

SYSTEMATIC REVIEW

Clinical presentation of painless pancreatitis: a systematic review

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Abstract

Painless pancreatitis is a slowly developing syndrome that involves inflammation, scarring and thickening of pancreatic cells and is often difficult to clinically diagnose due to lack of pain and indolent course. Thus, to increase awareness of this disease and improve its diagnosis, we conducted this study to investigate the epidemiology, clinical presentation and outcomes of painless pancreatitis. This systematic review was designed to investigate the epidemiology, clinical course and presentation, cause and comorbidities of painless pancreatitis. The PubMed database was used to search for the following keywords: “Clinical presentation”, “painless pancreatitis” and “case report” until August 2021. The following data were collected: country, age, gender, alkaline phosphatase, total bilirubin, lipase, amylase, comorbidity of hypertension, diabetes mellitus, alcohol consumption, symptoms of malaise, jaundice, diarrhea, vomiting, surgical intervention, drain and analyzed statistically. There are 23 cases from 22 case reports enrolled into study. The mean age of the included patients was 44.7 ± 20.6 years old. Males accounted for 73.9% of all cases. The rate of a personal history of smoking and alcohol drinking was 46.2% and 31.6%. A history of hypertension and diabetes was observed in 8.7% and 17.4% of the cases. Fever was documented in 75% of cases. A significant and positive correlation was observed between biochemistry results, including amylase and lipase, total bilirubin and direct bilirubin, and painless pancreatitis ($r = 0.571$ and $r = 0.193$). Alkaline phosphatase and the victim's age were negatively correlated with painless pancreatitis ($r = -0.183$, $p = 0.042$). In this study, we found that painless pancreatitis was predominant in males and presented mainly with fever, distended abdomen without pain. A personal history of smoking and alcohol drinking was observed in 46.2% and 31.6% of cases.

Keywords

Amylase; Gender; Lipase; Painless; Pancreatitis

1. Introduction

Painless pancreatitis, first described by Gambill *et al.* [1] in 1948, is considered as another presentation of chronic pancreatitis [1, 2]. It is a slowly developing syndrome involving inflammation, scarring and thickening of pancreatic cells. Chronic painless pancreatitis may present with painless but full or burning sensation of the abdomen, obstructive jaundice and weight loss, or via incidental images due to other complaints such as pancreatic insufficiency, pancreatic adenocarcinoma and new-onset of diabetes mellitus [3]. The incidence rate of painless pancreatitis may be up to 72% among people who have just been newly diagnosed with diabetes mellitus (DM) [4]. The etiology of painless pancreatitis is uncertain, but a systematic review showed up to 96% were caused by calcium deposits in the pancreatic system, followed by idiopathic or genetic etiology, diabetes mellitus and exocrine pancreatic insufficiency [5]. Thus, physicians need to be aware of the

possibility of painless pancreatitis to prevent the patient from disease exacerbation and avoid comorbidities such as adenocarcinoma of the pancreas, diabetes mellitus and exocrine insufficiency of the pancreas [6]. In this study, we investigated the epidemiology, clinical course and presentation, cause and comorbidities of painless pancreatitis.

2. Materials and Methods

This systematic review was designed to investigate the epidemiology, clinical course, incidence, cause, presentation, epidemiology, and comorbidity of painless pancreatitis. A search using keywords “Clinical presentation”, “painless pancreatitis” and “case report” was performed on PubMed until August 2021, which yielded a total of 44 potential articles. Of them, three case reports describing abdominal pain were excluded, and 19 case reports contained missing data on alkaline phosphatase (U/L), aspartate transaminase (AST) (U/L), alanine

aminotransferase (ALT) (U/L), total bilirubin (mg/dL), lipase (U/L), and amylase (U/L).

The following data were retrieved and systemically analyzed from the 22 eligible studies: country, age (years old), gender, alkaline phosphatase (U/L), aspartate transaminase (AST) (U/L), alanine aminotransferase (ALT) (U/L), total bilirubin (mg/dL), direct bilirubin (mg/dL), lipase (U/L), amylase (U/L), comorbidity of hypertension, diabetes mellitus, alcohol consumption, symptoms of malaise, jaundice, diarrhea, vomiting, surgical intervention and abdominal drainage.

The SPSS statistical software (SPSS Statistics for Windows, version 25.0. IBM Corp., Armonk, NY, USA) was used for regression analysis in biomarkers was performed, and $p < 0.05$ was used to indicate a statistically significant difference.

3. Results

After inspecting the retrieved studies, 22 case reports comprising of 23 patients were identified as eligible. The cases' past medical and personal history, laboratory results, subsequent management, clinical symptoms and signs, diagnoses are listed in Table 1. Of the retrieved studies, there were three cases reported from Germany, France and the United States. Two cases were reported from India and the United Kingdom, and one each from China, Greece, Israel, Italy, Japan, Korea, Singapore, Switzerland, Taiwan and Turkey.

Males accounted for 73.9% (17 in 23) of the whole cohort. The mean (\pm Standard deviation (SD)) age of the patients was 44.7 ± 20.6 years old. A personal history of smoking and alcohol drinking was observed in 46.2% and 31.6% of the cases. Further, a history of hypertension and diabetes was observed in 8.7% and 17.4% of the enrolled cases. Fever was documented in 75% (6 of 8) of the cases. Shock was reported in 2 of 4 patients by value of blood pressure. Tachycardia was observed in 28.6% (2 of 7) cases with a heart rate record. The reported signs and symptoms included abdomen distention, vomiting, jaundice, diarrhea, and lassitude, and their corresponding proportion are listed in Table 1. Seven of 23 cases (30.4%) accounted for immunoglobulin G4 (IgG4) elevation-related pancreatitis.

A significant correlation was observed between biochemistry results (amylase, lipase, bilirubin, and alkaline phosphatase) after analyses of linear regression. Amylase is significantly positively correlated to lipase ($r = 0.571, p < 0.001$) (Fig. 1). Direct bilirubin level showed a weakly positive correlation to total bilirubin ($r = 0.193, p = 0.036$) (Fig. 2). Alkaline phosphatase levels were negatively correlated to the painless pancreatitis patients' age ($r = -0.183, p = 0.042$) (Fig. 3). In regard to treatments, we found that 39% of the patients received non-surgical treatment, of whom 17.4% also had stent for bile duct insertions, while 47.8% of the patients treated by surgical intervention, of whom 13% had abdominal drainage.

4. Discussion

TABLE 1. Basic data of 23 painless pancreatitis cases.

Painless pancreatitis (23)	
Age (years old)	44.7 \pm 20.6
Gender (n, %)	
Male	17, 73.9%
Female	6, 26.1%
Autoimmune (7)	30.3%
Idiopathic (4)	17.4%
Infection related* (4)	17.4%
Acute (2)	8.7%
Acute on Chronic (2)	8.7%
Poisoning** (2)	8.7%
Hereditary (1)	4.4%
Tumor (1)	4.4%
Smoking	46.2%
Alcohol drinking	31.6%
Hypertension	8.7%
Diabetes mellitus	17.4%
Fever	75.0%
Jaundice	65.2%
Lassitude	40.9%
Vomiting	18.2%
Diarrhea	17.4%
Abdominal distension	13.0%
Tachycardia	28.6%
Shock	50.0%
Management	
Medical	39.0%
Surgery	47.8%
Stent	17.4%
Drain	13.0%
Lipase (U/L)	631.9 \pm 411.5
Amylase (U/L)	513.0 \pm 444.7
Aspartate transaminase (AST) (U/L)	179.7 \pm 119.0
Alanine aminotransferase (ALT) (U/L)	195.1 \pm 110.5
Alkaline phosphatase (ALP) (U/L)	518.7 \pm 303.4
Total bilirubin (mg/dL)	9.5 \pm 5.3
Direct bilirubin (mg/dL)	6.8 \pm 2.1

*, abscess, leptospirosis, pneumonia and tuberculosis.

**, mevinphos, mushroom.

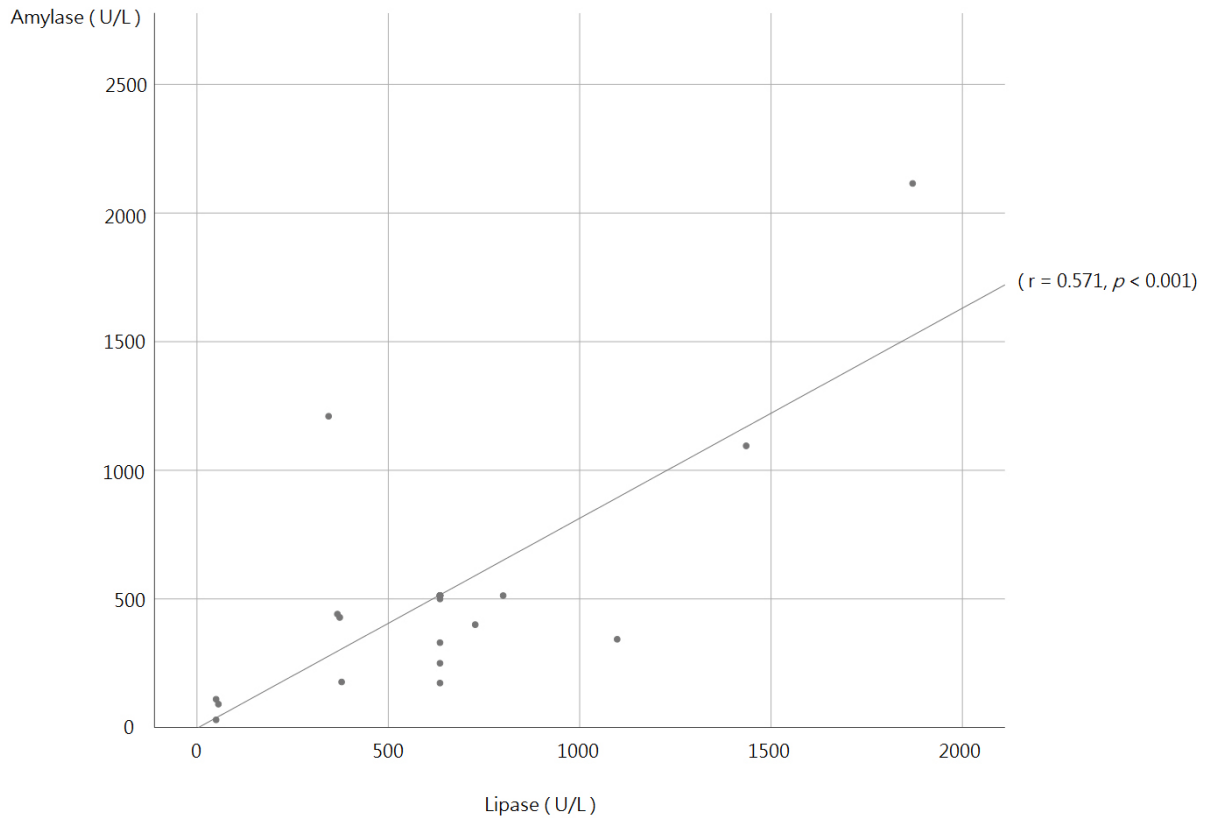


FIGURE 1. Amylase demonstrate a significant and positive correlation to lipase in patients with painless pancreatitis ($r = 0.571, p < 0.001$).

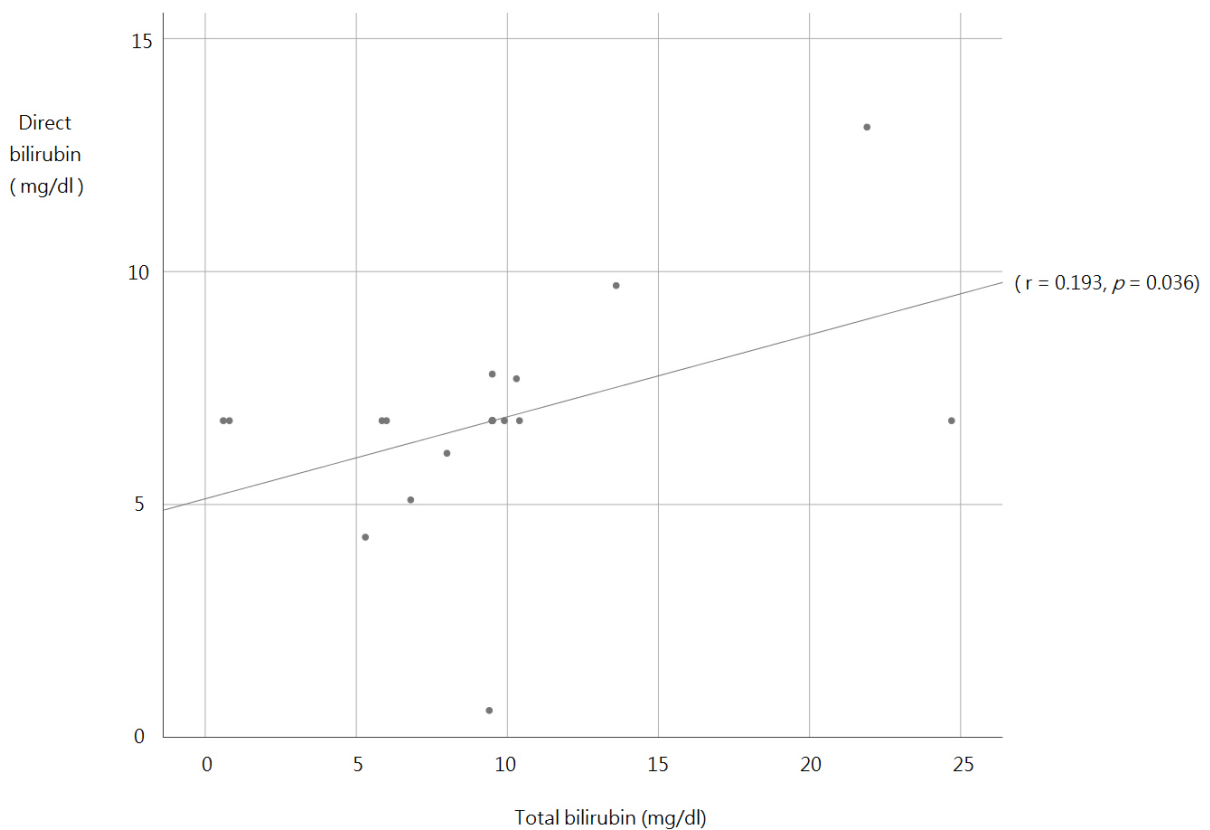


FIGURE 2. Total bilirubin and direct bilirubin demonstrate a significant positive correlation in patients with painless pancreatitis ($r = 0.193, p = 0.036$).

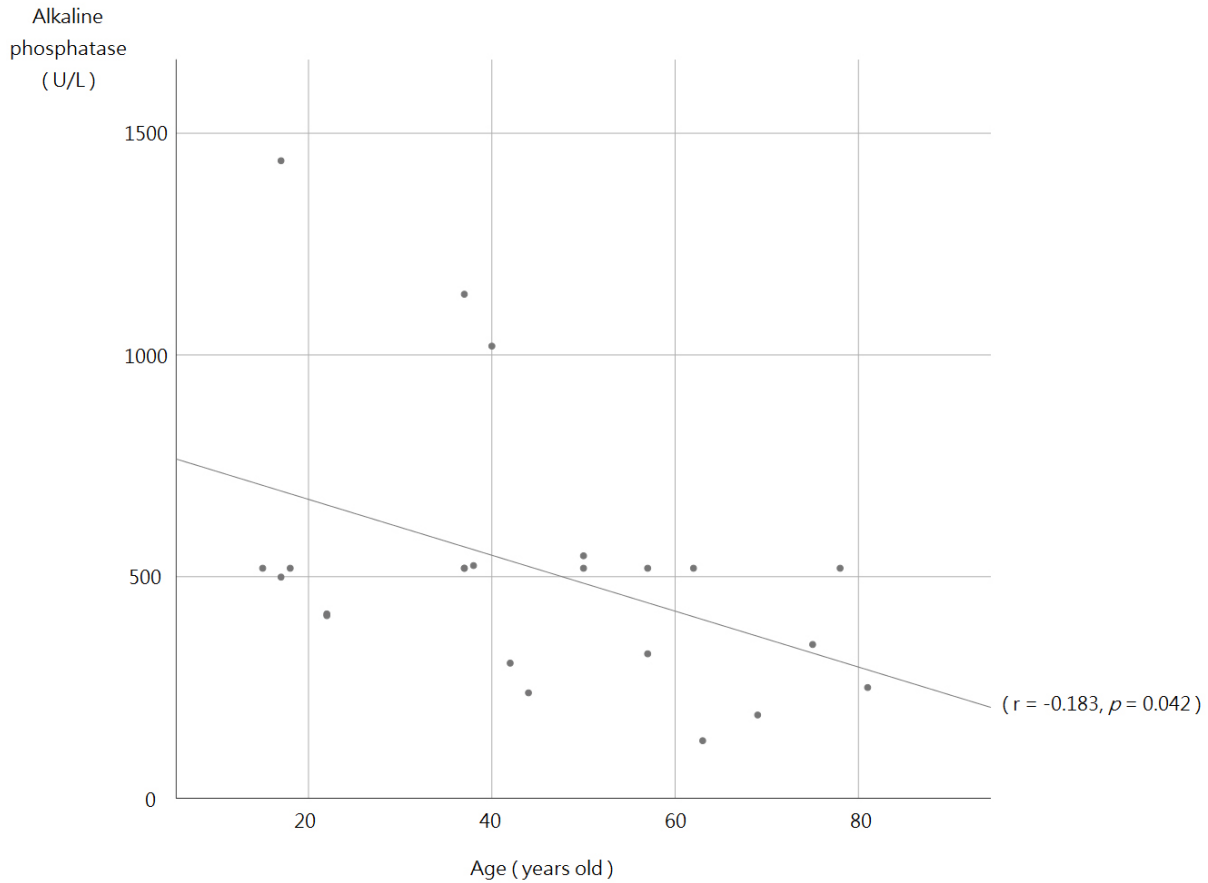


FIGURE 3. Alkaline phosphatase and the victim’s age demonstrate a negative correlation in patients with painless pancreatitis ($r = -0.183, p = 0.042$).

4.1 Epidemiology and etiology of painless pancreatitis

According to our results, the mean age of painless pancreatitis patients was 44.7 years old, which is very close to the common age of acute pancreatitis, especially in those who drink more than a threshold of five alcoholic drinks per day [7]. On the other hand, the mean age of 61 years was reported in a chronic painless pancreatitis study by Amodio *et al.* [4] Kamisawa *et al.* [5] also reported that painless pancreatitis was more often seen in elderly adults in Japan, especially in people older than 60 years old.

Our study found a higher proportion of males diagnosed with painless pancreatitis, with a male to female ratio of 2.8:1. Kamisawa and Ammann also reported that males in the general population were at higher risk for painless pancreatitis. We hypothesized that this gender predominance could be related to the association between painless pancreatitis and autoimmune diseases (as a causative role), such as Sjögren’s syndrome, sclerosing cholangitis and retroperitoneal fibrosis, which mainly affect males as well. However, the gap between males and females was reported to shrink slowly with age [5, 8].

The incidence of painless pancreatitis was first reported to be around 10–15% in 1948 but has now increased to up to 51% in recent studies, possibly because of the globalization of diagnostic computed tomography [1, 5]. Further, it was also reported that the incidence rate of painless pancreatitis

might be up to 72% among people who have just been newly diagnosed with diabetes mellitus [4].

The etiology of painless pancreatitis is multifactorial and may also be related to liquor consumption, genetic factor, lipid disorder and idiopathic [2]. The characteristics of painless pancreatitis are a full or burning sensation of the abdomen without pain, obstructive jaundice, weight loss often combined with the presence of excess fat in feces, calcium deposits in the pancreatic system followed by idiopathic or genetic etiology, diabetes mellitus and exocrine pancreatic insufficiency and impaired transport or excretion of bilirubin into the bile canaliculus or swollen pancreas [3, 5].

4.2 Comparison to painful pancreatitis

Pain is the obvious symptom of acute pancreatitis or an acute onset of chronic relapsing pancreatitis [9]. The pain is usually located in the upper abdomen and may radiate to the back. However, painless pancreatitis is mainly manifested by abdominal distension, obstructive jaundice and severe functional insufficiency of the exocrine or endocrine pancreas. Numerous factors, such as biliary tract disease, chronic alcoholism, pancreatic duct obstruction, infection, trauma, post-endoscopic retrograde cholangiopancreatography, hyperparathyroidism and hyperlipidemia, have been described as possible etiology of pancreatitis [10].

Although the cause of painless pancreatitis remains uncertain, it is believed that it could be the sequelae of repeated

episodes of acute pancreatitis. Further, it could result from an insidious chronic inflammatory process, which is thought to be related to an autoimmune mechanism [2]. Surgical indications include the presence of gallstones in the gallbladder or biliary tree, infected necrosis, and necrosectomy in symptomatic patients [11].

The main treatment of painless pancreatitis is conservative medication or endoscopic intervention because the absence of pain eliminates the main indication of surgery. The overall mortality rate of acute pancreatitis is about 21.1% and may differ based on the severity of the disease. Only 2.22% of the patients with a mild disease might succumb to the disease, as opposed to 45.63% of patients with the severe form of the disease [12]. However, there is currently no report suggesting painless pancreatitis as a cause of death.

4.3 Male is fragile to painless pancreatitis

Our results showed that painless pancreatitis was more prominent in males than females (male:female ratio, 2.8:1). The possible reasons could be because type 1 autoimmune pancreatitis, a systemic disease affecting the pancreas, bile ducts, salivary glands, kidneys, and other organs with infiltration of IgG4-bearing plasma cells, is often associated with elevations in serum levels of IgG4 [2]. Type 1 autoimmune pancreatitis is most commonly seen in middle-aged men presenting with painless obstructive jaundice [13, 14]. On the other hand, painless pancreatitis as a result of the repeated episodes of acute pancreatitis most commonly develops in men aged about 40 years old who are long-term heavy drinkers [7]. The two cases associated with chronic alcohol abuse were both in males [15, 16]. The reason for painless pancreatitis in women could be related to a genetic condition characterized by recurrent episodes of inflammation of the pancreas, such as hereditary pancreatitis or juvenile idiopathic pancreatitis; however, considering that these congenital problems are relatively rare, this might be the reason for the low prevalence of painless pancreatitis in women [17, 18].

4.4 Lipase is positively associated to amylase in painless pancreatitis

In a previous study on acute pancreatitis, the authors reported a positive correlation between lipase and amylase [19]. The result indicated that both tests were not necessary to be performed, and it was confirmed in a recent study that proved that testing with both tests at the same time did not increase their diagnostic precision [20].

In our study, we observed a positive correlation ($r = 0.571$) between serum amylase and lipase concentrations in painless pancreatitis. Therefore, we can speculate that clinicians could choose lipase or amylase to diagnose painless pancreatitis. As lipase assays are slightly more specific, offer a larger diagnostic window and are more sensitive in alcoholic pancreatitis and hypertriglyceridemia, testing lipase alone might be a reliable method to diagnose painless pancreatitis.

4.5 Weakly positive correlation between total and direct bilirubin in painless pancreatitis

In our study, direct bilirubin level showed a weakly positive correlation to total bilirubin ($r < 0.3$). Seven patients had elevated total and direct bilirubin levels, with the direct type exceeding half of the total bilirubin. Six patients had hyperbilirubinemia, and 66.7% were due to autoimmune pancreatitis. The only unconjugated hyperbilirubinemia was an IgG4-related disease presenting with painless obstructive jaundice, organomegaly and lymphadenopathy.

The reference range of alkaline phosphatase (ALP) is highly dependent on age [21]. A high bony growth rate during teenage years could cause bone isoenzyme fraction to reach peak levels. The reference level gradually decreases to the normal adult level after reaching their 20s and is similar between men and women. Our regression result showed a weakly negative correlation ($r < -0.3$) between ALP and age, which might reflect the background reference level and has no association with the severity of painless pancreatitis. Compared with classic pancreatitis, marked elevated lipase, direct bilirubin and ALP level in biliary pancreatitis, in non-biliary pancreatitis, elevated amylase and total bilirubin are more significantly observed [22].

4.6 Outcomes of painless pancreatitis are better than painful pancreatitis

The outcome of painless pancreatitis is at an average level. Three cases were admitted to the intensive care unit (ICU) due to hemodynamic instability, but all successfully recovered and were discharged from the hospital.

5. Conclusion

Painless pancreatitis is predominant in males and is a slowly developing syndrome characterized by inflammation, scarring and thickening of pancreatic cells. The mean age of the patients is 44.7 years old and may present with fever, burning sensation of the abdomen without pain, obstructive jaundice, weight loss, vomiting and diarrhea. The etiology could be related to liquor consumption, genetic factor and lipid disorder or might be idiopathic. A personal history of smoking and alcohol drinking was observed in 46.2% and 31.6% of the cases. A history of hypertension and diabetes was present in 8.7% and 17.4% of the enrolled cases. The outcome of painless pancreatitis was found to be less life-threatening compared with acute pancreatitis.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

YJS designed the research study. NHL, CC and HWY performed the research. YJS, NHL, and HWY analyzed the data. We all wrote the manuscript. All authors read and approved

the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the institution review board (IRB) of MacKay Memorial Hospital (approval number: 22MMHIS174e).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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