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Lipase elevation in serum of COVID-19 patients: frequency, extent of increase and clinical value

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Abstract

Objectives: Previous studies reported lipase elevations in serum of COVID-19 patients trying to establish a causal link between SARS-CoV-2 infection and pancreatic damage. However, the degree and prevalence of hyperlipasemia was not uniform across studies.

Methods: We retrospectively evaluated 1,092 hospitalized patients with COVID-19 and at least one available lipase result. The number and frequency of patients with lipase above the upper reference limit (URL), >3 URL, and >6 URL were estimated. Correlations between lipase values and other biomarkers of organ or tissue damage were performed to identify possible extra-pancreatic sources of lipase release. The potential prognostic role of lipase to predict death and intensive care unit (ICU) admission during hospitalization was also evaluated.

Results: Lipase was >URL in 344 (31.5%) of COVID-19 patients. Among them, 65 (5.9%) and 25 (2.3%) had a peak lipase >3 URL and >6 URL, respectively. In the latter group, three patients had acute pancreatitis of gallstone or drug-induced etiology. In others, the etiology of lipase elevations appeared multifactorial and could not be directly related to SARS-CoV-2 infection. No correlation was found between lipase and other tested biomarkers of organ and tissue damage. Lipase concentrations were not different between survivors and non-survivors; however, lipase was significantly increased ($p < 0.001$) in patients admitted to the ICU, even if the odds ratio for lipase as predictor of ICU admission was not significant.

Conclusions: Lipase was elevated in $\sim 1/3$ of COVID-19 patients, but the clinical significance of this finding is unclear and irrelevant to patient prognosis during hospitalization.

Keywords: acute pancreatitis; COVID-19; lipase; SARS-CoV-2.

Introduction

As the coronavirus disease 2019 (COVID-19) pandemic progressed, numerous epidemiological data regarding primary and secondary disease manifestations were accumulated worldwide. Typical presentations consist in pulmonary symptoms up to acute respiratory failure and severe progressive respiratory distress [1]. However, cases with a variety of extra-pulmonary manifestations, such as cardiac, neurological, gastrointestinal, ocular, cutaneous, and thromboembolic conditions, have been described [2]. It has been demonstrated that the ‘severe acute respiratory distress syndrome coronavirus 2’ (SARS-CoV-2), the novel coronavirus causing COVID-19, does not target only lung type 2 alveolar cells but also any other tissue cell expressing angiotensin converting enzyme 2 (ACE2) receptor, used as cell entry receptor by the virus, and transmembrane protease serine 2 (TMPRSS2), a protein needed for successful virus entrance. ACE 2 and TMPRSS2 are co-expressed not only in some lung cell-types, but also in other organs including ileum and colon in the gut, and pancreas [3].

Among COVID-19 biochemical signs of extra-pulmonary manifestations, lipase elevations in serum have been repeatedly reported [4–12]. Some studies were critically commented [13, 14], and pooled data concisely reviewed [15, 16] and even meta-analyzed [17]. Study limitations included a modest sample size with a huge selection bias of evaluated patients, the heterogeneity of hyperlipasemia definition across the studies, and the lack of attention to lipase analytical issues. Consequently, the prevalence of hyperlipasemia could be misunderstood and its clinical significance, if any, difficult to establish. Combining the evidence that messenger RNA levels of ACE2 were found to be higher in pancreas than the lung, and the high, even though not absolute, specificity of lipase for the pancreas, the immediate hypothesis would be that SARS-CoV-2

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directly targets the pancreatic acinar cells, resulting in organ damage and thus elevation of serum pancreatic markers [18]. Alternatively, the pancreas could be involved as part of the virus-triggered uncontrollable systemic hyperinflammatory response from cytokine storm syndrome, leading to multi-organ dysfunction that may trigger progression to a lipotoxic pancreatic damage [19]. Given this uncertainty in pathophysiologic hypotheses, to understand if the enzyme elevation in COVID-19 patients has a cause-effect relationship or is just an epiphenomenon, it is first critical to evaluate in a robust way the prevalence of hyperlipasemia. Furthermore, there have been reports of development of acute pancreatitis (AP) in patients with COVID-19 infection having respiratory symptoms as well as reports of patients with AP developing hospital acquired COVID-19 or just SARS-CoV-2 infection. Clearly, causality studies should focus on the former situation only.

To our knowledge, only one very recent study evaluated the prevalence of hyperlipasemia in a consistent number of COVID-19 patients, relating the enzyme values with D-dimer and adverse outcomes [11]. The study was however multicentric, therefore suffering of some analytical and post-analytical drawbacks, i.e., use of different assays for lipase measurements or different units of measurement for D-dimer, which may introduce some ambiguity in test result interpretation [20, 21]. Furthermore, the authors did not examine for comparison other biochemical markers, such as serum albumin and lactate dehydrogenase (LDH), which consistently showed powerful prognostic value in COVID-19 [22]. Therefore, we thought it useful to examine a cohort of more than a thousand COVID-19 patients, hospitalized in our national reference center for infectious diseases during the two 2020 pandemic waves, in order to describe: (a) the number and frequency of patients with lipase above different cut-off levels, i.e., the upper reference limit (URL), 3 URL, and 6 URL; (b) correlations between lipase values and other biomarkers of organ or tissue damage, i.e., alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), γ -glutamyltransferase (GGT), LDH, and serum creatinine, to identify possible extra-pancreatic sources of lipase release; and (c) the prognostic role of lipase to predict death and intensive care unit (ICU) admission during hospitalization, when compared with the two powerful biomarkers in this respect, i.e. LDH and serum albumin. Finally, the clinical history of COVID-19 patients with peak lipase >6 URL was specifically investigated to identify possible causes of marked enzyme increase.

Materials and methods

Study population

We performed a retrospective, observational study on a cohort of adult (age ≥ 18 years old) COVID-19 patients admitted between February and November 2020 to the “Luigi Sacco” academic hospital in Milan, one of the two national reference centers for infectious diseases in Italy. All patients had clinical and/or radiologic findings highly suggestive for COVID-19 at admission and SARS-CoV-2 infection was confirmed by detection of viral RNA on nasopharyngeal material, using a real-time reverse transcription polymerase chain reaction method. Electronic records of all patients were reviewed, and those having at least one lipase result during the hospitalization period were included in the study. The Institutional Review Board approved the study (Registration No. 2020/ST/159).

Methods

Patients’ data were extracted from the hospital information systems. In addition to lipase values, results obtained on the same serum sample of the lipase peak value for ALT, AST, ALP, GGT, LDH, and creatinine were retrieved, whenever available. Furthermore, for each patient, worst values during the whole hospitalization period of LDH and serum albumin (i.e., the highest and the lowest result for LDH and albumin, respectively), previously shown being the most powerful biochemical predictors of poor outcome in COVID-19 [22], were also retrieved and lipase prognostic role compared with them.

Serum lipase was determined by a colorimetric assay using the synthetic substrate 1,2-O-dilauryl-rac-glycero-3-glutaric acid-[4-methyl-resorufin]-ester [23], manufactured by Randox Laboratories and implemented on the Alinity c platform (Abbott Diagnostics). Results showed an average measurement uncertainty $\leq 6.2\%$ at a lipase concentration of 55 U/L [24]. To increase the robustness of the URL estimate, the routine URL of serum lipase was experimentally confirmed using samples obtained from 140 apparently healthy blood donors (aged 18–65 years). Other laboratory results were obtained on the Alinity c platform using proprietary reagents and calibrators provided by Abbott Diagnostics, except for serum albumin that was determined on Alinity by using an immunoturbidimetric assay manufactured by DiAgam. Data about performance of employed methods were previously published [25–27]. Adult reference intervals (all derived from previously performed ad hoc local studies) are: AST, up to 34 U/L; ALT, up to 49 (men) and 33 U/L (women); ALP, 43–115 U/L (men), 33–98 U/L (premenopausal women), and 53–141 U/L (post-menopausal women); GGT, up to 68 (men) and 40 U/L (women); LDH, 125–220 U/L; serum creatinine, 60–105 $\mu\text{mol/L}$ (men) and 45–85 $\mu\text{mol/L}$ (women); and serum albumin, 35–50 g/L.

Data analysis

Lipase reference intervals were derived according to the Clinical and Laboratory Standards Institute C28-A3 protocol [28]. Reed’s criterion was used for outlier detection and the Shapiro–Wilk test for testing

normality of data distribution. The 95% central reference interval was determined by the nonparametric statistical method.

The number and frequency of COVID-19 patients with peak lipase results above URL, 3 URL, and 6 URL were estimated. The 3 URL threshold was selected because it corresponds to the decision level reported in the revised Atlanta classification as one of the two out of three criteria that should be met to diagnose AP [29]. As in other critically ill patients [30], moderate hyperlipasemia in COVID-19 can be however difficult to interpret because of co-existent systemic inflammation; therefore, we also applied a greater lipase cut-off (6 URL) in evaluating our patients to increase the test positive predictive value for detecting pancreatic damage.

Linear regression analyses were performed between peak lipase values and values of other biomarkers mentioned above measured contextually, and coefficients of determination (R^2), which represent the proportion of the total variation in y (lipase) that can be explained by its regression on x (other biomarkers), were obtained to relate lipase release to extra-pancreatic organ and tissue damage.

A prognostic evaluation of lipase was performed by categorizing patients according to the following outcomes: a) death during hospitalization (non-survivors) vs. hospital discharge after clinical recovery (survivors), and b) hospitalization in ICU vs. hospitalization in non-intensive wards (non-ICU). Peak lipase values were compared with worst results for LDH and albumin between patients separated in these categories. Data were reported as median with interquartile range (IQR). Differences between variables in different categories were assessed by applying the Mann–Whitney rank-sum test. Furthermore, a logistic regression analysis was used to estimate variables' odds ratios (OR) and their 95% confidence intervals (CI) in relation to the selected outcome. A p -value <0.05 denoted statistical significance. All analyses were performed using MedCalc software.

Results

In the substudy aimed to determine the reference interval for lipase, 10 outlier results from 140 samples were detected and excluded from the analysis. Using the nonparametric statistical method (Shapiro–Wilk test rejected normality of data distribution, $p=0.0011$), the following reference interval (90% CI in parentheses) was found for lipase in serum: 16 (13–18) U/L to 43 (38–46) U/L, with no sex difference. Consequently, a rounded value of 45 U/L was applied as URL for lipase to define hyperlipasemia in the following clinical study. It is important to note that this experimentally defined URL confirmed the URL used in routine setting [24], so that the estimates in term of frequency and extent of increase of lipase did not change between the daily clinical practice and the data analysis in this specific study.

During the study period, 2,168 adult subjects affected by COVID-19 were hospitalized. Of these, 1,092 (50.4%) had at least one lipase result and were enrolled in the study. Median patient age was 64 years (IQR: 52–77), 692 (63.4%)

being males. A median of two lipase determinations (range: 1–76) in the hospitalization period were requested per patient. Figure 1 shows the lipase result distribution in the COVID-19 population compared with that in healthy group used to define the lipase reference interval. Table 1 reports the characteristics of patients included in the study, together with the number and percentage of patients with peak lipase values $>URL$, $>3 URL$, and $>6 URL$. Lipase was $>URL$ in 344 (31.5%) of COVID-19 patients. Among them, 65 (5.9%) and 25 (2.3%) had a peak lipase $>3 URL$ and $>6 URL$, respectively. 64% of patients admitted to the ICU displayed increased lipase values, while values remained more frequently inside the reference interval in patients who recovered well and were hospitalized in non-intensive wards. R^2 obtained by performing regressions between peak lipase and ALT (0.01), AST (0.003), ALP (0.001), GGT (0.01), LDH (0.02), and creatinine (0.003), measured at the same time, were all ≤ 0.02 , with at least 98% of the lipase variation remaining unexplained and not dependent on damage of tissues such as liver or on renal dysfunction depicted by other biomarkers.

Median lipase peak values were significantly higher in patients admitted to the ICU during hospitalization, while no difference was found between survivors and non-survivors (Table 2). On the other hand, median values of LDH and serum albumin were significantly different for both evaluated outcomes. Accordingly, the logistic regression analysis involving lipase was performed only in relation to the ICU outcome. As shown in Table 2, the univariate analysis gave however a not significant OR for lipase, while both LDH increase and serum albumin decrease remained highly predictive of ICU admission during hospitalization.

The clinical records of patients with lipase peak values $>3 URL$ (range: 137–6379 U/L) were revised to determine if Atlanta criteria for AP diagnosis were applicable to any of these subjects and to search for other features that may possibly explain the lipase increase. For most patients, no plausible involvement of pancreas could be highlighted neither by physical examination and anamnesis nor by imaging studies, when performed. Among 25 patients with lipase $>6 URL$, a cut-off expected to increase the test positive predictive value for detecting pancreatic involvement in critically ill patients, eight patients had a single lipase determination without any risk factor or symptom suggestive for development of AP during their hospital stay. Given the lack of clinical suspicion, the medical staff decided not to proceed with further examinations. Another patient, affected both by COVID-19 and an underlying advanced breast cancer, also having a single lipase result

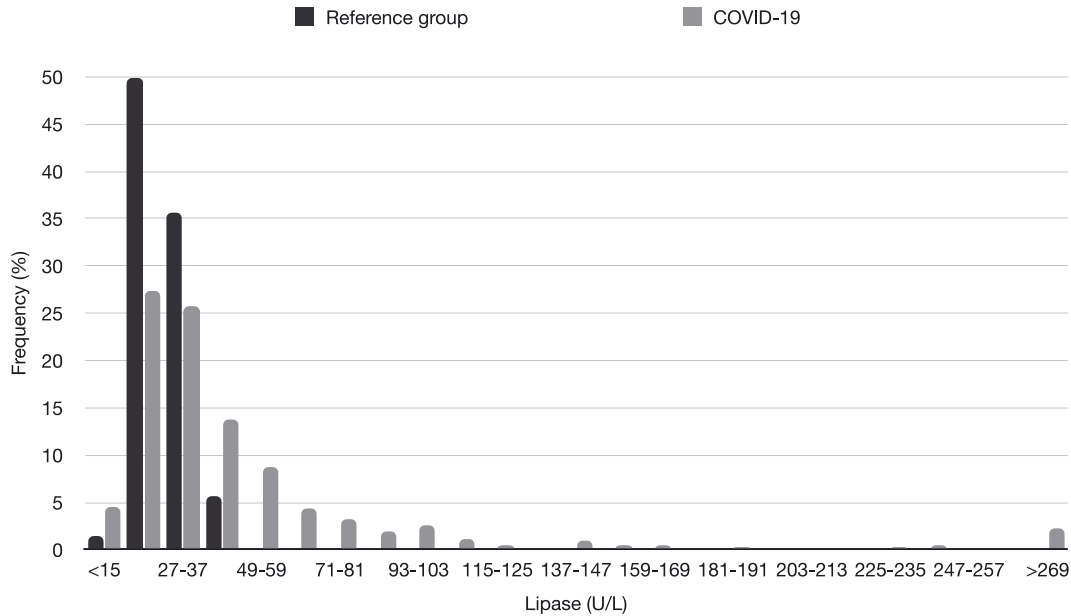


Figure 1: Comparison between lipase result distributions in the studied COVID-19 population and in the healthy group used to determine the lipase reference interval.

Table 1: Characteristics and lipase values of studied COVID-19 patients.

	Total	Non-survivors	Survivors	p	ICU	Non-ICU	p
Patients, n (%)	1,092 (100)	185 (16.9)	907 (83.1)	–	86 (7.9)	1,006 (92.1)	–
Age, years ^a	64 (52–77)	77 (69–85)	61 (50–74)	<0.001	61 (55–69)	64 (52–77)	0.08
Males, n (%)	692 (63.4)	114 (61.6)	578 (63.7)	0.59	70 (81.4)	622 (61.8)	<0.001
Lipase <URL, n (%)	748 (68.5)	112 (60.5)	636 (70.1)	0.01	31 (36.0)	717 (71.3)	<0.001
Lipase >URL, n (%)	279 (25.5)	52 (28.1)	227 (25.0)	0.38	35 (40.7)	244 (24.2)	<0.001
Lipase >3 URL, n (%)	40 (3.7)	12 (6.5)	28 (3.1)	0.02	12 (14.0)	28 (2.8)	<0.001
Lipase >6 URL, n (%)	25 (2.3)	9 (4.9)	16 (1.8)	0.01	8 (9.3)	17 (1.7)	<0.001

^aMedian and interquartile range.

(771 U/L), suddenly died the day after the lipase determination, making it impossible to ascertain if an acute inflammatory condition affecting the pancreas was in progress.

16 out of 25 patients with a peak lipase >6 URL (range: 273–6379 U/L) had multiple enzyme measurements. Among those, two were diagnosed as developing a classic AP of gallstone etiology, with typical acute abdomen and positive abdominal contrast enhanced computerized tomography examination. Both patients had a mild pulmonary COVID-19 picture, recovered, and were never admitted to the ICU. A third patient suffering of human immunodeficiency virus infection with several complications including a diffuse large B cell lymphoma showed a drug-induced AP when treated during hospitalization for COVID-19 with the anti-CD30 antibody brentuximab vedotin [31]. For the 13 remaining patients, despite the

finding of a peak lipase activity >6 URL, it was not possible to elicit history regarding abdominal pain or obtain proper imaging to evaluate the presence of pancreatic inflammation. Eight of them were however on mechanical ventilation that could have resulted in hypoperfusion, in turn believed to possibly cause AP as a complication [32]. Furthermore, in three of these mechanically ventilated patients the lipase peak (values from 459 and 638 U/L) was concomitantly detected at the start of therapies previously related, although rarely, to pancreatic injury (i.e., antibiotics such as linezolid or antiviral drugs such as remdesivir) [33, 34]. Figure 2 depicts the lipase trend of one of these three patients in parallel with the time of hospitalization and COVID-19 treatments. A drug-induced pancreatic injury could not be excluded also in a further patient treated by corticosteroids [35]. Among the remaining four patients with lipase activity >6 URL, one had acute

Table 2: Serum lipase, lactate dehydrogenase (LDH) and albumin concentrations (worst values) in COVID-19 patients included in the study and related regression analysis as predictor of admission in the intensive care unit (ICU) during hospitalization.

	Median (IQR) Non-survivors	Median (IQR) Survivors	p		
Lipase, U/L	33 (25–50)	36 (22–72)	0.16		
LDH, U/L	624 (458–811)	350 (275–464)	<0.001		
Albumin, g/L	21 (17–25)	28 (24–33)	<0.001		
	ICU	Non-ICU	p	OR (95% CI)	p
Lipase, U/L	65 (35–116)	32 (24–49)	<0.001	1.001 (0.999–1.001)	0.05
LDH, U/L	653 (517–806)	361 (280–484)	<0.001	1.003 (1.002–1.004)	<0.001
Albumin, g/L	18 (16–21)	28 (24–32)	<0.001	0.72 (0.68–0.77)	<0.001

IQR, interquartile range; OR, odds ratio; CI, confidence interval.

kidney injury likely contributing to reduced renal clearance of lipase, while for the last three, all directly admitted to the ICU from other hospitals, it was not possible to identify any known cause explaining their elevated lipase concentrations.

Discussion

Lipase measurement in serum is the recommended laboratory test to diagnose AP [36]. Increase of serum lipase activity to >3 URL, in the absence of renal failure, is a specific diagnostic finding but is however not exclusive. Lipase could be elevated in conditions other than AP, such as acute cholecystitis, gastrointestinal, and hepatobiliary disease [20]. Following the SARS-CoV-2 pandemic, several studies flourished investigating the spectrum of clinical presentations of this new disease. Multiple extra-pulmonary manifestations, often synchronous with a pulmonary picture of worsening respiratory failure, were described.

Studies reported that gastrointestinal symptoms may occur in up to 35% of COVID-19 cases [37]. Among other gastroenterology manifestations, several papers described lipase elevations in serum of hospitalized COVID-19 patients in a percentage ranging from 11 to 43% [4–12]. The wide range of frequencies reported in different studies may depend upon several aspects, starting from the population enrolled in terms of either selection criteria or number of patients, with higher frequencies estimated in larger populations [13]. Our study, the first performed monocentrically on more than one thousand COVID-19 patients, found a frequency of lipase increase of 31.5%, suggesting that approximately one third of patients hospitalized for COVID-19 illness may have abnormal lipase values. Previous authors did not give enough attention to the analytical and post-analytical aspects that may significantly influence the obtained data. Among the mentioned studies, only two explicitly reported the method used for measuring lipase [10, 12], and none experimentally derived the reference interval for lipase. Many lipase methods are commercially available, using a

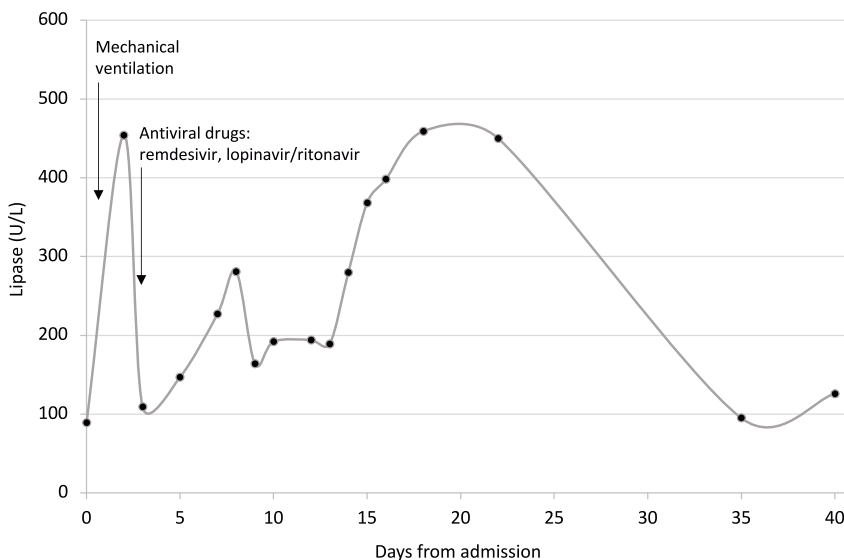


Figure 2: Lipase trend in serum of a patient in whom enzyme peaks were concomitantly detected in correspondence of COVID-19 treatments (mechanical ventilation and antiviral drugs) possibly related to pancreatic injury. Note the steeper lipase increase following the start of mechanical ventilation and the slower enzyme increase possibly related to the antiviral therapy administration, which needed approximately two weeks to produce the peak of lipase release.

wide variety of substrates and different detection technologies [20]. Unfortunately, these methods may show different analytical specificities, possibly contaminating study results with spurious enzyme elevations from extra-pancreatic sources. For instance, in the Ortho Clinical Diagnostics assay employed by Pezzilli et al. [12], the substrate is likely to be more specific for intestinal than pancreatic lipase potentially altering the lipase information as test of pancreatic injury [38]. Furthermore, lipase is among the more poorly standardized laboratory tests, so misdiagnosing AP and, more widely, pancreatic injury is a real possibility, especially if clinicians receive results from different measuring systems and interpret them according to cut-offs (i.e., URL or multiple of URL) that have not been properly derived. This may also lead to confusion in interpreting results of other studies and to the impossibility of extending study results to different settings.

Despite the confirmed high frequency of mild increases in serum lipase concentrations of COVID-19 patients, the clinical meaning of this biochemical sign is still object of wide controversy. Although in our study about two-thirds of patients admitted to the ICU displayed increased lipase values, it was clear that an isolated lipase >URL in COVID-19 had no clinical significance. Applying multiples of URL as cut-offs is the usual approach for increasing the positive predictive power of the test. In our study, a >3 URL cut-off decreased to around 6% the amount of hyperlipasemic COVID-19 patients to be evaluated for pancreatic injury and possibly fulfilling the Atlanta criteria for AP diagnosis. However, no patients with lipase between 3 and 6 URL showed typical findings of pancreatic inflammation neither by physical examination nor by imaging studies, when performed. As in all previous studies, the imaging evaluation of pancreas in this group of patients was however not addressed systematically but just based on clinical suspicion, bringing about a potential classification bias in the study population. The reported frequency of lipase elevations exceeding 3 URL was not surprising because it is known that critically ill patients may more frequently have hyperlipasemia [30]. These elevations, especially when coupled with hypotension and/or respiratory impairment, have been considered as the pancreatic manifestations of a systemic hyperinflammatory state and multi-organ failure.

Even when increasing the lipase cut-off to >6 URL, our patients rarely presented with typical abdominal symptoms and radiological findings of overt AP. Three patients (0.27%) had AP of gallstone or drug-induced etiology not primarily related to COVID-19. In others, the etiology of

lipase elevations appeared multifactorial and could not be directly related to SARS-CoV-2 infection itself. A recent large American study found a point prevalence of 0.27% of AP among patients hospitalized with COVID-19 [39]. Therefore, our results fully confirm this larger report unable to show an increase in the incidence of AP during the COVID-19 pandemic. Our experience demonstrates that etiology of markedly increased lipase in COVID-19 patients should be carefully investigated as several conditions in these patients, such as mechanical ventilation or shock resulting in hypoperfusion, can also develop acute pancreatic injury as a complication [30, 32]. One of the proposed mechanisms for pancreatic injury in these patients is that mechanical ventilation increases intrathoracic pressure, decreases venous return, and induces a relative splanchnic ischemia [40]. Furthermore, the available therapies used for the COVID-19 treatment may cause pancreas injury, including corticosteroids, antiviral drugs, such as remdesivir, and antibiotics, such as linezolid [33–35]. These drugs may account for the rise of pancreatic lipase rather than it being the direct effect of the virus on the pancreas.

Regardless of etiology, and more importantly, it remains to be determined if the increases of lipase values in COVID-19 patients have a relationship with disease severity and may independently predict clinical outcomes. A recent meta-analysis found that COVID-19 patients with hyperlipasemia, defined as any elevation of lipase above the URL, were at an approximately three-fold higher risk of poor clinical outcomes, including need for ICU admission, mechanical ventilation, or death [17]. This meta-analysis however suffered of major limitations, just considering four studies with heterogeneous populations, and many confounders, such as a modest sample size (a total of 756 patients) and a possible underestimation of the prevalence of hyperlipasemia (11.7%) due to a lack of testing and nonreporting of the data for many patients. In our study population, no difference in lipase values was found between survivors and non-survivors, suggesting that lipase determination, unlike other consolidated biomarkers such as LDH and serum albumin [21, 22, 27], is not useful for prediction of in-hospital death in COVID-19. Differently, patients admitted to the ICU had significantly higher lipase values. As discussed above, conditions, such as hyperinflammatory state, multi-organ failure, respiratory impairment, mechanical ventilation, and multi-drug therapies, which frequently affect patients admitted to the ICU, may result in pancreatic suffering of various degrees. The heterogeneity of causes may however explain the non-significance of OR for lipase in predicting ICU admission during hospitalization.

Conclusions

Despite the various hypotheses about the pathophysiology of a pancreatic injury resulting from SARS-CoV-2 infection [18, 19], this association remains uncertain and not-well defined, the involvement of the pancreas appearing not a peculiar prerogative of SARS-CoV-2 and actual evidence of clinical AP secondary to this virus more than dubious. Our study was unable to find a causality link between COVID-19 and acute pancreatic inflammation. For most, if not all, patients it seemed unlikely that the observed lipase elevations, even when of marked entity, were due to a direct pancreatic injury mediated by the virus rather than to a concomitant presence of other factors causing pancreatic suffering. Furthermore, the finding of elevated lipase results was unable to predict a poor outcome in COVID-19 patients during hospitalization. Akin to the described AST increases [41], lipase elevations in COVID-19 appear to be a disease nonspecific epiphenomenon.

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