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Research Article

The Effect of COVID-19 Infection on Severity of Acute Pancreatitis: A Prospective Cohort Study

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ABSTRACT

Background: Coronavirus Disease 2019 (COVID-19) is multisystemic disorder. It uses angiotensin converting enzyme 2 (ACE2) to gain access to human cells. The ACE2 receptor is present on cell types, one of them is pancreatic cell.
This study aimed to assess the impact of COVID 19 infection on severity of acute pancreatitis (AP).
Subjects and Methods: A prospective cohort study that was conducted at a major teaching hospital. The study group included all cases of AP with COVID 19. Medical records of randomly selected fifty cases of AP presented one year before COVID 19 pandemic with matching months of the year were considered as control. A comparison of the effect of COVID 19 on the severity of AP was done by measuring Glasgow and revised Atlanta scores.
Results: 37 cases of COVID 19 patients developed AP in this study. The serum calcium, and albumin were lower, while blood urea, sugar, and Glasgow score all were higher in cases of COVID 19 than control. Follow up, showed that 17 (19.5%) of the cases developed severe pancreatitis, 76.5% of severe cases of AP had COVID 19 on comparison to control. COVID 19 is an independent predictor for severity of AP.
Conclusions: COVID 19 is an independent predictor for severity of AP. More directed care to the cases of COVID 19 with superimposed AP, as they prone to develop severe form. Future studies to examine the effect of COVID 19 antiviral therapy on the severity of AP is recommended.

Introduction

The Coronavirus Disease of 2019 (COVID-19) is caused by the RNA virus(1,2). The respiratory symptoms are the most common clinical presentations of COVID-19, but as the cases of this pandemic increased across the globe, other presentations evolved, and it is now considered as a multi-organ disease(3).

COVID-19 has been shown to induce a range of inflammatory conditions in different organs, including the pancreas. Several studies have reported cases of COVID-19 patients developing acute pancreatitis(4-6). The underlying mechanisms linking COVID-19 and pancreatitis are still unclear, but it has been suggested that the virus

may directly infect pancreatic cells or trigger an immune response that leads to pancreatic inflammation(6,7). As in previous types of corona disease the virus had the ability to invade human cells by linking to the ACE2 receptors(8). Its attachment to these receptors on alveolar cells of the lung lead to its injurious effect. The expression of ACE2 receptor not exclusive to the lungs but also found on the cells of many organs and the pancreas is one of these organs(9). The pancreatic tissue had been found to harbor high levels of ACE2 mRNA to level exceed what found in the lung(9). Affinity of the virus to the ACE2 gates would lead to pancreatic injury(9). COVID-19-associated pancreatitis may also be linked to other inflammatory conditions that affect the pancreas, such as cytokine storm syndrome, which can cause systemic inflammation and damage to multiple organs(7).

Aggravated immune response was found in cases of severe COVID-19(10). To note that severe form of pancreatitis usually associated with elevated serum level of interleukin-6 (11), also the greatest pancreatic injury found in the severe cases of COVID-19 disease than the mild ones, this suggesting the link between the effect of immune alteration in the form of cytokine storm and severity of pancreatitis (9).

Severity of COVID 19 infection were investigated by many authors using radiological scoring as suggested by Wasilewski et al(12) or clinical scoring suggested by Son et al(13). The clinical scoring includes vital signs and level of consciousness, cases scored less than 5 were mild those with score 5 or 6 were moderate, and score of 7 or more considered severe cases(13).

This study aims to estimate the relation of COVID 19 infection to the severity of acute pancreatitis and to find the difference in AP course in the era of COVID 19.

Subjects and Methods

A prospective cohort study that conducted at a major teaching hospital, Iraq-Baghdad.

All cases of pancreatitis with COVID 19 infection that were admitted, over the period extended from 1st of April 2020 till the 1st of November 2021 (nineteen months) were included in the study.

Medical records of randomly selected fifty cases of acute pancreatitis admitted to above mentioned hospital one year before COVID 19 pandemic (with matching the months of admission done to overcome selection bias) considered as control.

Cases of acute on chronic pancreatitis, abdominal trauma, hypertriglyceridemia, infections other than COVID 19 were excluded from the study.

All participants were reviewed with recording the demographical information, past medical, surgical, drug and social histories, presenting illness vital signs, severity of COVID 19 infection were recorded depending on patient charts before development of AP, this done by using scoring system suggested by Son et al(13) into mild, moderate, and severe.

All participants subjected to the following investigations: real time polymerase chain reaction (RT-PCR) for diagnosis of COVID 19 infection, S. amylase, S. lipase for diagnosis of pancreatitis, if clinical features suggestive of AP but S. lipase does not elevate three times above the reference range the CT abdomen with IV contrast would be requested. Abdominal ultrasound for diagnosis of gallstone pancreatitis and if ultrasound show no gallstone magnetic resonance cholangio-pancreato-graphy (MRCP) done if the patient condition permits. Cases with no radiological signs of gallstone pancreatitis with no alcohol intake history then idiopathic pancreatitis considered the diagnosis.

Scoring of prediction of severity of pancreatitis was done using Glasgow criteria within first 48 hours by obtaining arterial blood gas analysis to estimate PaO2, WBC, S. calcium, blood urea, S. LDH, S. AST, S. albumin and blood sugar. Cases were followed for the first 4 weeks for reporting of complications, the final outcome of severity was divided according to revised Atlanta classification into: “mild (no organ failure, and no local complications), moderate (transient organ failure with or without local complications), and severe (permanent organ failure)”(14).

Data were compared according to the COVID 19 infection into group A (COVID 19 RT-PCR positive) and group B (control).

Group A further divided according to the severity of COVID 19 infection into A1: mild, A2: moderate, and A3: severe.

Definitions:

Acute pancreatitis: defined by the presence of two of three criteria (epigastric abdominal pain relived by leaning forward, three times elevated serum lipase, or radiological diagnosis using contrast enhanced CT).

local complications were defined as “radiological diagnosis of acute peripancreatic fluid collection, pancreatic pseudocyst, acute necrotic collection, and walled-off necrosis”. (15)

Organ failure was defined as “failure of at least one of the three organ systems (respiratory, cardiovascular, and renal). For each organ system, failure defined as score of two or more according to modified Marshall scoring system”(15).

Table 1: Modified Marshall scoring system(15).

Organ system	0	1	2	3	4
Respiratory (PaO2/FiO2)	>400	301–400	201–300	101-200	≤101
Renal (serum creatinine, mg/dl)	<1.4	1.4-1.8	1.9-3.6	3.6-4.9	>4.9
Cardiovascular (SBP, mmHg)	>90	<90, fluid responsive	<90, fluid nonresponsive	<90, pH <7.3	<9, pH <7.2

Statistical analysis: Data were introduced to IBM-SPSS v26 and results were presented in the form of tables, normality checked using “Shapiro wilk test”, p value was estimated using Chi square, fisher exact, student t test, and mann whitney u test. A Kruskall Wallis used as univariate test and Quantile regression analysis as multivariate analysis to estimate the effects of the variables on severity of AP. Binary logistic regression analysis was used to estimate the predictors of mortality. P value <0.05 was the mark of significance.

Ethical approval: the study registered in accordance with Declaration of Helsinki and had been approved by the ethical committee of the above-mentioned hospital (approval no. 1713 on the 19th of September 2019). All participants provided informed consents (could

be provided if needed). The access to medical records of the control group was approved by both scientific and ethical committees of the same hospital.

The study was reported in accordance to STROCSS criteria(16).

Results

The study included 37 cases of COVID 19 infected patients developed acute pancreatitis. The study included 50 cases of acute pancreatitis without COVID 19 infection as control.

Comparison of patient characteristics, and investigation between the two groups done, and showed that: no difference between the two groups regarding age, gender, BMI, S. Amylase, S. Lipase, PaO2, WBC, LDH, and AST. On the other hand, S. calcium and S. albumin were lower in cases of COVID 19 than control, while blood urea, sugar, Glasgow score, rate of idiopathic pancreatitis, and severe AP (by revised Atlanta classification) all were higher in cases of COVID 19 than control, as shown in Table 2.

Table 2: Distribution of patients' demographics, investigations, and severity of AP between case and control groups, with level of significance.

Variables		COVID 19	Control	P value
		Median (Min-Max)	Median (Min-Max)	
Age		41 (23-62)	39.5 (21-65)	0.952
BMI		30 (23-37)	30 (23-36)	0.705
s. amylase		1052 (308-1879)	1262.5 (311-1861)	0.233
s. lipase		363 (142-600)	314.5 (135-581)	0.680
PaO2		96 (73-99)	96 (94-99)	0.174
WBC		12.08 (2.6-22.3)	12.36 (10.61-22.3)	0.837
S. Calcium		8.45 (7.26-9.07)	8.69 (7.2-9.09)	**0.034**
Bl. Urea		41 (18-47)	33 (18-46.9)	**0.002**
LDH		459 (204-768)	344.5 (193-688)	0.057
AST		152 (89-366)	140 (92-186)	0.094
Albumin		3.5 (2.1-4.4)	3.8 (3.3-4.2)	**0.002**
Glucose		189 (120-366)	163 (123-208)	**0.046**
Glasgow score		2 (0-7)	1 (0-4)	**<0.0001**
		No. (%)	No. (%)	
Gender	Male	8 (21.6)	8 (16)	0.503*
	Female	29 (78.4)	42 (84)	
Cause of AP	Gallstone	20 (54.1)	41 (82)	**0.005**
	Idiopathic	17 (45.9)	9 (18)	
Revised Atlanta classification	Mild	7 (18.9)	37 (74)	**0.014***
	Moderate	17 (45.9)	9 (18)	
	Severe	13 (35.1)	4 (8)	

*Fisher exact test was used.

Cases of severe COVID 19 were associated with higher rate of severe pancreatitis when compared with mild and moderate COVID 19, as shown in Table 3.

Table 3: Distribution of severity according to revised Atlanta score according to the severity of COVID 19.

Variable		Revised Atlanta classification			P value
		Mild	Moderate	Severe	
		No. (%)	No. (%)	No. (%)	
Severity of COVID 19	Mild	7 (100)	1 (5.9)	0 (0)	**<0.0001***
	Moderate	0 (0)	13 (76.5)	5 (38.5)	
	Severe	0 (0)	3 (17.6)	8 (61.5)	

*Fisher exact test was used.

The comparison of the variables according to severity of AP in COVID 19 group using univariate analysis showed that significant difference in PaO_2, WBC, calcium, blood urea, Glasgow score, COVID 19 severity score, and cause of AP. For estimation the true effect of COVID 19 infection on the severity of AP, Quantile regression analyses was used.

Severity of COVID 19 was found to be the single independent predictor of severity of AP in COVID 19 infected patients, as shown in Table 4.

Table 4: Distribution of the variables of COVID 19 group according to the severity of pancreatitis with level of significance

Variables		Mild Median (Min-Max)	Moderate Median (Min-Max)	Severe Median (Min-Max)	P value* Univariate	P value* Multivariate
Age		39.5 (21-65)	34.5 (23-64)	44 (23-62)	0.232	0.217
BMI		30 (23-37)	28.5 (23-37)	30 (23-35)	0.885	0.521
s. amylase		1262.5 (311-1829)	1196 (308-1757)	998 (551-1879)	0.844	0.840
s. lipase		327 (135-581)	357 (161-522)	363 (142-600)	0.999	0.790
Pao2		96 (94-99)	96 (75-99)	95 (73-99)	**0.013**	0.996
WBC		11.93 (2.6-22.3)	11.7 (5.2-19.3)	17.5 (4.3-22.3)	**<0.0001**	0.558
calcium		8.84 (7.5-9.09)	8.49 (7.9-9.04)	8.23 (7.2-9.01)	**0.029**	0.249
urea		32.5 (18-46.1)	45 (18-47)	45 (21-46.9)	**0.017**	0.283
LDH		344.5 (193-587)	430 (215-768)	473 (255-749)	0.123	0.281
AST		145 (89-186)	145.5 (94-366)	142 (97-366)	0.273	0.636
albumin		3.6 (3.2-4.2)	3.7 (3.3-4.2)	3.6 (2.1-4.2)	0.839	0.943
sugar		156.5 (123-210)	188 (133-366)	183 (120-230)	0.160	0.112
Glasgow		1 (0-2)	2 (1-3)	4 (1-7)	**0.001**	0.827
COVID 19 score		0 (0-4)	5 (0-10)	6 (0-10)	**<0.0001**	**<0.0001**
		No. (%)	No. (%)	No. (%)		
Cause	Gallstone	6 (85.7)	11 (64.7)	3 (23.1)	**0.013****	0.087
	Idiopathic	1 (14.3)	6 (35.3)	10 (76.9)		
Gender	Male	3 (42.9)	3 (17.6)	2 (15.4)	0.314	0.457
	Female	4 (57.1)	14 (82.4)	11 (84.6)		

*Univariate analysis was done using Kruskal-Wallis test, while multivariate analysis was done using Quantile regression analyses.
**Fisher's exact test was used.

The mortality rate in this study was 16.1% (14 cases). The mortality was significantly higher in case of COVID 19 than control, as shown in Table 5.

Table 5: Comparison of mortality between the two groups.

Outcome	COVID 19	Control	P value
	No. (%)	No. (%)	
Died	10 (27)	4 (8)	**0.017**
Survived	27 (73)	46 (92)	

For estimation of the predictor of mortality in cases of COVID 19 that complicated by AP we applied logistic regression analysis and found that mortality in case of COVID 19 was dependent on the severity of AP (defined by revised Atlanta classification) and severity of COVID 19, but it was not dependent on Glascow score, as shown in Table 6.

Table 6: Analysis of mortality according to the severity of AP and COVID 19 in case group.

Variables		Died	Survived	P value	
		No. (%)	No. (%)	Univariate*	Multivariate**
Severity of COVID 19	**Mild**	0 (0)	8 (29.6)	<0.0001	**0.032**
	Moderate	2 (20)	16 (59.3)		
	Severe	8 (80)	3 (11.1)		
Severity of pancreatitis by Glascow score	**Mild**	3 (30)	19 (70.4)	<0.0001	0.104
	Severe	7 (70)	8 (29.6)		
Revised Atlanta classification	**Mild**	0 (0)	7 (25.9)	<0.0001	**0.003**
	Moderate	0 (0)	17 (63)		
	Severe	10 (100)	3 (11.1)		

*By Fisher's exact test. **By binary logistic regression analysis.

Discussion

The incidence of acute pancreatitis increasing globally in the recent years(17), as the pandemic progress more of the effect of the virus discovered. Previous studies had investigated acute pancreatitis as unusual presentation of the COVID 19(18), while in the current study we try to investigate the effect of COVID 19 infection on the severity of AP.

The current study included 37 cases of COVID 19 infected patients developed with features consistent with AP.

There was no age difference between the two groups, in literature multiple case reports was found as in the case presented by Cheung et al(19) as the patient age was 38 years with recurrent attacks of acute pancreatitis.

The BMI showed no difference regarding severity of acute pancreatitis. After application of Quantile regression analysis test also difference in the severity of AP regarding BMI. On the other hand, Soeroto et al(20) found that severity of COVID 19 increased with high BMI, and Dobszai et al(21) found that high BMI associated with severe form of pancreatitis. This variation could be due to the homogenous sample obtained in the current study to eliminate as possible the sampling bias.

All cases of pancreatitis were diagnosed after finding elevated S. Amylase and S. Lipase for at least three times the upper normal limit, thus no difference in their levels was found. Also, it was considered as poor predictor for the severity of pancreatitis as found by Loos et al (22).

The partial pressure of oxygen was found to be not different between case and control groups. Previous studies suggested that, PaO_2 lower in cases of COVID 19 infection, this attributed first to the effect of the infection second to the complication of pancreatitis that affect the lung (in the form of acute respiratory distress syndrome and plural effusion) as suggested by Iyer et al(23). The effect of COVID 19 infection may had the additional deleterious effect on the lung, as suggested by Alharmi et al (24) in their case report. This difference in the result may be attributed to the small number of cases of severe COVID 19 in the current study.

Although cases of COVID 19 associated with low lymphocyte count but overall increased WBC count as found by previous studies conducted by Naoum et al(25), and Pozdnyakova et al(26), and the severity of the infection was found to be associated with higher level of WBC as found by Zhu et al(27), in the current study no difference was found between cases of pancreatitis with and without COVID 19 infection as both groups associated with elevated WBC count.

The calcium level was significantly lower in cases of AP with COVID 19. Previous studies did not investigate the differences in calcium level in cases of pancreatitis with COVID 19 infection and without, although Alemzadeh et al(28) found that patients with low serum Calcium level were at risk to develop severe COVID 19 infection.

The mean blood urea level was higher in cases of COVID 19 infection than control, Cheng et al(29), found that severe form of COVID 19 infections associated with elevated levels of blood urea.

The LDH level was not different between the two groups, this probably because of both COVID 19 and AP in elevating LDH level thus no statistical difference was found. Li et al(30) found that cases of COVID 19 infection had higher LDH level.

The AST level was not different between the two groups, as AST would be elevated in pancreatitis. Wang et al(31) suggested that cases of COVID 19 had increased rate of liver injury and this may elevate AST level.

The albumin level was lower in cases of COVID 19 than control, albumin as acute phase protein tends to be lower in cases of severe inflammation that occurs in cases of COVID 19 infection as suggested by Aziz et al(32).

The blood sugar tends to be higher in cases of COVID 19 infection, this happened due to the increased inflammation that increase insulin resistance, also due to the side effect of the drugs (steroids) that consumed in cases of COVID 19 infection, similarly Sarvazad et al(33) found that COVID 19 infection associated with increased rate of hyperglycemia.

The predicted severity of pancreatitis (by Glascow score) was higher in cases with COVID 19 infection, cases of COVID 19 associated with higher rate of severe pancreatitis (according to Revised Atlanta classification). While comparison of severity of AP regarding severity of COVID 19, we found that the more severe COVD 19 the more severe AP, and by applying regression analysis we found that in cases of COVID 19 the single independent predictor of severity of AP was COVID 19 severity score (suggested by Son et al(13)).

The mortality rate in the current study was 16.1%, with majority of deaths happened in COVID 19 group. The mortality was dependent of both severity of COVID 19 and AP. Similarly found by Onoyama et al(34), that mortality rate was 12.7% in COVID 19 associated AP.

Strength of the study:

The sample size was larger than previous studies.

The severity of pancreatitis was divided according to revised Atlanta score rather than Glascow score.

Limitation of the study:

There is no well accepted method for classifying the severity of COVID 19.

The duration of stay in emergency department was prolonged after the diagnosis of acute pancreatitis in COVID 19 cases (delay in starting management), furthermore the discharge from hospital was also prolonged this and no definitive criteria for discharging patient with COVID 19 with concomitant pancreatitis this issue was faced by other researchers Akbulut et al(35), and stated that this delay was attributed to the increased workload during pandemic.

Conclusion

COVID 19 infection is an independent predictor for severity of acute pancreatitis. More directed care to the cases of COVID 19 infection with superimposed pancreatitis, as they prone to develop severe form. Future studies to examine the effect of COVID 19 antiviral therapy on the severity of pancreatitis is recommended.

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Conflict of Interest
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Data availability
Data are available upon reasonable request.

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