

The burden of acute pancreatitis on COVID-19 in the United States

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Abstract

Background Although SARS-CoV-2 primarily affects the respiratory system, gastrointestinal symptoms were also seen. Our study analyzed the prevalence and impact of acute pancreatitis (AP) on COVID-19 hospitalizations in the United States.

Methods The 2020 National Inpatient Sample database was used to identify patients with COVID-19. The patients were stratified into 2 groups based on the presence of AP. AP as well as its impact on COVID-19 outcomes were evaluated. The primary outcome was in-hospital mortality. Secondary outcomes were intensive care unit (ICU) admissions, shock, acute kidney injury (AKI), sepsis, length of stay, and total hospitalization charges. Univariate and multivariate logistic/linear regression analyses were performed.

Results The study population comprised 1,581,585 patients with COVID-19, from which 0.61% of people had AP. Patients with COVID-19 and AP had a higher incidence of sepsis, shock, ICU admissions, and AKI. On multivariate analysis, patients with AP had higher mortality (adjusted odds ratio [aOR] 1.19, 95% confidence interval [CI] 1.03-1.38; $P=0.02$). We also noted a higher risk of sepsis (aOR 1.22, 95%CI 1.01-1.48; $P=0.04$), shock (aOR 2.09, 95%CI 1.83-2.40; $P<0.001$), AKI (aOR 1.79, 95%CI 1.61-1.99; $P<0.001$), and ICU admissions (aOR 1.56, 95%CI 1.38-1.77; $P<0.001$). Patients with AP also had a longer length of stay (+2.03 days, 95%CI 1.45-2.60; $P<0.001$), and higher hospitalization charges (\$44,088.41, 95%CI \$33,198.41-54,978.41; $P<0.001$).

Conclusions Our study revealed that the prevalence of AP in patients with COVID-19 was 0.61%. Although this was not strikingly high, the presence of AP is associated with worse outcomes and higher resource utilization.

Keywords Acute pancreatitis, COVID-19, pandemic

Ann Gastroenterol 2023; 36 (X): 1-8

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Conflict of Interest: None

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Received 23 November 2022; accepted 4 January 2023; published online 3 February 2023

DOI: <https://doi.org/10.20524/aog.2023.0782>

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Introduction

SARS-CoV-2 infection was first described in December 2019 and it caused a global pandemic affecting millions worldwide [1]. As of October 2022, over 600 million cases had been confirmed globally and were responsible for more than 6.5 million deaths worldwide [2]. Respiratory complications are the most commonly reported sequelae and the predominant cause of morbidity and mortality. However, gastrointestinal symptoms have also been described [3-5]. Emerging data suggest the pancreas is a target organ, which might explain the cases of acute pancreatitis (AP) in patients with COVID-19 [6-8].

The exact pathogenesis of AP in COVID-19 remains unclear, but multiple theories have been postulated. Studies have hypothesized that COVID-19 infected and inflamed pancreatic glands, resulting in acute idiopathic pancreatitis [9]. This theory arises from the known ability of other microorganisms to affect the pancreas, leading to AP, which suggests a similar phenomenon in COVID-19 [10]. Several other studies have shown that both

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exocrine and endocrine functions can be affected. Liu *et al* studied the expression of angiotensin-converting enzyme 2 (ACE2), the receptor of COVID-19, in the pancreas [9]. They found that the messenger RNA level of ACE2 was higher in the pancreas than in the lung, which could explain the development of AP in COVID-19 patients. Others suggested that the cytokine storm associated with COVID-19 resembles the lipotoxicity process in AP and could also be a contributing factor to the pathogenesis [11].

The pooled prevalence of AP in COVID-19 in different regions of the world was estimated to be 3.1% in a meta-analysis using 11 studies done in various countries [12]. One meta-analysis included studies from the UK, China, Spain and the USA [13-23]. A study by Inamdar *et al* reported the prevalence of AP in COVID-19 patients to be 0.3%. Their study included 12 hospitals in New York [14]. To the best of our knowledge, no study has estimated the prevalence of AP or evaluated its effect on COVID-19 hospitalizations in the United States, using data representative of the national population. Given the limited data on outcomes of patients with COVID-19 who also have pancreatitis, our study aimed to assess the differences in mortality, severity, and resource utilization among these patients.

Materials and methods

Data source

The National Inpatient Sample (NIS), maintained by the Healthcare Cost and Utilization Project (HCUP) of the Agency

for Healthcare Research and Quality, is the largest database of inpatient hospital stays in the United States [24]. The NIS collects data from a 20% stratified sample of United States hospitals from 37 states and has been reliably used to estimate disease burden and outcomes. Each hospitalization is de-identified and maintained in the NIS as a unique entry with one primary discharge diagnosis and up to 39 secondary diagnoses during that hospitalization, depending on the year of data collection. Each entry includes patient demographics (age, sex and race), insurance status, primary and secondary procedures (up to 25), hospitalization outcomes, total charges and length of stay (LOS). Institutional Review Board approval was not required as the data are publicly available and de-identified.

Study population

The diagnosis codes of the International Classification of Diseases 10th Version, Clinical Modification (ICD-10 CM), were used to identify adult patients hospitalized with COVID-19 in 2020. Cases that lacked mortality, sex or other demographic information were excluded. In total, 1,581,585 cases met the inclusion criteria. Patients were stratified into 2 groups, those with and without AP. This inclusion flow diagram is presented in Fig. 1.

Study variables

Our primary exposure variable was AP. Other variables included age (divided into 3 groups: <44 years; 45-64 year; and

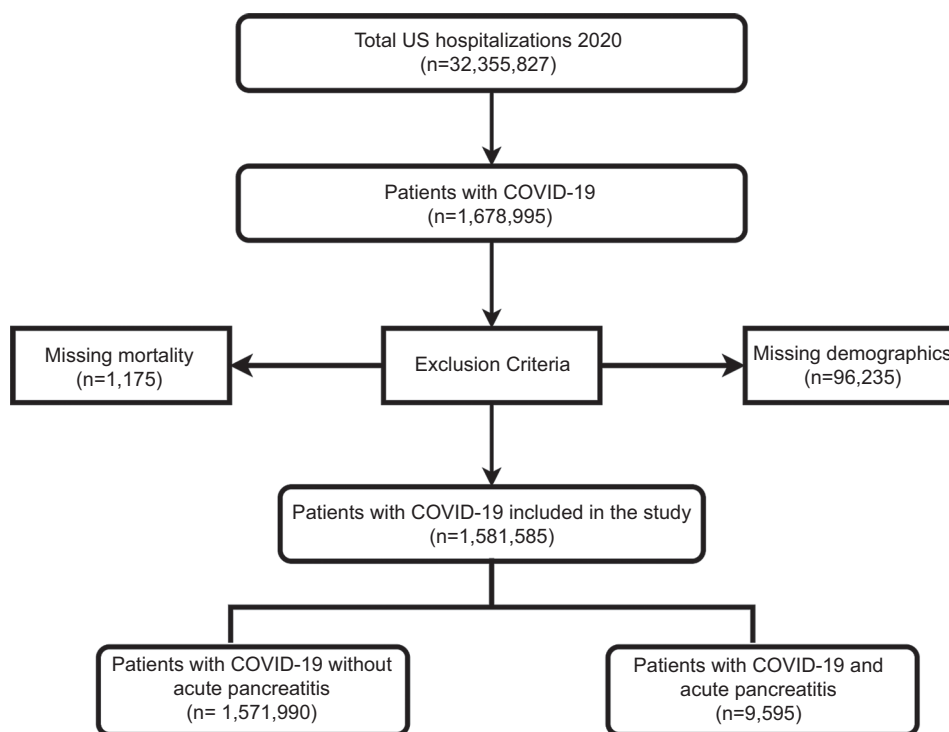


Figure 1 Inclusion flow diagram for the study

>65 years), sex, race, primary insurance and median income, as well as hospital characteristics such as region, size and rural/urban location, pre-specified by HCUP. Data were also collected on the etiology of AP, such as alcohol-related or biliary pancreatitis. We assessed for additional comorbidities that predispose to COVID-19, such as asthma, myelodysplastic syndrome, transplant history, immunosuppressive disorders, autoimmune diseases, neutropenia, hypertension, drug abuse, alcohol abuse, psychoses, depression, obesity, malnutrition, immunosuppressive disorders, autoimmune diseases, transplant status, neutropenia, and tobacco use. We collected information on additional infections, such as the presence of influenza, bacteremia and fungal infection. We further studied the Charlson/Deyo Comorbidity Index and comorbidities. This is a well-validated index based on ICD 10-CM codes meant to be used in association with large quantities of administrative data to predict mortality and hospital resource use [25]. We also collected information regarding the known complications of AP, such as pancreatic pseudocyst, portal vein thrombosis, ileus and pancreatic necrosis. A complete list of ICD-10 codes is presented in Supplementary Table 1.

Study outcomes

The primary outcome assessed the impact of AP on inpatient mortality in patients with COVID-19. Secondary outcomes studied included rates of shock, acute kidney injury (AKI), sepsis, and ICU admissions. We also compared the mean LOS and total hospitalization charges between COVID-19 and AP as surrogate markers for healthcare cost utilization. Hospital charges are defined as the dollar amount a hospital charges for services before negotiating discounts with insurance companies.

Statistical analysis

Hospital-level discharge weights provided by NIS were used to generate national estimates. Categorical variables were compared using the chi-square test, whereas an independent sample *t*-test was used for continuous variables. Multivariate logistic regression was performed with adjustments for patient demographics, hospital characteristics, Charlson/Deyo comorbidities, additional comorbidities associated with COVID-19 and complications in patients with COVID-19. Only confounding variables that had a *P*-value <0.01 were included in the final multivariate logistic regression model. The unadjusted and adjusted odds ratios (aOR) were calculated with a 95% confidence interval (CI). A type I error of <0.05 was considered statistically significant. Data analysis was carried out using STATA 17.0 (Texas).

Results

Demographics

The study comprised a total of 1,581,585 patients with COVID-19, of whom 0.61% had AP. Males accounted for

54.04% of the patients with AP, while the remaining were females. The age group 45-64 had the highest AP prevalence (38.41%), followed by patients aged over 65 (33.3%). AP was seen most commonly in Whites (39.24%), followed by Hispanics (31.06%), and African Americans (20.79%). A high prevalence of AP was seen in patients with 3 or more Charlson comorbidities (32%). Patient demographics, stratified by the presence of AP, are presented in Table 1.

Comorbidities

There was no significant difference between patients with and without AP in the comorbidities of rheumatoid disease, renal disease, cancer, immunosuppressive disorders and myelodysplastic disorders. Patients with AP had a higher prevalence of peptic ulcer disease (2.76% vs. 0.65%, *P*<0.001), moderate/severe liver disease (4.07% vs. 0.83%, *P*<0.001), and uncomplicated diabetes (33.09% vs. 30.77, *P*=0.029). Additionally, patients with AP had a higher incidence of fungal infections. Table 2 provides a complete list of comorbidities and additional infections, stratified by the presence or absence of AP.

Etiology and complications of AP

Of the patients admitted with AP, 1345 (14%) had gallstone pancreatitis, 1065 (11%) had alcohol-related pancreatitis, while 270 (2.8%) patients had idiopathic AP. No specific information was provided regarding the etiology of AP in other cases. These results are presented in Fig. 2. In addition, 235 (2.45%) patients had pancreatic necrosis, 360 (3.75%) patients developed pseudocyst, 315 (3.28%) patients developed ileus, while 65 (0.68%) patients had portal vein thrombosis.

Outcomes

All-cause mortality

Total in-hospital mortality in the study population was 211,810 (13.39%). The mortality rate in both patients with AP

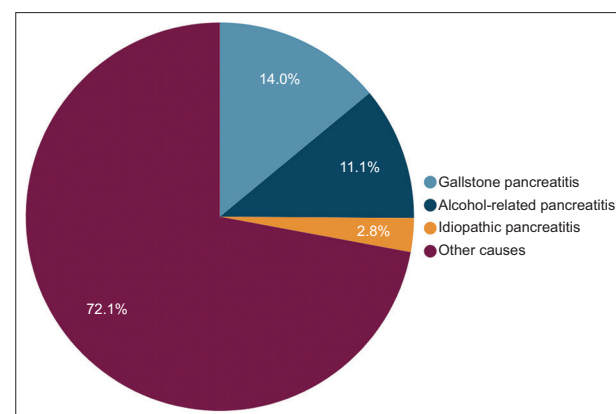


Figure 2 Etiology of acute pancreatitis

Table 1 Patient demographics, stratified by the presence of acute pancreatitis

| Demographics | Absence of acute pancreatitis n (%) | Presence of acute pancreatitis n (%) |
|--------------------------|-------------------------------------|--------------------------------------|
| Age category | | |
| 18-44 | 251,065 (15.97%) | 2715 (28.3%) |
| 45-64 | 502,590 (31.97%) | 3685 (38.41%) |
| >65 | 818,335 (52.06%) | 3195 (33.3%) |
| Sex | | |
| Male | 814,365 (51.8%) | 5185 (54.04%) |
| Female | 757,625 (48.2%) | 4410 (45.96%) |
| Race | | |
| White | 802,670 (51.06%) | 3765 (39.24%) |
| African American | 298,970 (19.02%) | 1995 (20.79%) |
| Hispanic | 336,890 (21.43%) | 2980 (31.06%) |
| Asian/Pacific Islander | 51,500 (3.28%) | 245 (2.55%) |
| Native American | 14,720 (0.94%) | 145 (1.51%) |
| Other | 67,240 (4.28%) | 465 (4.84%) |
| Primary expected payer | | |
| Medicare | 801,590 (50.99%) | 3310 (3.45%) |
| Medicaid | 224,305 (14.27%) | 2410 (25.12%) |
| Private | 414,670 (26.38%) | 2650 (27.62%) |
| Uninsured | 58,500 (3.72%) | 695 (7.24%) |
| Median household income | | |
| Lowest quartile | 534,425 (34%) | 3510 (36.58%) |
| Second quartile | 426,380 (27.12%) | 2700 (28.14%) |
| Third quartile | 349,750 (22.25%) | 2045 (21.31%) |
| Highest quartile | 261,435 (16.63%) | 1340 (13.97%) |
| Hospital region | | |
| Northeast | 294,405 (18.73%) | 1590 (16.57%) |
| Midwest | 343,860 (21.87%) | 1915 (19.96%) |
| South | 651,351 (41.43%) | 4045 (42.16%) |
| West | 282,374 (17.96%) | 2045 (21.31%) |
| Hospital location | | |
| Rural | 149,765 (9.53%) | 600 (6.25%) |
| Urban | 1,422,225 (90.47%) | 8995 (93.75%) |
| Hospital teaching status | | |
| Non-teaching hospitals | 445,151 (28.32%) | 2585 (26.94%) |
| Teaching hospitals | 1,126,839 (71.68%) | 7010 (73.06%) |
| Hospital size | | |
| Small | 380,470 (2.42%) | 2355 (24.54%) |
| Medium | 457,370 (29.09%) | 2630 (27.41%) |
| Large | 734,150 (4.67%) | 4610 (48.05%) |
| Charlson comorbidities | | |
| 0 | 438,230 (27.88%) | 2520 (26.26%) |
| 1 | 403,610 (25.68%) | 2545 (26.52%) |
| 2 | 238,380 (15.16%) | 1460 (15.22%) |
| >3 | 491,770 (31.28%) | 3070 (32%) |

(n=1285) and without (n=210,525) was 13.39%. The outcomes stratified by the presence of AP are presented in Fig. 3. On multivariate analysis, patients with AP had statistically significant higher mortality (adjusted odds ratio [aOR] 1.19, 95%CI 1.03-1.38; P=0.02).

Sepsis

The total incidence of sepsis in the study population was 5.02%. A total of 575 (5.99%) patients with AP and

78,820 (5.01%) without AP developed sepsis. On multivariate analysis, patients with AP had a statistically significant higher risk of sepsis (aOR 1.22, 95%CI 1.01-1.48; P=0.04). The results of the multivariate regression are presented in Table 3.

Shock

A total of 137,315 (8.68%) patients developed shock. The incidence of shock was 17.35% in patients with AP compared to 8.62% in patients without AP. On multivariate analysis,

Table 2 Comorbidities and infections in patients with COVID-19, stratified by the presence of acute pancreatitis

| Comorbidities | Absence of acute pancreatitis n (%) | Presence of acute pancreatitis n (%) | P-value |
|---------------------------------------|-------------------------------------|--------------------------------------|---------|
| Acute myocardial infarction | 130,410 (8.30%) | 635 (6.62%) | 0.009 |
| Congestive heart failure | 277,840 (17.67%) | 1300 (13.55%) | <0.001 |
| Peripheral vascular disease | 75,470 (4.80%) | 385 (4.01%) | 0.115 |
| Cerebrovascular disease | 82,815 (5.27%) | 410 (4.27%) | 0.059 |
| Dementia | 189,830 (12.08%) | 465 (4.85%) | <0.001 |
| Chronic obstructive pulmonary disease | 347,295 (22.09%) | 1420 (14.8%) | <0.001 |
| Rheumatoid disease | 42,245 (2.69%) | 230 (2.40%) | 0.437 |
| Peptic ulcer disease | 10,195 (0.65%) | 265 (2.76%) | <0.001 |
| Moderate/severe liver disease | 12,970 (0.83%) | 390 (4.07%) | <0.001 |
| Diabetes | 483,675 (30.77%) | 3175 (33.09%) | 0.029 |
| Complicated diabetes | 259,260 (16.49%) | 1605 (16.73%) | 0.78 |
| Hemiplegia/paraplegia | 21,055 (1.33%) | 105 (1.09%) | 0.371 |
| Renal disease | 332,185 (21.13%) | 2085 (21.73%) | 0.524 |
| Cancer | 60,865 (3.87%) | 360 (3.75%) | 0.777 |
| Metastatic cancer | 17,605 (1.12%) | 110 (1.14%) | 0.911 |
| Tobacco use | 467,710 (29.75%) | 2805 (29.23%) | 0.623 |
| Myelodysplastic syndrome | 2,770 (0.18%) | 10 (0.10%) | 0.453 |
| Neutropenia | 10,810 (0.69%) | 50 (0.521%) | 0.378 |
| Asthma | 123,895 (7.90%) | 540 (5.62%) | <0.001 |
| Immunosuppressive disorders | 23,530 (1.50%) | 115 (1.20%) | 0.276 |
| Anemia from blood loss | 7,180 (4.56%) | 65 (0.68%) | 0.18 |
| Deficiency anemia | 60,590 (3.85%) | 415 (4.32%) | 0.271 |
| Alcohol abuse | 39,695 (2.52%) | 1525 (15.89%) | <0.001 |
| Drug abuse | 38,755 (2.46%) | 490 (5.1%) | <0.001 |
| Depression | 184,785 (11.75%) | 955 (9.93%) | 0.015 |
| Psychosis | 39,745 (2.53%) | 130 (1.35%) | 0.0016 |
| Hypertension without complications | 600,020 (38.17%) | 3265 (34.03%) | 0.002 |
| Hypertension with complications | 427,705 (27.21%) | 2340 (24.39%) | 0.005 |
| Obesity | 404,680 (25.74%) | 2170 (22.62%) | 0.002 |
| Malnutrition | 123,445 (7.85%) | 1230 (12.82%) | <0.001 |
| Infections | | | |
| Bacteremia | 13,520 (0.86%) | 115 (1.19%) | 0.109 |
| Fungal infection | 37,440 (2.38%) | 390 (4.06%) | <0.001 |
| Influenza | 4,285 (0.27%) | 35 (0.36%) | 0.435 |

patients with AP had a statistically significant higher risk of shock (aOR 2.09, 95%CI 1.83-2.40; P<0.001).

significant higher risk of AKI (aOR 1.79, 95%CI 1.61-1.99; P<0.001).

AKI

A total of 453,060 (28.65%) patients developed AKI. Among patients with AP, 3790 (39.5%) developed AKI compared to 4,49,270 (28.58%) patients without AP. On multivariate analysis, patients with AP had a statistically

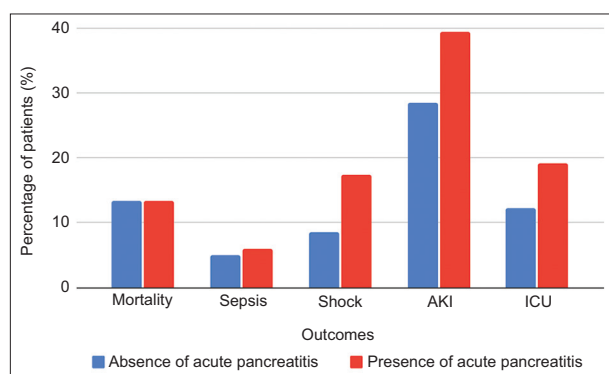
ICU admission

A total of 195,535 (12.36%) patients required ICU admission. There were 1845 (19.23%) patients with AP who required ICU admission compared to 1,93,690 (12.32%) patients without AP. On multivariate analysis, patients with AP had a statistically

Table 3 Adjusted odds ratio/coefficient after adjusting for patient demographics, comorbidities, Charlson Comorbidity Index and infections in COVID-19

| Categorical variables | Adjusted odds ratio | 95%CI | P-value |
|-------------------------------|----------------------|-----------------------|---------|
| Mortality | 1.19 | 1.03-1.38 | 0.021 |
| Sepsis | 1.22 | 1.01-1.48 | 0.04 |
| Shock | 2.09 | 1.83-2.40 | <0.001 |
| AKI | 1.79 | 1.61-1.99 | <0.001 |
| ICU | 1.56 | 1.38-1.77 | <0.001 |
| Continuous variables | Adjusted coefficient | 95%CI | P-value |
| Length of stay | 2.03 | 1.45-2.60 | <0.001 |
| Total hospitalization charges | \$44,088.41 | \$33,198.41-54,978.41 | <0.001 |

AKI, acute kidney injury; ICU, intensive care unit; CI, confidence interval

**Figure 3** Outcomes of patients, stratified by the presence or absence of acute pancreatitis.

AKI, acute kidney injury; ICU, intensive care unit

significantly higher risk of ICU admission (aOR 1.56, 95%CI 1.38-1.77; $P < 0.001$).

LOS

The mean LOS in patients with AP was 10.53 days (± 0.32) compared to 8.01 days (± 0.03) in patients without AP. On multivariate analysis, patients with AP had a statistically significant longer stay than those without (adjusted coefficient 2.03, 95%CI 1.45-2.60; $P < 0.001$).

Total charges

The total hospitalization charges in patients with AP were \$149,911.7 (± 6462.41) compared to \$91,451.85 (± 1191.55) in patients without AP. On multivariate analysis, patients with AP had statistically significant higher total hospitalization charges than those without (adjusted coefficient 44,088.41, 95%CI \$33,198.41-54,978.41; $P < 0.001$).

Discussion

COVID-19 is a highly contagious viral illness that has been proved to have catastrophic effects on the human body.

It was initially thought to affect only the respiratory system, but the discovery of its association with ACE-2 cell receptors led to the realization that there can be multiple organ involvement [26]. While a correlation has been recognized between gastrointestinal manifestations and COVID-19 [27], further research is needed to assess the association between AP and its effect on disease severity and outcomes in COVID-19 patients. Our retrospective analysis aims to further investigate this association.

Our study revealed a 0.6% prevalence of AP in patients with COVID-19 in the United States using NIS data, representative of the total hospitalizations in the United States. Inamdar *et al* performed a study in New York hospitals and found a prevalence of 0.27% and similar mortality in those with and without COVID-19 [14]. In our study, we included hospitalizations from all regions of the United States, thereby minimizing the risk of sampling bias. A meta-analysis by Yang *et al* reported a prevalence of 3.1% (95%CI 1.6-5.1%) [12]. Their study included patients from the USA, China and European countries. Another international multicenter cohort study by Pandanaboyana revealed the prevalence of AP in COVID-19 to be 8.3% [13].

Our study reports a statistically significant association between mortality and AP in 1.5 million patients with COVID-19 in the United States. Various studies have assessed the association between the development of AP and mortality in patients with COVID-19. A systematic review by Mutneja *et al* revealed a significantly greater mortality rate (OR 4.10, 95%CI 2.03-8.29) in patients with AP and COVID-19 [28]. Similar results were seen in a study by Yang *et al*, who found significantly greater mortality in patients with AP and COVID-19 (aOR 5.75, 95%CI 3.62-9.14) [12]. Given that the majority of these studies were performed outside the United States, the possibility of regional variations could not be ruled out. Inamdar *et al*, in their study on patients from 12 hospitals in New York, reported a higher mortality in patients with concomitant AP and COVID, although their results were not statistically significant (aOR 2.19, 95%CI 0.44-10.95; $P = 0.34$) [14]. The smaller sample size might have contributed to the association not being statistically significant. SARS-CoV-2 can aggravate the ongoing inflammatory state of pancreatitis and contribute to worse outcomes [29]. Furthermore, a higher incidence of fungal infection in patients with AP was also

noted compared to patients without AP, which could also have contributed to higher mortality.

On analysis of the etiologies of AP, 25.1% were classified as biliary/alcohol-related pancreatitis, while no specific etiology was reported for the remaining cases. It is well known that viral infections such as Coxsackie, mumps and measles have been implicated as causes of AP, further extending this theory to COVID-induced pancreatitis [10]. Furthermore, there is a high likelihood that COVID-19 or drugs used for its treatment contributed to the development of pancreatitis in patients without a diagnosis of biliary/alcohol-related pancreatitis [30-32].

Overall, morbidity and mortality were significantly greater in patients with AP and COVID-19, suggesting a deleterious relationship between the 2 processes. AKI was noted to be 78% higher in patients with AP than in those without. AKI is a frequent complication of severe AP and carries a poor prognosis. Battle *et al* suggested that the hypercoagulable state in COVID-19 could foster the progression of acute tubular necrosis, leading to irreversible kidney dysfunction [33]. Thus, it is difficult to ascertain whether AKI in these patients is due to AP or COVID-19. Furthermore, the kidneys are fundamental in eliminating amylase and lipase and their malfunction can lead to a transient increase in pancreatic enzymes [11].

Sepsis and shock were also noted to be 22% and 109% higher, respectively, in patients with AP. Development of sepsis and shock can be seen as a result of marked arterial vasoconstriction in AP, leading to volume deficit and subsequently shock. Wilson *et al* described another mechanism via which angiotensin-2 levels caused endothelial cell dysfunction and vascular leak syndrome, leading to sepsis and shock [34]. There was a 98% higher likelihood of ICU admissions in patients with concomitant AP and COVID-19, which can be explained by higher rates of sepsis, AKI, and shock. Furthermore, aggressive early fluid resuscitation is essential in the management of AP [35,36]. Cautious use of intravenous fluids in patients with COVID-19, due to concern for worsening of respiratory status, might have led to under-resuscitation and worse outcomes.

Patients with AP were also noted to have longer hospital stays and higher hospitalization costs, indicating higher resource utilization. As previously described, AP has been associated with a higher rate of sepsis, shock, ICU admission and mortality, indicating greater disease severity. Furthermore, the LOS was also noted to be longer in patients with COVID who developed AP. Hospitals nationwide saw a greater LOS due to quarantine guidelines associated with COVID-19 infection, thus a clear conclusion cannot be drawn as to whether the longer LOS was due to greater severity or quarantine guidelines. Further research identifying the factors associated with LOS in COVID-19 patients is warranted.

We acknowledge the following limitations of our study. The NIS database lacks objective data, limiting our ability to calculate common risk stratification scores such as APACHE-II or BISAP. It also lacks information on pharmaceutical therapies used during hospitalization. Since NIS is an administrative database using ICD-10 codes, the possibility of coding errors cannot be excluded. Furthermore, we are unable to identify patients with acute vs. long COVID-19 infection. Additional

causes of AP, such as hypertriglyceridemia, hypercalcemia and endoscopic retrograde cholangiopancreatography, could not be ascertained, given the paucity of ICD-10 codes available for these factors. Finally, data from NIS only include acute hospitalization episodes; therefore, the patients could not be followed longitudinally. It was also difficult to ascertain whether the COVID-19 or AP episode was a primary admission or a readmission. Despite these limitations, the study's strength comes from the large population size and the exclusion of a sample bias from data collected from a single region or hospital. Further studies capturing more granular clinical data, including information on treatment, and long-term mortality, are encouraged.

In summary, the consequence of pancreatic injury in COVID-19 can be potentially serious. Our study expands on the impact of AP in patients who developed COVID-19. We found that, although the prevalence of AP is low in patients with COVID-19, its presence was associated with higher rates of mortality, sepsis, shock, ICU admission and AKI. Patients with AP also had a greater LOS and higher total hospitalization charges. Physicians should be aware of this association, as the presence of pancreatic injury in patients with COVID-19 can lead to worse outcomes.

Summary Box

What is already known:

- Acute pancreatitis is associated with significant morbidity and mortality
- Acute pancreatitis is the leading cause of gastrointestinal-related hospitalizations in the United States
- No study has estimated the prevalence of acute pancreatitis (AP) or evaluated its effect on COVID-19 hospitalizations in the United States, using data representative of the national population

What the new findings are:

- The prevalence of AP in patients with COVID-19 was low
- AP in patients with COVID-19 was associated with higher mortality, sepsis, and shock
- Patients with AP also required higher resource utilization, as evidenced by higher intensive care unit admissions, hospitalization charges, and a longer length of stay

References

1. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. *Lancet* 2020;395:470-473.
2. WHO COVID-19 Dashboard. Geneva: World Health Organization, 2020. Available online: <https://covid19.who.int/>

- [Accessed 30 January 2023].
3. Leal T, Costa E, Arroja B, Gonçalves R, Alves J. Gastrointestinal manifestations of COVID-19: results from a European centre. *Eur J Gastroenterol Hepatol* 2021;**33**:691-694.
 4. Groff A, Kavanaugh M, Ramgobin D, et al. Gastrointestinal manifestations of COVID-19: a review of what we know. *Ochsner J* 2021;**21**:177-180.
 5. El Ouali S, Achkar JP, Lashner B, Regueiro M. Gastrointestinal manifestations of COVID-19. *Cleve Clin J Med* 2021 Feb 17 [Online ahead of print]. doi: 10.3949/ccjm.87a.ccc049
 6. Abramczyk U, Nowaczyński M, Słomczyński A, Wojnicz P, Zatyka P, Kuzan A. Consequences of COVID-19 for the pancreas. *Int J Mol Sci* 2022;**23**:864.
 7. Bacaksiz F, Ebik B, Ekin N, Kılıc J. Pancreatic damage in COVID-19: Why? How? *Int J Clin Pract* 2021;**75**:e14692.
 8. Goyal H, Kopel J, Ristić B, et al. The pancreas and COVID-19: a clinical conundrum. *Am J Transl Res* 2021;**13**:11004-11013.
 9. Liu F, Long X, Zhang B, Zhang W, Chen X, Zhang Z. ACE2 Expression in pancreas may cause pancreatic damage after SARS-CoV-2 infection. *Clin Gastroenterol Hepatol* 2020;**18**:2128-2130.
 10. Rawla P, Bandaru SS, Vellipuram AR. Review of infectious etiology of acute pancreatitis. *Gastroenterology Res* 2017;**10**:153-158.
 11. Zippi M, Hong W, Traversa G, et al. Involvement of the exocrine pancreas during COVID-19 infection and possible pathogenetic hypothesis: a concise review. *Infez Med* 2020;**28**:507-515.
 12. Yang F, Huang Y, Li T, et al. Prevalence and outcomes of acute pancreatitis in COVID-19: a meta-analysis. *Gut* 2022;**71**:1451-1453.
 13. Pandanaboyana S, Moir J, Leeds JS, et al; COVID PAN collaborative group. SARS-CoV-2 infection in acute pancreatitis increases disease severity and 30-day mortality: COVID PAN collaborative study. *Gut* 2021;**70**:1061-1069.
 14. Inamdar S, Benias PC, Liu Y, Sejpal DV, Satapathy SK, Trindade AJ; Northwell COVID-19 Research Consortium. Prevalence, risk factors, and outcomes of hospitalized patients with coronavirus disease 2019 presenting as acute pancreatitis. *Gastroenterology* 2020;**159**:2226-2228.
 15. Akarsu C, Karabulut M, Aydin H, et al. Association between acute pancreatitis and COVID-19: could pancreatitis be the missing piece of the puzzle about increased mortality rates? *J Invest Surg* 2022;**35**:119-125.
 16. Dirweesh A, Li Y, Trikidanathan G, Mallery JS, Freeman ML, Amateau SK. Clinical outcomes of acute pancreatitis in patients with coronavirus disease 2019. *Gastroenterology* 2020;**159**:1972-1974.
 17. Bulthuis MC, Boxhoorn L, Beudel M, et al. Acute pancreatitis in COVID-19 patients: true risk? *Scand J Gastroenterol* 2021;**56**:585-587.
 18. Kumar V, Barkoudah E, Souza DAT, Jin DX, McNabb-Baltar J. Clinical course and outcome among patients with acute pancreatitis and COVID-19. *Eur J Gastroenterol Hepatol* 2021;**33**:695-700.
 19. Miró, Llorens P, Jiménez S, et al; Spanish Investigators on Emergency Situations TeAm (SIESTA) network. A case-control emergency department-based analysis of acute pancreatitis in Covid-19: results of the UMC-19-S6. *J Hepatobiliary Pancreat Sci* 2021;**28**:953-966.
 20. Szatmary P, Arora A, Thomas Raraty MG, Joseph Dunne DF, Baron RD, Halloran CM. Emerging phenotype of severe acute respiratory syndrome-coronavirus 2-associated pancreatitis. *Gastroenterology* 2020;**159**:1551-1554.
 21. Vatansev H, Yıldırım MA, Kuccukturk S, Karaselek MA, Kadiyoran C. Clinical evaluation of acute pancreatitis caused by SARS-CoV-2 virus infection. *Gastroenterol Res Pract* 2021;**2021**:5579795.
 22. Ding P, Song B, Liu X, et al. Elevated pancreatic enzymes in ICU patients with COVID-19 in Wuhan, China: a retrospective study. *Front Med (Lausanne)* 2021;**8**:663646.
 23. Karaali R, Topal F. Evaluating the effect of SARS-Cov-2 infection on prognosis and mortality in patients with acute pancreatitis. *Am J Emerg Med* 2021;**49**:378-384.
 24. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP). Available from: <https://www.ahrq.gov/data/hcup/index.html> [Accessed 30 January 2023].
 25. Glasheen WP, Cordier T, Gumpina R, Haugh G, Davis J, Renda A. Charlson Comorbidity Index: ICD-9 update and ICD-10 translation. *Am Health Drug Benefits* 2019;**12**:188-197.
 26. Salamanna F, Maglio M, Landini MP, Fini M. Body localization of ACE-2: on the trail of the keyhole of SARS-CoV-2. *Front Med (Lausanne)* 2020;**7**:594495.
 27. Zeng W, Qi K, Ye M, et al. Gastrointestinal symptoms are associated with severity of coronavirus disease 2019: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol* 2022;**34**:168-176.
 28. Mutneja HR, Bhurwal A, Arora S, Goel A, Vohra I, Attar BM. Acute pancreatitis in patients with COVID-19 is more severe and lethal: a systematic review and meta-analysis. *Scand J Gastroenterol* 2021;**56**:1467-1472.
 29. Shaharuddin SH, Wang V, Santos RS, et al. Deleterious effects of SARS-CoV-2 infection on human pancreatic cells. *Front Cell Infect Microbiol* 2021;**11**:678482.
 30. Khadka S, Williams K, Solanki S. Remdesivir-associated pancreatitis. *Am J Ther* 2022;**29**:e444-e446.
 31. Meyers MH, Main MJ, Orr JK, Obstein KL. A case of COVID-19-induced acute pancreatitis. *Pancreas* 2020;**49**:e108-e109.
 32. Vara-Luiz F, Pé D'Arca Barbosa F, Antunes Albuquerque A, Valada Marques A, Spencer V. An uncommon cause of acute pancreatitis in a patient with COVID-19. *Cureus* 2022;**14**:e27910.
 33. Batlle D, Soler MJ, Sparks MA, et al; COVID-19 and ACE2 in Cardiovascular, Lung, and Kidney Working Group. Acute kidney injury in COVID-19: emerging evidence of a distinct pathophysiology. *J Am Soc Nephrol* 2020;**31**:1380-1383.
 34. Wilson A, Phillips A, Woods K, Stello K, Binion D, Whitcomb D. Severe acute pancreatitis and shock: are high angiotensin-2 levels causing endothelial cell dysfunction and a vascular leak syndrome? *Am J Gastroenterol* 2017;**112**:S13.
 35. Yamashita T, Horibe M, Sanui M, et al. Large volume fluid resuscitation for severe acute pancreatitis is associated with reduced mortality: a multicenter retrospective study. *J Clin Gastroenterol* 2019;**53**:385-391.
 36. Liu L, Wang C, Luo T, Li L. Effects of fluid resuscitation on the occurrence of organ failure and mortality in patients with acute pancreatitis. *Pancreas* 2020;**49**:1315-1320.

Supplementary material

Supplementary Table 1 ICD-10 codes used in the analysis

| Diagnosis | ICD-10 codes |
|---------------------------------------|---|
| <i>Clostridioides difficile</i> | A047 |
| COVID-19 | U071 |
| Acute myocardial infarction | I21.x, I22.x, I25.2 |
| Congestive heart failure | I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.x, I50.x, P29.0 |
| Peripheral vascular disease | I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9 |
| Cerebrovascular disease | G45.x, G46.x, H34.0, I60.x-I69.x |
| Dementia | F00.x-F03.x, F05.1, G30.x, G31.1 |
| Chronic obstructive pulmonary disease | I27.8, I27.9, J40.x-J47.x, J60.x-J67.x, J68.4, J70.1, J70.3 |
| Rheumatoid disease | M05.x, M06.x, M31.5, M32.x-M34.x, M35.1, M35.3, M36.0 |
| Peptic ulcer disease | K25.x-K28.x |
| Mild liver disease | B18.x, K70.0-K70.3, K70.9, K71.3-K71.5, K71.7, K73.x, K74.x, K76.0, K76.2-K76.4, K76.8, K76.9, Z94.4 |
| Diabetes | E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9 |
| Complicated diabetes | E10.2-E10.5, E10.7, E11.2-E11.5, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9 |
| Hemiplegia/paraplegia | G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0-G83.4, G83.9 |
| Renal disease | I12.0, I13.1, N03.2-N03.7, N05.2-N05.7, N18.x, N19.x, N25.0, Z49.0-Z49.2, Z94.0, Z99.2 |
| Cancer | C00.x-C26.x, C30.x-C34.x, C37.x-C41.x, C43.x, C45.x-C58.x, C60.x-C76.x, C81.x-C85.x, C88.x, C90.x-C97.x |
| Moderate/Severe liver disease | I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7 |

(Contd...)

Supplementary Table 1 (Continued)

| Diagnosis | ICD-10 codes |
|-----------------------------|---|
| Metastatic cancer | C77.x-C80.x |
| AIDS | B20.x-B22.x, B24.x |
| Tobacco abuse | F17 Z71 Z720 Z87 |
| Asthma | J45 J46 |
| Autoimmune diseases | G35 G70 K90 L93 M05 M35 |
| Cystic fibrosis | E84 |
| Immunosuppressive disorders | D80 D81 D82 D83 D84 D85 D86 D87 D88 D89 |
| Myelodysplastic syndrome | D46 |
| Neutropenia | D70 |
| H/o transplant | Z94 |
| Idiopathic pancreatitis | K85.0 |
| Biliary pancreatitis | K85.1 |
| Alcoholic pancreatitis | K85.2 |
| Pancreatic necrosis | K85.91, K85.92 |
| Pseudocyst | K86.3 |
| Ileus | K560, K563, K67 |
| Portal vein thrombosis | I81 |
| Bacteremia | R7881 |
| Fungal infections | B44 B37 B38 B45 B39 B46 B59 B35 B36 B40 B41 B42 B43 B47 B48 B49 |
| Influenza | J09 J10 J11 |
| Pneumonia | J12 J13 J14 J15 J16 J17 J18 |
| Sepsis | R6510 R6511 R6520 |
| Shock | R6521 R571 R578 R579 |
| Pressor use | 3E030XZ 3E033XZ 3E040XZ 3E043XZ 3E050XZ 3E053XZ 3E060XZ 3E063XZ |
| Mechanical ventilation | 5A1935Z 5A1945Z 5A1955Z |
| ICU admission | Pressor and mechanical ventilation |
| Acute kidney injury | N170 N171 N172 N178 N179 |
| Death | Information provided by HCUP |

ICU, intensive care unit; HCUP, Healthcare Cost and Utilization Project