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High lipasemia is frequent in Covid-19 associated acute respiratory distress syndrome

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ABSTRACT

Background: Covid-19 is a rapidly spreading viral disease that can cause severe acute respiratory distress syndrome (ARDS). Besides the lungs it can also affect other organs like the heart or the liver. Whether there is a pancreatic manifestation as well is currently unclear.
Methods: and aims: We prospectively collected patient information of patients with Covid-19 associated ARDS in a registry (COvid Registry REChts der Isar intensive care Trial – CORRECT) and analyzed this patient cohort for signs of acute pancreatitis (e.g. lipase activity >3 times the upper limit).
Results: 12/38 (31.6%) patients with Covid-19 associated ARDS had a serum lipase activity >180 U/l. Median lipase activity was 422 U/l (186–1127). No patient showed typical findings of acute pancreatitis on imaging studies. On hemodynamic monitoring no patient had signs of intravascular fluid demand regarding MAP, GEDVI and therapy with vasopressors. To avoid worsening respiratory function no treatment with crystalloids was initiated. Lipasemia was not explained by gastroenteritis or renal insufficiency, occurred before as well as after viral clearance and 16.1 ± 6.0 days after the first symptoms. No patient developed severe acute pancreatitis during the follow up period of 35.8 ± 8.3 days.
Conclusion: High lipasemia without typical signs of acute pancreatitis is a frequent finding in severe Covid-19 associated ARDS. Considering the markedly high levels of serum lipase activity, we think impaired microcirculation in severely ill patients can explain this finding rather than extra-pancreatic co-morbidities (UTN: DRKS00021612).

Introduction

Corona virus disease 2019 (Covid-19) is a rapidly spreading viral disease caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) that challenges health care systems all around the world. The main site of infection are the alveolar cells of the lungs, around 5% of the patients develop a severe disease with acute respiratory distress syndrome (ARDS) and 71% of these critically ill patients require mechanical ventilation [1,2]. However, SARS-CoV-2 can affect other organs as well. Acute kidney injury, myocarditis and liver dysfunction are frequent complications of severe SARS-CoV-2 infections [3–5]. In autopsy studies the SARS-CoV-1 virus of the same virus family was found in pancreatic tissue. Furthermore pancreatic enzymes like lipase and amylase are frequently elevated in patients with SARS-CoV-2 infections [6,7]. Viral infections are a rare but frequently described etiology of acute pancreatitis. Mainly mumps, coxsackie B and hepatitis viruses are known to cause acute pancreatitis [8]. However, treatment of acute pancreatitis with volume expansion would hamper treatment of Covid-19 associated ARDS.

Nevertheless it has not been evaluated so far whether SARS-CoV-2 only affects the pancreas and causes pancreatic tissue damage or whether it really induces a typical acute pancreatitis requiring volume treatment.

With this study we want to analyze if severe SARS-CoV-2 infections are associated with acute pancreatitis and if these patients require treatment for acute pancreatitis.

Materials and methods

We prospectively collected information about patient history, diagnostics and treatment of patients who were treated with severe Covid-19 at our intensive care unit (ICU) in a central registry.

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The so called 'COvid Registry RECht der Isar intensive care Trial – CORRECT' was approved by the ethical review board of Technische Universität München (Project 178/20 S) on 30/03/2020.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Written, informed consent was obtained from each patient or its legal representative included in the study. All authors had access to the study data and reviewed and approved the final manuscript. The study is registered in the WHO approved German Clinical Trials Register (DRKS - https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00021612) with the universal trial number DRKS00021612.

Klinikum rechts der Isar der Technischen Universität München is a tertiary referral center in Munich, southern Germany.

Patients

Acute pancreatitis is defined according to the revised Atlanta classification [9]. During the SARS-CoV-2 pandemic we established a standard laboratory panel for all patients at admission on ICU and on day 3 and 7 every week thereafter. This panel includes lipase serum activity. Our laboratory reference range is 0–60 U/l. Patients with a lipase activity at least three times greater than the upper limit of normal (>180 U/l) during their treatment of Covid-19 at our ICU in March and April 2020 were recruited for this analysis.

The exclusion criteria are as follows: a pre-existing pancreatic disease; patients unable to provide informed consent to participate in the study including those less than 18 years of age; and those who had received abdominal surgery within the last year.

As control group serve 38 consecutive SARS-CoV-2 negative patients on mechanical ventilation with ARDS that did not have acute pancreatitis or history of chronic pancreatitis and were treated at our ICU from March till June according to the same standards that were set for the Covid-19 patients.

Within 24 h after lipase elevation >180 U/l all patients received either a computed-tomography (CT) scan or an abdominal ultrasound or both to look for typical findings of acute pancreatitis and to exclude bile duct obstruction in case of elevated serum levels of bilirubin, alkaline phosphatase (AP) or gamma-glutamyltransferase (GGT). The indication for an ultrasound or a CT scan was a clinical decision and is not part of the study protocol. The diagnosis of a SARS-CoV-2 infection was established by PCR of a nasal swab or bronchoalveolar fluid. Viral clearance is defined as two consecutive negative PCR test of nasal swabs or bronchoalveolar fluid.

Besides invasive arterial pressure measurement transpulmonary thermodilution and pulse contour analysis was used for extended hemodynamic monitoring (PiCCO-2 and PulsioFlex with PiCCO module, PULSION Medical Systems SE, Feldkirchen, Germany). Decreased intravascular volume was assessed using the global end-diastolic volume index (GEDVI – reference range 680–800 ml/m^2) and in patients with pressure controlled ventilation and sinus rhythm using the stroke volume variation (SVV – reference range <10%).

Serum lipase activity

Lipase serum activity was measured using the LIPC lipase colorimetric kit on a cobas c 701/702 analyzer (Roche Diagnostics International AG, Rotkreuz, Swiss) according to the manufacturer's instructions. In this assay triglyceride - cholic acid - mixed micelles (1,2-O-Dilauryl-rac-glycero-3-glutaracid-(6-methylresorufin)-ester, tauro- and Na-desoxycholat) are the substrate of lipase and co-lipase is added as cofactor in the reagent. In addition, pancreatic lipase acts at the interface of the hydrophobic substrate and the aqueous phase, a condition that is present in the reaction mixture of the LIPC reagent [10,11]. Co-lipase activates pancreatic lipase but not extra-pancreatic lipases. As activities of adipose triglyceride lipase or lipoprotein lipase are not inhibited, interference of extra-pancreatic lipases with the assay cannot be excluded. Our laboratory reference range is 0–60 U/l.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 25 (SPSS Inc, Chicago, Illinois, USA). Samples were checked for normal distribution by the Shapiro-Wilk test. Normally distributed parameters are presented as mean ± standard deviation and accordingly, descriptive data without normal distribution as median and range. For the analysis of quantitative variables, the *t*-test and the Mann-Whitney-U test were employed. All statistical tests were two-sided with a level of significance (p-value) of 5%.

Results

In total 40 patients with severe Covid-19 were treated at our ICU. Two patients or their legal representatives declined informed consent and 38 patients were included in the CORRECT registry in March and April 2020. Patient characteristics of the patients with Covid-19 associated ARDS and the control group are displayed in Table 1. None of the recruited patients is still on ICU.

In total, 10/38 (26%) of the Covid-19 positive patients had a lipase serum activity between 60 and 180 U/L (mean 104.5 ± 29.6) and 12/38 patients (31.6%) developed relevant lipasemia with serum activity levels above three times the upper limit (>180 U/l), 10 male and 2 female patients. Patient characteristics of the 12 patients with Covid-19 associated ARDS are summarized in Table 2. Lipasemia with a serum lipase activity of >180 U/l was significantly more frequent in patients with Covid-19 associated ARDS than in the control group (12/38 [31.6%] versus 2/38 [5.3%], p = 0.003). There was no association between lipasemia >180 U/l and outcome parameters like days on ventilation or mortality in the 38 patients with Covid-19. All patients were ventilated due to respiratory failure, but in 2/12 (16.7%) lipasemia manifested after extubation. In 5/12 (41.7%) patients lipasemia occurred after virus clearance. Highest lipase activity occurred in 10/12 (83.3%) patients after the highest inflammatory activity according to C-reactive protein (CRP) serum levels and the time between highest lipase and highest CRP serum levels was 5.2 ± 6.7 mg/dl days. Fig. 1 shows the time course of serum lipase and CRP levels.

At the highest serum lipase activity 2/12 (16.7%) patients had elevated creatinine levels (1.5 and 2.7 mg/dl) and one of these two patients was on hemodialysis because of anuresis. At the same time, 1/12 (8.3%) patients suffered from diarrhea as additional gastrointestinal symptom.

Patients with lipasemia were significantly longer on mechanical ventilation than patients with Covid-19 associated ARDS and no lipasemia >180 U/l (60.1 ± 60.1 days versus 9.1 ± 7.9 days, p < 0.001). One patient had the highest serum lipase activity at the time of intubation, two patients after extubation. In the remaining 9 patients mean time from intubation to highest serum lipase activity was 9.7 ± 4.7 days.

As 9/12 (75%) patients developed high lipase levels during sedation for mechanical ventilation only three patients were able to adequately report pain. Two of these three (66.6%) patients reported acute abdominal pain. Clinical parameters to evaluate symptoms of acute pancreatitis are displayed in Table 3. In this patient cohort only noradrenalin was administered as vasopressor. Hemodynamic parameters did not differ significantly between the day with the highest serum lipase activity and 24 h later (MAP: p = 0.07; GEDVI: p = 0.95; vasopressor dose: p = 1.00). At the

Table 1
Characteristics of the patients with Covid-19 associated ARDS and the control group of patients suffering ARDS without Covid-19 (ARDS: acute respiratory distress syndrome, BMI: body mass index).

	Covid-19 associated ARDS	control group	P
n	38	38	
age	68.5 (26–85)	67 (22–88)	0.819
female/male	8/30	14/24	0.129
BMI	26.2 ± 8.4	25.0 ± 4.5	0.675
smoker	9/38 (23.7%)	11/38 (28.9%)	0.602
alcohol abuse	4/38 (10.1%)	8/38 (21.1%)	0.208
mortality	12/38 (31.6%)	10/38 (26.3%)	0.613
Lipasemia >60 and < 180 U/l	10/38 (26.3%)	12/38 (31.6%)	0.256
lipasemia > 180 U/l	**12/38 (31.6%)**	**2/38 (5.3%)**	**0.003**

Table 2
Characteristics of the patients with Covid-19 associated ARDS and lipase serum activity >180 U/l versus <180 U/L (BMI: body mass index).

Patients with Covid-19 associated ARDS and lipase activity		>180 U/l	<180 U/l	P
Age (range)		70.5 (51–84)	60.5 (26–84)	0.710
Gender m:f		6:1	4.3:1	0.709
BMI		26.9 ± 6.0	24.9 ± 7.7	0.809
Days till viral clearance		22.5 ± 7.3	17.3 ± 10.4	0.149
Follow up in days		35.8 ± 8.3	29.8 ± 15.3	0.135
at last follow up consultation	Necrotic collection or walled of necrosis	0/12 (0%)		
	serum glucose level > 200 mg/dl	0/12 (0%)		
Symptoms				
	Fever	7/12 (58.3%)	19/26 (73.1%)	0.363
	Malaise	7/12 (58.3%)	21/26 (80.8%)	0.144
	Dyspnea	5/12 (41.7%)	15/26 (57.7%)	0.358
	Cough	3/12 (25%)	15/26 (57.7%)	0.060
	Acute renal failure	3/12 (25%)	5/26 (19.2%)	0.685
	Diarrhea	1/12 (8.3%)	5/26 (19.2%)	0.392
	Somnolence	1/12 (8.3%)	0/26	0.316
Comorbidities				
	Hypertension	5/12 (41.7%)	21/26 (80.8%)	**0.016**
	COPD or lung fibrosis	3/12 (25%)	5/26 (19.2%)	0.685
	Chronic kidney disease	2/12 (16.7%)	7/26 (26.9%)	0.489
	Diabetes	1/12 (8.3%)	11/26 (42.3%)	**0.036**
	No comorbidities	3/12 (25%)	3/26 (11.5%)	0.290
	Others include:	leukemia, lymphoma, chronic heart failure, hepatic steatosis, pericardial effusion, alcohol abuse		
Organ failure				
	Respiratory failure	12/12 (100%)	26/26 (100%)	
	Days on mechanical ventilation	19.3 ± 11.7	14.7 ± 12.1	0.053
	Renal failure	7/12 (58.3%)	11/26 (42.3%)	0.358
	Liver failure	2/12 (16.7%)	3/26 (11.5%)	0.664

highest lipase activity 11/12 (91.7%) patients were under hemodynamic monitoring.

Discussion

The largest group of pathogens causing infectious pancreatitis are viruses. In former times it was mumps but more recently hepatitis B virus, particularly after liver transplantation, accounts for the majority of reported viral pancreatitis cases. One theory is, that inflammation and edema leads to the destruction of pancreatic acinar cells [8,12]. In our patient cohort, high serum lipase activity of up to 1100 U/l suggests pancreatic acinar cell damage. SARS-CoV-2 interacts with angiotensin-converting enzyme 2 (ACE2) to enter human cells [13,14]. While ACE2 is expressed on pancreatic islet β-cells, reports of ACE2 expression on acinar cells are the exception [15,16]. Only recently one Chinese study described ACE 2 expression on both pancreatic acinar and islet cells [17]. Without high glucose levels and new onset diabetes in our patients an isolated infection of β-cells seems unlikely.

By definition all 12 patients fulfilled already one criterion for the diagnosis of acute pancreatitis [9]. But only two patients reported abdominal pain and no patient had typical imaging findings. Consequently, the criteria to diagnose acute pancreatitis according to the revised Atlanta classification were fulfilled in only two cases. Because sedated patients can hardly report pain, examining those patients for typical symptoms of acute pancreatitis is difficult. About 15–20% of the patients with acute pancreatitis suffer a severe course of the disease. In the early phase of acute pancreatitis patients are mainly at risk of a systemic inflammatory response with organ failure [9,18]. To prevent a severe pancreatitis, appropriate treatment consists of intravascular volume expansion by crystalloids. Excessive fluid administration, however, can worsen respiratory function in patients with Covid-19 associated ARDS [19]. We monitored our sedated patients for intravascular volume

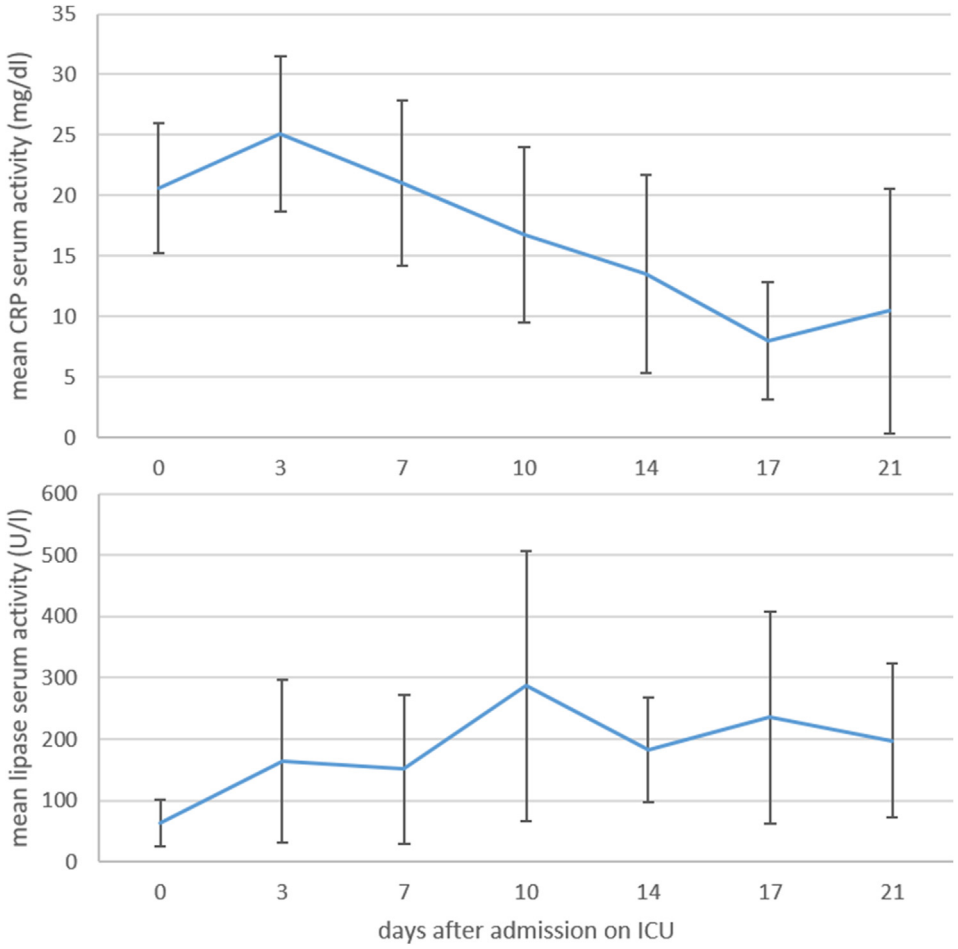

Fig. 1. Time course of serum lipase (U/l) and C-reactive protein (CRP in mg/dl) levels with error bars (95% confidence interval).

Table 3
Hemodynamics and clinical parameters of the patients with a lipase serum activity >180 U/l (GGT: gamma-glutamyltransferase; AP: alkaline phosphatase; CRP: C-reactive protein; MAP: mean arterial pressure; GEDVI: global end-diastolic volume index; SVV: stroke volume variation).

Laboratory findings	reference range	unit	
highest serum lipase activity	13–60	U/l	422 (186–1127)
onset of symptoms to highest lipase level		days	16.1 ± 6.0
highest CRP level	<0.5	mg/dl	33.0 ± 8.9
hematocrit at highest lipase activity		%	31.1 ± 4.6
Physical examination			
abdominal tenderness and guarding		2/12 (16.7%)	
Imaging			
Computed tomography		4/12 (33.3%)	
- with contrast		3/12 (25%)	
Abdominal Ultrasound		10/12 (83.3%)	
Signs of pancreatitis		0/12 (0%)	
Choledocholithiasis		0/12 (0%)	
Dilated biliary duct		0/12 (0%)	
Hemodynamic monitoring			
at highest lipase activity	MAP	mmHg	84 ± 8.6
	Therapy with vasopressors		5/12 (41.7%)
	Noradrenalin dose (μg/h)		167 (0–800)
	GEDVI		822 (635–1279)
	Volume expansion with crystalloids		0/12 (0%)
24 h after highest lipase activity	MAP	mmHg	89 ± 16.6
	Therapy with vasopressors		6/12 (50%)
	Noradrenalin dose (μg/h)		148 (0–800)
	GEDVI	11/12	806 ± 162

demand with transpulmonary thermodilution. As none of our patients showed signs of hemoconcentration or signs of intravascular fluid demand on extended hemodynamic monitoring, we avoided additional fluid administration as treatment of acute pancreatitis in this patient cohort. Without further clinical signs of severe acute pancreatitis, we relied on abdominal ultrasound as preferred imaging modality for infection control reasons and only performed a CT scan if indicated for other reasons. Liu et al. reported that 7% of the patients with severe Covid-19 had typical imaging findings of acute pancreatitis like focal enlargement or dilatation of the pancreatic duct [17]. In contrast, none of our patients had typical imaging signs of pancreatitis. However, Lax et al. reported that, without clinical suspicion, focal pancreatitis with necrosis of pancreatic parenchyma was found in 4/11 (36%) patients in an autopsy series of 12 patients with Covid-19 [20]. So laboratory and radiologic diagnostics have their limitations and pancreatic tissue damage in patients with severe Covid-19 may occur even without typical clinical signs. Taken together without signs of inflammation on ultra sound or CT imaging and without the typical clinical course, acute pancreatitis seems an unlikely cause of hyperlipasemia in patients with Covid-19 associated ARDS. Several recent publications also report hyperlipasemia in patients with Covid-19 and support this conclusion. Although Wang et al. refer hyperlipasemia to pancreatic injury patterns, Barlass et al. and McNabb-Baltar et al. do not report typical signs of pancreatitis in patients with hyperlipasemia and Covid-19 in their cohorts. Due to the retrospective design lipase was measured as decided by the clinician and not according to a predefined protocol. So both studies are limited by a selection bias and results regarding the outcome of patients with hyperlipasemia are arbitrary [7,21,22]. Nevertheless, close monitoring of patients with hyperlipasemia remains important in case a patient actually develops an acute pancreatitis or in case of concomitantly elevated biliary markers a bile duct obstruction. In addition, lipasemia usually occurred after the highest systemic inflammatory activity and in both, patients who were persistently SARS-CoV-2 positive, and patients, who had cleared the virus. If hyperlipasemia occurs independently from viral clearance, one has to question whether hyperlipasemia actually results from acinar damage by infection of the pancreas by SARS-CoV-2. On the contrary, recent reports suggested pancreatic tissue damage because of mild elevation of pancreatic enzymes – mainly amylase – in patients with Covid-19 [7,17]. Unlike this publication we analyzed not amylase but lipase. According to our study hyperlipasemia is a frequent finding in Covid-19 associated ARDS. Almost every third patient with Covid-19 associated ARDS had a lipasemia of more than three times the upper limit of normal, which is significantly more frequent than in a control group of patients with ARDS of other causes. However, amylase and lipase can be secreted by other organs than the pancreas like the lungs [23]. Also, increased serum activity of amylase and lipase are reported in conditions like severe gastroenteritis, diabetes, after cardiovascular surgery, trauma, burns and, because of the renal clearance of pancreatic enzymes, in renal insufficiency [24–27]. While trauma, burns and surgery were not present in our patient cohort, SARS-CoV-2 is known to affect the gastrointestinal tract and serum lipasemia might be the result of gastrointestinal inflammation. But the fact that only one patient had gastrointestinal symptoms like diarrhea and five patients developed hyperlipasemia after virus clearance compromises this explanation. In addition, at the time of the highest lipase activity only one patient had renal insufficiency. Apart from pancreatic lipase, serum lipase activity can derive from extra-pancreatic lipases like adipose triglyceride lipase or lipoprotein lipase. Obesity is a risk factor for a severe course of Covid-19 and adipose tissue expresses ACE2 as well. But it still has to be elucidated whether SARS-CoV-2 affects adipose cells and whether affection of adipose cells by SARS-CoV-2 would result in the release of adipose triglyceride lipase. In addition our patient cohort was overweight but not particularly obese according to the definition by the world health organization and BMI did not differ significantly between the Covid-19 and the control group. Although, there are case reports of serum lipase levels above 3 times the upper limit of normal e.g. in severe infections or diabetes, extra-pancreatic causes of elevated pancreatic enzymes usually result in mild elevation of lipase activity [25,28]. Also, most of the potential extra-pancreatic causes of lipasemia are present in our control group as well. Taken together, we think that the frequently increased serum lipase activity of up to 1100 U/l in Covid-19 associated ARDS is unlikely to be caused by extra-pancreatic co-morbidities alone.

Impaired microcirculation is a well accepted concept in the pathogenesis of acute pancreatitis [29,30]. Regarding the time on mechanical ventilation as surrogate marker for severity of Covid-19 associated ARDS, hyperlipasemia is associated with a severe course of the infection. In ARDS capillary leakage and in severe cases reduced systemic perfusion are typical findings. A recent autopsy study reported pronounced endothelial damage and widespread capillary microthrombi in Covid-19 associated ARDS [31]. Impaired microcirculation by capillary leakage, reduced end-organ perfusion and endothelial damage with capillary microthrombi could result in pancreatic cell dysfunction and is a possible explanation of hyperlipasemia in Covid-19 associated ARDS.

Finally, further studies preferably including histology samples are required to clarify the actual cause of hyperlipasemia in Covid-19 associated ARDS.

To our knowledge this is the largest reported patient cohort of patients on intensive care unit with severe Covid-19 associated ARDS and hyperlipasemia. Also, we describe not only an indefinite laboratory finding of elevated pancreatic enzymes but evaluate clinically relevant increased serum lipase activity and its consequence for the management of the patients. However, by the nature of its design this study has some limitations. As a monocentric, observational trial it is prone to a selection bias. Correlation to autopsy findings could clarify the cause of hyperlipasemia and if there is a direct pancreatic infection by SARS-CoV-2. Finally, interference of extra-pancreatic lipases with the lipase assay cannot be totally excluded and our results do only refer to severe Covid-19 cases.

Conclusion

High lipasemia without typical signs of acute pancreatitis is a frequent finding in severe Covid-19 associated ARDS. Considering the markedly high levels of serum lipase activity, we think impaired microcirculation in severely ill patients can explain this finding rather than extra-pancreatic co-morbidities.

Author contributions

Guarantor of the article: SR.
SR, AH, RMS, WH and TL contributed to the design of the study.
SR, AH and TL were responsible for data collection.
SR analyzed the data.
SR drafted the manuscript; all authors edited this and approved its final version.

Declaration of competing interest

Tobias Lahmer received travel grants from Gilead, Pfizer and MSD. Sebastian Rasch received travel grants from Gilead. Wolfgang Huber collaborated with Pulsion Medical Systems SE, Feldkirchen,

Germany as member of the Medical Advisory Board. All other authors declare that there is no conflict of interest.

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Abbreviations

ACE2: angiotensin-converting enzyme 2
AP: alkaline phosphatase
ARDS: acute respiratory distress syndrome
BMI: body mass index
Covid-19: Corona virus disease 2019
CRP: C-reactive protein
GEDVI: global end-diastolic volume index
GGT: gamma-glutamyltransferase
ICU: intensive care unit
MAP: mean arterial pressure
SARS-CoV-2: severe acute respiratory syndrome corona virus 2
SVV: stroke volume variation