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LETTERS TO THE EDITOR

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Serum Lipase Elevations in COVID-19 Patients Reflect Critical Illness and not Acute Pancreatitis

Dear Editor:

We read with interest the article "ACE2 Expression in Pancreas May Cause Pancreatic Damage After SARS-CoV-2 Infection" by Liu et al.[1] The authors noted abnormalities of serum amylase and lipase values among nearly 20% of hospitalized patients with COVID-19 and concluded that these enzyme abnormalities represent pancreatic injury and might even lead to chronic pancreatitis. However, many conditions may cause elevations in serum lipase, and these should not be attributed to pancreatic injury in the absence of acute pancreatitis (AP).[2] We sought to establish the prevalence of abnormal serum lipase values and the prevalence of AP among a large cohort of patients hospitalized with COVID-19.

Consecutive patients hospitalized with COVID-19 at 36 North American medical centers during the earliest phase of the pandemic were identified and their charts were reviewed for clinical characteristics and outcomes, as previously described.[3] AP was diagnosed according to the Revised Atlanta Criteria (2012), requiring 2 out of 3 of the following: characteristic abdominal pain, imaging abnormalities, or serum pancreas enzyme level greater than 3 times the upper limit of normal (ULN). For the outcome of elevated lipase, an extensive (n = 112 variables) univariable analysis was performed that included patient characteristics, comorbidities, medications, COVID-19 severity parameters and treatment regimens, and gastrointestinal symptoms (Table 1). Subsequently, a multivariable logistic regression model was fit for elevated lipase using stepwise selection among all variables with a significant difference between subjects with and without an elevated lipase at a level of $P = .2$.

Among 1992 subjects with polymerase chain reaction–confirmed COVID-19, serum lipase values were measured on the day of admission in 316 (15.9%). Although 58 subjects had an elevated value, only 9 (2.8%) were 3 times the ULN. Only 2 patients had both lipase >3 times the ULN and abdominal pain. Neither subject underwent cross-sectional imaging during the hospitalization, but an abdominal ultrasound in both cases demonstrated cholecystitis providing an alternative and more likely cause for AP than COVID-19. Serum lipase values were recorded during hospitalization in 400 (20.1%) subjects. Although in 100 subjects the levels were elevated, only 26 patients (6.5%) had a value greater than 3 times the ULN. Among these, 6 subjects met 2 of 3 Revised Atlanta Criteria and did not have an obvious alternative explanation for AP other than COVID-19 infection.

Within our cohort of patients hospitalized with COVID-19, there was no association between preexisting diabetes and elevated lipase values during hospitalization ($P = .81$). Furthermore, patients with diabetes with increased lipase values experienced similar mortality rates to patients with diabetes with normal lipase values (38.5% vs 24.0%; $P = .08$). There was no significant association between elevated lipase value and the use of angiotensin-converting enzyme inhibitors (13.7% vs 17.9%; $P = .344$) or angiotensin receptor blockers (12.5% vs 15.8%; $P = .44$) before admission (Table 1). Multivariable analysis demonstrated that elevated lipase values were associated with mechanical ventilation (n = 173; odds ratio, 2.55; 95% confidence interval, 1.6–4.08) and biliary disease (n = 9; odds ratio, 5.49; 95% confidence interval, 1.3–23.15).

Our findings demonstrate that AP occurs rarely in hospitalized subjects with COVID-19, despite the presence of angiotensin converting enzyme-2 receptors in both exocrine and endocrine cells. Mild elevations in pancreas enzymes were seen in approximately 20% of patients hospitalized with COVID-19; these were associated with severity of illness and did not indicate AP.

Since the start of the COVID-19 pandemic, there have been several reports on the development of AP among subjects with COVID-19 and its relation to AP severity.[4] However, a systematic review determined that the work-up to accurately determine the cause of pancreatitis was suboptimal.[5] Subsequent studies have posited that impaired circulation in the pancreas might explain the elevated serum lipase values among critically ill patients with COVID-19.[6] Among critically ill patients with acute respiratory distress syndrome before the pandemic, elevations in lipase were common, but were not specific to the pancreas.[7] Data from our cohort also suggest that elevated lipase values are associated with critical illness, rather than being directly related to pancreatic injury qualifying as AP.

In conclusion, elevations of pancreatic enzymes are relatively common (20%) in COVID-19 hospitalized patients, but rarely signify a clinical diagnosis of AP (1.5%). When AP is diagnosed, further investigation into the cause is warranted. As in other examples of critical

Table 1. Univariable Associations with Elevated Lipase

	Normal lipase (n = 300)		Elevated lipase (n = 100)		*P* value[a]
Patient characteristics					
Age, *y*	60.27	15.48	59.43	14.90	.637[b]
Body mass index at presentation, kg/m^2	30.29	7.76	31.67	8.55	.171[b,c]
Male sex	190	63.33	67	67.00	.508
Race					.774[d]
American Indian or Alaska Native	2	0.67	1	1.00	
Asian	29	9.67	8	8.00	
Black or African American	97	32.33	40	40.00	
Native Hawaiian or other Pacific Islander	111	37.00	32	32.00	
White	4	1.33	1	1.00	
Multiple	57	19.00	18	18.00	
Unknown					
Hispanic ethnicity	49	18.22	18	19.35	.807
Cigarette smoking status					.112
Current smoker	12	4.26	9	9.57	
Ex-smoker	83	29.43	30	31.91	
Nonsmoker	187	66.31	55	58.51	
Vaping status					.043[d]
Current vaping	1	0.54	3	4.55	
Does not vape	183	98.92	62	93.94	
Prior vaping	1	0.54	1	1.52	
Alcoholism					.189
Current	19	7.14	11	12.94	
No	233	87.59	68	80.00	
Prior	14	5.26	6	7.06	
Cannabis use					.530[d]
Current user	9	3.88	2	2.82	
No	216	93.10	65	91.55	
Prior user	7	3.02	4	5.63	
Illicit drug use					1.000[d]
Current user	5	1.98	1	1.20	
No	237	93.68	78	93.98	
Prior user	11	4.35	4	4.82	
Comorbidities					
Hypertension	190	63.33	64	64.00	.905
Coronary artery disease/prior or current myocardial infarction	46	15.33	17	17.00	.692
Congestive heart failure	32	10.67	12	12.00	.712
Pulmonary hypertension	1	0.33	2	2.00	.156[d]
Chronic pulmonary obstructive disease	31	10.33	9	9.00	.700
Asthma	37	12.33	11	11.00	.722
Obstructive sleep apnea	37	12.33	10	10.00	.530
Interstitial lung disease/pulmonary fibrosis	4	1.33	0	0.00	.576[d]
Peripheral vascular disease	17	5.67	5	5.00	.800
Prior or current cerebrovascular accident or transient ischemic attack	25	8.33	7	7.00	.670
Dementia	10	3.33	1	1.00	.305[d]
Collagen vascular/rheumatologic disease	18	6.00	7	7.00	.721
Chronic liver disease	13	4.33	6	6.00	.587[d]

Table 1. Continued

	Normal lipase (n = 300)		Elevated lipase (n = 100)		*P* value[a]
Cirrhosis	5	1.67	2	2.00	1.000[d]
MELD score before COVID-19 illness	14.00	8.89	20.00	0.00	
Diabetes mellitus, uncomplicated	93	31.00	30	30.00	.851[d]
Diabetes mellitus with end-organ damage	28	9.33	9	9.00	.921
Moderate to severe kidney disease (creatinine >3 mg/dL before admission, end-stage renal disease, dialysis)	35	11.67	14	14.00	.538
Active/current malignancy, excluding nonmelanoma skin cancer	13	4.33	5	5.00	.783[d]
Prior malignancy	26	8.67	8	8.00	.836
Human immunodeficiency virus/AIDS	5	1.67	0	0.00	.338[d]
Solid organ transplant recipient	14	4.67	0	0.00	.026[d]
Bone marrow transplant recipient	4	1.33	1	1.00	1.000[d]
Irritable bowel syndrome	5	1.67	1	1.00	1.000[d]
Chronic diarrhea	2	0.67	2	2.00	.261[d]
Chronic constipation	8	2.67	1	1.00	.461[d]
Celiac disease	0	0.00	0	0.00	n/a
Prior biliary disease, including cholelithiasis, cholecystitis, choledocholithiasis, or cholangitis	7	2.33	1	1.00	.685[d]
Prior pancreatitis	4	1.33	2	2.00	.643[d]
Etiology					.400[d]
Acute pancreatitis	3	100.0	1	50.00	
Recurrent acute pancreatitis	0	0.00	1	50.00	
Chronic pancreatitis	0	0.00	0	0.00	
Inflammatory bowel disease	2	0.67	1	1.00	1.000[d]
Other, not fitting into an above category	143	47.67	49	49.00	.817
Medications (within 1 mo of admission or current)					
Angiotensin-converting enzyme inhibitor use	52	17.87	13	13.68	.344
Angiotensin receptor blocker use	46	15.75	12	12.50	.438
Nonsteroidal anti-inflammatory drug use	86	39.09	29	36.25	.655
Antibiotic use	85	30.14	27	29.03	.839
Proton pump inhibitor use	82	29.18	17	18.68	.049
H_2 blocker use	39	13.88	8	8.70	.194
COVID-19 parameters					
Highest level of care					.002
Inpatient ward	155	51.67	34	34.00	
ICU	145	48.33	66	66.00	
Duration of symptoms before first seeking medical attention, *d*	5.10	4.26	5.11	4.47	.924[b,c]
Duration of symptoms before hospitalization, *d*	6.68	4.85	6.29	4.90	.709[b,c]
Duration of hospitalization, *d*	14.84	13.60	19.86	15.73	.082[b,c]
If admitted to ICU, duration of ICU stay, *d*	14.23	12.29	19.21	13.06	.004[b,c]
Required mechanical ventilation	112	37.33	61	61.00	< .001
Required extracorporeal membrane oxygenation	6	2.00	4	4.00	.276[d]

Table 1. Continued

	Normal lipase (n = 300)		Elevated lipase (n = 100)		*P* value[a]
Required vasopressor support	97	32.33	53	53.00	< .001
Final discharge disposition					.038
Deceased	57	19.00	28	28.00	
Discharged to rehabilitation or nursing facility	48	16.00	21	21.00	
Recovered (or almost recovered)	189	63.00	47	47.00	
Still hospitalized at end of study	6	2.00	4	4.00	
COVID-19-specific treatments					
Remdesivir	16	5.33	9	9.00	.190
Hydroxychloroquine	168	56.00	66	66.00	.079
Chloroquine	2	0.67	0	0.00	1.000[d]
Azithromycin	178	59.33	64	64.00	.408
Glucocorticoids	41	13.67	15	15.00	.739
Interferon-α	0	0.00	0	0.00	n/a
Intravenous immunoglobulin	0	0.00	1	1.00	.250[d]
Lopinavir/ritonavir	7	2.33	3	3.00	.716[d]
Oseltamivir	16	5.33	5	5.00	.897
Tocilizumab	20	6.67	16	16.00	.005
Convalescent plasma	4	1.33	8	8.00	.002[d]
Anakinra	0	0.00	1	1.00	.250[d]
Ribavirin	1	0.33	0	0.00	1.000[d]
Sarilumab	3	1.00	2	2.00	.603[d]
Other	47	15.67	19	19.00	.437
None	59	19.67	13	13.00	.133
Gastrointestinal symptoms or signs					
Anorexia	84	28.00	22	22.00	.239
Nausea	122	40.67	35	35.00	.315
Vomiting	79	26.33	24	24.00	.644
Abdominal pain (including cramps)	73	24.33	29	29.00	.354
Type					
Diffuse	22	7.33	6	6.00	.651
Periumbilical	2	0.67	1	1.00	1.000[d]
Epigastric	10	3.33	8	8.00	.089[d]
Right upper quadrant	12	4.00	2	2.00	.532[d]
Left upper quadrant	6	2.00	2	2.00	1.000[d]
Right lower quadrant	5	1.67	1	1.00	1.000[d]
Left lower quadrant	9	3.00	2	2.00	.738[d]
Not specified	19	6.33	10	10.00	.221
Diarrhea	113	37.67	42	42.00	.441
Bloody diarrhea	1	0.33	0	0.00	1.000[d]
Hematemesis	2	0.67	3	3.00	.102[d]
Melena	4	1.33	3	3.00	.373[d]
Hematochezia (including bright red blood per rectum)	5	1.67	5	5.00	.130[d]
Dysphagia	6	2.00	2	2.00	1.000[d]
Odynophagia	1	0.33	0	0.00	1.000[d]

Table 1. Continued

	Normal lipase (n = 300)		Elevated lipase (n = 100)		*P* value[a]
Constipation	21	7.00	3	3.00	.145
Hiccups	1	0.33	1	1.00	.438[d]
Jaundice	0	0.00	1	1.00	.250[d]
Other	11	3.67	3	3.00	1.000[d]
None	68	22.67	30	30.00	.140
Timing of gastrointestinal symptoms (if any) relative to respiratory/systemic symptoms (if any)					.813
Cannot tell from medical records review	24	10.34	5	7.14	
GI symptoms came on concurrently with other symptoms	77	33.19	26	37.14	
GI symptoms followed other symptoms	87	37.50	25	35.71	
GI symptoms preceded other symptoms	42	18.10	14	20.00	
GI symptoms were the only manifestation	2	0.86	0	0.00	
Duration of gastrointestinal symptoms					.824
Cannot tell from medical records review	36	15.52	12	17.14	
GI symptoms were present for a short portion (<25% of the duration) of the entire COVID-19 illness	92	39.66	24	34.29	
GI symptoms were present for a significant portion (25%–75% of the duration) of the entire COVID-19 illness	69	29.74	21	30.00	
GI symptoms were present for the entire/almost entire COVID-19 illness	35	15.09	13	18.57	
Did gastrointestinal symptoms remain after resolution of other COVID-19 symptoms?					1.000[d]
No	132	89.80	43	91.49	
Yes	15	10.20	4	8.51	
If yes, how long?, *d*	9.67	9.07	—	—	n/a
Prominence of gastrointestinal symptoms					.156
Cannot tell from medical records review	12	5.17	1	1.43	
GI symptoms were equally prominent to other symptoms related to COVID-19	48	20.69	16	22.86	
GI symptoms were less prominent than other symptoms related to COVID-19	153	65.95	42	60.00	
GI symptoms were less prominent than other symptoms related to COVID-19	19	8.19	11	15.71	
Gastrointestinal diagnoses established shortly before, during, or shortly after COVID-19 illness					
Esophagitis/esophageal ulcers	4	1.33	1	1.00	1.000[d]
Gastritis	3	1.00	3	3.00	.168[d]
Peptic ulcer disease	0	0.00	0	0.00	n/a
New enteritis	0	0.00	2	2.00	.062[d]
New colitis	2	0.67	3	3.00	.102[d]
Biliary disease, including cholelithiasis, cholecystitis, choledocholithiasis, or cholangitis	3	1.00	6	6.00	.009[d]
Hepatitis	10	3.33	4	4.00	.756[d]
Pancreatitis	0	0.00	6	6.00	< .001[d]
Other	26	8.67	11	11.00	.486[d]
None	258	86.00	75	75.00	.011

GI, gastrointestinal; ICU, intensive care unit; MELD, Model for End-Stage Liver Disease; n/a, not available.
[a]Chi-square test unless otherwise noted.
[b]Student *t* test.
[c]Variable log transformed for analysis.
[d]Fisher exact test.

illness, elevated serum lipase in COVID-19 patients likely reflects the overall disease severity.

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Conflicts of interest
The authors disclose no conflicts.

Most current article

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Tailored Treatment in Obese Patients With Achalasia: Endoscopic or Surgery Treatment?

Dear Editor:

We read with great interest the systematic review and meta-analysis by Oude Nijhuis et al[1] that identified factors associated with achalasia treatment outcomes. The goal of achalasia treatment is to provide symptom relief, prevent the occurrence of late complications, and improve the quality of life of patients. Although there is no curative treatment, there has been considerable advances in the management of achalasia over the past decade, mainly with the introduction of per-oral endoscopic myotomy (POEM).

Recently, the 2019 Seoul Consensus and the European and American guidelines[2–4] were published and they all agreed that pneumatic dilation, laparoscopic Heller myotomy (LHM), and POEM have comparable efficacy and should be used as first-line therapeutic options in achalasia patients. Despite these recommendations, the choice of therapeutic modality often is based on patient preference, possible side effects, and/or complications and center expertise. In this setting, clinical factors can guide treatment strategy, with the manometric type and age being the most important factors that are predictive of treatment outcome.[2]

The systematic review and meta-analysis by Oude Nijhuis et al[1] confirmed that older age and manometric subtype III are associated with clinical response. Despite the lack of evidence on other potential predictive factors, Oude Nijhuis et al[1] proposed an expert-opinion–based algorithm to guide treatment in achalasia patients. This original approach is innovative, and it may allow physicians to choose the best therapeutic modality based on patient characteristics. They also suggested that more definitive treatments such as LHM and POEM will be more effective in younger adults and patients with type III achalasia. Current guidelines[3,4] also advise that POEM could be a preferred option for patients with type III achalasia. However, there is still no established consensus on which patients would benefit from LHM instead of POEM.

Oude Nijhuis et al[1] suggested that performing LHM is less reasonable compared with POEM in patients with previous extensive surgery or a history of peritonitis, but also with severe obesity, because it is a more invasive surgical procedure. However, obesity is associated with a 2.5 times higher risk of developing gastroesophageal reflux disease (GERD), because of increased intragastric pressure and anatomic disruption of the gastroesophageal junction caused by high amounts of visceral fat.[5] A recent meta-analysis[6] showed a higher incidence of GERD after POEM compared with LHM with fundoplication. Although the management of morbidly obese patients with achalasia may be complex and the most effective treatment remains controversial, LHM appears to have the advantage of adding an antireflux procedure, unlike POEM. Instead of performing LHM with partial fundoplication, a recent review[7] suggested that the preferred approach in these patients would be to address both disease processes simultaneously with LHM and a Roux-en-Y gastric bypass (RYGB). Besides the additional health benefits associated with weight loss and improvement in obesity-related comorbidities, RYGB results in a significant decrease in reflux symptoms (31% preoperatively vs 5% postoperatively), esophagitis (24% preoperatively vs 10% postoperatively), and incidence of GERD (34% preoperatively vs 12% postoperatively).[5]

In addition, Oude Nijhuis et al[1] suggested different approaches among patients with obesity and severe obesity, mentioning that physicians should advise POEM only in patients with severe obesity because it is less