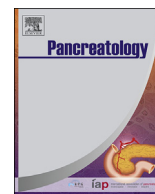




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## Prevalence and prognosis of increased pancreatic enzymes in patients with COVID-19: A systematic review and meta-analysis



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### ABSTRACT

**Introduction:** The prevalence of increased pancreatic enzymes (elevated serum amylase and/or lipase) and its relationship to clinical outcomes in patients with coronavirus disease 2019 (COVID-19) infection is not known.

**Methods:** A systematic review and meta-analysis of relevant studies reporting prevalence and impact of increased pancreatic enzymes (defined as an elevation in amylase and/or lipase levels above the upper limit of normal [ULN] value) in COVID-19 was undertaken.

**Results:** A total of 36,496 patients from 21 studies were included for this meta-analysis. The overall prevalence and mortality for increased pancreatic enzymes (>ULN) in COVID-19 were 25.4% (95% CI, 15.8%–36.2%) and 34.6% (95% CI, 25.5%–44.4%), respectively. The overall prevalence and mortality for increased pancreatic enzymes (>3 × ULN) were 6.1% (95% CI, 3.6%–9.2%) and 39.2% (95% CI, 18.7%–61.6%), respectively. Patients with increased pancreatic enzymes, including elevated serum lipase or amylase of either type, had worse clinical outcomes, including need for ICU admission, mechanical ventilation and mortality.

**Discussion:** Increased pancreatic enzymes is frequent and may exacerbate the consequences of COVID-19 infection.

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### 1. Introduction

Increased pancreatic enzymes (elevated serum amylase and/or lipase) is not necessarily diagnostic for acute pancreatitis and can occur during acute and critical illness [1], including coronavirus disease 19 (COVID-19) infection [2–4]. Subclinical direct pancreatic damage due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection of the exocrine pancreas has been demonstrated in previous studies [5,6]. The elevation of pancreatic enzymes has been initially reported in approximately 17% of

patients with COVID-19, but none of the patients met the revised Atlanta criteria for a diagnosis of acute pancreatitis [2]. It can be due to both increased uptake into portal vein and mesenteric lymphatics with gut injury and decreased excretion due to renal impairment [7]. Although acute pancreatitis has been reported to be associated with worse outcomes in COVID-19 [8,9], it is not known whether this is true for increased pancreatic enzymes [3,10–12]. Understanding the disease course of concomitant COVID-19 and increased pancreatic enzymes may identify patients at risk of poor outcomes and indicate early intervention. The aim of this systematic review was to determine the pooled prevalence and prognostic significance of increased pancreatic enzymes in adult patients with COVID-19.

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## 2. Methods

The PubMed, Embase, Scopus databases, and Cochrane library were systematically searched using the PRISMA framework for relevant reports on COVID-19 and hyperenzymemia. One of the reviewers (YTF), who is proficient in database search, designed the search strategies (Supplementary Material). The search terms used “2019-nCoV” or “SARS-CoV-2” or “COVID-19” AND “amylase” or “lipase” or “hyperamylasemia” or “hyperlipasemia” or “pancreas” or “pancreatic injury” or “pancreatitis”. The records were imported into Covidence for screening. Observational studies published in English or Chinese from inception to January 20, 2022, and reported outcomes in adult patients with COVID-19 were eligible for inclusion. Duplicate reports, case reports, reviews, commentaries, editorials, small case series (<5 cases), and studies of other coronavirus-related diseases such as Middle East Respiratory Syndrome (MERS) were excluded. Two reviewers (YTH and TL) independently reviewed the records of possible relevance and assessed their eligibility. Discrepancies were resolved by a senior reviewer (FY). The references of relevant studies were manually screened for additional records. Quality assessment of included studies was performed using the Newcastle-Ottawa Scale independently by two reviewers (YCX and TL), with discrepancies resolved by another reviewer (FY).

Two reviewers (YLD and YCX) independently collected data from the included studies. Discrepancies were resolved by consensus or by a third reviewer (FY). The following variables were collected when available: authors, study location and institution, study design, study period, sample size, demographic data, comorbidities, gastrointestinal symptoms on admission, clinical outcomes including intensive care unit (ICU) admission, mechanical ventilation, and mortality. Increased pancreatic enzymes, which varied among studies due to different normal ranges, was defined as an elevation in amylase and/or lipase levels above the upper limit of normal (ULN) value. Levels higher than  $3 \times$  ULN were also collected for further analysis. The primary outcome was prevalence of increased pancreatic enzymes in COVID-19. Effect of increased pancreatic enzymes on the outcomes was also assessed. A random-effects model was used to pool the effect sizes by providing more conservative results of odds ratio (OR) and 95% confidence intervals (CI). In studies that reported both estimates of hyperamylasemia and hyperlipasemia, we combined them into a single value whenever possible, or selected the one with a higher prevalence. Statistical heterogeneity was estimated using the Cochran Q test and  $I^2$  statistic. We used R (version 4.1.0) for pooling single-armed rates with Freeman-Tukey double arcsine transformation, and Review Manager (version 5.4) for other analyses. A two-tailed p-value < 0.05 was considered statistically significant.

## 3. Results

The initial search yielded 3,088 studies, among which 21 were included [2–4,10–27] (Fig. 1). Except for one study, all included studies had a cohort study design, and most were conducted in Europe ( $n = 11$ ) or the United States ( $n = 5$ ). All of the studies were retrospective in nature except two, and eight were multi-center studies (Table 1). The median score of the Newcastle-Ottawa scale was 6.

The estimated pooled prevalence of increased pancreatic enzymes (>ULN) in COVID-19 was 25.4% (95% CI, 15.8%–36.2%), whereas that of increased pancreatic enzymes ( $>3 \times$  ULN) was 6.1% (95% CI, 3.6%–9.2%) (Fig. 2A and B). Only a small fraction of patients were diagnosed with acute pancreatitis ( $n = 594/35,906$ , 1.7%). The pooled prevalence of hyperlipasemia (>ULN) was 21.5% (95% CI,

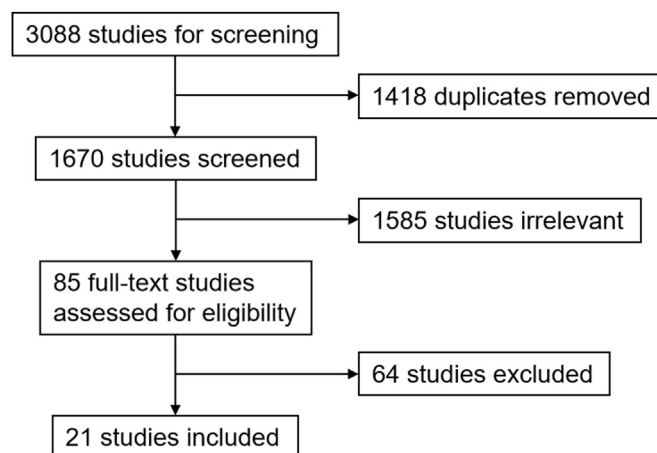


Fig. 1. Study selection.

10.9%–34.3%), whereas that of hyperlipasemia ( $>3 \times$  ULN) was 5.6% (95% CI, 2.8%–9.3%) (Fig. 3A and B). The pooled prevalence of hyperamylasemia (>ULN) was 21.9% (95% CI, 13.0%–32.3%), whereas that of hyperamylasemia ( $>3 \times$  ULN) was 4.0% (95% CI, 0.9%–8.7%) (Supplementary Figs. 1A and 1B).

Subgroup analyses among hospitalized non-ICU patients revealed that the pooled prevalence of increased pancreatic enzymes (>ULN and  $>3 \times$  ULN) was 19.4% (95% CI, 10.9%–29.5%) and 4.7% (95% CI, 2.4%–7.5%), respectively (Supplementary Figs. 2A and 2B). The pooled prevalence of hyperlipasemia (>ULN and  $>3 \times$  ULN) was 17.0% (95% CI, 7.3%–29.7%) and 4.7% (95% CI, 2.1%–8.2%), respectively (Supplementary Figs. 3A and 3B). The pooled prevalence of hyperamylasemia (>ULN and  $>3 \times$  ULN) was 16.7% (95% CI, 12.1%–21.9%) and 2.0% (95% CI, 0.5%–4.1%), respectively (Supplementary Figs. 4A and 4B). Among ICU patients, the pooled prevalence of increased pancreatic enzymes (>ULN and  $>3 \times$  ULN) was 63.9% (95% CI, 57.0%–70.6%) and 24.5% (95% CI, 16.6%–33.3%), respectively. The pooled prevalence of hyperlipasemia (>ULN) was 58.1% (95% CI, 47.8%–68.0%).

The pooled mortality of increased pancreatic enzymes (>ULN) in COVID-19 was 34.6% (95% CI, 25.5%–44.4%), and that of increased pancreatic enzymes ( $>3 \times$  ULN) was 39.2% (95% CI, 18.7%–61.6%) (Fig. 2C and D). The pooled mortality of hyperlipasemia (>ULN) was 31.7% (95% CI, 23.6%–40.2%), and that of hyperlipasemia ( $>3 \times$  ULN) was 30.3% (95% CI, 13.9%–49.0%) (Fig. 3C and D). The pooled mortality of hyperamylasemia (>ULN) was 37.6% (95% CI, 19.5%–57.5%), and that of hyperamylasemia ( $>3 \times$  ULN) was 59.8% (95% CI, 19.4%–94.7%) (Supplementary Figs. 1C and 1D).

Subgroup analyses among hospitalized non-ICU patients revealed that the pooled mortalities of increased pancreatic enzymes (>ULN and  $>3 \times$  ULN) were 31.1% (95% CI, 21.5%–41.4%) and 38.8% (95% CI, 16.4%–63.5%), respectively (Supplementary Figs. 2C and 2D). The pooled mortalities of hyperlipasemia (>ULN and  $>3 \times$  ULN) were 26.4% (95% CI, 21.0%–32.1%) and 30.3% (95% CI, 13.9%–49.0%), respectively (Supplementary Figs. 3C and 3D). The pooled mortalities of hyperamylasemia (>ULN and  $>3 \times$  ULN) were 38.0% (95% CI, 14.6%–64.4%) and 71.0% (95% CI, 24.0%–100%), respectively (Supplementary Figs. 4C and 4D). Among ICU patients, the pooled mortality of increased pancreatic enzymes (>ULN) was 56.2% (95% CI, 15.5%–92.5%).

Compared with normal patients, those having amylase and/or lipase > ULN were more likely to have hypertension (OR, 1.27; 95% CI, 1.05–1.53;  $p = 0.01$ ) and diabetes (OR, 1.48; 95% CI, 1.10–2.00;  $p = 0.009$ ) (Supplementary Table 1). They had increased rates of

**Table 1**  
Baseline characteristics of included studies with hyperenzymemia in coronavirus disease 2019.

First author	Country	Study design	Centers	Study period	Patients with COVID-19	No. of severe COVID-19 <sup>§</sup>	Patients with AP <sup>†</sup>	ULN of amylase (U/L)	ULN of lipase (U/L)	Quality assessment*
Wang [2]	China	Retrospective	Single	2020.1.20–2020.2.28	52	4 MV	NA	90	70	4
McNabb-Baltar [3]	USA	Retrospective	Multi	2020.1.23–2020.4.2	71	17 ICU, 17 MV, 18 death	0	NA	60	7
Troncone [4]	Italy	Retrospective	Single	2020.3.6–2020.5.6	254	48 ICU, 65 death	2	125 for <70 yrs, 160 for >70 yrs	78	5
Ahmed [10]	USA	Retrospective	Multi	2020.3.1–2020.5.1	992	81 ICU <sup>&amp;</sup> , 65 MV <sup>&amp;</sup> , 264 death	2	NA	60 in BILH, 78 in NYULH	3
Bansal [11]	Indian	Retrospective	Single	NA	42	18 death	NA	100	81	6
Barlass [12]	USA	Retrospective	Single	2020.3.12–2020.4.3	83	35 ICU <sup>#</sup> , 27 MV <sup>#</sup>	NA	NA	52	6
Bulthuis [13]	Netherlands	Prospective	Multi	2020.3.4–2020.5.26	432	160 ICU, 86 death	8	NA	NA	7
Aghemo [14]	Italy	Retrospective	Single	2020.2.22–2020.3.30	292	27 ICU, 56 death	NA	100	68	3
Akkus [15]	Turkey	Retrospective	Single	2020.3.20–2020.6.9	127	18 ICU, 15 MV, 6 death	2	NA	60	5
Bruno [16]	Italy	Retrospective	Single	2020.2.25–2020.5.10	70	NA	0	100	393	3
Liu [17]	China	Retrospective	Multi	2020.1.1–2020.2.15	121	6 ICU, 7 MV, 5 death	NA	135	78	6
Pezzilli [18]	Italy	Retrospective	Single	2020.4.1–2020.4.30	110	20 MV, 9 death	0	53	300	4
Ramsey [19]	USA	Retrospective	Multi	NA	400	211 ICU, 173 MV, 85 death	6	NA	NA	8
Rasch [20]	Germany	Prospective	Single	2020.3–2020.4	38 <sup>§</sup>	38 ICU, 38 MV, 12 death	2	NA	60	6
Stephens [21]	UK	Retrospective	Multi	2020.3.14–2020.5.22	234 <sup>§</sup>	234 ICU, 87 death	4	100	NA	5
Benias [22]	USA	Retrospective	Multi	2020.3.1–2020.6.1	11883	391 MV <sup>1</sup> , 313 death <sup>1</sup>	89	NA	NA	7
Singh [23]	International	Retrospective	Multi	2020.1.1–2020.12.31	17255	127 MV <sup>2</sup> , 263 death <sup>2</sup>	467	NA	80	6
Ding [24]	China	Retrospective	Single	2020.1.1–2020.3.30	55 <sup>§</sup>	55 ICU, 31 MV, 37 death	3	135	78	5
Bacaksız [25]	Turkey	Retrospective	Single	2020.3–2020.12	1378	469 death	6	105	65	6
Li [26]	China	Retrospective	Single	2020.1.18–2020.3.18	1515	156 ICU, 258 MV, 118 death	0	115	NA	8
Caruso [27]	Italy	Retrospective	Single	2020.2–2020.11	1092	86 ICU, 185 death	3	NA	55	5

AP, acute pancreatitis; BILH, Beth Israel Lahey Health; ICU, intensive care unit; MV, mechanical ventilation; NA, not available; NYULH, New York University Langone Health; ULN, upper limit of normal.

<sup>§</sup> The study population was ICU patients and all other studies were hospitalized patients.

<sup>§</sup> Severe COVID-19 included admission to the ICU, need for MV, or death.

<sup>†</sup> Diagnosis of acute pancreatitis was in accordance with the revised Atlanta criteria.

\* According to the Newcastle-Ottawa Scale.

<sup>&</sup> Among 157 patients with COVID-19.

<sup>#</sup> Among 82 patients with COVID-19.

<sup>1</sup> Among 1560 patients with COVID-19.

<sup>2</sup> Among 2812 patients with COVID-19.

ICU admission (OR, 3.90; 95%CI, 2.59–5.87;  $p < 0.00001$ ), need for mechanical ventilation (OR, 2.90; 95%CI, 2.03–4.14;  $p < 0.00001$ ), and mortality (OR, 2.36; 95%CI, 1.58–3.51;  $p < 0.0001$ ). Comparing amylase and/or lipase  $>3$  vs  $<3 \times$  ULN, the ORs (95%CI) of ICU admission, need for mechanical ventilation and mortality were 7.04 (3.86–12.86), 2.76 (1.26–6.03), and 2.35 (1.32–4.16), respectively (Supplementary Fig. 5).

Compared with normal patients, those having lipase  $> ULN$  were more likely to have hypertension (OR, 1.26; 95%CI, 1.01–1.58;  $p = 0.04$ ) (Supplementary Table 1). They had increased rates of ICU admission (OR, 3.30; 95%CI, 2.30–4.72;  $p < 0.00001$ ), need for mechanical ventilation (OR, 2.24; 95%CI, 1.81–2.77;  $p < 0.00001$ ), and mortality (OR, 1.66; 95%CI, 1.42–1.94;  $p < 0.00001$ ). Comparing lipase  $>3$  vs  $<3 \times ULN$ , the ORs (95%CI) of ICU admission, need for mechanical ventilation and mortality were 6.10 (3.86–9.65), 2.76 (1.26–6.03), and 1.70 (1.22–2.38), respectively (Fig. 4).

#### 4. Discussion

The exact pathophysiologic mechanism regarding pancreatic involvement of COVID-19 remains fully unknown. Based on the results of this meta-analysis, increased pancreatic enzymes was found in about 20% of hospitalized patients with COVID-19, which was notably higher than earlier studies [2,3,14–17,28]. The obvious reason for increased pancreatic enzymes in COVID-19 patients is concomitant acute pancreatitis, which is thought to be related to rich expression of angiotensin converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) in pancreatic ductal cells [29,30]. Autopsy findings showed that pancreatitis and fat necrosis occurred in 20–40% cases of lethal patients with COVID-19 [31,32]. However, consistent with the result of a previous meta-analysis [9], acute pancreatitis occurred in very few patients (1.7%) in this study. The high prevalence may also be due to COVID-

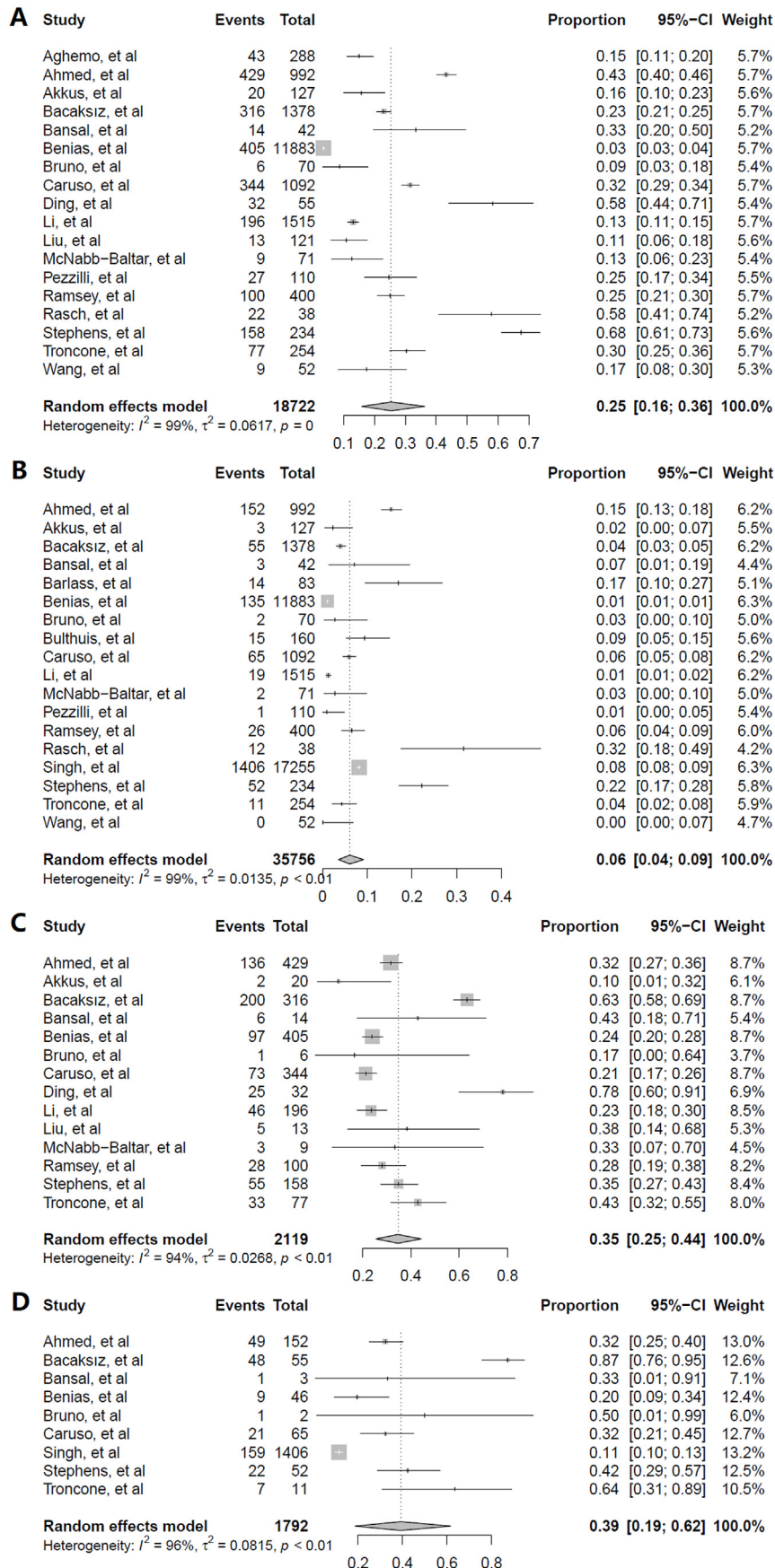


Fig. 2. Pooled prevalence of increased pancreatic enzymes (A > ULN, B > 3 × ULN) and mortality (C > ULN, D > 3 × ULN) in patients with COVID-19. ULN, upper limit of normal.



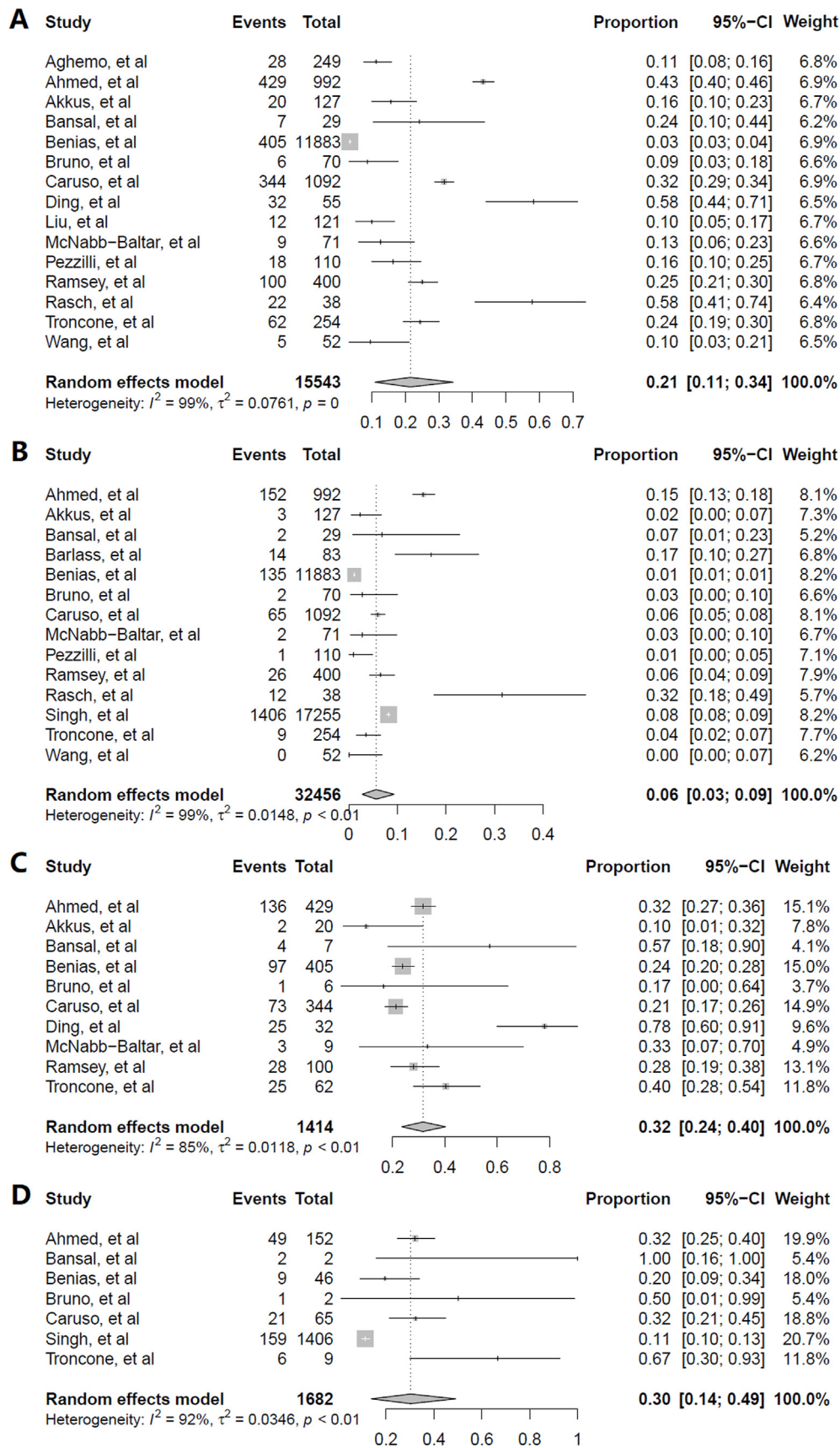
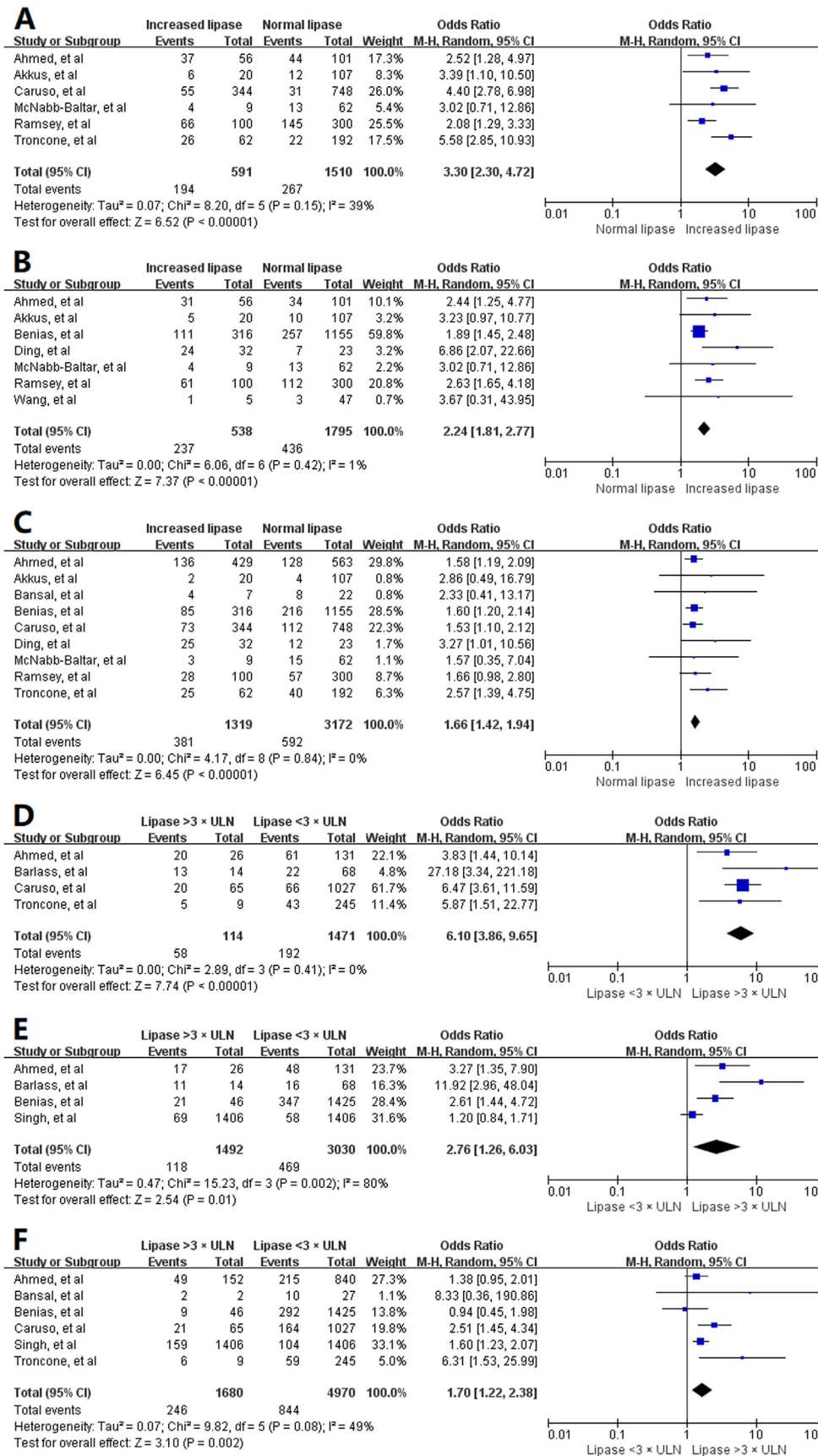


Fig. 3. Pooled prevalence of hyperlipasemia (A > ULN, B > 3 × ULN) and mortality (C > ULN, D > 3 × ULN) in patients with COVID-19.



**Fig. 4.** Forest plot for clinical outcomes of patients with concomitant COVID-19 and hyperlipasemia. Increased (>ULN) vs normal levels: ICU admission (A), need for mechanical ventilation (B), and mortality (C). >3 × ULN vs <3 × ULN levels: ICU admission (D), need for mechanical ventilation (E), and mortality (F).

19 infection causing hypotension and ischemic gut injury, mechanical ventilation, renal injury, and other consequences that can give rise to the elevation of pancreatic enzymes [4,12,19]. This is well illustrated by the higher prevalence in ICU patients compared to hospitalized non-ICU patients by subgroup analyses. In addition, comorbidities such as diabetes, which has been identified as an independent predictive factor for increased pancreatic enzymes [33], may also contribute to the difference. However, the significant between-study heterogeneity requires more prospective studies to validate our results.

This study also showed that patients with concomitant COVID-19 and increased pancreatic enzymes had a significantly worse outcome, including need for ICU admission, mechanical ventilation, and mortality. In addition, the pooled mortality of patients with increased pancreatic enzymes (either > ULN or >3 × ULN) was higher than that of patients with acute pancreatitis reported in a previous meta-analysis [9]. The reason is unknown, but it suggests that elevation of serum pancreatic enzymes in some patients may be from critical illness. Altered gut lymph (from gut injury in acute illness) has been shown to cause enhanced systemic inflammatory response and multiple organ dysfunction [34]. For example, it is known that elevated levels of pancreatic lipase in the thoracic duct increase the risk of acute respiratory distress, possibly via toxic free fatty acids [35], which have been observed to increase in COVID-19 [36]. Fatty acids may worsen outcomes during COVID-19 by inducing cytokine storm and causing organ damage as in pancreatitis [37,38]. While the underlying mechanisms require further investigation, data from this study highlights the clinically important association between COVID-19 and increased pancreatic enzymes. The worse outcome of COVID-19 patients in whom pancreatic enzyme >3 × ULN supported the view of Inamdar et al. [39], who divided patients with concomitant COVID-19 and increased pancreatic enzymes into 3 groups: (1) patients with serum lipase and/or amylase of <3 × ULN, (2) patients with serum lipase and/or amylase of >3 × ULN, but do not meet the Atlanta criteria for acute pancreatitis, and (3) patients with acute pancreatitis meeting the Atlanta criteria.

The main limitation of the present study was lack of high-quality studies. Most of them were retrospective in nature, and some had a small sample size with a low event rate, leading to heterogeneity between studies. In addition, the included studies had neither uniform study population nor uniform control groups, making the results possibly distorted. Since confounding factors may affect the prognosis of COVID-19, we may have not shown the real effect of increased pancreatic enzymes on COVID-19 in absence of multivariable analyses. But at least it reminds clinicians that these patients should be taken seriously. Despite these limitations, the rigorous inclusion criteria and size of the total cohort provide us a clear picture of patients with concomitant COVID-19 and increased pancreatic enzymes.

In conclusion, increased pancreatic enzymes should be studied as a risk factor for severity in COVID-19 infection. As such, serum lipase could prove to be helpful in monitoring COVID-19 and predicting outcomes as it has higher specificity.

#### Author contributions

Feng Yang: study concept, study design, data analysis, statistical analysis, drafting the manuscript, study supervision.

Yinlei Dong: data acquisition, data analysis.

Yecheng Xu: data acquisition, data analysis.

Yuting Huang: data acquisition, data analysis.

Yunting Fu: data acquisition, data analysis.

Tian Li: data acquisition, data analysis.

Chenyu Sun: data analysis, statistical analysis.

Sanjay Pandanaboyana: data analysis, critical revision of the manuscript.

John A Windsor: data analysis, critical revision of the manuscript.

Deliang Fu: study concept, critical revision of the manuscript; study supervision.

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#### Declaration of competing interest

We declare no conflicts of interest.

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pan.2022.03.014>.

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