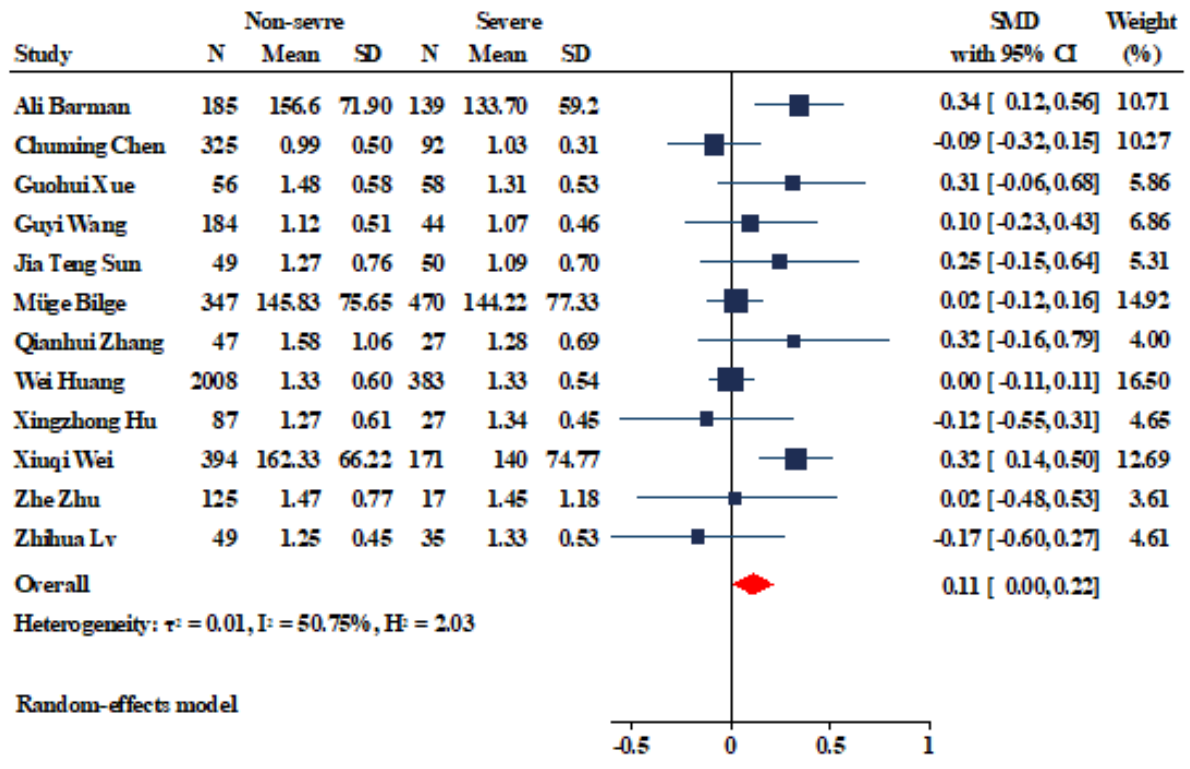


**Figure 2:** Forest plots showing the random effects meta-analysis for the concentrations of triglyceride between non-severe and severe cases with COVID-19; SMD, standardized mean difference.

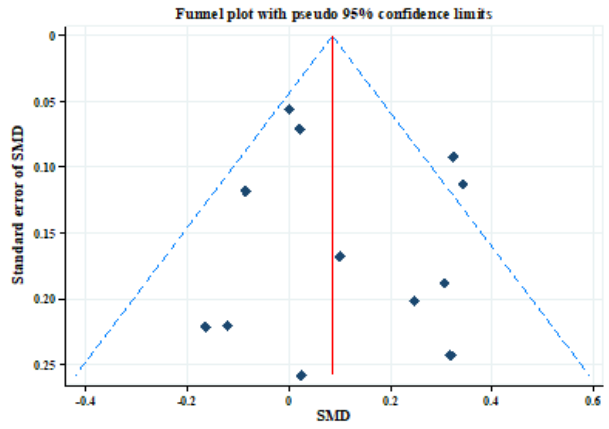


**Figure 3:** Funnel plot for the assessment of the publication bias using Egger's test.

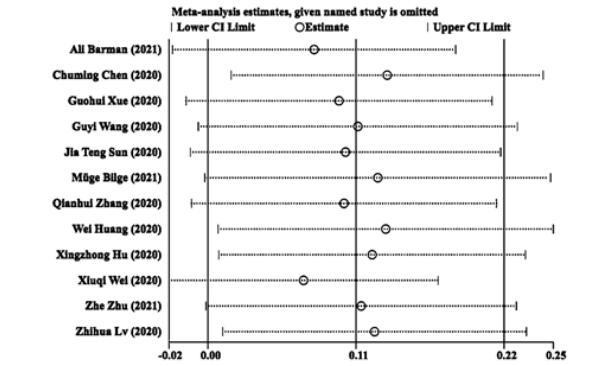


**Figure 4:** Sensitivity analysis of the association between TG and the severity of COVID-19.

include decreased food intake, medication use, and the development of disorders that affect triglyceride levels [31]. Additionally, the cytokine storm associated with COVID-19 may cause excessive production of pro-inflammatory cytokines, leading to endothelial dysfunction, which is a key factor in COVID-19 pathogenesis [32]. Fatty acids, which are breakdown products of triglycerides, can activate the NF-κB pathway, increasing the expression of pro-inflammatory cytokines. Furthermore, triglyceride-rich particles can increase inflammation, activate the complement pathway, and compromise the integrity of the endothelium [33]. Conversely, severe COVID-19 patients may have decreased triglyceride concentrations due to the excessive release of pro-inflammatory cytokines, which can decrease the synthesis and secretion of apolipoproteins in hepatic cells [34,35]. One case report described hypertriglyceridemia in a non-severe COVID-19 infection due to autoantibodies against lipoprotein lipase, which transiently inhibited its activity [27].

### Limitations

Our analysis suggests that triglyceride levels are lower in severe COVID-19 patients, caution should be taken in interpreting these results, and the limitations of this study should be considered. Firstly, the majority of the studies included in this analysis were conducted in China, with only two studies from Turkey, which may limit the generalizability of our results to other populations. Secondly, all studies included in this analysis were retrospective cohort hospital-based studies, which may not reflect the true population prevalence of elevated triglyceride levels and COVID-19 severity. Thirdly, although a pooled analysis of adjusted estimates is desirable, variations in triglyceride units and continuous variables descriptions may affect the results of pooled analysis. Lastly, none of the included studies presented data on serum triglyceride-rich lipoprotein (TRL) or TRL remnants levels such as chylomicrons and very low-density lipoproteins. Therefore, the observed association between decreased triglyceride levels and COVID-19 severity may not be solely attributed to triglyceride levels but could be confounded by other factors. Additionally, the possibility of publication bias cannot be ruled out, as studies reporting significant findings are more likely to be published than studies with null findings.

## Conclusion

In conclusion, our study sheds light on an inverse association between serum triglyceride levels and COVID-19 severity. Although the precise mechanisms underlying this relationship are not yet fully understood, our findings suggest that monitoring triglyceride levels may have clinical relevance in predicting COVID-19 outcomes and tailoring treatment strategies. Clinicians should be mindful of the potential influence of medications and comorbidities on triglyceride levels and consider individualizing COVID-19 treatment based on these levels. Future research could explore the predictive role of triglyceride levels in COVID-19 prognosis, investigate potential protective effects of triglyceride-lowering treatments, and further elucidate the underlying mechanisms linking triglycerides to COVID-19 pathogenesis. These efforts may ultimately contribute to improved patient care and outcomes in the context of the COVID-19 pandemic.

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## Author's Contribution

Liu Jinsong: Conceptualization, Methodology, Investigation, Data Curation, Formal analysis, Writing - Original Draft and Writing - Review & Editing. Zhang Manli: Conceptualization, Methodology, Investigation, Formal analysis, Visualization and Writing - Original Draft. Yan Renqing: Methodology, Investigation and Data Curation. Chen Zhuyi: Methodology, Investigation and Formal analysis. He Ziyun: Methodology, Investigation and Writing - Original Draft. Dai Haibing: Methodology, Investigation and Writing - Original Draft. Zhu Yonglin: Methodology, Investigation and Writing - Original Draft. Zhang Feng: Methodology, Investigation and Writing - Original Draft. Zhang Lin: Methodology, Investigation, Supervision and Writing - Original Draft. Yan Shengkai: Conceptualization, Methodology, Writing - Review & Editing, Visualization and Supervision.

## Ethics approval and consent to participate

Not applicable.

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## Conflict of Interests

The authors do not have any conflicts of interest to declare.

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