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Original research

SARS-CoV-2 infection in acute pancreatitis increases disease severity and 30-day mortality: COVID PAN collaborative study

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ABSTRACT

Objective There is emerging evidence that the pancreas may be a target organ of SARS-CoV-2 infection. This aim of this study was to investigate the outcome of patients with acute pancreatitis (AP) and coexistent SARS-CoV-2 infection.

Design A prospective international multicentre cohort study including consecutive patients admitted with AP during the current pandemic was undertaken. Primary outcome measure was severity of AP. Secondary outcome measures were aetiology of AP, intensive care unit (ICU) admission, length of hospital stay, local complications, acute respiratory distress syndrome (ARDS), persistent organ failure and 30-day mortality. Multilevel logistic regression was used to compare the two groups.

Results 1777 patients with AP were included during the study period from 1 March to 23 July 2020. 149 patients (8.3%) had concomitant SARS-CoV-2 infection. Overall, SARS-CoV-2-positive patients were older male patients and more likely to develop severe AP and ARDS (p<0.001). Unadjusted analysis showed that SARS-CoV-2-positive patients with AP were more likely to require ICU admission (OR 5.21, p<0.001), local complications (OR 2.91, p<0.001), persistent organ failure (OR 7.32, p<0.001), prolonged hospital stay (OR 1.89, p<0.001) and a higher 30-day mortality (OR 6.56, p<0.001). Adjusted analysis showed that length of stay (OR 1.32, p<0.001), persistent organ failure (OR 2.77, p<0.003) and 30-day mortality (OR 2.41, p<0.04) were significantly higher in SARS-CoV-2 co-infection.

Conclusion Patients with AP and coexistent SARS-CoV-2 infection are at increased risk of severe AP, worse clinical outcomes, prolonged length of hospital stay and high 30-day mortality.

Significance of this study

What is already known on this subject?

- Emerging data suggest that the pancreas could be target organ for SARS-CoV-2 infection with increase in severity of pancreatitis.
- However, there is limited data on the clinical outcomes of patients with coexistent SARS-CoV-2 and acute pancreatitis (AP).

What are the new findings?

- Patients with AP and coexistent SARS-CoV-2 have a significantly high 30-day inpatient mortality.
- These patients also have significantly worse clinical outcomes including increased severity of pancreatitis, length of stay and organ failure.

How might it impact on clinical practice in the foreseeable future?

- Data from the largest international multicentre study will enable clinicians to better prognosticate for patients with concomitant AP and SARS-CoV-2 infection, optimise resource allocation and target treatment options.

INTRODUCTION

Respiratory complications due to SARS-CoV-2 infection are the most commonly reported sequelae and the predominant cause of significant morbidity and mortality.[1] However extrapulmonary symptoms and presentations have also been described with GI symptoms frequently reported as presenting symptoms.[2–4] Emerging data suggest that the GI tract and pancreas are target organs of SARS-CoV-2 because ACE2 receptor is expressed in the GI tract including pancreas acinar and islet cells.[5–7] This is supported by several published reports of AP in patients with SARS-CoV-2 infection.[8–16] It has also been postulated that infection leads to increased expression and distribution of ACE2, particularly on the pancreatic islet cell, increasing the risk of pancreatic injury and hyperglycaemic.[7] It is however unknown if SARS-CoV-2 infection causes pancreatic injury and acute pancreatitis or cause an aggravated inflammatory response, and increased risk of organ failure and pancreatic complications leading to increased patient morbidity and mortality.[17] The published evidence to date is largely from small case series and reports, which is insufficient to answer these questions.

This study reports the results of a multicentre international collaborative project to investigate the aetiology, clinical trajectory and outcomes in consecutive patients admitted with AP during the current SARS-CoV-2 pandemic.

METHODS

Study design, ethics approval and protocol

This was an international prospective multicentre collaborative cohort study of consecutive patients admitted with AP during the current SARS-CoV-2 pandemic.

Data were collected online in real time and stored on a secure data server running the Research Electronic Data Capture (REDCap) database. The database was held and monitored at the Newcastle Joint Research Office. No patient identifiable information was entered.

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advice on interpretation or writing up of results. We plan to disseminate the results of the research to the relevant patient community.

Participating centres

The study was initiated and developed at the Freeman Hospital, Newcastle upon Tyne, UK. All hospitals admitting patients with acute pancreatitis in the UK and other global pancreatic units were eligible for the study and were invited to input their data on REDCap. Enrolment of consecutive patients commenced from the start of the SARS-CoV-2 pandemic in the respective hospitals.

Patients and procedures

Consecutive adult patients (18 years and over) admitted with AP during the SARS-CoV-2 pandemic were included in the study. The recruitment period was between 1 March 2020 and 23 July 2020. All patients who had clinical symptoms consistent with SARS-CoV-2 or who were confirmed to have SARS-CoV-2 infection (by quantitative reverse transcription PCR (RT-PCR) and/or positive imaging by CT thorax in the first 72 hours[18] within admission) were all included. To avoid duplication of data, units were advised to inform us about patients who were being transferred to a regional tertiary care hospital for specialist input.

Definitions

SARS-CoV-2 infection was defined as a positive swab, positive CT thorax or a clinical diagnosis of symptomatic SARS-CoV-2 in patients for whom a swab test and CT scan were unavailable. The rationale behind this methodology was the fact that during the initial stages of the current pandemic the swab test had a high false negative rate ~30% and some patients globally were diagnosed based on clinical symptoms and findings on cross-sectional imaging.

WHO case definitions were employed to further classify patients into confirmed SARS-CoV-2 case, probable SARS-CoV-2 case and suspected SARS-CoV-2 case.[19]

Idiopathic pancreatitis was defined as patients who have been investigated prior to this admission and no cause found for pancreatitis.

Pancreatitis of unknown aetiology was defined as patients who during this particular admission did not have a defined aetiology despite multiple investigations at the time of discharge/death.

Severity of AP was defined as per the revised Atlanta criteria[20] which included:

Mild acute pancreatitis

- No organ failure.
- No local or systemic complications.

Moderately severe acute pancreatitis

- Organ failure that resolves within 48 hours (transient organ failure).
- Local or systemic complications without persistent organ failure.

Severe acute pancreatitis

- Persistent organ failure (>48 hours).
  - Single or multiple organ failure.

The Eastern Cooperative Oncology Group (ECOG) score was used to describe the patient's level of functioning in terms of their ability to care for themselves, daily activity and physical ability (walking, working and so on) and the scale runs from 0 to 5.[21]

Data variables

Multiple variables were collected, including demographic data, aetiology of acute pancreatitis at discharge, blood parameters including amylase on admission, serum bilirubin on admission, serum ferritin, lymphocyte count, D-dimer levels, C reactive protein, presenting symptoms, severity of AP (based on the revised Atlanta criteria), premorbid ECOG score, endoscopic or surgical interventions for drainage of pancreatic pseudocyst or walled off necrosis and 30-day mortality. In addition, duration of ICU stay and length of hospital stay were recorded (online supplemental file 1).

Outcome measures

The primary outcome measure was the severity of AP based on the revised Atlanta criteria. Secondary outcome measures included aetiology of AP, admission to intensive care unit and length of hospital stay, development of acute pancreatic fluid collections, pancreatic necrosis, pseudoaneursyms, pancreatic ascites, pancreaticopleural fistula, mesenteric-portal vein thrombosis, overall local complications, persistent organ failure and 30-day mortality.

A further comparative analysis of baseline characteristics and outcomes of patients with SARS-CoV-2 infection and unknown aetiology of AP to those with known aetiology of AP was undertaken.

Statistical analysis

To allow for the clustering of patients within different centres, all analyses were performed using multilevel regression methods. Two-level models were used with patients nested within centres.

Initially, the baseline/demographic characteristics of SARS-CoV-2-positive SARS-CoV-2-negative patients were compared. Continuous variables were analysed using multilevel linear regression, with variables found to have a positively skewed distribution analysed on the log scale. Multilevel logistic regression was used to compare the binary factors between the two groups, while multilevel ordinal logistic regression was preferred for those variables measured on an ordinal scale.

Subsequently, patient outcomes were compared between groups. Two analyses were performed for each outcome. Initially, a raw, unadjusted, comparison between groups was made. A second analysis compared the groups after adjusting for baseline/demographic factors found to show some evidence of a difference between the groups (all factors with p value of <0.2, providing that they were measured on the majority of patients). The SARS-CoV-2-positive SARS-CoV-2-negative groups were compared without considering any potential bias for: age, sex, smoking status, alcohol aetiology, idiopathic aetiology, unknown aetiology, other aetiology, ECOG and revised Atlanta criteria. Multilevel logistic regression was used for all binary outcomes. Multilevel linear regression was used for length of stay, which was analysed on the log scale due to the positively skewed distribution. Additional analyses compared the characteristics of positive patients with and without an unknown aetiology. Comparisons were again made using multilevel logistic regression.

A series of sensitivity analyses were performed using multiple imputation methods to impute missing data values for the baseline/demographic factors and key outcomes (online supplemental file 2).

RESULTS

Over the study period, 1777 patients with AP were included in the REDCap database with last date for data entry on 23 July 2020. Countries with contributing centres included England, Wales, Scotland, Northern Ireland, Malta, Italy, Pakistan, Turkey and Lithuania (online supplemental file 3).

One hundred forty-nine patients (8.3 %) developed concomitant AP and SARS-CoV-2 infection.

Symptoms and diagnosis of SARS-CoV-2 infections

The predominant symptoms, apart from abdominal pain, in those diagnosed with a swab alone were fever in 9.4%, shortness of breath in 6.6% and cough in 4.7%. In all those with a clinical suspicion of infection, patients had fever in 13.6%, shortness of breath in 27.3% and cough in 22.7% of cases; 2.7% of patients presented with no abdominal pain, and rather only fever, shortness of breath or a cough.

Based on WHO case definitions, 118/149 (79%) of patients were *confirmed cases* with laboratory confirmation of SARS-CoV-2 testing on a positive swab; 16/149 (10.7%) of patients were classed as *probable cases* based on clinical criteria and suspicious chest imaging showing findings suggestive of SARS-CoV-2 infection. A further 15/149 (10%) patients were classed as suspicious *cases* based on clinical criteria alone.

Among the 118 patients with infection confirmed on a positive swab, 56 (56/118, 47.4%) patients had a positive swab on the day of admission, a further 31 (31/118, 26.2%) patients within 72 hours of admission, 14 (14/118, 11.8%) patients between 4 and 14 days of admission and 15 patients (15/118, 12.7%) 14–90 days of admission.

Two patients had a positive swab in the community before hospital admission. Overall, 87% (88/101) of patients with a positive swab within 14 days of admission had hyperamylasaemia and abdominal pain suggestive of concomitant SARS-CoV-2 infection and acute pancreatitis.

In the group of patients who had confirmed diagnosis of SARS-CoV-2 with a known aetiology (91/112, 81%), 2 patients had a positive swab (2/91, 2.2%) prior to admission, 44 patients (44/91, 48.3%) had a positive swab on the day of admission, 20 patients (20/91, 22%) within 72 hours of admission, 13 patients (13/91, 14.3%) between 4 and 14 days of admission and 12 patients (12/91, 13.2%) after 14 days from admission. Overall, 84% of patients in the known aetiology group had a positive swab within 14 days of admission suggestive of concomitant SARS-CoV-2 infection in addition to an underlying aetiology to pancreatitis; 43/91 (47%) patients in this group developed moderate-to-severe or severe pancreatitis.

Hyperamylasaemia was noted at admission in 47/56 patients with positive swab on the day of admission, in 28/31 patients with a positive swab with 72 hours and in 13/14 patients with a positive swab between 4 and 14 days. Overall, 87% (88/101) of patients with a positive swab within 14 days of admission had hyperamylasaemia and abdominal pain.

Baseline characteristics of SARS-CoV-2-negative and SARS-CoV-2-positive patients with AP

The demographic details are shown in table 1.

There were 294 patients with missing data on one or more of the baseline factors that were excluded from these analysis (255 SARS-CoV-2-negative patients, 39 SARS-CoV-2-positive patients). This amounted to 26.2% loss in the SARS-CoV-2-positive cohort and 15.6% in the SARS-CoV-2-negative cohort.

Gallstones were the most common aetiology of AP in both groups. SARS-CoV-2-positive patients were found to be older by approximately 5 years. The positive group also had a higher proportion of males when compared with the negative group. There was no significant difference in the ethnicity of the groups.

The number of patients with an alcohol aetiology was significantly higher in the SARS-CoV-2-negative group (26.7% vs 18.8%, p=0.04). The number of patients with an unknown aetiology was more common in the SARS-CoV-2-positive group (24.8% vs 19.4%), but this difference was not statistically significant (p=0.08).

The ECOG score was significantly higher in the SARS-CoV-2-positive patients, with 15% having a score of 3 or 4, compared with only 4% of SARS-CoV-2-negative patients (p<0.001). There was no significant difference in liver steatosis or body mass index between groups.

The severity of AP was significantly worse in SARS-CoV-2-positive patients, with over 22.6% of patients in this group developing severe pancreatitis, compared with only 6.3% of SARS-CoV-2-negative patients (p<0.001). The occurrence of ARDS was also significantly higher in the SARS-CoV-2-positive group (13.6% vs 4%, p<0.001).

Necrosectomy was more likely to be performed in the SARS-CoV-2-positive patients, occurring in over 5%, compared with 1% in the SARS-CoV-2-negative patients (p<0.001). Conversely, an index cholecystectomy was less frequent in the SARS-CoV-2-positive patients (p<0.02).

Furthermore, 49% (43/88) of patients with a positive SARS-CoV-2 swab within 14 days of admission and

Table 1 Comparison of the baseline characteristics of all SARS-CoV-2-positive SARS-CoV-2-negative patients

		SARS-CoV-2 negative		SARS-CoV-2 positive		
Variable	**Category**	**N**	**Summary**	**N**	**Summary**	**P value**
Number of patients*		1628	–	149	–	
Age	–	1618	54.5±18.1	147	59.9±17.2	0.001
Sex	Female	1620	786 (48.5%)	148	55 (37.2%)	0.009
	Male		834 (51.5%)		93 (62.8%)	
Ethnicity	White	1358	1202 (88.5%)	122	104 (85.3%)	0.76
	Asian		92 (6.8%)		11 (9.0%)	
	Black		19 (1.4%)		2 (1.6%)	
	Mixed/Other		45 (3.3%)		5 (4.1%)	
Smoker	No	1517	1043 (68.7%)	132	100 (75.8%)	0.05
	Yes		474 (31.3%)		32 (24.2%)	
Aetiology	Gallstones	1628	696 (42.8%)	149	60 (40.3%)	0.37
(dis)†	Alcohol		434 (26.7%)		28 (18.8%)	0.04
	Idiopathic		93 (5.7%)		13 (8.7%)	0.14
	Hereditary		4 (0.3%)		0 (0.0%)	‡
	Post-ERCP		43 (2.6%)		3 (2.0%)	0.64
	Post-EUS		2 (0.1%)		0 (0.0%)	‡
	Steroid		8 (0.5%)		1 (0.7%)	0.77
	Hypercalcaemia		2 (0.1%)		0 (0.0%)	‡
	Hyperlipidaemia		49 (3.0%)		6 (4.0%)	0.47
	Unknown		315 (19.4%)		37 (24.8%)	0.08
	Other		5 (0.3%)		2 (1.3%)	0.11
Premorbid	0	1534	945 (61.6%)	125	58 (46.4%)	<0.001
ECOG status	1		373 (24.3%)		31 (24.8%)	
	2		153 (10.0%)		17 (13.6%)	
	3 or 4		63 (4.1%)		19 (15.2%)	
Ferritin	–	77	246 (106, 742)	20	910 (478, 1362)	0.001
LDH	–	508	375 (242, 540)	52	370 (276, 610)	0.53
Revised Atlanta	Mild	1600	1244 (77.7%)	146	71 (48.6%)	<0.001
Criteria	Moderate-to-severe		256 (16.0%)		42 (28.8%)	
	Severe		100 (6.3%)		33 (22.6%)	
ARDS	No	1387	56 (96.0%)	140	121 (86.4%)	<0.001
	Yes		56 (4.0%)		19 (13.6%)	
Liver steatosis	No	739	541 (73.2%)	62	48 (77.4%)	0.45
	Yes		198 (26.8%)		14 (22.6%)	
BMI	–	845	27.4 (23.7, 32.1)	91	28.4 (24.5, 33.1)	0.41
Necrosectomy	No	1605	1585 (98.7%)	145	137 (94.5%)	<0.001
	Yes		20 (1.3%)		8 (5.5%)	
Index	No	1551	1467 (94.6%)	145	144 (99.3%)	0.02
Cholecystectomy	Yes		84 (5.4%)		1 (0.7%)	

Summary statistics are mean±SD, median (p75–p25) or number (percentage). (*) Patients could have >1 aetiology so each aetiology considered as a separate variable.
*Includes all patients.
†Patients could have >1 aetiology so each aetiology considered as a separate variable.
‡Insufficient occurrences to enable a formal group comparison.
ARDS, acute respiratory distress syndrome; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase.

hyperamylasaemia developed moderate-to-severe or severe pancreatitis.

Specific data on fluid resuscitation protocols were not available however, the fluid resuscitation for patients with acute pancreatitis in the UK is based on National Institute for Health and Care Excellence guidance on resuscitation of acutely ill patients.[22]

Outcomes for SARS-CoV-2-positive SARS-CoV-2-negative patients with AP

The SARS-CoV-2-positive SARS-CoV-2-negative groups were compared without considering any potential confounding factors, and then repeated with adjustments for factors found to show some evidence of a difference between positive and negative patients. The factors included as part of the adjusted analysis were age, sex, smoking status, alcohol status, idiopathic aetiology and unknown aetiology at discharge, ECOG status and severity of AP.

There were 294 patients with missing data on one or more of the baseline factors that were excluded from these analysis (255 SARS-CoV-2-negative patients, 39 SARS-CoV-2-positive patients). This left a total of 1483 patients for analysis (1373 negative, 110 positive) (table 2).

Pandanaboyana S, *et al*. *Gut* 2021;**70**:1061–1069. doi:10.1136/gutjnl-2020-323364

Table 2 Comparison of outcomes between SARS-CoV-2-positive SARS-CoV-2-negative patients

	COVID	Unadjusted analysis*				Adjusted analysis†		
Outcome	Status	N	n (%)	OR (95% CI)	P value	N	OR (95% CI)	P value
ICU admission	Negative	1367	100 (7.3%)	1	<0.001	1367	1	0.09
	Positive	110	27 (24.6%)	5.21 (3.06 to 8.85)		110	1.89 (0.91 to 3.95)	
30-day mortality	Negative	1328	34 (2.6%)	1	<0.001	1328	1	0.04
	Positive	102	15 (14.7%)	6.56 (3.44 to 12.5)		102	2.41 (1.02 to 5.71)	
Length of hospital stay‡	Negative	1341	4 (3, 8)	1	<0.001	1341	1	<0.001
	Positive	101	9 (5, 17)	1.89 (1.64 to 2.19)		101	1.32 (1.16 to 1.50)	
Pancreatic necrosis	Negative	1188	177 (12.2%)	1	0.001	1188	1	0.48
(suspected or +ve)	Positive	103	24 (23.3%)	2.35 (1.41 to 3.90)		103	0.79 (0.41 to 1.52)	
Acute pancreatic fluid collections	Negative	1190	253 (21.3%)	1	<0.001	1190	1	0.05
(suspected or +ve)	Positive	103	47 (45.6%)	3.33 (2.15 to 5.16)		103	1.70 (1.00 to 2.88)	
Pseudoaneurysms	Negative	1185	12 (1.0%)	1	0.97	1185	1	0.27
(suspected or +ve)	Positive	103	1 (1.0%)	0.96 (0.12 to 7.44)		103	0.30 (0.03 to 2.59)	
Pancreato-pleural fistula	Negative	1188	10 (0.8%)		(§)	1188		(§)
(suspected or +ve)	Positive	102	0 (0.0%)			102		
Enteric fistula	Negative	1185	10 (0.8%)	1	0.22	1185	1	0.99
(suspected or +ve)	Positive	102	2 (2.0%)	2.61 (0.56 to 12.3)		102	0.99 (0.18 to 5.48)	
Pancreatic ascites	Negative	1187	86 (7.3%)	1	0.006	1187	1	0.47
(suspected or +ve)	Positive	103	15 (14.6%)	2.45 (1.29 to 4.65)		103	1.33 (0.62 to 2.85)	
Portal vein thrombus	Negative	1180	35 (3.0%)	1	0.89	1180	1	0.19
(suspected or +ve)	Positive	101	3 (3.0%)	1.09 (0.32 to 3.75)		101	0.40 (0.10 to 1.55)	
Any local complication¶	Negative	1180	380 (26.1%)	1	<0.001	1180	1	0.22
	Positive	101	50 (49.5%)	2.91 (1.89 to 4.49)		101	1.40 (0.81 to 2.40)	
Persistent organ failure	Negative	1338	73 (5.5%)	1	<0.001	1338	1	0.003
	Positive	144	37 (25.7%)	7.32 (4.48 to 12.0)		144	2.77 (1.43 to 5.39)	

*Two hundred ninety-four patients with missing data on one or more of the baseline factors that were excluded from the analysis (255 SARS-CoV-2-negative patients, 39 SARS-CoV-2-positive patients); 1483 patients were included in the analysis (1373 SARS-CoV-2-negative patients, 110 SARS-CoV-2-positive patients).
†Adjusted for: age, sex, smoking status, alcohol aetiology, idiopathic aetiology, unknown aetiology, other aetiology, ECOG, Atlanta classification.
‡Summary statistics are: median (p75–p25). Group differences reported as: ratio (95% CI).
§Insufficient occurrences to enable a formal group comparison.
¶Defined as any of: acute pancreatic fluid collection, pseudoaneurysm, pancreatic pleural fistula, enteric fistula, pancreatic ascites or portal vein thrombus.
ECOG, Eastern Cooperative Oncology Group; ICU, intensive care unit.

The overall 30-day mortality rate in the SARS-CoV-2-positive cohort was 14.7% compared with 2.6% in the SARS-CoV-2-negative group ($p<0.04$).

Unadjusted analyses of outcomes showed that patients with concomitant SARS-CoV-2 infection and AP were more likely to require ICU admission (OR 5.21, 95% CI 3.06 to 8.85), develop acute pancreatic fluid collections (OR 3.33, 95% CI 2.15 to 5.16), pancreatic necrosis (OR 2.35, 95% CI 1.41 to 3.90), local complications (OR 2.91, 95% CI 1.89 to 4.49), persistent organ failure (OR7.32, 95% CI 4.48 to 12.0), prolonged length of hospital stay (OR 1.89, 95% CI 1.64 to 2.19) and increased 30-day mortality (OR 6.56, 95% CI 3.44 to 12.5).

Potential confounding variables were then adjusted for some of the differences between the positive and negative groups. The 30-day mortality was higher in the SARS-CoV-2-positive group with an OR of 2.4 (95% CI 3.44 to 12.5). The length of hospital stay (OR 1.32, 95% CI 3.44 to 12.5) and persistent organ failure (OR 2.77, 95% CI 1.43 to 5.39) were worse in the SARS-CoV-2-positive group.

Respiratory failure was the predominant organ failure in the majority of SARS-CoV-2-positive patients. Thirty-one patients developed respiratory failure, seven patients a combination of renal, respiratory and cardiovascular failure, four patients renal, respiratory failure and cardiovascular failure, two patients renal and respiratory failure and two patients renal failure. In patients who died in the SARS-CoV-2-positive group, pulmonary complication secondary to SARS-CoV-2 infection was the cause of death.

We analysed portal vein thrombus rates in SARS-CoV-2-positive SARS-CoV-2-negative group and found no significant difference and these data. We have further reviewed the CT scan data and there were no reported instances of ischaemic damage especially in the intestine.

A further subgroup analysis of outcomes between specialist pancreatic centres and non-specialist centres was undertaken. Sixty-four patients were transferred to specialist units for further management. These only accounted for 3.6% of patients in the study group. Furthermore for the purpose of analysis, when comparing outcomes for specialist and non-specialist centres, these patients were considered to be in specialist centres. There was no significant difference in outcomes between the specialist and non-specialist centres for both SARS-CoV-2-positive SARS-CoV-2-negative patients (online supplemental file 4).

Comparison of outcomes between confirmed SARS-CoV-2 swab-positive (true positives) patients and SARS-Cov-2 swab-negative patients (true negatives)

A further subgroup analysis comparing confirmed SARS-CoV-2 swab-positive (true positives) patients and SARS-Cov-2 swab-negative patients (true negatives) was undertaken. Among the 1131/1777 (63.6%) patients tested, data on swab results were available for 1101 patients (61.9%); 983/1101 confirmed cases had a negative swab test and were considered as confirmed negative patients and 118/1101 confirmed cases had confirmed positive swab test and were considered as confirmed positive cases.

Of the 1101 confirmed patients, some patients were excluded from the analysis due to missing values for the baseline factors/covariates. One hundred fifty-six patients were excluded from the negative group and 36 from the positive group. This left 909 patients for analysis, 827 negative and 82 positive patients.

Comparisons of outcomes between the groups were made, and a summary of both the unadjusted and adjusted analyses are presented in online supplemental file 5.

The outcomes were again are comparable to the original outcomes including all patients. The outcomes again showed increased risk of persistent organ failure, increased hospital stay and 30-day mortality in confirmed SARS-CoV-2-positive patients (online supplemental file 5).

An additional sensitivity analyses was undertaken including only those patients without confirmed SARS-CoV-2 infection. Six hundred forty-five of the 1628 negative patients (39.2%) had no swab test result and were considered as unconfirmed negative patients. Thirty-one of the 149 positive patients (20.8%) had unconfirmed positive status based on the WHO classification. Of the 676 unconfirmed cases, some cases were excluded from the analysis due to missing values for the baseline factors/covariates. Ninety-nine were excluded from the negative group and three from the positive group. This left 574 patients for analysis, 546 negative and 28 positive patients. The unadjusted analysis again showed the SARS-CoV-2 positive group is at increased risk of ICU admission, 30-day mortality, organ failure, increased local complications and prolonged hospital stay. The adjusted analysis showed a prolonged hospital stay (online supplemental file 6).

Outcome data of unknown aetiology in SARS-CoV-2-positive patients

A further subgroup analysis of patients with unknown aetiology of AP was undertaken in comparison to those with known aetiology of AP. This analysis focused only on the SARS-CoV-2-positive patients (n=149). Of these, 37 (25%) had an unknown aetiology (at discharge), while the remaining 112 (75%) had a defined aetiology.

None of the outcome variables was different between the two different aetiology groups (*p>0.05*) (table 3).

DISCUSSION

This multicentre, international cohort study is the largest in the literature to study the impact of SARS-CoV-2 in patients presenting with AP. Patients with concomitant AP and SARS-CoV-2 tented to be older, male and with higher ECOG score. SARS-CoV-2-positive patients with AP were at a significantly increased risk of developing moderate-to-severe or severe AP, local complications, ARDS, persistent organ failure, prolonged ICU stay and high inpatient 30-day mortality. Of note, the 30-day mortality of 14.7% is significantly higher than in patients with AP without SARS-CoV-2 infection (2.6%).

At the outset of the SARS-CoV-2 pandemic, the symptoms of SARS-CoV-2 were considered predominantly respiratory with GI symptoms significantly less common.[5 23–25] However, as the pandemic evolved and with accumulating evidence on various presentations of SARS-CoV-2 infection, the GI tract and pancreas were identified as potential target organs of SARS-CoV-2 on the basis of expression of ACE2, the major receptor of SARS-CoV-2, on the pancreatic islet cells.[7] Furthermore, the rate of the severe/critical SARS-CoV-2 disease was noted to be significantly higher in patients with GI symptoms.[25 26] However, the impact of these observations on AP severity and clinical trajectory was unknown.

The first reported series of pancreatic injury from SARS-CoV-2 was reported from China in January 2020 at the outset of the SARS-CoV-2 pandemic.[1–3] Liu *et al*[7] described a series of 121 patients with SARS-CoV-2, of which 13 patients developed pancreatitis with the risk of developing pancreatitis being much higher in patients with severe SARS-CoV-2 infection. Wang *et al*[4] described 138 patients with SARS-CoV-2 pneumonia and 9 patients developed pancreatic injury with more severe illness at admission. With the spread of the pandemic outside China, further cohort studies were reported from the USA and UK.[14 16] Gubatan *et al*[15] reported 102 patients with a history of pancreatitis and found 8 patients developed SARS-CoV-2 speculating that patients with previous history of pancreatitis may be susceptible to SARS-CoV-2 infection. Szatmary *et al*[16] in a series of 35 patients with acute pancreatitis identified 5 patients with SARS-CoV-2 infection who were predominantly male,

Table 3 Comparison of outcomes between known and unknown aetiology of pancreatitis in SARS-CoV-2-positive patients

	Known aetiology		Unknown aetiology			
Outcome	N*	n (%)	N	n (%)	OR (95% CI)†	P value
ICU admission	111	20 (18.0%)	37	9 (7.3%)	1.49 (0.59 to 3.79)	0.40
30-day mortality	103	12 (11.7%)	35	6 (17.1%)	1.57 (0.54 to 4.56)	0.41
Length of stay‡	100	8 (5, 16)	35	12 (5, 21)	1.26 (0.91 to 1.73)	0.16
Pancreatic necrosis	105	22 (21.0%)	34	9 (26.5%)	1.36 (0.55 to 3.32)	0.50
Acute pancreatic fluid collections	107	43 (40.2%)	34	17 (50.0%)	1.54 (0.68 to 3.50)	0.30
Pseudoaneurysm	107	1 (0.9%)	34	0 (0.0%)	–	§
Pancreato-pleural fistula	106	0 (0.0%)	33	0 (0.0%)	–	§
Enteric fistula	107	2 (1.9%)	32	0 (0.0%)	–	§
Pancreatic ascites	107	14 (13.1%)	34	6 (17.7%)	1.77 (0.50 to 6.22)	0.37
Portal vein thrombus	105	1 (1.0%)	34	2 (5.9%)	6.50 (0.57 to 74.0)	0.13
Any local complication¶	105	47 (44.8%)	34	18 (52.9%)	1.41 (0.63 to 3.20)	0.41
Persistent organ failure	111	29 (26.1%)	36	15 (41.7%)	2.09 (0.88 to 4.95)	0.09

*Indicates the number of patients included in the analysis.
†ORs expressed as odds in unknown aetiology group relative to the odds in known aetiology group.
‡Summary statistics are: median (p75–p25). *Group differences reported as: ratio (95% CI)*.
§Insufficient occurrences to enable a formal group comparison.
¶Defined as any of: acute pancreatic fluid collection, pseudoaneurysm, pancreatic pleural fistula, enteric fistula, pancreatic ascites or portal vein thrombus.

overweight or obese with elevated triglycerides and glucose at admission with no apparent aetiology for the pancreatitis. The present study did not show a significant difference between the groups for severity of liver steatosis.

The present study has shown that patients with concomitant SARS-CoV-2 and AP are at significantly increased risk of developing moderate-to-severe or severe AP. In addition, these patients also appear to be at a higher risk of developing local complications secondary to AP. These results therefore raise the important question of whether SARS-CoV-2 infection directly causes increased severity of AP. Recent published evidence on expression of ACE2 receptors suggests that messenger RNA level of ACE2 expression were noted to be higher in the pancreas than in the lung and ACE2 receptors are expressed both on endocrine and islet cells of the pancreas.[27] This increased expression of ACE2 receptors in the pancreas may increase viral load and worsen the clinical trajectory of AP, especially in the presence of severe SARS-CoV-2 infection.[28] An exaggerated immune response with subsequent cytokine storm and endothelial damage may worsen the clinical trajectory similar to other pro-inflammatory conditions with concomitant SARS-CoV-2 infection such as multisystem inflammatory syndrome in children and adolescents.[29–31] Neutrophils play a significant role in innate response after acute pancreatitis through formation of neutrophil extracellular traps (NETs). NETs have been shown to worsen pancreatic inflammation, and promoting pancreatic duct obstruction in patients with acute pancreatitis. Recent studies have shown increased concentrations NETs in plasma of patients with SARS-CoV-2 infection and much higher concentration in patients with ARDS and respiratory failure. The generation of NETs by neutrophils can be triggered by viral infections and although their predominant function is to trap viruses, virus-induced NETs can trigger inflammatory and immunological responses leading to exaggerated systematic inflammatory response.[32 33]

Furthermore, endothelial damage and severe endothelitis is frequent in SARS-CoV-2 infection,[34] although further data are needed to determine whether marked prothrombotic changes seen in these patients are specific to SARS-CoV-2 infection or secondary to the cytokine storm. The thrombotic complications and abnormal coagulopathy reported in patients with severe SARS-CoV-2 may have further contributed to the worsening of acute pancreatitis. Autopsy data on pancreatic damage are not available as this was not the remit of the study, however given the published lung and intestine autopsy data in patients with SARS-CoV-2 infection has consistently shown presence of platelet–fibrin thrombi in small arterial vessels and coagulopathy, it is highly likely similar changes are expected within the pancreas.[33] The UK Randomised Evaluation of COVID-19 Therapy (RECOVERY) Trial has shown the use of dexamethasone reduces death rate by a third of patients by suppressing the immune response further supporting the hypothesis of a hyper-immune response and tissue injury from SARS-CoV-2 infection.[35]

The present series also identified a higher number of patients with SARS-CoV-2 infection having AP of unknown aetiology (24.8%). The absence of definite aetiology further raises questions regarding the potential role of SARS-CoV-2 inducing primary pancreatic damage or worsening the course of underlying AP. Viral-induced pancreatic damage is well studied and causes inflammation by acinar cell necrosis and damage early in the course of infection.[36] In the present series, the majority of patients with concomitant AP and SARS-CoV-2 infection, especially in those with a SARS-CoV-2 infection conformed on a positive swab with 14 days of admission presented with abdominal pain and respiratory symptoms and hyperamylasaemia in support of the hypothesis that SARS-Cov-2 may cause pancreatic injury and pancreatitis. However, this association can only be substantiated by use of a pancreas organoid model to study the pancreas-specific effects of SARS-CoV-2.[37]

The mortality rate in the SARS-CoV-2-positive group is much higher ($p<0.001$) than published series reporting early mortality after acute AP.[24 38] The increased mortality is most likely secondary to the fact that patients in the SARS-CoV-2-positive group were older patients with worse ECOG score with moderate-to-severe and severe AP, ARDS and persistent organ failure.

The present study has limitations. There are several participating centres in the UK and overseas with varied testing protocols. During the early phase of the pandemic when routine testing was not available the diagnosis of SARS-CoV-2 was made using symptoms and CT criteria. However, this was the case only in a small number of patients with the majority of SARS-CoV-2 infection confirmed on laboratory testing. The poor sensitivity of testing during the early phase of the pandemic means there may be a small fraction of patients who were presumed negative for SARS-CoV-2 infection included in the group of patients with acute pancreatitis with no SARS-CoV-2 infection. However, this study used several methods to make a diagnosis of SARS-CoV-2 and therefore this number is likely to be small.

However, the study has several strengths. To the best of our knowledge, this is the largest international prospective cohort of patients with concomitant AP and SARS-CoV-2 infection reported to date. This has enabled a more detailed analysis to quantify the impact of SARS-CoV-2 infection on the course of AP. This is also the first study to highlight the significantly high inpatient morbidity and mortality within 30 days in the presence of SARS-CoV-2 infection and could potentially help target treatments including dexamethasone or remdesevir.

In conclusion, patients presenting with concomitant SARS-CoV-2 infection and acute pancreatitis are at higher risk of developing severe AP with associated increased morbidity and mortality. These findings have implications for management of patients with acute pancreatitis during the current pandemic. If the infection continues to be prevalent without an effective treatment or vaccine, these data help clinicians to better prognosticate for patients with concomitant AP and SARS-CoV-2 infection and optimise resource allocation.

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terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

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