

Does Hyperlipasemia Predict Worse Clinical Outcomes in COVID-19? A Multicenter Retrospective Cohort Study

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Goal: We aim to perform a multicenter retrospective cohort study to determine if elevated serum lipase determines clinical outcomes in patients with coronavirus disease 2019 (COVID-19).

Background: Several cases of acute pancreatitis (AP) have recently been reported in association with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Most of the evidence is based on elevated serum lipase values without objective demonstration of pancreatic inflammation or necrosis.

Materials and Methods: A population-based, multicenter, retrospective cohort study utilizing TriNetX was performed to obtain aggregated health records of ~69 million patients from 49 health care organizations from January 1, 2020, to December 31, 2020. Adult patients (18 y and above) diagnosed with COVID-19 were identified using appropriate *International Classification of Diseases, 10th Revision* (ICD-10) codes and were stratified into 2 groups, with elevated (≥ 180 U/L) and with normal (≤ 80 U/L) serum lipase. The primary outcome was 30-day mortality; other outcomes were 30-day rehospitalization, need for mechanical ventilation, need for vasopressor use, acute kidney injury.

Results: A total of 435,731 adult patients with COVID-19 were identified, and 1406 of them had elevated serum lipase which was associated with higher 30-day mortality [risk ratio (RR)=1.53, $P < 0.001$], risk of acute kidney injury (RR=1.5, $P = 0.003$), and vasopressor use (RR=1.69, $P < 0.001$) without any difference in 30-day rehospitalization (RR=0.98, $P = 0.54$), or need for mechanical ventilation (RR=1.20, $P = 0.26$). The negative predictive value of normal serum lipase for 3-month mortality in patients with COVID-19 was 91%.

Conclusions: Patients with COVID-19 who have elevated serum lipase experience worse clinical outcomes even in the absence of AP. If these findings can be replicated in prospective studies, serum lipase can be utilized as a marker of disease severity in patients with COVID-19.

Key Words: lipase, acute pancreatitis, COVID-19, SARS-CoV-2
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Coronavirus disease 2019 (COVID-19) is a serious disease caused by a novel strain of coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). While acute respiratory illness predominates the clinical presentation of COVID-19, the spectrum of organ involvement and illness is broad.^{1–3} Multiple studies have shown that gastrointestinal (GI) symptoms like abdominal pain, vomiting, and diarrhea can be the presenting manifestations of COVID-19.^{4,5} The biological plausibility of GI manifestations is understandable since angiotensin-converting enzyme II (ACE II) receptors, implicated in the SARS-CoV-2 viral entry pathway, are highly expressed in the enterocytes of the small bowel, colon, and upper esophageal stratified epithelial cells.⁶ High expression of ACE II messenger RNA has also been demonstrated in pancreatic tissue and thus the potential for virus-induced pancreatic injury.⁷

Retrospective studies have shown evidence of pancreatic injury in 1% to 2% of patients with nonsevere COVID-19 and in ~17% of those with severe disease.^{7,8} Besides, there have been multiple case reports highlighting the role of SARS-CoV-2 as an etiologic agent for acute pancreatitis (AP).^{9–12} However, it is questionable whether these reports are true events of AP attributable to COVID-19 or represent the mere elevation of serum lipase without clinical consequences of AP. A recently published retrospective study has shown that elevated lipase is common in patients with SARS-CoV-2 infection without evidence of AP and without any influence on clinical outcome.¹³

Here, we aim to perform a large multicenter retrospective study to determine the rate of elevated serum lipase in patients with COVID-19 and if it predicts worse clinical outcomes.

MATERIALS AND METHODS

We performed a population-based, multicenter, retrospective cohort study utilizing TriNetX (Cambridge, MA), “A global federated health research network that provides deidentified data from electronic medical records. Protected Health Information (PHI) is not available on this platform” (www.trinetx.com/page/4/#home-slider-3-copy). To fortify protected health information, TriNetX rounds up number of patients to the nearest 10 for analytic purposes.¹⁴ We searched the TriNetX platform to obtain aggregated health records of ~69 million patients from 49 health care organizations from January 1, 2020, to December 31, 2020. The study data was shared with all the authors who reviewed and approved the final manuscript.

Study Population

Adult patients (18 y and above) diagnosed with COVID-19 were identified using appropriate ICD-10 codes, COVID-19 (U07.1), pneumonia due to SARS-associated coronavirus (J12.81) or Coronavirus infection, unspecified (B34.2). Patients with the most recent positive test result for

TABLE 1. Baseline Characteristics and Common Comorbidities Before and After Propensity Matching

Demographics	Before Matching				After Matching			
	Mean (\pm SD)	n (%)		P	Mean (\pm SD)	n (%)		P
		Elevated Lipase	Normal Lipase			Elevated Lipase	Normal Lipase	
Age (y)	58.2 (\pm 16.8) 57.2 (\pm 18.6)	1406 (100)	15,849 (100)	0.04	58.2 (\pm 16.8) 58.5 (\pm 16.8)	1406 (100)	1406 (100)	0.69
Female		641 (45.6)	8349 (52.7)	<0.001		641 (45.6)	631 (44.9)	0.70
Race								
White		691 (49.15)	7754 (48.9)	0.87		—	—	—
Black		380 (27.0)	3902 (24.6)	0.04		380 (27.0)	383 (27.2)	0.89
Diagnoses								
Diabetes mellitus		429 (30.5)	4308 (27.2)	0.007		429 (30.5)	425 (30.2)	0.87
Obesity		328 (23.3)	3671 (23.2)	0.89		—	—	—
Malnutrition		95 (6.8)	854 (5.4)	0.03		95 (6.8)	74 (5.3)	0.09
Chronic kidney disease		284 (20.2)	2235 (14.1)	<0.001		284 (20.2)	273 (19.4)	0.60
Ischemic heart disease		278 (19.8)	3004 (18.9)	0.45		—	—	—
Heart failure		195 (13.9)	2121 (13.4)	0.60		—	—	—
Chronic pulmonary disease		236 (16.8)	3298 (20.8)	<0.001		236 (16.8)	227 (16.1)	0.65
Symptoms								
Abdominal pain		25 (1.8)	241 (1.5)	0.45		—	—	—
Nausea/vomiting		45 (3.2)	50 (3.6)	0.60		—	—	—

CRP indicates C-reactive protein; N, number of patients; SD, standard deviation.

SARS-CoV-2 RNA (TriNetX:LAB code 9088) was also identified. COVID-19 patients with elevated serum lipase above 3 times the upper limit of normal (ULN or ≥ 180 U/L) and those with normal serum lipase (≤ 80 U/L) were identified. Serum lipase levels within 1 week of COVID-19 diagnosis were identified using laboratory code (TriNetX:LAB code 9069). A subgroup of patients with idiopathic (K85.0), other (K85.8), or unspecified AP (K85.9) during acute illness due to COVID-19 was also identified. Common etiologies of AP were excluded. Serum ferritin level was considered markedly elevated when it was ≥ 1000 ng/mL and C-reactive protein was considered significantly elevated when it was ≥ 150 mg/L. The query builders for both the groups with elevated and normal serum lipase are available as Supplemental Files (Supplemental Digital Content 1, <http://links.lww.com/JCGE/A754>).

Outcome Measures

We compared the group with normal serum lipase with those who had elevated serum lipase. A subgroup of patients with AP during acute illness from COVID-19 was analyzed and compared with patients who had elevated serum lipase. The primary outcome was 30-day mortality. Other outcomes were the need for mechanical ventilation, vasopressor use, acute kidney injury, and rehospitalization within 30 days. We also calculated the sensitivity, specificity, positive predictive value, and negative predictive value of elevated serum lipase in predicting mortality within 3 months in patients with COVID-19. The analyses were performed in the cohort of patients who had serum lipase value available during acute illness with COVID-19.

Statistical Analyses

Mean and SD were calculated for continuous variables and proportion and percentage for dichotomous and categorical variables. Propensity score matching (1:1) was performed for baseline characteristics (age, gender, race) and

common comorbidities (diabetes mellitus, obesity, malnutrition, chronic kidney disease, chronic pulmonary diseases, coronary artery disease, and heart failure). For clinical outcomes, relative risk, risk difference, and odds ratio were calculated, and Kaplan-Meier analysis with survival curve was obtained where appropriate. The statistical significance was set at a 2-sided P -value < 0.05 . All the statistical analyses were performed using the TriNetX platform.

RESULTS

We found 435,731 adult patients from 45 health care organizations who were diagnosed with COVID-19 during the study period. Patients with elevated serum lipase values ($N = 1406$) and those with normal values ($N = 15,849$) were identified. Male patients (53% vs. 46%, $P < 0.001$) and those of black race (27% vs. 24%, $P = 0.04$) were more likely to have elevated serum lipase. Diabetes, chronic kidney disease, and chronic pulmonary disease were more frequent in patients with elevated serum lipase. A small proportion of patients with elevated serum lipase had documented abdominal pain (1.8%) and nausea or vomiting (3.2%) which was similar to those with normal serum lipase (Table 1). AP was diagnosed in 11.8% of patients with elevated lipase compared with 1.9% of those with normal or mildly elevated lipase.

After propensity score matching, elevated serum lipase was associated with significantly higher 30-day mortality [11.31% vs. 7.40%; risk ratio (RR)=1.53, $P < 0.001$] (Fig. 1), risk of acute kidney injury (9.46% vs. 6.47%; RR=1.52, $P = 0.003$), and vasopressor use (12.52% vs. 7.40%; RR=1.69, $P < 0.001$) without any difference in 30-day rehospitalization (41.96% vs. 42.82%; RR=0.98, $P = 0.64$), risk of acute respiratory failure or acute respiratory distress syndrome (11.45% vs. 12.02%; RR=0.95, $P = 0.64$), or need for invasive mechanical ventilation (4.91% vs. 4.13%; RR=1.2, $P = 0.26$). Frequency of

markedly elevated serum ferritin (14.5% vs. 13.5%, $P=0.51$) and C-reactive protein (9.8% vs. 10.8%, $P=0.49$) levels were not different between the 2 groups (Tables 2, 3). Comparing COVID-19 patients who had a diagnosis of AP with all patients with elevated serum lipase, there was no difference in clinical outcomes including 30-day mortality (7.2% vs. 7.9%, $P=0.91$), rehospitalization ($P=0.60$), acute kidney injury ($P=0.57$), vasopressor use ($P=0.73$), acute respiratory failure ($P=0.90$), or ventilator use ($P=0.71$).

The sensitivity, specificity, positive predictive value, and negative predictive value of elevated serum lipase in predicting mortality in the first 3 months among COVID-19 patients with available serum lipase values was 13.2%, 91.9%, 8.9%, and 91.3%, respectively.

DISCUSSION

This is the largest study looking at the relationship between hyperlipasemia and clinical outcomes in patients with COVID-19, to the best of our knowledge. We found that elevated serum lipase (> 3 times ULN) in patients with COVID-19 predicts worse clinical outcomes including short-term (30-d) mortality, acute kidney injury, and vasopressor use, even after propensity score matching for demographic characteristics and common chronic illnesses. We also performed separate analyses with serum lipase values 1 to 2 times ULN and 2 to 3 times ULN. However, there was no difference in mortality, rehospitalization, risk of acute kidney injury, or vasopressor use between those with either 1 to 2 times serum lipase elevation or 2 to 3 times serum lipase elevation compared with patients with normal serum lipase during acute COVID-19 illness (Supplement Table 1, <http://links.lww.com/JCG/A754>).

While our study adds to the emerging knowledge of hyperlipasemia in AP, its association with the worse clinical outcome has yet to be replicated in prospective studies. Our results are contrary to the results from prior retrospective

studies that have shown no relationship between hyperlipasemia and clinical outcomes in patients with COVID-19; however, these results are limited by small patient samples ($N < 10$) and were conducted in a small geographic area.^{8,13}

Our findings suggest that hyperlipasemia is not uncommon in patients with COVID-19, and there is no significant difference in the frequency of abdominal symptoms between patients who had elevated serum lipase and those with normal serum lipase. We found no difference in the clinical outcomes between COVID-19 patients who were labeled as having AP (idiopathic or other AP) when compared with all patients with elevated serum lipase. This is interesting as it might point towards overdiagnosis of AP in the setting of COVID-19 solely based on elevated serum lipase. Multiple cases of AP have been reported in association with COVID-19, however, most of these cases did not have any evidence of interstitial or necrotizing pancreatitis on cross-sectional imaging (computed tomography scan or magnetic resonance imaging).^{9,12,15} The diagnoses were solely based on elevated serum pancreatic enzyme levels, which has been shown to be a common phenomenon in patients with COVID-19. Besides, COVID-19 is associated with several nonspecific GI symptoms making it difficult to correlate abdominal pain as a symptom of AP in the absence of imaging findings.^{4,5} Some of the above cases had demonstration of AP on imaging without clear known etiology, nonetheless, it is likely that these patients represent 15% to 25% of patients with AP in whom the etiology is unknown.¹⁶

A multicenter study has shown higher rate of idiopathic AP in patients with COVID-19 compared with those without COVID-19 (24% vs. 14%, $P=0.001$).¹⁷ Nonetheless, there are confounders and bias involved in the study that have to be considered before making any conclusions about this causal relation. Moreover, there has been a trend towards less frequent utilization of imaging modalities and invasive endoscopic procedures including endoscopic retrograde cholangiopancreatography and endoscopic ultrasound in

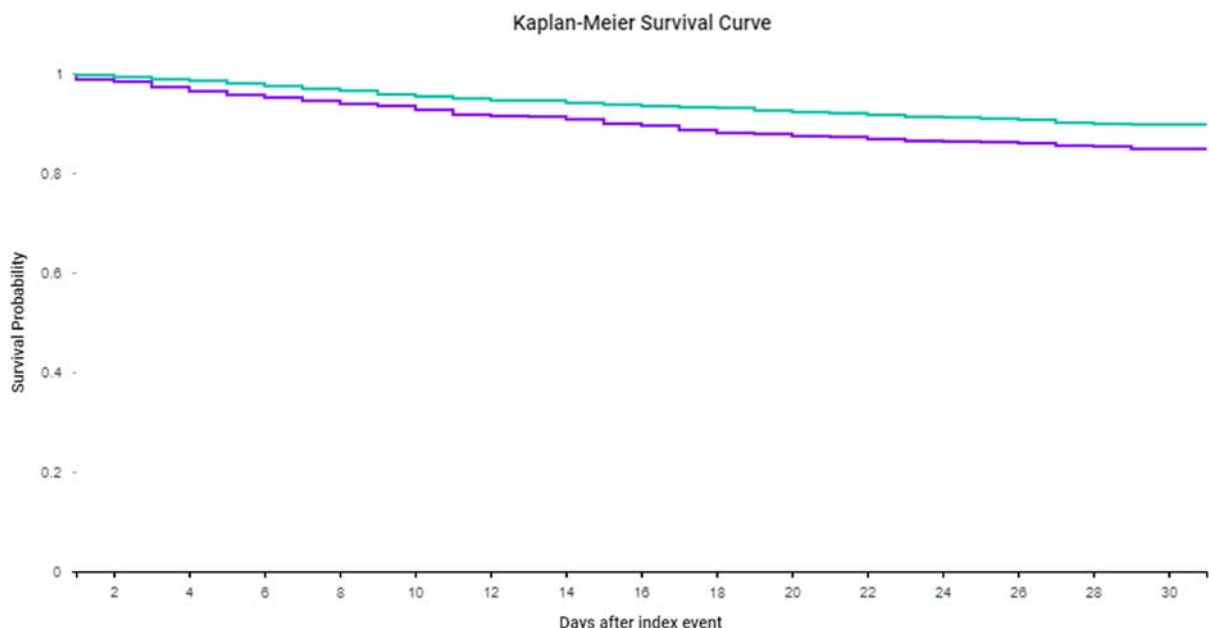


FIGURE 1. The Kaplan-Meier survival curve for 30-day mortality. Light gray curve indicates COVID-19 with normal S. lipase and dark gray curve indicates COVID-19 with elevated S. lipase.

TABLE 2. Clinical Outcomes of Patients With Elevated Serum Lipase Compared With Those With Normal Serum Lipase

Outcomes	n (%)		Risk Ratio (Risk Difference, %)	P	Odds Ratio	95% Confidence Interval
	COVID-19 With Elevated Serum Lipase	COVID-19 With Normal Serum Lipase				
Mortality	159 (11.31)	104 (7.40)	1.53 (3.9)	<0.001	1.60	1.23-2.07
Rehospitalization	590 (41.96)	602 (42.82)	0.98 (-0.85)	0.64	0.97	0.83-1.12
Need for mechanical ventilation	69 (4.91)	58 (4.13)	1.2 (0.8)	0.26	1.29	0.82-2.00
Vasopressor use	176 (12.52)	104 (7.40)	1.69 (5.1)	<0.001	1.79	1.39-2.31
Acute kidney injury	133 (9.46)	91 (6.47)	1.5 (2.9)	0.003	1.51	1.14-1.99
Acute respiratory failure*	161 (11.45)	169 (12.02)	0.95 (-0.57)	0.64	0.95	0.75-1.19
Serum ferritin ≥ 1000 ng/mL	204 (14.51)	190 (13.51)	1.07 (0.99)	0.76	1.09	0.87-1.34
Elevated CRP†	134 (9.53)	152 (10.81)	0.88 (-1.3)	0.26	0.87	0.68-1.11

*Includes acute respiratory distress syndrome and other acute respiratory failure.

†CRP ≥ 150 mg/L.

COVID-19 indicates coronavirus disease 2019; CRP, C-reactive protein.

patients with active COVID-19 to limit the transmission of the virus. This practice probably explains both, overreporting of AP solely based on elevated serum lipase and increased frequency of idiopathic AP due to missed cases of biliary sludge, microlithiasis, pancreatic cystic lesions, and early pancreatic cancer.¹⁷ Furthermore, a multicenter, retrospective study from Spain reported a lower frequency of AP in patients with COVID-19 (odds ratio=0.44, 95% confidence interval: 0.33-0.60).¹⁸ Thus, the data on the incidence of AP in patients with COVID-19 appears to be inconsistent, questioning the probability of a true causal relationship.

Elevated serum lipase is considered more specific than serum amylase for the diagnosis of AP; nonetheless, there are conditions other than AP that can lead to mild to moderate lipase elevation. Among GI illnesses any form of bowel injury including enteritis, colitis or perforation can lead to hyperlipasemia without AP. Pancreatic ischemia due to systemic hypoperfusion can cause lipase elevation with or without AP.¹⁹ Among non-GI acute illnesses, diabetic ketoacidosis has been shown to be associated with elevated lipase even in the absence of true AP.²⁰

We found that elevated serum lipase level had high specificity and negative predictive value for mortality (both >90%) among patients who had serum lipase values available. This is an important finding as having a normal or near-normal serum lipase may predict better clinical outcomes and lower probability of short-term mortality in

patients with COVID-19. Previous studies have shown adverse clinical outcomes in COVID-19 patients with hyperlipasemia (in the absence of AP) have not evaluated elevated serum lipase in predicting mortality or any other clinical outcome.^{21,22} While our findings are interesting and may have clinical implications in prognosticating some of the patients with COVID-19, the results must be validated in a prospective studies before clinical application.

We found that there was no difference in the rates of markedly elevated serum ferritin or C-reactive protein between patients who had elevated serum lipase compared with those who had normal serum lipase. This finding is interesting as serum lipase can complement other biomarkers of inflammation to predict disease course in patients with COVID-19.

Our study has some limitations. The retrospective study design brings with it an inherent risk of bias. Details on individual patients is lacking as the clinical data was extracted from a large database without access to protected health information. Besides, the cause of death or readmission cannot be determined in individual patients due to the study design. Nonetheless, the multicenter study design along with a large population size makes it a strong study.

CONCLUSIONS

Serum lipase is commonly elevated in patients with COVID-19, and it can serve as a predictor of disease severity.

TABLE 3. Clinical Outcomes in COVID-19 Patients With AP Compared With Those With Elevated Serum Lipase

Outcomes	n (%)		Risk Ratio (Risk Difference, %)	P	Odds Ratio	95% Confidence Interval
	COVID-19 With AP	COVID-19 With Elevated Serum Lipase				
Mortality	19 (7.18)	21 (7.95)	0.91 (-0.8)	0.91	0.89	0.47-1.71
Rehospitalization	145 (54.92)	139 (52.65)	1.04 (2.2)	0.60	1.09	0.78-1.54
Acute respiratory failure*	41 (15.53)	40 (15.15)	1.02 (0.38)	0.90	1.03	0.64-1.65
Need for mechanical ventilation	14 (5.30)	16 (6.06)	0.88 (-0.76)	0.71	0.87	0.42-1.81
Vasopressor use	45 (17.05)	48 (18.18)	0.94 (-1.1)	0.73	0.93	0.59-1.45
Acute kidney injury	26 (9.85)	30 (11.36)	0.87 (-1.5)	0.57	0.85	0.49-1.48

*Including acute respiratory distress syndrome.

AP indicates acute pancreatitis; COVID-19, coronavirus disease 2019.

Elevated serum lipase may be a novel marker that can complement serum ferritin, C-reactive protein, and other markers of inflammation to identify patients at the highest risk of adverse outcomes from this deadly disease. AP during acute illness with COVID-19 has probably been overreported due to the common occurrence of elevated serum lipase and GI symptoms in this population, and it is important to exercise caution when making a diagnosis of AP in these patients and in attributing it to COVID-19. Our findings must be validated in prospective studies before serum lipase can be utilized as a marker of disease severity in COVID-19.

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