Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Pancreatology 21 (2021) 698–703

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Hyperlipasemia in absence of acute pancreatitis is associated with elevated D-dimer and adverse outcomes in COVID 19 disease

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ARTICLE INFO

Article history:
Received 4 October 2020
Received in revised form
20 February 2021
Accepted 23 February 2021
Available online 4 March 2021

Keywords:
Hyperlipasemia
Pancreatitis
covid 19
Outcomes
D dimer

ABSTRACT

Background: Coronavirus SARS-CoV-2 affects multiple organs. Studies have reported mild elevations of lipase levels of unclear significance. Our study aims to determine the outcomes in patients with COVID-19 and hyperlipasemia, and whether correlation with D-dimer levels explains the effect on outcomes.
Methods: Case-control study from two large tertiary care health systems, of patients with COVID-19 disease admitted between March 1 and May 1, 2020 who had lipase levels recorded. Data analyzed to study primary outcomes of mortality, length of stay (LOS) and intensive care utilization in hyperlipasemia patients, and correlation with D-dimer and outcomes.
Results: 992 out of 5597 COVID-19 patients had lipase levels, of which 429 (43%) had hyperlipasemia. 152 (15%) patients had a lipase > 3x ULN, with clinical pancreatitis in 2 patients. Hyperlipasemia had a higher mortality than normal lipase patients (32% vs. 23%, OR = 1.6,95%CI = 1.2–2.1, P = 0.002). In subgroup analysis, hyperlipasemia patients had significantly worse LOS (11vs.15 days, P = 0.01), ICU admission rates (44% vs. 66%,OR = 2.5,95%CI = 1.3–5.0,P = 0.008), ICU LOS (12vs.19 days,P = 0.01), mechanical ventilation rates (34% vs. 55%,OR = 2.4,95%CI = 1.3–4.8,P = 0.01), and durations of mechanical ventilation (14 vs. 21 days, P = 0.008). Hyperlipasemia patients were more likely to have a D-dimer value in the highest two quartiles, and had increased mortality (59% vs. 15%,OR = 7.2,95%CI = 4.5–11,P < 0.001) and LOS (10vs.7 days,P < 0.001) compared to those with normal lipase and lower D-dimer levels.
Conclusion: There is high prevalence of hyperlipasemia without clinical pancreatitis in COVID-19 disease. Hyperlipasemia was associated with higher mortality and ICU utilization, possibly explained by elevated D-dimer.

Introduction

The global COVID-19 pandemic caused by the novel coronavirus SARS-CoV-2 has affected upwards of 25 million people, resulting in over 900,000 deaths globally, a fifth of which have occurred in the United States [1]. Although thought to be primarily a respiratory illness, emerging evidence demonstrates that the infection can variably manifest itself within multiple organ systems [2–6]. In fact, the first reported patient with COVID-19 in the United States had gastrointestinal symptoms of abdominal pain and diarrhea [7]. Early reports showed a 3.8% prevalence of gastrointestinal symptoms but more recent studies show the prevalence to be up to 17% [8,9]. Furthermore, there have been a few small studies which have shown an elevation of lipase, without any obvious clinical significance, especially as it pertains to the pancreas [10,11]. To our knowledge, there are only seven case reports of COVID-19 associated clinical pancreatitis, as defined by the revised Atlanta criteria [12–14].

COVID-19 associated pancreatic injury may be a consequence of the virus entering host cells via the transmembrane angiotensin-

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https://doi.org/10.1016/j.pan.2021.02.021
1424-3903/

converting enzyme 2 (ACE-2) receptor, which is highly expressed in pancreatic acinar cells, and for which the virus appears to have a high affinity [15]. Wang et al. first described the presence of hyperlipasemia in 17% of their cohort of 52 patients, with a subsequent US study reporting a prevalence of 12% in 71 patients [10,11]. The significance of these findings was unclear as there was no obvious correlation with radiographic pancreatic injury or signs and symptoms to suggest clinical pancreatitis, and also no clear correlation to outcomes. Moreover, the combined number of patients with hyperlipasemia across both studies was only 18.

In critically ill patients, hyperlipasemia can be difficult to interpret as there is often co-existent systemic inflammation, shock and decreased renal clearance, all of which significantly reduce its positive predictive value for clinical pancreatitis [16]. Moreover, patients with COVID-19 illness have coagulation abnormalities, thrombotic events and elevated D-dimer levels which may contribute to pancreatic injury and hyperlipasemia [17,18]. D-dimer is a fibrinogen degradation product in the coagulation cascade, and although not an independent risk factor of mortality, it is a well-established marker of poor outcomes in critical illness, including COVID-19 disease.

While hyperlipasemia has been reported in a small number of patients with COVID-19 infection, its clinical significance remains unclear. The focus of our study was to determine the outcome in COVID-19 disease patients with hyperlipasemia when compared to patients with normal lipase levels, measured by mortality, length of stay (LOS), and intensive care unit (ICU) utilization. We also examined the correlation between D-dimer levels in patients with elevated lipase as a surrogate marker for outcomes and microthrombotic disease resulting in pancreatic injury and thus hyperlipasemia.

Methods

The study was a collaborative multicenter effort conducted across two major tertiary medical systems in New York and Boston, between New York University Langone Health (NYULH, 4 hospitals) and Beth Israel Lahey Health (BILH, 3 hospitals) systems. Institutional Review Board approval was obtained at both institutions independently, followed by a data use agreement to facilitate collaboration between the two institutions.

Study design and patient selection (Fig. 1)

An *a priori* study collection tool was created independently at both institutions for data review and collection. Adult patients, older than 18 years of age, were included in the study if they were diagnosed and hospitalized for COVID-19 illness at their respective institutions, from March 1st to May 3rd, 2020, and had a lipase level drawn. Patients evaluated and treated/observed in the emergency department with an overall length of stay less than 48 h were excluded from analysis. SARS-CoV-2 infection was diagnosed via polymerase chain reaction analysis of nasopharyngeal swabs. Normal laboratory reference ranges for lipase at BILH was 0–60 IU/L, and NYU Langone Health was 8–78 IU/L. Patients were further divided into 4 groups for analysis: 1) Normal range lipase level, 2) Lipase levels elevated to less than 3x upper limit of normal (<3xULN), 3) Lipase levels elevated to greater than 3xULN (>3xULN), and 4) Hyperlipasemia (all levels > ULN; sum of group 2 and 3). Normal laboratory reference ranges for D-dimer at BILH was 0–500 ng/mL FEU and for NYULH was 0–230 ng/mL DDU. To facilitate categorical comparisons of D-dimer results that were based off two different institutional assays, D-dimer values were subdivided into institution-specific quartiles (Supplemental Table A).

Data collection

Electronic medical records for COVID-19 patients were reviewed. Data regarding demographics, presenting complaints, presence of gastrointestinal and non-gastrointestinal symptoms, comorbid illnesses, vital signs, laboratory tests, including d-dimer levels, radiological testing and hospital course were recorded. The peak values for lipase and D-dimer were identified as the single highest level during the hospitalization and used for analysis. D-dimer was used as it has strongly been associated with poor outcomes in COVID-19 disease. Routine testing for serum lipase was not included by default in initial admission orders, and was performed based at the discretion of the primary treatment team. Outcome data recorded for both health systems included mortality and overall LOS. Additional outcome data were recorded for the subgroup of BILH patients that included ICU utilization (number of ICU admissions, ICU LOS, number of patients who were mechanical ventilated, and duration of mechanical ventilation). Inspection of all study variables identified no missing data among those selected for primary analysis. Patients with missing data for secondary analyses were excluded from the denominator during comparison of select variables, with revised denominators indicated where relevant.

Statistical analysis

Prior to comparative analyses, continuous variables were evaluated for distribution normality using a Shapiro-Wilk statistic and normality plots to guide nonparametric testing. Data were then analyzed using Student's t-test, Mann-Whitney U, or Fisher's exact testing. Results containing continuous variables are presented as means with standard deviations or medians with interquartile ranges (IQR) based on normality distribution. Odds ratios and 95% confidence intervals are provided for pertinent categorical comparisons. Statistical significance was assumed at $P < 0.05$. Data analyses were performed using IBM Statistical Package for the Social Sciences (IBM SPSS 25.0, Armonk, NY).

Results

We identified 5597 patients with COVID-19 disease admitted to seven hospitals across two health systems during the study period. After excluding 101 patients with a LOS of less than 48 h, 992 patients (18%) had lipase levels checked during their hospitalization and were included for analysis. A total of 563 (57%) patients had a normal lipase and 429 (43%) had hyperlipasemia. Among patients with hyperlipasemia, 152 (15%) patients had a lipase level > 3xULN. A total of 803 patients had both lipase levels and D-dimer levels recorded. The basic demographics of patient groups are presented in Table 1. There were no differences in the mean age, body mass index (BMI), or smoking status of patients across all groups. Notably, there was a significant male predominance in the hyperlipasemia group (66% vs. 58%, OR = 1.4, 95%CI = 1.09–1.8, P = 0.01). As would be expected, a higher number of cross-sectional imaging studies were performed in patients with lipase >3XULN; only 2 out of 43 patients in this group who had imaging studies demonstrated radiological evidence of pancreatitis. As shown in Supplemental Table B, patients with hyperlipasemia had lower prevalence of major cardiopulmonary and vascular disease at baseline; we observed a higher percentage of patients with zero comorbidities in the hyperlipasemia cohort compared to the normal lipase group (34% vs. 13%, OR = 3.5, 95%CI = 1.6–7.8, P = 0.003). There was no difference in the renal function between patients with normal lipase and hyperlipasemia. Presence of gastrointestinal symptoms on admission was not statistically different across all lipase groups

Table 1
Patient demographics, by lipase cohort.

	Normal Lipase [Group 1] (N = 563)	Elevated Lipase <3x ULN [Group 2] (N = 277)	Elevated Lipase >3x ULN [Group 3] (N = 152)	All Elevated Lipase [Group 4] (N = 429)	1 vs. 4 OR (95%CI)	1 vs. 4 P
Age (years)[a]	64 ± 17	65 ± 17	61 ± 17	64 ± 17	n/a	0.97
Male Gender	324 (58%)	175 (63%)	107 (70%)	282 (66%)	1.4 (1.09–1.8)	0.01
Lifetime Smoking History[b]	156/490 (32%)	65/220 (30%)	34/117 (29%)	99/337 (29%)	0.89 (0.66–1.2)	0.49
Current Smoker	21 (3.7%)	9 (3.2%)	3 (2.0%)	12 (2.8%)	0.74 (0.36–1.5)	0.47
Body Mass Index[a]	29.4 ± 8.3	29.9 ± 7.6	29.7 ± 5.4	29.9 ± 6.8	n/a	0.57
Number of patients with CT or MRI	115 (20%)	51 (18%)	43 (28%)	94 (22%)	1.09 (0.80–1.5)	0.58

[a] Data presented as mean with standard deviation.
[b] Revised denominators reflect patients excluded for missing data on this variable.

(Supplemental Table C); however, of the 2 patients in the >3xULN group who had cross-sectional imaging suggestive of pancreatitis, one had characteristic abdominal pain and was diagnosed with acute pancreatitis with gallstones, while the etiology in the second patient with interstitial pancreatitis, and without abdominal pain was undetermined.

Primary outcomes

Outcome data showing mortality and LOS across the entire study sample are outlined in Table 2. We observed significantly higher mortality in all three elevated lipase cohorts when compared to patients with normal lipase levels. However, LOS among patients with normal lipase and across all groups with hyperlipasemia was found to be similar. Sub-group analysis of only the BILH patients is reported in Table 3. In contrast to the larger study sample, the LOS in the BILH subset was significantly greater for hyperlipasemia patients. The BILH subgroup also demonstrated more ICU admissions among patients with hyperlipasemia, with longer ICU LOS, more patients requiring mechanical ventilation, and increased duration on mechanical ventilation when compared to patients with normal lipase levels. The subgroup of patients with lipase >3ULN had maximum intensive care utilization. A clear ICU and ventilator utilization analysis was not possible for the NYULH cohort due to multiple location assignments in the EMR system as many units and beds were variably flexed into ICU levels of care during the study period.

D-dimer and hyperlipasemia

Although D-dimer levels above normal were seen equally across all groups, Table 4 demonstrates that among patients with normal lipase levels, we observed a smaller percentage of elevated D-dimer in the 3rd and 4th quartiles when compared to hyperlipasemia patients, where a higher percentage of elevated D-dimer was noted (45% vs. 56%, OR = 0.63, 95%CI = 0.48–0.84, P = 0.001). Furthermore, patients with both hyperlipasemia and the highest D-dimer quartile had an increased mortality and longer LOS when compared to patients who had both normal lipase levels and D-dimer levels in the lower 3 quartiles (Table 5). This effect was seen consistently, irrespective of level of lipase elevation (i.e., <3xULN or >3x ULN) (Supplemental Tables D1 and D2). Additionally, independent of lipase elevation, elevated D-dimer predicted a poor outcome with significantly higher mortality and longer LOS (Supplemental Table E) but with a lower odds ratio for mortality when compared to patients with combined highest D-dimer quartile and hyperlipasemia.

There was no impact on mortality across all groups when examining the effect of hyperlipasemia alone by controlling for D-dimer levels (Supplemental Tables F1 and F2). Table 6a (NYULH) and 6b (BILH) demonstrate the median peak lipase and D-dimer values according to survival cohort at each institution (separate analyses by institution required due to different assays/reference ranges). Higher levels of both lipase and D-dimer were observed among NYULH patients who did not survive, whereas in the BILH data, non-survivors demonstrated higher peak D-dimer values, with no differences observed in median peak lipase levels.

Discussion

In this multicenter analysis of 992 patients with COVID-19 illness across two large tertiary care health systems comprised of 7 hospitals in New York and Boston, we examined the prevalence of hyperlipasemia and its association with survival, LOS and ICU utilization. We report that 43% patients had hyperlipasemia, and 15% of patients had lipase levels >3xULN. This is a significantly higher prevalence of hyperlipasemia than previously reported in studies of much smaller sample sizes [10,11]. Even though 152 patients had lipase levels >3ULN, a criteria necessary for the diagnosis of acute pancreatitis, only 2 patients (within the BILH subgroup) had evidence for acute pancreatitis by the revised Atlanta criteria. One patient had classic gallstone pancreatitis while the other was on mechanical ventilation when diagnosed with biochemical and radiological pancreatitis of undetermined etiology.

We also report that patients with hyperlipasemia had a 39% higher mortality rate when compared to patients with normal lipase levels (32% vs 23%). With the available data, we were able to demonstrate that patients with hyperlipasemia in the BILH group

Table 2
Outcomes across entire study population, by lipase cohort.

	Normal Lipase [Group 1] (N = 563)	Elevated Lipase <3x ULN [Group 2] (N = 277)	Elevated Lipase >3x ULN [Group 3] (N = 152)	All Elevated Lipase [Group 4] (N = 429)	1 vs. 2 OR (95%CI), P	1 vs. 3 OR (95%CI), P	1 vs. 4 OR (95%CI), P
LOS (days)[a]	7.0 (4.0–13)	6.0 (3.0–11)	7.0 (3.0–13)	6.0 (3.0–12)	n/a, 0.03	n/a, 0.79	n/a, 0.08
Mortality	128 (23%)	87 (31%)	49 (32%)	136 (32%)	1.6 (1.1–2.1), 0.009	1.6 (1.1–2.4), 0.02	1.6 (1.2–2.1), 0.002

[a] Data presented as medians with interquartile ranges.

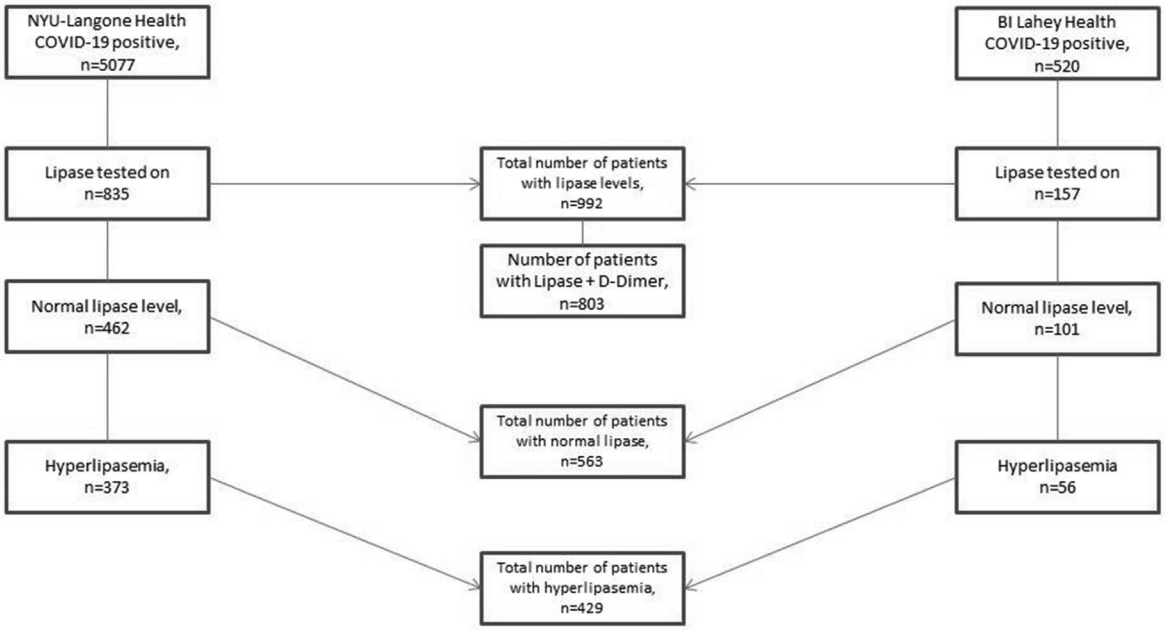

Fig. 1. Patient flow diagram.

Table 3
Outcomes for BILH sub-group only, by lipase cohort.

	Normal Lipase [Group 1] (N = 101)	Elevated Lipase <3x ULN [Group 2] (N = 30)	Elevated Lipase >3x ULN [Group 3] (N = 26)	All Elevated Lipase [Group 4] (N = 56)	1 vs. 4 OR (95%CI)	1 vs. 4 P
LOS (days)[a]	11 (5.5–20.5)	12 (7.0–23.8)	23 (10–38.8)	15 (8.3–30)	n/a	0.01
ICU Admissions	44 (44%)	17 (57%)	20 (77%)	37 (66%)	2.5 (1.3–5.0)	0.008
ICU LOS (days)[a]	12 (3.3–20)	15 (6.5–21.5)	26 (10.3–40)	19 (7.5–33.5)	n/a	0.01
Patients requiring mechanical ventilation	34 (34%)	14 (47%)	17 (65%)	31 (55%)	2.4 (1.3–4.8)	0.01
Duration Mechanical Ventilation (days)[a]	14 (7.3–20)	15 (10–23.5)	28 (19–39)	21 (13.3–31)	n/a	0.008

[a] Data presented as medians with interquartile ranges.

Table 4
Correlation between lipase and D-dimer levels.

	Normal Lipase [Group 1] (N = 438)	Elevated Lipase <3x ULN [Group 2] (N = 230)	Elevated Lipase >3x ULN [Group 3] (N = 135)	All Elevated Lipase [Group 4] (N = 365)	1 vs. 4 OR (95%CI)	1 vs. 4 P
D-Dimer Above ULN	383 (87%)	208 (90%)	122 (94%)	365 (90%)	1.4 (0.87–2.1)	0.22
D-Dimer in 3rd+4th Quartile	196 (45%)	128 (56%)	77 (57%)	205 (56%)	0.63 (0.48–0.84)	0.001
D-Dimer in 4th Quartile	91 (21%)	66 (29%)	43 (32%)	109 (30%)	0.62 (0.45–0.85)	0.003

Table 5
Outcomes for select combinations of lipase and D-dimer levels.

	Normal Lipase [Group 1] & D-Dimer 1st-3rd Quartile (N = 347)	All Elevated Lipase [Group 4] & D-Dimer 4th Quartile (N = 109)	OR (95% CI)	P
LOS (days)[a]	7.0 (4–12)	10 (6–21)	n/a	<0.001
Mortality	57 (16%)	64 (59%)	7.2 (4.5–11.6)	<0.001

[a] Data presented as medians with interquartile ranges.

had a more complicated hospitalization course with a higher number of ICU admissions, longer ICU LOS, more patients requiring mechanical ventilation, and longer durations of mechanical ventilation, especially in the group with lipase >3ULN. Some of these findings such as increased ICU admissions and intubations are similar to the study by Barlass et al. [19] Although the same maybe true for the NYULH cohort, ICU and ventilator utilization data were not collected in the same manner in the EMR system, so a similar

Table 6a
Peak lipase and D-dimer values for NYULH survivors and non-survivors.

NYULH	Survivors (Lipase N = 613) (D-Dimer N = 485)	Deceased (Lipase N = 222) (D-Dimer N = 185)	P
Peak Lipase Level (IU/L)[a]	57 (29–149)	87 (38–189)	0.002
Peak D-Dimer Level (ng/mL)[a]	622 (310–2507)	4011 (876–10,001)	<0.001

[a] Data presented as medians with interquartile ranges.

Table 6b
Peak lipase and D-dimer values for NYULH and BILH survivors and non-survivors.

BILH	Survivors (Lipase N = 115) (D-Dimer N = 94)	Deceased (Lipase N = 42) (D-Dimer N = 39)	P
Peak Lipase Level (IU/L)*	37 (23–87)	51 (32–104)	0.11
Peak D-Dimer Level (ng/mL)*	1640 (872–4185)	7164 (2500–18,835)	<0.001

analysis could not be done. However, the overall LOS did not vary significantly between the two groups in the combined cohort from both health systems, with no clear explanation provided by the data analyzed. These results differ from the findings of Barlass et al. who found an increased LOS in patients with hyperlipasemia. It is possible that the LOS in severe disease was shorter due to early demise of these patients in our study, but this was not confirmed.

Further analyses revealed that a higher proportion of patients with hyperlipasemia had elevated D-dimer levels, particularly in the 3rd and 4th quartiles, as compared to patients with normal lipase levels. These patients with hyperlipasemia and elevated D-dimer had a significantly higher odds ratio for mortality. However, when controlled for D-dimer elevation, hyperlipasemia alone had little impact on survival as compared to normal lipase level. D-dimer is a soluble fibrinogen degradation product, which characteristically marks the presence of vascular thrombosis, especially in inflammatory disease states. COVID-19 infection is increasingly recognized as a multi-system inflammatory process, resulting in a cytokine storm and coagulation disorders leading to organ damage [18]. Microthrombotic injury has been reported in the post mortem examination of multiple organs in COVID 19 infection, which similarly to the pancreas, express the ACE-2 receptor. While our study is unable to identify the cause of the direct relationship, we speculate that elevated D-dimer levels among patients with hyperlipasemia may represent similar microthrombotic vascular injury occurring in the pancreas that results in elevated lipase levels but does not lead to overt clinical pancreatitis. This would be consistent with several studies that point to severity of COVID-19 infection directly corresponding to D-dimer levels in these patients [20,21]. Thus, we speculate that hyperlipasemia may reflect subclinical injury to the pancreas, and serve as a surrogate marker for poor outcomes in COVID-19 infected patients and further studies are needed to investigate this possibility. Alternatively, hyperlipasemia could represent a non-specific acute phase reactant finding in the setting of severe COVID-19 disease in patients with markedly elevated D-dimer levels.

There are several strengths of our study, most notably, the number of patients with reported hyperlipasemia. This is the highest prevalence of hyperlipasemia reported in COVID-19 patients, allowing for a more detailed analysis. The study was conducted across two major health care systems in the United States, in cities that were significantly affected, and also representing a large and geographically diverse population. This is also the first study to report poor outcomes in patients with hyperlipasemia. There are a few limitations of our study, including that this is a retrospective study and the results of this study are inherently not generalizable to other centers. There was lack of evaluation of non-pancreatic causes of lipase elevations such as renal failure or shock, even though the renal function in all groups of patients studied was similar [16,22]. However, while these additional factors may have played a role in contributing to hyperlipasemia, it also supports the presence of hyperlipasemia as a marker for disease severity and poor outcomes. Only half the patients had GI symptoms, and the clinical indications for lipase testing was not determined for the entire cohort. Also, not all patients who had COVID-19 disease had lipase levels checked, creating a potential selection bias. Moreover, even though the peak lipase level was selected for analysis, there was inadequate data on the trending of lipase levels during the hospital course to sufficiently align specific clinical events (i.e. transfer to ICU) against specific points on a patient's lipase curve. Finally, we did not examine other inflammatory markers such as ferritin, C-reactive protein, calcium levels and interleukin 6, which have shown promise in demonstrating prognostic value in COVID-19 as these were not consistently available in our study cohort for adequate analysis [23,24].

In conclusion, we report a high prevalence of hyperlipasemia, including levels >3xULN in patients with COVID-19 illness, without evidence of clinical pancreatitis. Although not a predictor, hyperlipasemia is a surrogate marker for poor outcomes in these patients. Further investigation with post-mortem evaluation of the pancreas would be important to identify if asymptomatic pancreatic injury occurs in patients with hyperlipasemia.

Declaration of competing interest

The authors of this study have no relevant conflict of interests to declare.

Acknowledgement

Awais Ahmed MD is a fellow of the Barbara Janson and Arthur Hilsinger Pancreatology Fellowship at Beth Israel Deaconess Medical Center.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.pan.2021.02.021.

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