Prevalence and outcomes of acute pancreatitis in COVID-19: a meta-analysis

The study by Pandanaboyana et al showed that acute pancreatitis (AP) patients with COVID-19 had a significantly higher mortality than those without COVID-19. Nevertheless, a similar trend of mortality was found by another observational cohort study. The true prevalence and outcomes of AP in patients with COVID-19 are not known. The aim of this study was to conduct a meta-analysis to determine the pooled prevalence and clinical outcomes of AP in patients with COVID-19.

PubMed, Embase, Scopus and Cochrane library were searched for outcome studies of adult patients with AP and COVID-19 published before 15 September 2021 (online supplemental file 1). Excluded were studies that either did not use the revised Atlanta criteria for AP diagnosis or reported patients with COVID-19 with a prior history of pancreatitis. Patients were divided into three groups: group I—AP with COVID-19, group II—AP without COVID-19 and group III—COVID-19 without AP. The primary endpoint was mortality (both in-hospital or 30-day). Secondary endpoints were pooled prevalence of AP and other clinical outcomes. The overall pooled prevalence and mortality were assessed for group I with a random-effects model and Freeman–Tukey double arcsine transformation using R statistical software (V4.1.0). Heterogeneity was assessed using the I² statistic and Cochran Q test. Publication bias was assessed using the funnel plots and Egger’s test. Other analyses were performed using Review Manager (V5.4).

Eleven studies were included (online supplemental file 1), of which six were multicentre and eight were retrospective. The pooled prevalence of AP in patients with COVID-19 was 3.1% (95% CI 1.6% to 5.1%, I²=98.3%; figure 1A) comprising 183 with AP among 88635 patients with COVID-19 in seven studies. The pooled mortality was 18.5% (95% CI 12.6% to 25.1%, I²=40%; figure 1B) comprising 74 patients out of 384 who had both AP and COVID-19 in 11 studies. The visual inspection of the funnel plot indicated relative symmetry (online supplemental file 1), and Egger’s test showed no evidence of significant publication bias for mortality (p=0.087).

Compared with AP patients without COVID-19 (group II), patients with AP and COVID-19 (group I) had a higher proportion of males (five studies), unknown/idiopathic aetiology (five studies), greater severity of AP (Bedside Index of Severity in Acute Pancreatitis [BISAP] in four studies), increased risk of pancreatic necrosis (four studies), ICU admission (three studies), persistent organ failure (two studies) and need for mechanical ventilation (two studies). The mortality of group I was increased compared with group II (five studies) and group III (four studies; table 1).

Figure 1 Forest plots for the pooled prevalence (A) and mortality (B) of acute pancreatitis in patients with COVID-19.
This meta-analysis is the first systematic evaluation of the prevalence and outcome of AP in patients with COVID-19. Comparing AP patients with or without COVID-19 is striking. The increased prevalence of unknown/idiopathic aetiology in patients with concomitant disease suggests that SARS-CoV-2 might itself cause AP in some patients (possibly via a higher density of ACE2 receptors). The overall pooled prevalence was low (possibly via a higher density of ACE2 receptors) at 3.1%, but this might be an underestimate as two studies27 excluded patients that developed AP during hospitalisation. Sensitivity analysis with these two studies excluded showed that the pooled prevalence of AP was 6.7%. Patients with AP and COVID-19 had a high pooled mortality (18.5%) and significantly worse clinical outcomes. There was no significant difference in ICU admission rate between groups I and III who both had COVID-19 even though AP and COVID-19 both cause systemic inflammatory response and multiple organ dysfunction.

This study does not necessarily represent the global situation, drawing data only from the USA, China and European countries. However, it clearly shows that patients with concomitant AP and COVID-19 have a high risk of adverse outcomes and almost a 20% chance of dying. This study is limited by the small number of included studies, the low event rate and high heterogeneity due to differences in study design and methodology. However, this is the best available data and the meta-analysis can be updated after publication of more prospective studies.

### Table 1

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No of studies</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
<th>I²</th>
<th>P H</th>
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<tr>
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<td></td>
<td></td>
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<td></td>
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<tr>
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<tr>
<td>Male</td>
<td>5</td>
<td>1.51</td>
<td>1.18 to 1.94</td>
<td>0.001</td>
<td>0</td>
<td>0.80</td>
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<tr>
<td>BISAP≥3</td>
<td>4</td>
<td>2.71</td>
<td>1.04 to 7.06</td>
<td>0.04</td>
<td>80</td>
<td>0.002</td>
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<td>Hypertension</td>
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<td>0.99</td>
<td>0.36 to 2.74</td>
<td>0.98</td>
<td>76</td>
<td>0.04</td>
</tr>
<tr>
<td>Diabetes</td>
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<td>1.23</td>
<td>0.72 to 2.09</td>
<td>0.45</td>
<td>0</td>
<td>0.80</td>
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<td>Aetiology</td>
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<tr>
<td>Alcohol</td>
<td>4</td>
<td>0.28</td>
<td>0.11 to 0.72</td>
<td>0.009</td>
<td>65</td>
<td>0.04</td>
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<tr>
<td>Gallstone</td>
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<td>0.74</td>
<td>0.54 to 1.02</td>
<td>0.06</td>
<td>20</td>
<td>0.29</td>
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<tr>
<td>Unknown/idiopathic</td>
<td>5</td>
<td>3.36</td>
<td>1.43 to 7.90</td>
<td>0.006</td>
<td>82</td>
<td>0.0002</td>
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<tr>
<td>Drug-induced</td>
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<td>1.57</td>
<td>0.49 to 5.03</td>
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<td>0</td>
<td>0.93</td>
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<td>Hyperlipidaemia</td>
<td>4</td>
<td>0.92</td>
<td>0.31 to 2.76</td>
<td>0.88</td>
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<td>0.48 to 3.53</td>
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<td>Persistent organ failure</td>
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<td>7.37</td>
<td>3.48 to 15.60</td>
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<td>ICU admission</td>
<td>3</td>
<td>3.91</td>
<td>2.53 to 6.05</td>
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<td>0.52</td>
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<td>Mechanical ventilation</td>
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<td>3.23 to 17.49</td>
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<td>0.33</td>
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<tr>
<td>Mortality</td>
<td>5</td>
<td>5.75</td>
<td>3.62 to 9.14</td>
<td>&lt;0.00001</td>
<td>0</td>
<td>0.66</td>
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<td>I vs III</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>3</td>
<td>1.74</td>
<td>1.09 to 2.80</td>
<td>0.02</td>
<td>0</td>
<td>0.45</td>
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<tr>
<td>ICU admission</td>
<td>2</td>
<td>3.80</td>
<td>0.95 to 15.18</td>
<td>0.06</td>
<td>77</td>
<td>0.04</td>
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<tr>
<td>Mortality</td>
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<td>2.76</td>
<td>1.17 to 6.54</td>
<td>0.02</td>
<td>61</td>
<td>0.05</td>
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</table>

BISAP, Bedside Index of Severity in Acute Pancreatitis; ICU, intensive care unit.

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**Competing interests** None declared.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; internally peer reviewed.

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**Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2021-325941).**
(AF). The main use of such algorithms is not to identify those at low risk of AF who can undergo liver biopsies to stage fibrosis among the few patients with laboratory parameters suggestive of cirrhosis (platelet count, INR) most fall above the liver stiffness measurement (LSM) cut-off of 20 kPa recommended by Baveno VI.4 The positive predictive value of the LSM cut-off of 20 kPa is only 44%, whereas the percentage of patients who have LSM cut-offs of 8, 15, and 20 kPa is 7%, 6%, and 3%, respectively.

Based on our data, if those with LSM cut-offs of 8, 15, and 20 kPa are entered into HCC surveillance, only 44% will have cirrhosis, while nearly a quarter will have F0–2 fibrosis (table S6). We therefore believe that screening patients with cirrhosis by the 20 kPa recommended by Baveno VI 4 could identify those with cirrhosis who should undergo monthly ultrasound scans. The presence of cirrhosis rather than high LSM cut-offs is the main driver of the HCC risk.7 Long-term surveillance without a histological diagnosis of cirrhosis is not justified.

In conclusion, diagnosis of liver cirrhosis, but can be seen in earlier stages of disease.3 Our data show that features for cirrhosis, as these patients do not include patients with overt hepatic encephalopathy. We therefore believe that screening patients with laboratory features of cirrhosis according to histological and imaging-based classification is the main driver of the HCC risk.7 Long-term surveillance without a histological diagnosis of cirrhosis is not justified.


The literature to date has examined two steps forward and one step back? disease in NAFLD: two steps ahead and one step forward? Majumdar and Tsochatzis1 and Majumdar and Tsochatzis1 suggest that the LSM cut-off of 20 kPa recommended by Baveno VI 4 could identify those with cirrhosis who should undergo monthly ultrasound scans. The positive predictive value of the LSM cut-off of 20 kPa is only 44%, whereas the percentage of patients who have LSM cut-offs of 8, 15, and 20 kPa is 7%, 6%, and 3%, respectively.

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Supplementary Material

Search Strategies

All results were imported to Covidence. Duplicates were removed by Covidence.

PubMed


AND

("pancreatitis"[MeSH Terms] OR "Pancreatitis, Acute Hemorrhagic"[Mesh] OR "Pancreatitis, Acute Necrotizing"[Mesh] pancreatitis OR interstitial pancreatitis OR acute pancreatitis OR pancreatic injur* OR pancreas OR pancreatic damage OR amylase OR lipase OR hyperamylasemia OR hyperlipasemia)

NOT

(animals[mesh] NOT humans[mesh])

Embase

('coronavirus disease 2019'/exp OR 'Severe acute respiratory syndrome coronavirus 2'/exp OR covid OR 'covid 19' OR coronavirus OR 'sars-cov-2' OR '2019 ncov' OR '2019 novel coronavirus' OR 'severe acute respiratory syndrome coronavirus 2')

AND

('pancreatitis'/exp OR 'acute pancreatitis'/exp OR pancreatitis OR 'pancreas injury'/exp OR 'interstitial pancreatitis' OR 'acute pancreatitis' OR 'pancreatic injur*' OR pancreas OR 'pancreatic damage' OR amylase OR lipase OR hyperamylasemia OR hyperlipasemia)

NOT ((animal/exp OR nonhuman) NOT human/exp)

AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)

Scopus

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AND
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Cochrane Library

("coronavirus disease 2019" OR "severe acute respiratory syndrome coronavirus 2" OR “covid 19” OR covid OR coronavirus OR “sar-cov-2” OR “2019 ncov” OR “2019 novel coronavirus”)

AND

(pancreatitis OR “acute pancreatitis” OR “pancreas injur*” OR “interstitial pancreatitis” OR “pancreas” OR “pancreatic damage” OR amylase OR lipase OR hyperamylasemia OR hyperlipasemia)

In All Text
Table 1. Characteristics of included studies about acute pancreatitis in patients with COVID-19.

<table>
<thead>
<tr>
<th>First author</th>
<th>Country</th>
<th>Study design</th>
<th>Centers</th>
<th>Study period</th>
<th>Sample size</th>
<th>No. of AP with COVID-19</th>
<th>Quality assessment†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akarsu</td>
<td>Turkey</td>
<td>Prospective cohort study</td>
<td>Single center</td>
<td>2020.3.25-2020.4.25</td>
<td>316 with COVID-19</td>
<td>40</td>
<td>5</td>
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<tr>
<td>Bulthuis</td>
<td>Netherlands</td>
<td>Prospective cohort study</td>
<td>Bi-center</td>
<td>2020.3.4-2020.5.26</td>
<td>432 with COVID-19</td>
<td>8</td>
<td>5</td>
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<tr>
<td>Dirweesh</td>
<td>USA</td>
<td>Retrospective cohort study</td>
<td>Multi-center</td>
<td>2020.3.1-2020.6.30</td>
<td>339 with AP</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Inamdar</td>
<td>USA</td>
<td>Retrospective cohort study</td>
<td>Multi-center</td>
<td>2020.3.1-2020.6.1</td>
<td>189 with AP</td>
<td>32</td>
<td>7</td>
</tr>
<tr>
<td>Kumar</td>
<td>USA</td>
<td>Retrospective cohort study</td>
<td>Multi-center</td>
<td>2020.2.1-2020.6.30</td>
<td>985 with COVID-19</td>
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<td>7</td>
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<tr>
<td>Miró</td>
<td>Spain</td>
<td>Retrospective case control study</td>
<td>Multi-center</td>
<td>2020.3.1-2020.4.30</td>
<td>74814 with COVID-19*</td>
<td>54</td>
<td>5</td>
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<tr>
<td>Pandanaboyana</td>
<td>Multiple</td>
<td>Prospective cohort study</td>
<td>Multi-center</td>
<td>2020.3.1-2020.7.23</td>
<td>1777 with AP</td>
<td>149</td>
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<tr>
<td>Szatmary</td>
<td>UK</td>
<td>Case series</td>
<td>Single center</td>
<td>2020.3.14-2020.4.30</td>
<td>35 with AP</td>
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<td>Vatansev</td>
<td>Turkey</td>
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<td>Single center</td>
<td>2020.4-2020.6</td>
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<td>Ding</td>
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<td>Retrospective cohort study</td>
<td>Single center</td>
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<td>55 with COVID-19</td>
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<td>Karaali</td>
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<td>2020.3-2020.12</td>
<td>189 with AP</td>
<td>83</td>
<td>7</td>
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</tbody>
</table>

† According to the modified Newcastle-Ottawa Scale.
* Including patients with COVID-19 diagnosed exclusively based on clinical criteria.
Modified Newcastle-Ottawa Quality Assessment Scale (Cohort studies)

Selection
1) Representativeness of the exposed cohort
   a) truly representative of the average population with acute pancreatitis / COVID-19 in the community
   b) somewhat representative of the average population with acute pancreatitis / COVID-19 in the community
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort
2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort
3) Ascertainment of exposure
   a) clearly record using the standardized diagnostic criteria
   b) record without details on the diagnostic criteria
   c) written self report
   d) no description
4) Demonstration that outcome of interest was not present at start of study
   a) yes
   b) no

Comparability
1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for age
   b) study controls for any additional factor

Outcome
1) Assessment of outcome
   a) independent blind assessment
   b) record linkage
   c) self / family report
   d) no description
2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest)
   b) no
3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for
   b) subjects lost to follow up unlikely to introduce bias
   c) subjects lost to follow up may introduce bias
   d) no statement
Supplementary Figures

Supplementary Figure 1. Flowchart of study selection.

Supplementary Figure 2. Funnel plot of the arcsine transformed mortality.
The visual inspection of the funnel plot indicated relative symmetry.