Acute pancreatitis as a complication of acute COVID-19 in kidney transplant recipients

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ORIGINAL ARTICLE

Retrospective Study Acute pancreatitis as a complication of acute COVID-19 in kidney transplant recipients

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Abstract

BACKGROUND

Acute pancreatitis is a rare extrapulmonary manifestation of coronavirus disease 2019 (COVID-19) but its full correlation with COVID-19 infection remains unknown.

AIM

To identify acute pancreatitis' occurrence, clinical presentation and outcomes in a cohort of kidney transplant recipients with acute COVID-19.

METHODS

A retrospective observational single-centre cohort study from a transplant centre in Croatia for all adult renal transplant recipients with a functioning kidney allograft between March 2020 and August 2022 to record cases of acute pancreatitis during acute COVID-19. Data were obtained from hospital electronic medical records. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was proven by a positive SARS-CoV-2 real-time reverse transcriptase-polymerase chain reaction on the nasopharyngeal swab.

RESULTS

Four hundred and eight out of 1432 (28.49%) patients who received a renal allograft developed COVID-19 disease. The analyzed cohort included 321 patients (57% males). One hundred and fifty patients (46.7%) received at least one dose of the anti-SARS-CoV-2 vaccine before the infection. One hundred twenty-five



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(39.1%) patients required hospitalization, 141 (44.1%) developed pneumonia and four patients (1.3%) required mechanical ventilation. Treatment included immunosuppression modification in 233 patients (77.1%) and remdesivir in 53 patients (16.6%), besides the other supportive measures. In the study cohort, only one transplant recipient (0.3%) developed acute pancreatitis during acute COVID-19, presenting with abdominal pain and significantly elevated pancreatic enzymes. She survived without complications with a stable kidney allograft function.

CONCLUSION

Although rare, acute pancreatitis may complicate the course of acute COVID-19 in kidney transplant recipients. The mechanism of injury to the pancreas and its correlation with the severity of the COVID-19 infection in kidney transplant recipients warrants further research.

Key Words: Acute pancreatitis; COVID-19; Kidney transplant; Angiotensin-converting enzyme-2 receptor; Immunosuppressive agents

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Core Tip: The attention to the effect of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus on pancreatic tissue has been arising. It is hypothesized that the SARS-CoV-2 virus can directly affect pancreatic tissue via angiotensinconverting enzyme 2 receptors which are heavily expressed in pancreatic cells. Our single-centre retrospective study aimed to identify the occurrence of acute pancreatitis, clinical presentation and outcomes in a cohort of kidney transplant recipients with acute coronavirus disease 2019 (COVID-19) between March 2020 and August 2022. 28.49% of transplant recipients developed COVID-19 disease and only 0.3% developed acute pancreatitis during the acute COVID-19 presenting with abdominal pain and elevated pancreatic enzymes with no imaging features. The mechanism of injury to the pancreas and its correlation with the severity of the COVID-19 infection in kidney transplant recipients warrants further research.

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INTRODUCTION

Acute pancreatitis is an acute inflammation of the pancreas characterized by typical upper abdominal pain, vomiting and nausea. Clinical, biochemical and/or radiologic findings are required to establish a diagnosis[1]. The most common causes of pancreatitis are gallstones, alcohol, hypertriglyceridemia, post-endoscopic retrograde cholangiopancreatography pancreatitis, medications and pancreatic duct injury[2]. Since March 2020, when the WHO declared the novel coronavirus disease 2019 (COVID-19) outbreak a global pandemic[3], many studies investigated its effect on different organ systems and tissues, showing that 15% of patients with acute COVID-19 infection develop digestive symptoms[4]. COVID-19-associated pancreatic injury has been suggested, but its correlation with pancreatic disease remains unclear. It is hypothesized that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus affects pancreatic tissue via angiotensin-converting enzyme 2 receptors, which are heavily expressed in pancreatic cells and indirectly by locoregional inflammation as a part of systemic inflammation[5]. A recent United States study on a total of 1659040 hospitalized COVID-19 patients showed that the incidence of pancreatitis is 0.6% and that is followed by worse in-hospital outcomes, including increased episodes of septic shock, acute kidney injury and requirement for hemodialysis compared to patients without pancreatitis, but without increased mortality[6]. In the COVID-19 setting, transplanted patients carry an additional disease burden due to immunosuppression; however, the data on the transplant population on acute COVID-19 and pancreatitis is lacking. Therefore, this study aims to identify the occurrence of acute pancreatitis, its clinical presentation and outcomes in a cohort of kidney transplant recipients with acute COVID-19.

MATERIALS AND METHODS

Study design

A retrospective observational single-centre cohort study recruited study participants from the largest kidney transplant centre in Croatia to record cases of acute pancreatitis during acute COVID-19 infection. Data were retrospectively obtained from hospital charts and records. The study included all adult renal transplant recipients with a functioning kidney allograft between March 2020 and August 2022.



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SARS-CoV-2 infection

SARS-CoV-2 infection was proven by a positive SARS-CoV-2 real-time reverse transcriptase-polymerase chain reaction (RT-PCR) on the nasopharyngeal swab. No data on SARS-CoV-2 genotyping were available.

Acute pancreatitis

The diagnosis of acute pancreatitis was based on the fulfilment of two of three criteria: (1) Upper abdominal pain; (2) serum amylase and/or lipase of at least three times the upper limit of normal; and/or (3) findings consistent with acute pancreatitis on imaging studies (abdominal ultrasound, computed tomography or magnetic resonance imaging)[1]. The study was approved by the University Hospital Center Zagreb Ethics committee.

RESULTS

In the study period, 408 out of 1432 (28.49%) patients who received a renal allograft at our institution developed COVID-19 disease, proved by the positive SARS-CoV-2 RT-PCR on the nasopharyngeal swab. Twenty-five patients died in the period during or after the infection and 62 patients had not been assessed in our clinic and were therefore excluded from the study population, which finally included 321 patients (57% males) (Table 1). One hundred and fifty patients (46.7%) received at least one dose of the anti-SARS-CoV-2 vaccine before the infection. Regarding the severity of SARS-COV-2 infection, 21 (6.6%) patient was completely asymptomatic, while 125 (39.1%) patients required hospitalization, 141 (44.1%) developed pneumonia and 4 patients (1.3%) required mechanical ventilation. The most common presenting symptom was febrility (76.6%), followed by respiratory symptoms (71.9%) and diarrhoea (12.2%).

Treatment included immunosuppression modification in 233 patients (77.1%) and remdesivir in 53 patients (16.6%), besides the other supportive measures. Additionally, thirteen patients (4.4%) received intravenous immunoglobulins, eight (2.5%) received convalescent plasma and 30 patients (9.4%) received hyperimmune anti- cytomegalovirus (CMV) globulin (in exchange for convalescent plasma) as a passive immune augmentation. Three patients (0.9%) were treated with tocilizumab. In the study cohort only one patient (0.3%) developed acute pancreatitis during acute COVID-19.

COVID-19 and acute pancreatitis-a case description

A 68-year-old female with a kidney allograft from a deceased donor 127 months ago due to end-stage renal disease caused by rapidly progressive glomerulonephritis presented with a three-week history of productive cough, inapatency, abdominal pain, vomiting and diarrhoea. Her immunosuppressive regimen included cyclosporine, mycophenolate mofetil and steroids. The posttransplant course was complicated with new-onset diabetes after transplantation and an episode of E. coli sepsis. At admission, her abdomen was tender and painful on palpation. SARS-CoV-2 polymerase chain reaction was tested positive by RT-PCR on the nasopharyngeal swab and laboratory investigations revealed elevated serum amylase (187 IU/L, reference range 23-91 IU/L) and lipase (179 IU/L, reference range 13-60 IU/L). Her temperature was 37.5 °C, O₂ saturation was 98%, and her blood pressure was 158/82 mmHg. Chest X-rays revealed bilateral COVID-19 pneumonia. Over the following days, serum amylase increased to 1203 IU/L and lipase to 1489 IU/L with C-reactive protein within the normal range. Computerized tomography did not show any changes in the pancreatic or peripancreatic tissue.

Treatment included hydration, broad-spectrum antibiotics, proton pump inhibitors and low molecular weight heparin with temporary cessation of mycophenolate. She recovered entirely without complications with a stable allograft function

DISCUSSION

Our retrospective analysis shows that acute pancreatitis in a COVID-19 setting is a rare (0.3%) complication in kidney transplant recipients. Data on the transplant population are scarce and are based only on a few case reports from which no data about the incidence and characteristics of this specific group of patients can be extracted[7].

Also, in a non-COVID-19 setting, acute pancreatitis is rare after kidney transplantation and is mainly associated with the use of steroids and other immunosuppressive drugs[8] without traditional risk factors like gallstones and alcohol consumption. Furthermore, as renal transplant recipients are immunocompromised, they are more vulnerable to viral infections such as CMV, Epstein-Barr virus and varicella zoster, which can cause viral pancreatitis[9].

During acute SARS-CoV-2 infection, acute pancreatitis was diagnosed in only one kidney transplant recipient from our cohort. Current guidelines recommend monitoring the presence of systemic inflammatory response syndrome or organ failure at admission for a minimum of 48 h to predict the development of a severe course of the disease[1]. Her symptoms were present at the hospital admission; however the three-week history disables precise determination of the timing between the SARS-CoV-2 infection and the development of acute pancreatitis.

In the non-transplant population, the literature demonstrates cases of acute pancreatitis at COVID-19's initial presentation and those that developed during hospitalization [10,11]. In the study of Wang et al [12], 17% of the patients with severe COVID infection had elevated levels of serum amylase and lipase, indicating pancreatic injury. Elevated levels of pancreatic enzymes in intensive care unit COVID-19 patients were reported in several studies[13,14], however, there were no reporting details on the clinical data or radiological imaging for evaluating pancreatitis severity and treatment. The prevalence of acute pancreatitis among critically ill patients presenting with COVID-19 is significantly higher (7.9%)



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Table 1 Coronavirus disease 2019 kidney transplant recipients characteristics (n = 321)			
Characteristics	Number (%) of patients	Range	
Sex			
Male/female	183/138 (57/43)		
Age (yr) [Median (IQR)] Primary kidney disease	55 (44-64)	22-81	
Glomerulonephritis	9 + 8 (30.6)		
Diabetic nephropathy	12 (3.8)		
ADPKD	48 (15)		
Pyelonephritis	26 (8.1)		
Nephroangiosclerosis	26 (8.1)		
Other	110 (34.4)		
Time from transplantation (months) [Median (IQR)]	94.5 (52-135.8)	1-368	
Height (cm) [Median (IQR)]	171 (163-180)	124-199	
Body weight (kg) [Median (IQR)]	79 (67-92)	42-150	
BMI [Median (IQR)]	26.5 (23.9-29.2)	17.36-45.79	
Nutritional status			
Underweight (BMI < 18.5)	4 (1.3)		
Normal weight	105 (32.8)		
Pre-obesity (25-29.9)	144 (45)		
Obese (≥ 30)	67 (20.9)		
Previous thrombosis	30 (9.4)		
Previous myocardial infarction or stroke	32 (10)		
Previous CMV infection	36 (11.3)		
Previous BK infection	68 (21.3)		
Previous EBV infection	28 (8.8)		
Allograft rejection	46 (14.4)		
Creatinine value [Median (IQR)]	129 (98-165.8)	45-430	
CKD EPI [Median (IQR)]	49 (35-64)	0.23-133	
Biuret [Median (IQR)]	0.2 (0.1-0.5)	0-79	
Vaccinated against COVID-19	246 (76.9)		
Before COVID-19 infection	149 (46.6)		
After COVID-19 infection	97 (30.3)		
Number of vaccine doses [Median (IQR)]	2 (2-3)	1-4	
Number of vaccine doses ($n = 246$)			
One	21 (8.5)		
Two	138 (56.1)		
Three	83 (33.7)		
Four	4 (1.6)		
COVID-19 initial symptoms			
Febrility	245 (76.6)		
Diarrhea	39 (12.2)		
Respiratory	230 (71.9)		

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	Intravenous immunoglobulin	13 (4.4)	

COVID-19: Coronavirus disease 2019; ADPKD: Autosomal dominant polycystic kidney disease; CMV: Cytomegalovirus; EBV: Epstein-Barr virus; BKV: BK virus; MMF: Mycophenolate mofetil; Aza: Azathioprine; CyA: Cyclosporine; Tac: Tacrolimus; BMI: Body mass index.

compared to 1.4% in patients without COVID-19 but with no significant differences in outcomes, including the need for mechanical ventilation, hospital stay and a 50-d follow-up survival rate[15].

A growing body of evidence reveals the relationship between SARS-CoV-2 infection and acute pancreatitis[12,16]. The virus has been isolated from the pancreatic pseudocyst of a patient with acute pancreatitis[17]. The receptor theory suggests that expression of the angiotensin-converting enzyme-2 receptor and transmembrane serine protease 2, which are receptors for the SARS-CoV-2 are more pronounced within the gastrointestinal tract comparable to the respiratory mucosa, thus enabling the transfer of the virus into the tissue with consequent pancreatic tissue damage[18]. This increased pancreatic SARS-CoV-2 affinity may lead to the elevation of pancreatic enzymes without manifesting as acute pancreatitis. Therefore, it is important to interpret data in the clinical context to prevent overdiagnosis/misdiagnosis and patient harm[19].

Besides potential direct and indirect viral effects, antiviral drugs may induce pancreatic lesions. For example, remdesivir, used in COVID-19 treatment, may increase serum triglycerides, thus increasing the risk for acute pancreatitis^[20].

Our immunocompromised patient had two out of three criteria for acute pancreatitis. Typical clinical presentation and laboratory findings without radiological changes indicate serous pancreatitis that may be viral aetiology.

Similar to our experience, Kumar et al^[21] report that patients with acute pancreatitis on admission had a better clinical outcome when compared to patients who developed acute pancreatitis during hospitalization for acute COVID-19.

Our study has several limitations, mainly due to the retrospective nature of this study. We are missing data for 25 transplant recipients who died in the period during or after the infection outside the hospital and 62 transplant recipients who had not been assessed in our clinic and were therefore excluded from the study population, leading to possible underdiagnosis of pancreatitis. Considering that we described only one case with acute pancreatitis and COVID-19, we cannot analyse the specific characteristics of this group of patients. Furthermore, we did not measure amylase and lipase in our patient's cohort to see whether they had increased values compared to the non-COVID population.

CONCLUSION

The incidence of acute pancreatitis in the COVID-19 setting in the transplant population is low. However, the mechanism of injury to the pancreas and its correlation with the severity of the COVID-19 infection in kidney transplant recipients warrants further research.



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ARTICLE HIGHLIGHTS

Research background

Acute pancreatitis, an infrequent extrapulmonary manifestation of coronavirus disease 2019 (COVID-19), raises uncertainties about its association with the viral infection. Existing literature presents conflicting evidence, with some studies indicating elevated mortality in COVID-19 patients with acute pancreatitis while others report no significant impact.

Research motivation

No prior literature explores the occurrence of acute pancreatitis in the kidney transplant population in the context of COVID-19.

Research objectives

To describe the occurrence, clinical presentation and outcomes of acute pancreatitis in a cohort of kidney transplant recipients with acute COVID-19.

Research methods

A retrospective observational single-center cohort study conducted at a single transplant center in Croatia, encompassing all adult renal transplant recipients with a functioning kidney allograft between March 2020 and August 2022. Data, including cases of acute pancreatitis during acute COVID-19, were retrieved from electronic medical records.

Research results

Out of 1432 renal allograft recipients, 28.49% developed COVID-19. Hospitalization was necessary for 39.1% of patients, with 44.1% developing pneumonia and 1.3% requiring mechanical ventilation. Treatment involved immunosuppression modification in 77.1% and remdesivir in 16.6%, alongside other supportive measures. Acute pancreatitis occurred in one transplant recipient (0.3%). The patient recovered without complications, maintaining stable kidney allograft function.

Research conclusions

Although uncommon, acute pancreatitis may complicate the course of acute COVID-19 in kidney transplant recipients.

Research perspectives

Further research is warranted to explore the mechanism of pancreatic injury and its correlation with the severity of COVID-19 infection in kidney transplant recipients.

FOOTNOTES

Author contributions: Basic-Jukic N was involved in conceptualization of the study; Juric I, Katalinic L, Furic-Cunko V were responsible for data curation; Juric I and Katalinic L drafted the original version of the manuscript; Basic-Jukic N, Furic-Cunko V, Mrzljak A and Sesa V reviewed and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

Institutional review board statement: The study was reviewed and approved by the Ethic Committee of University Hospital Centre Zagreb (Approval No. 8.1-21/252-2).

Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at: nina_basic@net.hr. Participants gave informed consent for data sharing.

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