Original Paper

Pleural Effusion as a Negative Prognostic Factor in Patients with Acute Pancreatitis and COVID-19

PATRICIA MIHAELA RADULESCU[1], ALEXANDRA FLORIANA NEMEŞ[2], CRISTINA CALARASU[3], ION GEORGESCU[4], DUMITRU RADULESCU[4]

[1]*UMF Craiova Doctoral School, University of Medicine and Pharmacy of Craiova, Romania*

[2]*Department of Neonatology, Louis Ţurcanu Clinical Emergency Hospital for Children, Timişoara, Romania*

[3]*Department of Pulmonology, University of Medicine and Pharmacy of Craiova, Romania*

[4]*General Surgery Department, University of Medicine and Pharmacy of Craiova, Romania*

ABSTRACT: We conducted a retrospective multicentre study to investigate the association between acute pancreatitis, COVID-19, and pleural effusion. The study involved a total of 433 patients. Among them, 405 patients did not have COVID-19 infection, while 28 patients had both acute pancreatitis and COVID-19. Out of the 28 patients with both conditions, 12 also had pleural effusion. Among the 405 patients with acute pancreatitis without COVID-19, 48 had pleural effusion. The results showed that the relative risk of death associated with pleural effusion was approximately 4 times higher in patients with COVID-19 and pleural effusion compared to those with pleural effusion without COVID-19.

KEYWORDS: *Acute pancreatitis, COVID-19, pleural effusion, prognostic analysis.*

Introduction

COVID-19 (2019 coronavirus disease) is a respiratory illness caused by infection with the SARS-CoV-2 virus [1].

It was first identified in December 2019 in the city of Wuhan, Hubei Province, China [2].

The SARS-CoV-2 virus is an RNA virus belonging to the coronavirus family [3].

Common symptoms include fever, dry cough, fatigue, shortness of breath, and loss of taste or smell [4].

The majority of individuals infected with the SARS-CoV-2 virus experience mild to moderate symptoms and recover without requiring specific medical treatment [5].

However, older adults and individuals with pre-existing medical conditions are at a higher risk of developing severe forms of the disease [6].

The infection with SARS-CoV-2 not only affects the respiratory system but also other organs that express the ACE-2 receptor (angiotensin-converting enzyme 2 receptor), such as the gastrointestinal tract, liver, kidneys, and pancreas [7].

COVID-19-associated pancreatitis can be caused by several factors, including systemic inflammation induced by infection, the formation of blood clots that affect pancreatic perfusion, or an exaggerated immune response to the infection [8].

It is important to note that pancreatitis can be a rare complication of COVID-19 and does not occur in all patients infected with the virus [9].

Patients with COVID-19 have been found to be more predisposed to pleural effusion secondary to pneumonia and systemic inflammatory response [10].

Acute pancreatitis (AP) is an inflammatory condition of the pancreas characterized by inflammation and injury to the pancreatic gland [11].

It can be caused by various factors, such as gallstones, excessive alcohol consumption, trauma, infections, or certain medications [12].

Common symptoms of AP include severe abdominal pain in the upper abdomen, nausea, vomiting, and abdominal distension [13].

In some cases, systemic symptoms such as fever, tachycardia, and decreased blood pressure may also occur.

In severe cases of AP, complications such as abscess formation, extensive pancreatic necrosis, and pseudocyst formation can occur.

These conditions often require medical or surgical intervention to prevent further complications and promote healing of the affected pancreas [14].

Pleural effusion is a condition characterized by the excessive accumulation of fluid in the pleural space, which is the area between the membranes that cover the lungs and the chest wall.

It can be a result of various causes, including respiratory infections, congestive heart failure,

10.12865/CHSJ.49.02.08

pulmonary embolism, tumors, or inflammatory diseases [15].

Common symptoms of pleural effusion include dyspnoea (difficulty breathing), chest pain, cough, and fatigue [16].

In some cases, pleural effusion can be asymptomatic and may be discovered incidentally during a medical examination or imaging tests [17].

The diagnosis of pleural effusion involves evaluating symptoms, physical examination, blood tests (such as laboratory tests to assess the composition of the pleural fluid), and medical imaging such as chest X-ray or computed tomography [18].

Material and Methods

Study design

We conducted a retrospective multicentre study involving 561 consecutive patients with AP admitted to two university medical centres, the Emergency County Hospital No. 1 Craiova and the Emergency Military Hospital Craiova "Dr. Stefan Odobleja", after obtaining approval from the ethics committees of each institution, between January 1, 2018, and April 30, 2022.

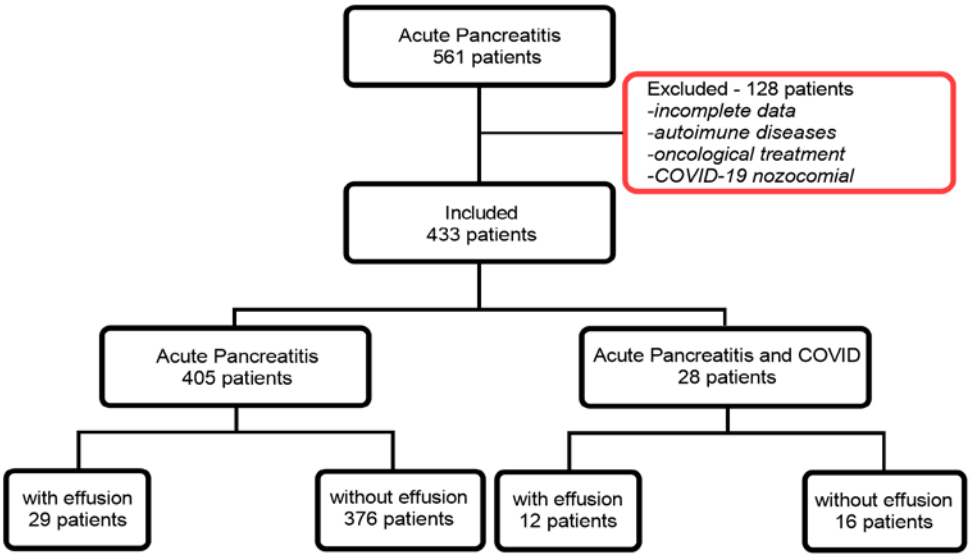

Figure 1. Flowchart of patient inclusion.

Out of the 561 patients with AP admitted to the surgical department, after applying the exclusion criteria, 433 patients remained eligible for the study.

The clinical and paraclinical data of AP patients were obtained by examining the recorded data in the two electronic health records of the two hospital units.

The diagnosis of COVID-19 was established through real-time reverse transcription polymerase chain reaction (RT-PCR) testing of nasopharyngeal swabs.

Only patients with a positive result upon admission were included in the study.

Pleural effusion was identified and diagnosed using imaging diagnostic methods, particularly chest computed tomography (CT).

We included consecutive patients with a confirmed biological and imaging diagnosis of AP according to the Revised Atlanta Criteria [17], from January 1, 2018, to May 30, 2022, including the first blood test performed before initiating any medical treatment.

Exclusion Criteria

Patients excluded from the study were those with insufficient hospitalization-related data in the system, those with chronic treatment of corticosteroids and immunosuppressive drugs in the past three months, those with autoimmune diseases, those with incomplete oncologic treatment, those with recurrent AP, and those with chronic pancreatitis.

Statistical Analysis

Quantitative variables are presented as medians (interquartile ranges) and were analysed using the Mann-Whitney U test.

Categorical variables were reported as frequencies and percentages and were statistically compared using the chi-square test.

A p-value<0.05 was considered statistically significant.

All statistical analyses were performed using SPSS version 26.0, and the graphs were created using GraphPad Prism v.9.3.0.

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Results

The study analysed a total of 433 patients (225 males, 52%) resulting from the application of the exclusion criteria from a consecutive series of 561 patients.

Among them, 28 patients had COVID-19 and AP upon admission.

Demographic and clinical data in patients with AP and COVID-19

Comparing patients with AP without COVID-19 (n=405) to those with AP and COVID-19 (n=28) (Table 1), a higher median age was found in the group of patients with AP and COVID-19, [63 (51-74) vs. 46.5 (39-62); p<0.001].

Table 1. Comparison of demographic characteristics between patients with AP and those with AP and COVID-19.

	Total n=433	**Without COVID n=405**	**With COVID n=28**	***P* value**
Age	49 (41-63)	63 (51-74)	46.5 (39-62)	<0.001*†
Genre				0.082
M	225(52%)	206(50.9%)	19 (67.9%)	
W	208(48%)	199(49.1%)	9 (32.1%)	
Ethyology				0.084
Biliary	120(27.7%)	117(28.8%)	3(10.7%)	
Alcoholic	184(42.5%)	171(42.4%)	13(46.4%)	
unknown	129(29.8%)	117(28.8%)	12 (42.9%)	
Hours onset	24 (12-72)	24 (12-48)	24 (12-72)	0.438†
Hosp_days	9 (7-15)	9 (7-14)	9 (7-15)	0.989†
Complications with surgical risk				<0.001*
Yes	56 (12.9%)	46(11.4%)	10 (32.1%)	
No	377(87.1%)	359(88.6%	18(67,9%)	
HTN				0.170
Yes	144 (33.3%)	138(35.1%)	6 (21.4%)	
No	289(66.7%)	267(64.9%)	22(78.6%)	
Diabetes				0.267
Yes	62 (21.4%)	56(13.8%)	6 (21.4%)	
No	371(78.6%)	349(86.2%)	22(78.6%)	
MSOF				0.029*
Yes	32 (7.4%)	27(6.7%)	3(25%)	
No	401(92.6%)	378(93.3%)	9(75%)	
Effusion				<0.001*
Yes	42 (9.7%)	30 (7.4%)	12 (42.9%)	
No	391 (90.3%)	375 (92.6%)	16 (57.1%)	
Mortality				<0.001*
Yes	60 (13.9%)	48(11.9%)	12 (42.9%)	
No	373(86.1%)	357(88.1%)	16(57,1%)	

*p<0.05-statistically significant; † Chi-square test; HTN-high blood pressure; MSOF-Multiple organ failure;

Regarding the gender of the patients, aetiology of AP, hours since symptom onset, and length of hospital stay, no statistically significant differences were identified.

However, concerning complications with surgical risk, an increased incidence was observed in patients with AP and COVID-19, from (46/405, 11.4%) to (10/28, 32.1%) (p<0.001).

Multiple Organ System Failure (MSOF) showed an increased incidence in patients with COVID-19, from (27/405, 6.7%) to (3/28, 10.7%) (p<0.029).

There was a substantial increase in the incidence of pleural effusion in patients with AP and COVID-19, from (30/405, 7.4%) to (12/28, 42.9%) (p<0.001).

Mortality had a very high incidence among patients with COVID-19, with an increase from (30/405, 7.4%) to (12/28, 42.9%) (p<0.001) (Figure 2).

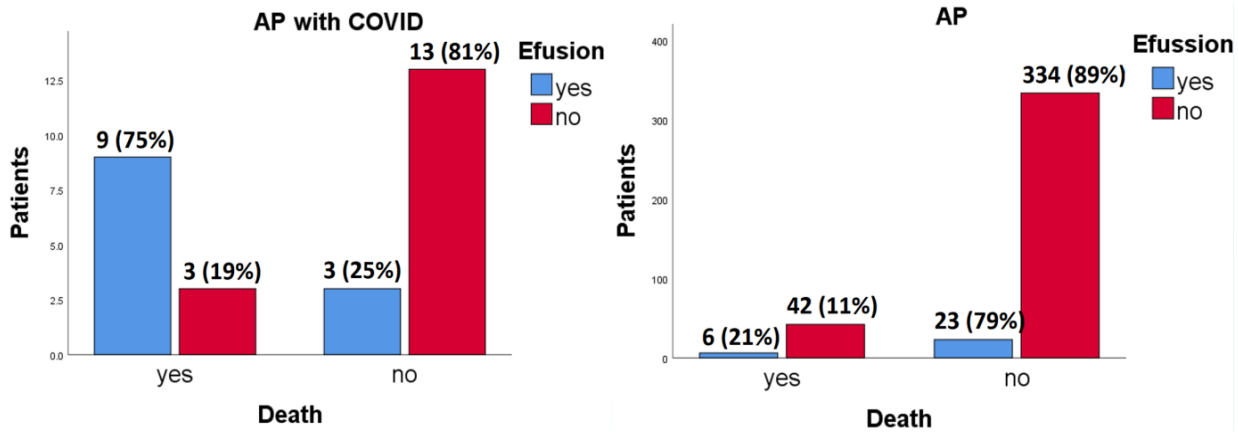

Figure 2. Comparison of mortality in patients with pleural effusion between patients with AP and patients with AP and COVID-19.

Because pleural effusion had a very high incidence in patients with AP and COVID-19, we wanted to determine if it influenced mortality.

After conducting univariate analysis, we performed multivariate analysis, which confirmed that pleural effusion independently increases the risk of death (Table 2).

Table 2. Univariate and multivariate analysis of variables associate with mortality in patients with AP and patients with AP and COVID-19.

Variable	Univariate analysis	*p* value	Multivariate analysis	*p* value
	OR		OR	
AP without COVID				
Age	0.98 (0.96-1.00)	0.115		
Complications	1.97 (0.75-5.16)	0.165		
MSOF	19.31 (8.08-46.18)	0.001*	37.1 (12.45-110.55)	0.001*
Effusion	2.47 (1.00-6.13)	0.050		
AP with COVID				
Age	0.92 (0.85-0.99)	0.027*	0.94 (0.85-1.03)	0.220
Complications	9.43 (1.43-62.17)	0.020*	1.49 (0.77-2.86)	0.228
MSOF	5.25 (0.59-46.13)	0.083		
Effusion	13 (2.12-79.59)	0.006	9.30 (1.40-61.91)	0.021*

*p<0.05-statistically significant.

To determine the extent of the increased risk of death, we performed the Chi-Square test, which yielded a value of 8.859 with df (1), p=0.003*.

Subsequently, we calculated the relative risk, which was 4, indicating that patients with AP and COVID-19 who have pleural effusion are four times more likely to die compared to patients with AP without COVID-19 and pleural effusion. (Table 3)

Table 3. Chi-Square test and Relative Risk (RR) of death in patients with AP and COVID-19, based on the presence or absence of pleural effusion.

Compared groups	Odd ratio CI 95%	Relative risk (RR) Of death	X 2	df	*p* value
PA with COVID effusion vs. No effusion	13,00 (2,12-79,59)	4,00 (1,37-11,67)	8.859	1	0,003*

*p<0,05-statistically significant.

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Discussions

Both AP and COVID-19 are associated with significant systemic inflammation [19].

This can lead to increased production of inflammatory mediators and cytokines, which can affect multiple organs and systems, including the pleura [20], resulting in the accumulation of fluid in the pleural space [21].

The inflammatory response in AP and COVID-19 can cause increased vascular permeability [22].

This allows fluid, proteins, and cells to leak from blood vessels and accumulate in the pleural space, leading to pleural effusion [23].

Both AP and COVID-19 can affect the normal functioning of the lymphatic system [24].

The lymphatic system plays a crucial role in draining fluid and cellular debris from tissues, including the pleural space [25].

When lymphatic drainage is compromised, fluid can accumulate in the pleural space, resulting in pleural effusion [26].

Respiratory complications can arise from both AP and severe cases of COVID-19 [27].

AP can result in lung injury and acute respiratory distress syndrome (ARDS) due to the release of pancreatic enzymes and inflammatory mediators [28].

Similarly, COVID-19 can lead to pneumonia and ARDS, causing severe respiratory symptoms [29].

Consequently, these respiratory complications play a role in the development of pleural collections [30].

Patients with AP and COVID-19 are susceptible to secondary infections, including bacterial pneumonia [31].

Secondary infections can further contribute to the development of pleural effusion [32].

Although there is an increased incidence of pleural diseases in patients with AP and COVID-19, not all individuals with these conditions will develop pleural complications [33].

The occurrence of pleural effusion depends on various factors, including the severity of the underlying condition and individual patient characteristics [34].

Study Limitation

The main limitation of the study is that it is retrospective and does not allow for direct control of independent and dependent variables.

This means that a causal relationship between the factors studied and the observed outcomes cannot be established.

After applying the exclusion criteria, a large number of patients were no longer included in the study, which may affect the representativeness of the results and their generalizability to the general population.

External sources, such as pre-hospital treatment or other environmental factors that could have modified the inflammatory state of patients and thereby influence their progression during hospitalization, could not be excluded.

This may introduce confounding factors in the interpretation of the results and the assessment of the direct impact of the variables of interest.

Further large cohort studies are needed to generalize the results of this study and to gain a better understanding of the causal relationships and mechanisms involved in the association between the variables studied.

Conclusions

The results obtained in our study indicate that pleural effusion is a rare complication in both AP (AP) and COVID-19 infection.

However, among patients diagnosed with both conditions (AP and COVID-19), a significant increase in the rate of pleural effusion, approximately 5-fold, was observed compared to those who had only one of these conditions.

Additionally, the relative risk of death was approximately 4 times higher in these patients with pleural effusion compared to patients with pleural effusion and AP.

Based on these findings, we can conclude that pleural effusion can be considered a predictive marker of mortality in patients affected by both AP and COVID-19.

However, it is important to emphasize that the interaction between AP and COVID-19, including their combined impact on mortality, is not yet fully understood, as research in this field is still ongoing.

Furthermore, it should be noted that pleural effusion associated with COVID-19 infection represents only one of the possible complications, and its impact on overall mortality will be influenced by the individual characteristics of the patient and the course of the disease.

Conflict of interests

None to declare

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Corresponding Author: Cristina Calarasu, Department of Pulmonology, University of Medicine and Pharmacy of Craiova, 200349 Craiova, Romania, e-mail: cristina.calarasu@umfcv.ro