Journal Pre-proof

Emerging phenotype of SARS-CoV2 associated pancreatitis.

Peter Szatmary, Ankur Arora, Michael Godwin Thomas Raraty, Declan Francis Joseph Dunne, Ryan David Baron, Christopher Michael Halloran

PII: S0016-5085(20)34741-7
DOI: https://doi.org/10.1053/j.gastro.2020.05.069
Reference: YGAST 63511

To appear in: *Gastroenterology*
Accepted Date: 27 May 2020

Please cite this article as: Szatmary P, Arora A, Raraty MGT, Dunne DFJ, Baron RD, Halloran CM, Emerging phenotype of SARS-CoV2 associated pancreatitis., *Gastroenterology* (2020), doi: https://doi.org/10.1053/j.gastro.2020.05.069.

Title: Emerging phenotype of SARS-CoV2 associated pancreatitis.

Short title: SARS-CoV2 associated pancreatitis.

Szatmary, Peter[1,2]; Arora, Ankur[3]; Raraty, Michael Godwin Thomas[2]; Dunne, Declan Francis Joseph[2]; Baron, Ryan David[2]; Halloran, Christopher Michael[1,2]

Affiliations:

[1] Department of Molecular & Clinical Cancer Medicine, University of Liverpool, UK

[2] Department of General and Pancreatic Surgery, Liverpool University Hospitals NHS Foundation Trust, UK

[3] Department of Radiology, Liverpool University Hospitals NHS Foundation Trust, UK

Grant Support:

PS has grants from the NIHR, Wellcome Trust & PSGBI

RB has received travel grants from Mylan

DD has grants from PCUK

CMH has grants from CRUK, PCUK, NIHR & RCS(Eng)

Abbreviations:

SARS-CoV2	**Severe acute respiratory syndrome coronavirus 2**
CECT	**Contrast-enhanced computerised tomography**
HU	**Hounsfield units**
ACE2	**Angiotensin converting enzyme 2**

Corresponding author: Professor C.M.Halloran

Address for Correspondence:

Institute of Systems, Molecular & Integrative Biology.

Department of Molecular & Clinical Cancer Medicine,

University of Liverpool, 2nd Floor Sherrington Building,

Ashton Street, Liverpool, L69 3GE, UK

Email: halloran@liverpool.ac.uk

Tel: ++44 (0) 151 795 8031

Disclosures: There are no conflicts of interest to disclose.

Author Contributions:

Conceptualization (PS, DD, RB, CMH); data curation and formal analysis (PS, AA); writing - draft (PS, CMH); writing – review and editing of manuscript (PS, AA, MGTR, DD, RB, CMH).

Word count 999.

Introduction. As the global pandemic of **severe acute respiratory syndrome coronavirus 2** (SARS-CoV2) continues, nuances of the disease it precipitates in humans continue to emerge. Following early reports of presentation with gastro-intestinal-type symptoms in China[1] and Italy[2], a group from Wuhan reported a series of 9 patients with purported pancreatic injury in the context of SARS-CoV2 infection[3], but did not provide robust evidence for pancreatitis relying on mild hyperamylasaemia alone. Current international consensus for a diagnosis of acute pancreatitis requires two of the following three features: 1) Abdominal pain consistent with pancreatitis; 2) Serum amylase/lipase greater than 3 times the upper limit of normal and 3) Characteristic findings on cross sectional imaging[4]. Simply put, there are too many causes for hyperamylasaemia in the context of systemic illness, with or without SARS-CoV2, for its use in isolation as a marker of pancreatic injury. None the less, we report here 5 cases of atypical but proven acute pancreatitis in the context of SARS-CoV2 infection.

Methods. This review was registered with the Liverpool University Hospitals NHS Foundation Trust audit department (ID TA0002744). Cases were identified searching admission diagnoses (ICD10 K85) or radiology requests and reports for 'acute pancreatitis'. SARS-CoV2 was diagnosed when either swabs were positive on rapid PCR (VIASURE^{TM}) or patients had radiological evidence of SARS-CoV2 infection (supplementary figure 1). Cases with pre-existing pancreatic pathology or where the etiology was clearly non-SARS-CoV2 related were excluded. Data extracted from patient and radiology records was used to calculate clinical scores as well as hepatic steatosis estimates by analysis of contrast-enhanced computerised tomography (CECT) images as previously described[5]. Imaging findings were re-reported by an expert pancreatic radiologist.

Results. Between 14th of March and 30th of April 2020, 35 patients with acute pancreatitis were assessed at the Royal Liverpool University Hospital. 25 patients were negative for SARS-CoV2 and were excluded. Of the remaining 10 patients who were deemed positive for SARS-CoV2 a further 5 were excluded because they presented with a clearly defined etiology (e.g. choledocholithiasis). The remaining 5 patients, all with SARS-CoV2, presented atypically yet homogenously with a distinct metabolic-pancreatitis phenotype. These 5 patients form the cohort subsequently discussed (supplementary figure 1).

All 5 patients were young adult males (median age 42 years; IQR 15) who were either overweight or obese (median BMI 30; IQR 6.7). Serum amylase was elevated but non-diagnostic in all cases (median 149 U/L; IQR 238), contrast-enhanced abdominal CT (CECT) was used to confirm the diagnosis. Patients had no sonographic evidence of gallstones on this admission. No patient had known cardiovascular disease. On admission patients had evidence of metabolic distress; median (IQR) levels of triglycerides and glucose were 2.7 (18.2) mmol/L and 10 (8.6) mmol/L respectively. 1 patient had sustained ethanol use without hypertriglyceridemia or hyperglycaemia, but importantly had no prior pancreas symptoms. 1 patient had a long term medication history (Atorvastatin and Sertraline) again without prior pancreatitis symptoms. However, in all patients, CECT showed transient moderate to severe hepatic steatosis (<104 HU), which rapidly regressed in patients for whom follow-up CECT was available. Median attenuation (IQR) on admission was -3.5 (55.8) HU with a median (IQR) improvement at 7 days of 31.12 HU (3.1). The pattern of pancreatic inflammation was similarly unusual in these patients: Mild pancreatic edema without significant pancreatic or peripancreatic necrosis, with distinct duodenal/periduodenal inflammation involving the second and third part of the duodenum. Radiological findings were accompanied by a profound systemic inflammatory response (1-2 SIRS criteria on admission; 2-4 after 48

hours) and dramatic elevation of C-reactive protein (median 31 mg/L, IQR 141 on admission vs. 485 mg/L, IQR 286.5 after 48 hours).

All patients were treated with intra-venous fluids; 3 out of 5 received insulin and/or fibrate therapy. Abdominal pain was managed with opiate analgesia and all patients were tolerant of oral diet from admission. 4 out of 5 patients with CT findings suggestive of pneumonitis received broad-spectrum intra-venous antibiotics. None of the patients received corticosteroids and none required organ support, beyond low-flow oxygen, or admission to a level 2/3 care setting. Thus, all were classed as moderate pancreatitis based on the presence of acute fluid collections alone. 2 Patients required pancreatic enzyme replacement therapy to control their abdominal pain and steatorrhea, indicating a true exocrine component to their disease. Median length of stay (range) was 14 days (6-16).

Discussion. Despite the dramatic way these 5 patients presented, with multiple metrics predictive of severe disease, their pathway was much more benign than anticipated and not dissimilar from a typical attack of moderate pancreatitis. We therefore propose the combination of male sex, abdominal pain, metabolic stress and CT-findings of predominantly pancreatico-duodenal inflammation with steatosis represent a distinct subset of pancreatitis in patients infected with SARS-CoV2. Furthermore, we postulate that the endocrine pancreas is particularly vulnerable to this infection. While we cannot deduce causality based on data presented here, we note that the human pancreas is known to express high concentrations of angiotensin-converting enzyme 2 (ACE2)[6], especially (but not exclusively) in the pancreatic islets where binding to SARS-CoV1 has been shown to induce acute diabetes[7]. Persons with pre-existing metabolic syndrome, even if not formally diagnosed, may be at particular risk in light of the high BMIs and HbA1c in our case series.

Acute pancreatitis secondary to hypertriglyceridemia is uncommon in Western populations and more often associated with severe disease, organ failure and death than other etiologies[8]. None of the patients presented here had transient or persistent organ failure and the main reason for the prolonged length of stay in all cases was poor diabetic control or persistent elevation of serum inflammatory markers. We speculate that due to the low levels of free pancreatic enzymes (as evidenced by near normal levels of circulating pancreatic amylase), toxic lipolysis does not occur, and the liver is able to absorb the majority of triglycerides resulting in the changes in hepatic steatosis observed. These patients likely represent the severe end of the pancreatopathy spectrum, but transient dyslipidaemias and impaired glucose tolerance may be common in SARS-CoV2 patients and warrant further investigation.

1. Guan WJ, et al. *N Engl J Med.* 2020; 382: 1708-1720.

2. Spinelli A, et al. *Br J Surg*. 2020.

3. **Wang F**, **Wang H**, **Fan J**, **Zhang Y**, et al. *Gastroenterology*. 2020.

4. Banks PA, et al. *Gut*. 2013; 62: 102-111.

5. Monjardim RdF, et al. Radiologia Brasileira 2013; 46: 134-138.

6. Liu F, et al. *Clin Gastroenterol Hepatol*. 2020.

7. Yang JK, et al. *Acta Diabetol*. 2010; 47: 193-199.

8. Zhang R, et al. *HPB (Oxford)*. 2019; 21: 1240-1249.

Author names in bold designate shared co-first authorship

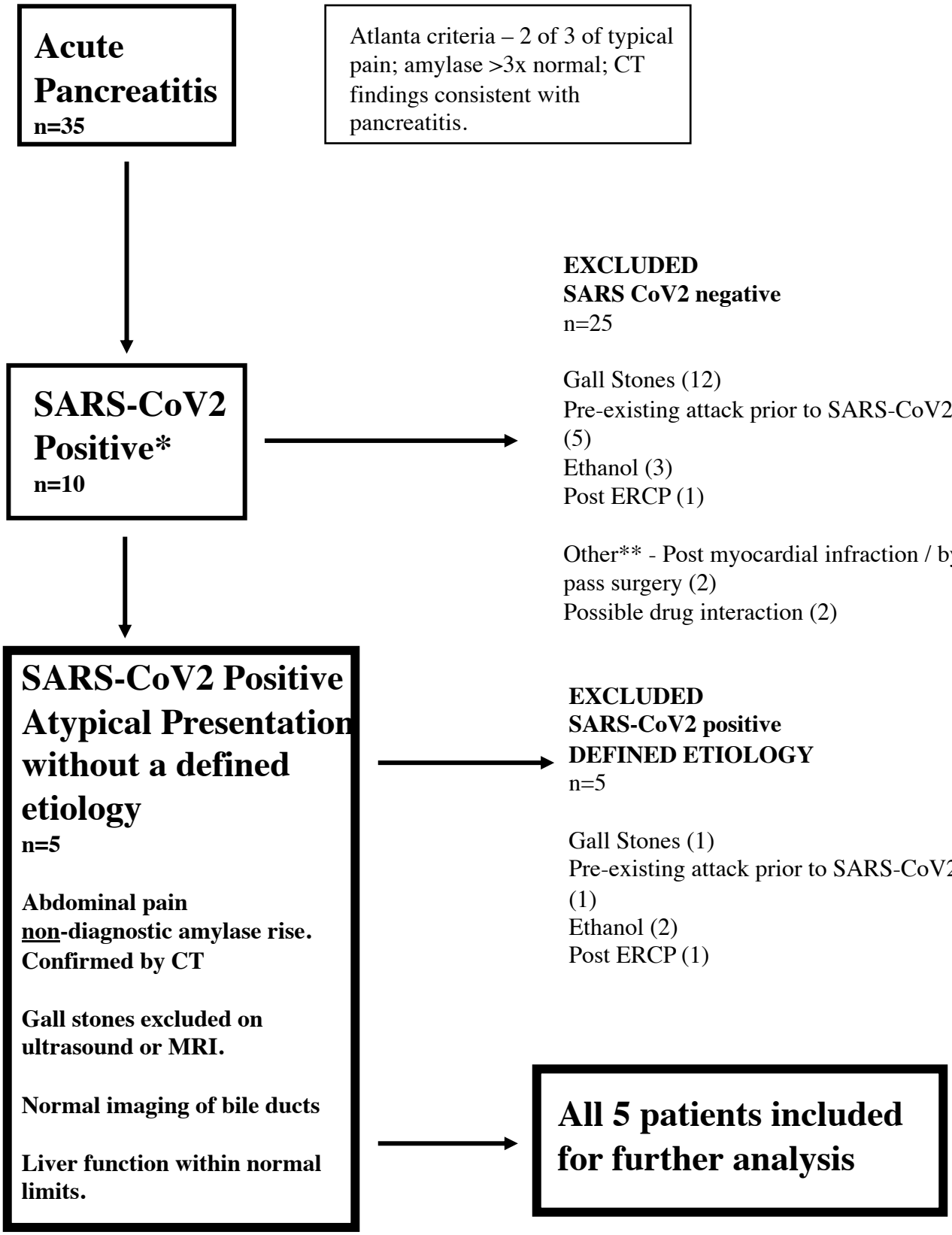

Figure1. Flow Diagram. * A diagnosis was made by either a rapid PCR (VIASURE™) or radiological evidence of SARS-CoV2, the COVID CT score is based on the British Society of Thoracic Imaging criteria where changes are classed as 'probable' where there is >70 % confidence of COVID infection[1]. Patients excluded with gall stones had either biliary dilatation, abnormal liver function tests or confirmed ductal stones. Patients excluded with ethanol use had a history of stable chronic alcohol use/abuse, with/without recent binge, with/without pre-existing neurological/liver/pancreas injury. Patients excluded with pre-existing attacks had Recurrent acute or acute-on-chronic pancreatitis with at least one attack prior to Nov 2019. Patients excluded with post ERCP pancreatitis, 1 suspected gallstones, but trawl negative, 1 head of pancreas mass/stent). **Patients negative for SARS-CoV2 and excluded for other reasons had Gallstones excluded on ultrasound or MRI; had no history of significant alcohol intake OR recently reducing alcohol intake in the absence of pre-existing alcohol-related organ damage.

[1][https://www.bsti.org.uk/media/resources/files/BSTI_COVID-19_Radiology_Guidance_version_2_16.03.20.pdf].

		Patient					Summary statistic	
		1	**2**	**3**	**4**	**5**	**Median**	**IQR**
Demographics	Age	29	41	42	47	53	42	15
	Sex	M	M	M	M	M	-	-
	BMI	32.9	35.8	29.7	25.7	30	30	6.7
	Ethnicity	Other Asian	White British	White British	White British	Other White	-	-
	HTN	No	No	No	No	No	-	-
	DM	No	No	No	No	No	-	-
	Respiratory Disease	No	No	Asthma	No	No	-	-
	Charlston Index	0	0	0	0	1	-	-
COVID status	CT score	Normal (CVCT0)	Classic/Probable (CVCT1)	Classic/Probable (CVCT1)	Non-COVID (CVCT3)	Classic/Probable (CVCT1)		
	Throat swab	Positive	Negative	Unknown	Positive	Negative		
							Median	**IQR**
Pancreatitis diagnostics	Typical pain	Yes	Yes	Yes	Yes	Yes	-	-
	Amylase *(U/L)*	77	149	378	211	36	149	238
	Amylase timing (hours after pain)	27	20	6	16	23	20	14
	CT on admission	Pancreatitis	Pancreatitis	Pancreatitis	Pancreatitis	Pancreatitis	-	-
							Median	**IQR**
Pancreatitis risk factors	Gallstones *(Ultrasound)*	No	No	No	No	No	-	-
	Alcohol intake *(g / week)*	0	80	400	50	0	50	240
	Smoker	Never	Yes	Never	Ex	Yes	-	-
	Medication	None	None	Omeprazole; Thiamine; Hydroxycobalamin	Atorvastatin; Sertraline	None	-	-
							Median	**IQR**
Clinical characteristics of pancreatitis	SIRS *(admission)*	2	2	1	2	2	-	-
	SIRS *(48h peak)*	4	2	3	4	2	-	-
	CRP *(admission)*	258	37	5	8	31	31	141
	CRP *(peak)*	597	550	292	485	282	485	286.5
	Peak CRP time *(days from admission)*	0	2	9	2	0	2	5.5
	Organ failure	No	No	No	No	No	-	-
	Activity index *(admission)*	250	220	-	245	145	232.5	85
	Activity index *(48 h)*	205	150	-	175	25	162.5	141.3
							Median	**IQR**
Imaging findings	Focus of inflammation	Periduodenal (D1-D4) and pancreatic head	Periduodenal (D2-D3) and pancreatic head	Periduodenal (D1-3) and peripancreatic	Duodenal thickening (D2-3) and peripancreatic	Duodenum spared; peripancreatic		
	Peripancreatic necrosis	No	No	No	No	No	-	-
	Pancreatic necrosis	None	None	None	Pancreatic tail (<30 %)	None	-	-

	Acute fluid collections	Paraduodenal	None	Peripancreatic	Pancreatic tail	Paraduodenal		
	Modified Balthasar score	6	2	4	8	4	4	4
							Median	**IQR**
Metabolic parameters	New onset diabetes	Yes	Yes	No	No	Yes	-	-
	Glucose on admission *(mmol/L ; mg/dL)*	14.3 ; 257.4	16.6 ; 298.8	7.9 ; 142.2	5.9 ; 106.2	10 ; 180	10 ; 180	8.6 ; 154.8
	HbA1c *(IFCCmmol /mol)*	86	-	-	36	47	-	-
	Urinalysis on admission	Glucose 4+	Glucose +; Ketones +	-	-	-	-	-
	Insulin therapy	Yes	Yes	No	No	No	-	-
	Triglycerides on admission *(mmol/L ; mg/L)*	30.9 ; 2740	8.4 ; 743	1.65 ; 146	2.7 ; 239	1.3 ; 115	2.7 ; 239	18.2 ; 1610
	Hepatic steatosis *(admission; HU)*	18.0	-46.7	-18.1	11.1	-	-3.5	55.8
	Hepatic steatosis *(7 days; HU)*	50.6	-15.6	8.30	42.2	-	25.2	50.1
	ΔHepatic steatosis	32.7	31.1	26.4	31.1	-	31.1	3.1
							Median	**IQR**
Outcome parameters	Severity of pancreatitis	Moderate	Moderate	Moderate	Moderate	Moderate	-	-
	LOS *(days)*	16	14	16	12	6	14	7
	Intervention	No	No	No	No	No	-	-
	New therapy on discharge	Insulin; PERT; Fibrate	Insulin	No	PERT; Fibrate	No	-	-

Table 1. Clinical characteristics of patients with acute pancreatitis in the context of COVID19 infection. All summary parameters are median (IQR). Ethnicity labels are those used by the Office of National Statistics of the UK. COVID CT score is based on the British Society of Thoracic Imaging criteria where changes are classed as 'probable' where there is >70 % confidence of COVID infection. SIRS score is calculated by presence of the following – Temperature >38^{o}C or <36^{o}C; Heart rate >90; Respiratory rate >20 or $PaCO_2$ < 32 mmHg; WBC > 12000/mm^3. Organ failure is defined as a SOFA score of 2 or more. Pancreatic activity index is a composite score including organ failure, tolerance to oral diet, SIRS, abdominal pain and intra-venous morphine equivalent dose on any given day. Hepatic steatosis is based on CECT image evaluation as previously reported. Severity of pancreatitis is defined by the Revised Atlanta Classification 2012.