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Hyperlipasemia and potential pancreatic injury patterns in COVID-19: A marker of severity or innocent bystander?

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Introduction

Coronavirus disease 2019 (COVID-19) is caused by Severe Acute Respiratory Syndrome (SARS-CoV-2). Gastrointestinal symptoms are increasingly being reported in COVID-19¹. Data on the involvement of the pancreas in COVID-19 has been emerging, and multiple case reports of SARS-CoV-2-induced acute pancreatitis have been published in the literature². The angiotensin-converting enzyme-2 (ACE-2) is the target receptor of SARS-CoV-2 and is expressed abundantly by both the exocrine and endocrine pancreatic tissues³. The presence of ACE-2 in the pancreas could make it susceptible to SARS-CoV-2 resulting in interstitial leakage of pancreatic lipase, adipose tissue lipolysis, and potentially toxic fatty acid-induced damage. These changes can at least contribute to cytokine storm, multiorgan dysfunction, and COVID-19 morbidity⁴. Due to its non-specificity, lipase could be elevated in a myriad of conditions such as infections, renal dysfunction, medication-related, gastrointestinal, and hepatobiliary disease⁵. Given this, it is critical to evaluate the prevalence of hyperlipasemia in COVID-19 and predict clinical outcomes.

Methods

We conducted a systematic search using PubMed, Embase, Ovid, and Google Scholar databases from December 1st, 2019 to October 9th, 2020, to evaluate hyperlipasemia in COVID-19 patients. The following search terms were used- 'COVID-19', 'SARS-CoV-2', 'lipase,' 'pancreatic injury,' 'pancreas.' The articles with relevant data on the prevalence of hyperlipasemia and its effect on COVID-19 severity were examined. All adult patients with nasopharyngeal RT-PCR positive for SARS-CoV-2 were included in the analysis. Severe COVID-19 was defined as clinical deterioration resulting in adverse clinical outcomes such as admission to the intensive care unit (ICU), need for mechanical ventilation, or death. Hyperlipasemia was defined as any elevation in the lipase levels above the upper limit of the normal (ULN) reference level. The definition of hyperlipasemia varied among the

studies because of differences in the range of lipase levels, as was the definition of severe COVID-19.

The OpenMeta[Analyst] software was used to estimate the pooled prevalence of lipase elevations among COVID-19 patients and the pooled odds ratio (OR) for severe COVID-19 among this subset of patients. Results were reported with a 95% confidence interval (CI), and a p-value of <0.05 was considered statistically significant. Heterogeneity was assessed using the I^2 test, and $I^2 >50\%$ was taken as a measure of moderate inter-study variation.

Results

The initial search yielded 52 articles. After excluding duplicates and reviews articles, seven studies (6 retrospective observational studies and one prospective observational study) were included in the pooled analysis. A flow chart depicting the study screening and selection process is represented in Supplemental Figure 1.

Data on the point-prevalence of hyperlipasemia was available in all seven studies, whereas only 4 reported clinical outcomes, ICU admission status, and need for mechanical ventilation, or death. The normal range of serum lipase levels differed among studies. While four studies had an average upper limit of 50-60 U/L; two had a higher cut-off ($>300\text{U/L}$) for lipase levels. Data about 756 COVID-19 patients were reported in these studies, out of which 92 patients had hyperlipasemia. All were single center experiences, except one. Two studies reported severe COVID-19 as patients needing ICU admission, one study with a need for mechanical ventilation, and only one study used a combination of all three as severe COVID-19. Supplemental Table 1 outlines the baseline characteristics of the included studies.

The results of this pooled analysis are shown in Figure 1 (A & B). Among 756 COVID-19 patients with available lipase levels, the pooled prevalence of hyperlipasemia was 11.7% (95% CI: 0.094-0.140, $P=0.001$), and $I^2 = 0\%$. The pooled OR for severe COVID-19 in these patients was 3.143 (95% CI: 1.543-6.400, $P=0.003$); mild inter-study heterogeneity was observed ($I^2 = 27\%$).

Discussion

Based on the result of our pooled analysis, hyperlipasemia was found to be in 11.7% of patients affected by SARS-CoV-2. COVID-19 patients with hyperlipasemia are at a ~3-fold higher risk of poor clinical outcomes, including the need for ICU admission, mechanical ventilation, or death.

Although multiple mechanisms have been proposed for pancreatic injury in COVID-19, the exact etiology remains unclear. Some of the mechanisms include direct pancreatic tissue damage by SARS-CoV-2 and intense inflammatory response (interleukin [IL]-1 β , IL-6, and tumor necrosis factors) with cytokine storm mediated tissue injury. Furthermore, studies showed COVID-19 patients with pancreatic injury had a higher prevalence of severe illness on admission, lower levels of CD3+, CD4+ T cells, and higher levels of aspartate aminotransferase, γ -glutamyl transferase, creatinine, lactate dehydrogenase, and erythrocyte sedimentation rate⁶.

Limitations of this study include a modest sample size of 756 COVID-19 patients, of which 92 patients had elevated serum lipase levels. The degree of hyperlipasemia was not uniform across all studies. Potential confounders such as age, comorbidities, and medication use could alter the results of this study. Furthermore, a lack of high-quality randomized controlled trials with adjustment of potential confounders is a notable limitation. Given the inclusion of observational studies, selection bias, information bias, and confounding bias are possible. The prevalence of hyperlipasemia could be underestimated due to a lack of testing and non-reporting of the data in many patients.

Severe pancreatic injury resulting in acute pancreatitis may not be a common event in COVID-19. As evidenced by lipase elevation, mild to moderate pancreatic injury is a clinically significant finding in these patients. Future prospective studies are warranted to ascertain the exact impact of lipase elevation in COVID-19 and guide management strategies for these patients.

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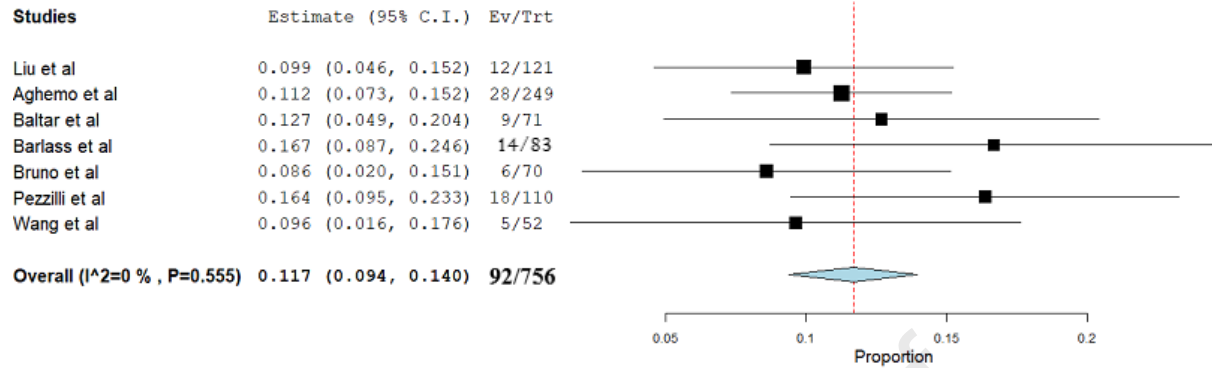


Figure 1-A: Pooled Incidence Rate of Hyperlipasemia in COVID-19 patients

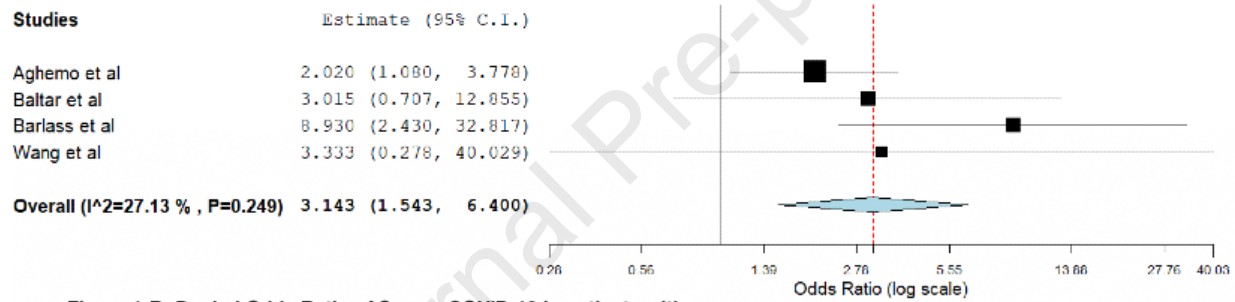


Figure 1-B: Pooled Odds Ratio of Severe COVID-19 in patients with hyperlipasemia