ACUTE PANCREATITIS IN CHILDREN IN UNIVERSITY MALAYA MEDICAL CENTRE: A DESCRIPTIVE STUDY

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ABSTRACT

ACUTE PANCREATITIS IN CHILDREN IN UNIVERSITY MALAYA MEDICAL CENTRE: A DESCRIPTIVE STUDY

Background: Acute pancreatitis in children is uncommon but when it occurs, it can be associated with severe morbidity and mortality. The purpose of this study was to describe the clinical presentation, etiology, diagnosis, severity, management, outcome and follow up of acute pancreatitis in children in UMMC.

Methods: Children and adolescent less than 18 years old, diagnosed with acute pancreatitis were recruited by searching DSM-ICD 10 code for acute pancreatitis in UMMC beginning from 1st January 2007 till 31st July 2017. Most patients recruited were gastroenterology and oncology patients. Patients were included if they are less than 18 years old and diagnosed with acute pancreatitis for the first time. Data described include clinical presentation, etiology, severity, diagnosis, management, outcome and follow up of acute pancreatitis

Results: There were 36 cases diagnosed with acute pancreatitis included. On average there were 3 cases per year diagnosed with acute pancreatitis in children in UMMC. Age range from 2 to 18 years old (median age 10.5 years old). The most common cause of acute pancreatitis in UMMC is idiopathic (n=16). Other causes include drug-induced (n=4), congenital biliary anomalies (n= 5), gallstones (n=3), post-ERCP (n=1), pancreaticobiliary anomaly (n=1) and hereditary (n=2). The most common presenting symptoms were abdominal pain (n= 33) which were mainly epigastric pain followed by vomiting (n=18). Thirty six children diagnosed with acute pancreatitis in UMMC met at least 2 out 4 diagnostic criteria for acute pancreatitis thirty three children had typical abdominal pain, 23 had high urine amylase, 23 had high serum amylase, 18 had both high serum and urine amylase and 23 patients had abnormal radiological imaging. Pancreatic enlargement is the

most common radiological finding suggestive of acute pancreatitis in children in UMMC (n=13). Other abnormal radiological findings were dilated pancreatic duct (n=4), pancreatic pseudocyst (n=3), peripancreatic fluid (n=1) and pancreatic mass (n=1). There were a total of 33 children had mild disease and 3 with severe acute pancreatitis. Twenty-nine children with acute pancreatitis were given supportive treatment in which 27 of them had mild disease and 2 had severe disease. Seven children with mild disease were 4 patients with choledochal cyst and 3 with gallstones. All seven patients undergo surgery. Only one patient with severe disease underwent pseudocyst drainage because of worsening abdominal distension and peritonitis. Most common acute complication in children in UMMC were pancreatic pseudocsyt (n=3). From 36 children with acute pancreatitis, 18 resolved spontaneously, 8 had acute recurrent pancreatitis and 9 had chronic pancreatitis. Two children with chronic pancreatitis developed long term complications. One patient had Diabetes Mellitus requiring insulin and the other had malabsorption on CREON. There were 3 deaths but it was not related to acute pancreatitis, 2 due to relapse ALL and 1 due to hypovolaemic shock post choledochal cyst resection. Out of 33 children who are still alive, 20 children still continue their follow up and 13 were lost to follow up.

Conclusion: Paediatric pancreatitis is rare in children in UMMC. Most acute pancreatitis in children is mild and resolve spontaneously with medical and supportive treatment. Approximately about 5% of patients with acute recurrent and chronic pancreatitis may develop complications. Proper monitoring and follow up is important in patient with acute pancreatitis.

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LIST OF SYMBOLS AND ABBREVIATIONS

UMMC	University Malaya Medical Centre
AP	Acute Pancreatitis
ARP	Acute Recurrent Pancreatitis
CP	Chronic Pancreatitis
INSPPIRE	International Study Group of Pediatric Pancreatitis: In Search for Cure
JPN	Japanese
US	Ultrasound
CT	Computed Tomography
MRCP	Magnetic Resonance Cholangiopancreaticography
ERCP	Endoscopic Retrograde Cholangiopancreaticography
ALL	Acute Lymphoblastic Leukemia
IBD	Inflammatory Bowel Disease
SLE	Systemic Lupus Erythematous
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
SPINK1	Serine Protease Inhibitor Kazal-type1
SIRS	Systemic Inflammatory Response Syndrome
APACHE	Acute Physiology and Chronic Health Evaluation
NASPHGAN	North American Society for Pediatric Gastroenterology Hepatology and Nutrition
TPN	Total Parenteral Nutrition
EBV	Epstein-Barr virus
EMR	Electronic Medical Record
ICD-10	International Classification of Disease
NAI	Non accidental injury

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CHAPTER 1: INTRODUCTION

Pancreatitis is an inflammatory process in which pancreatic enzymes auto digest the gland. Pancreatitis is common in adults but relatively rare in the pediatric population. INSPPIRE (International Study Group of Pediatric Pancreatitis: In Search for Cure), has divided pancreatitis into 3 groups: acute pancreatitis (AP), acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP).

Table 1: Classification of pancreatitis

Classification	Definition
Acute Pancreatitis(AP)	fulfill 2 out of 3 criteria which are: 1) Abdominal pain compatible with AP(vague abdominal pain may or may not radiate to the back) 2) Serum amylase and/or lipase values 3 times upper limits of normal 3) Imaging finding compatible with AP (pancreatic edema, pancreatic or peripancreatic necrosis, peripancreatic inflammation, acute fluid collections, pancreatic hemorrhage, peripancreatic abscess and pancreatic pseudocyst.
Acute Recurrent Pancreatitis (ARP)	2 distinct episodes of AP with intervening return to baseline
Chronic Pancreatitis(CP)	the presence of typical abdominal pain plus characteristic imaging findings (pancreatic fibrosis) or exocrine insufficiency (malabsorption) plus imaging findings or endocrine insufficiency plus imaging findings

Acute pancreatitis is one of the common gastrointestinal disorders requiring acute hospitalization worldwide in adults, with a reported annual incidence of 13-45 cases per

100,000 in US(Chris et al 2016). However, acute pancreatitis in pediatrics is uncommon but when it occurs, it can be associated with severe morbidity and mortality. The causes of acute pancreatitis in pediatric patients are different from in adults. A few recent studies done in several countries, including Asian countries, showed that the incidence has increased possibly due to improvement in diagnostic tests including biochemistry and imaging and also possibly due to increased awareness of the disease(Goh, 2003, Ibrahim, 2011, Mitsuyoshi et al, 2014, MaonMen et al, 2002).

In Malaysia, available data for acute pancreatitis are only from adult patients(Kandasami 2002, Thamilselvam P 2008, Nadesan 1999). There is no local data for pediatric population. University Malaya Medical Centre (UMMC) is a tertiary care hospital with an established Pediatric Gastroenterology unit in Malaysia. The aim of this study is to describe the clinical presentation, diagnosis, etiology, severity, treatment and outcome of acute pancreatitis in pediatric patients in UMMC over past 10 years.

CHAPTER 2: LITERATURE REVIEW

2.1 Incidence of Pediatric Acute Pancreatitis

Acute pancreatitis(AP) is one of the common gastrointestinal disorders requiring acute hospitalization worldwide in adults, with a reported annual incidence of 13-45 cases per 100, 000 in United states(Chris et al 2016). Acute pancreatitis in pediatrics has been diagnosed more frequently in the past few decades, possibly due to an increase in health care provider awareness of pancreatitis which lead to a more thorough evaluation of this children. The incidence of pediatric AP in United States over the past few decades was estimated to be 13.2 cases per 100,000 per year (Monica et al 2017). This increase in the incidence of AP in the pediatric population has caused a significant health and economic burden from the hospitalization.

A few retrospective studies done in Asian countries showed the prevalence of acute pancreatitis is uncommon in pediatric patients (Maonmen et al 2002). Best comparison with Malaysian population for AP in pediatric patients is Singapore. Even though Singapore has smaller population (5 million) compared to Malaysia (31 million), both countries have many similarities. A 3 year retrospective study in KK Women and Child's Hospital, Singapore, found 12 pediatric patients with acute pancreatitis (Goh 2003) and there are more male diagnosed with acute pancreatitis compare to female and their mean age is 9 years old . A similar single center study in Taiwan found a total of 61 pediatric patients in Taiwan with acute pancreatitis over a period of 15 years (Maonmen et al 2002). Maonmen et al showed difference in sex ratio compared to Goh et al study but both study showed similar mean age. However, the median age reported by Henedina et al is higher compared to other study which is 15 years old and for Steven L et al is 12 years old. Both of these studies have shown that female is more predominant to get acute pancreatitis compared to male.

2.2 Etiology of Pediatric Acute Pancreatitis

The etiologies of acute pancreatitis in pediatric patients are different from adult. In adult , the most common etiologies are gallstones(40%) and alcohol(30%)(Chris et al, 2016). In children, common etiologies are trauma, congenital biliary anomalies and gallstones (Nydegger et al 2006).

Malaysia is a country with three main ethnic groups which include Malay, Indian and Chinese. In Malaysia, a few studies conducted to look for the common etiology among different ethnic groups for acute pancreatitis in adult patients(P Kandasami 2002, Thamilselvam P 2008, S. Nadesan June 1999). The common etiology for acute pancreatitis in Indian patients is alcohol while gallstone is common among Malay and Chinese patients. It is possibly due to different food habit or alcohol consumption between the ethnicity(Thamilselvam P 2008). Studies also show that female and male adult patients have different causes of acute pancreatitis. Common cause of acute pancreatitis in adult patients for male is alcohol and gallstone for female. However in pediatric, all studies show no difference between male and female(Goh 2003, Ibrahim 2011, Henedina et al 2014). No study has been done to look for etiologies among children of different ethnic groups.

Table 2: Etiologies of acute pancreatitis in pediatric (Nydegger et al 2006, Henedina et al 2014, Mitsuyoshi et al 2014)

Classification	Common Etiologies
Biliary	Choledochol cyst, cholecystitis, gall stones, pancrease divisum, pancreabilary maunion and tumor
Systemic	Shock, sepsis, haemolytic uremic syndrome, Kawasaki disease
Autoimmune	Inflammatory bowel disease(IBD), Systemic lupus Erythematous(SLE)
Trauma	Abdominal trauma, post ERCP
Infections	Measles, mumps, coxsackievirus, echovirus, influenza, Ebstein-Barr virus (EBV), mycoplasma, Salmonella, Hepatitis A and Escherichia coli
Metabolic	Hyperlipidemia, hypertriglyceridemia, diabetes mellitus, hypercalcemia,
Genetic mutation	Cystic fibrosis(mutation in CFTR) has been associated with autosomal recessively inherited pancreatitis, , mutation in the serine protease inhibitor Kazal type1(SPINK1), mutation in chymotrypsin
Medication	L-asparaginase, Valproic Acid, Azathioprine, Mercaptopurine and Mesalamine
Idiopathic	Unknown cause

Goh from Singapore and MaonMen et al from Taiwan reported that the most common etiology is trauma. Trauma can be either non-accidental or accidental injury. Based on Goh et al observation, home accidents and child abuse contributed to acute pancreatitis. The study suggest that the clinician should aware the possibility of acute pancreatitis in non accidental injury especially when handling children presenting with abdominal discomfort. However, in Western countries such Portugal, Henedina et al showed that congenital biliary anomalies are common in pediatric pancreatitis. Acute pancreatitis is thought as idiopathic when the cause is unknown after thorough investigations have

been done. Idiopathic acute pancreatitis is only reported as common in a study by Ibrahim et al.

2.3 Diagnosis of Pediatric Acute Pancreatitis

Diagnosis of acute pancreatitis is based on three criteria and to confirm the diagnosis, the patients need to fulfill two out three criteria which are (INSPPIRE criteria):

1) Abdominal pain compatible with AP

2) Serum amylase and/or lipase values three times upper limit or normal

3) Imaging finding compatible with AP.

Hence, laboratory and imaging investigations facilitate in the diagnosis of acute pancreatitis. Goh et al, Maonmen et al, Steven L et al, and Ibrahim et al use INSPPIRE criteria as diagnostic criteria to diagnose acute pancreatitis in their studies and their patients fulfilled the criteria.

2.3.1 Clinical Manifestation

Clinical manifestation for acute pancreatitis may vary from mild abdominal pain to the systemic presentations such as shock. All studies agree that abdominal pain is the commonest clinical presentation in acute pancreatitis both in adult and children. Studies done in Singapore, Taiwan and Western countries including United State, Portugal and United Kingdom reported that approximately 90% of children diagnosed with acute pancreatitis present with abdominal pain (Werlin et al 2003, Henedina et al 2014, Goh 2003, Maonmen et al 2004). Pain localised at the upper abdomen is most commonly reported by Goh and Henedina et al. However, Maonmen et al reported different findings in which abdominal pain is mostly generalised in their children during

presentation. Only a few patients have typical abdominal presentation like adult. It is rarely children presented with typical epigastric pain which radiated to the back. Non specific abdominal pain usually occurred among infants and young children and it is reported by Mitsuyoshi et al and Dabirian et al study.

In severe acute pancreatitis, the patients present with severe abdominal pain (generalized abdominal tenderness with guarding) associated with signs of shock (hypotension, tachycardia) followed by multi organ failure such as dyspnea, poor urine output, hemorrhage or changes in mental status(Dabirian 2016). Signs suggestive of hemorrhagic pancreatitis, Grey Turner and Cullen discolorations of the flanks are rare in pediatric(Nydegger 2006).

2.3.2 Laboratory parameters

Serum amylase and serum lipase are the biochemical markers that are used to diagnose acute pancreatitis(Matull 2006). They are used because these test are quick, cheap and reliable(HS Batra 2015). However, many studies showed that serum lipase is a better marker in diagnosing acute pancreatitis because serum lipase has longer half-life, better sensitivity and specificity(HS Batra 2015).Serum amylase is widely used to diagnose and easily available in most hospital because it is cheaper that serum lipase. All patients in the study by Goh have high serum amylase with one third of the patients has high serum amylase three times above the upper limit. Whereas, Maonmen et al reported, 52 out of 61 patients have high serum amylase. There is no difference found in serum amylase level between mild and severe acute pancreatitis. In acute pancreatitis, lipase starts to increase within 4-8 hours after the onset, peak at 24 hours and starts to decrease within 8-14 days. Serum amylase levels start to increase by 2 to 4 hours after the onset on acute pancreatitis, usually peaks at 48 hours and starts to decrease within 5 to 7 days. It is reported that serum lipase sensitivity range between 85% and 100% and specificity

95%(Matull 2006, HS Batra 2015). Serum amylase specificity is 95% and sensitivity is as low as 61%(Matull 2006). Serum lipase appears to be more specific than amylase because the levels remain elevated longer after the onset of acute pancreatitis. Increase in serum amylase can also be seen in other intra and extra-abdominal condition. Most studies reported that serum amylase or lipase levels has no role in determining the etiology, severity and prognosis of acute pancreatitis(Chang et al 2011, HS Batra 2015, Babyatsky 2015).

The molecular weight of amylase is 50,000 Daltons. It has low molecular weight and as a result, amylase can easily pass through the glomerulus into the urine(Mumtaz et al 2017). Urine amylase is also used to diagnose acute pancreatitis although non pancreatic disease can cause elevated urine amylase. Previous studies show urine amylase is more sensitive than serum amylase as it remains elevated for several days even though serum concentration has returned to normal (Hakayawa et al 1970). However in comparison to serum amylase and serum lipase, urine amylase is found not to have superior diagnostic availability(Babyatsky 2015). The specificity of urine amylase is very poor and there is also no cut off level for urine amylase to diagnose acute pancreatitis. Recent study by Mumtaz et al reported that urine amylase is highly sensitive indicator for acute pancreatitis because it remains abnormal even after serum concentration has returned to normal. Other than that, urine amylase has good correlation with serum amylase on admission. Therefore, urine amylase can be an alternative to serum amylase in diagnosing patient with acute pancreatitis(Mumtaz et al 2017).

2.3.3 Imaging

Radiological imaging is rarely necessary in patients with mild acute pancreatitis except for identifying the cause of acute pancreatitis. Imaging can be used as a supportive investigation in patients who fulfill the clinical criteria but not the biochemical markers.

The types of imaging studies includes transabdominal ultrasound (US), CT scan with contrast (CT), Magnetic Resonance Cholangiopancreatography(MRCP) or Endoscopic Retrograde Cholangiopancreatography(ERCP).

Transabdominal ultrasound is preferred in pediatric patients as it has no radiation exposure, no contrast agent and noninvasive. Furthermore, transabdominal ultrasound is inexpensive, widely available, quick and easy to perform. However, the limitations were limited window due to bowel gas. Transabdominal ultrasound is one the best modalities to detect gallstones, the sensitivity is about 95% (Thomas L Bollen 2016). It is helpful in identifying inflammation and enlargement of pancreas but not pancreatic necrosis.

Abdominal CT with contrast is the best radiological imaging used to diagnose acute pancreatitis and the local complications of the disease. Enlargement of pancreas, necrosis and peripancreatitis inflammation, pseudocyst, abscess, interpancreatic or pre pancreatic haemorrhage can be identified in abdominal CT with contrast. The sensitivity of CT scan is about 90% compared to US which is about 70%(Dabirian 2016).It is highly sensitive for detection of gas bubble and calcification. Furthermore, it is readily available in most tertiary institutions, and less expensive compared to MRI(Bollen et al 2016, Pathway 2012). The greatest limitation for CT scan is radiation exposure to children.

MRCP is useful in detecting intrahepatic and pancreatic ductal abnormalities, common bile duct abnormalities, choledocholithiasis, strictures, pancrease divisum, long common channel and pancreatic and biliary tumour. MRCP delineates the bile and pancreatic ducts better than CT and has a higher sensitivity in detecting choledocholitiasis. However, the detection of gas bubble is inferior compare to CT scan. (Thomas et al 2016). MRCP is an excellent alternative imaging for pediatric and pregnant mother as it has no radiation exposure. The major disadvantages for MRCP

are longer scanning time (not suitable for ill patient) and cost. For pediatric patient, sedation may be needed.

ERCP is particularly useful for the diagnosis and treatment non-resolving and recurrent biliary obstruction. ERCP is not beneficial in the absence of biliary obstruction (persistent bile duct stone), in mild cases of acute gallstone pancreatitis or as a diagnostic test before cholecystectomy(Chris et al 2016).

Ultrasound abdomen is used as the first choice of diagnostic imaging in Goh, Maonmen et al, Henedina et la, Ibrahim et al. However, CT abdomen has been shown to be superior to ultrasound in all these studies because most of the abnormal findings are seen in CT. Most common radiological findings seen are enlargement of pancreas and the most common complications seen are pancreatic pseudocyst.

2.4 Severity of Pediatric Acute Pancreatitis

Revised Atlanta 2012 Classification has classified acute pancreatitis based on the degree of severity into mild, moderately severe and severe acute pancreatitis(Peter et al 2013). The severity is based on the presence of local complications, systemic complications or organ failure. Local complications include peripancreatic fluid collections, necrotic fluid collections, pancreatic and peripancreatic necrosis and development of pseudo cyst and walled off necrosis. These changes can be seen in CT scan or MRI. Systemic complications in pediatric acute pancreatitis is defined as exacerbation of pre-existing underlying chronic disease precipitated by acute pancreatitis such as chronic lung disease, heart disease or renal disease(Banks 2013, Maissam et al 2017). Organ failure in adult is defined by a score of more than 2 or equal on modified Marshall scoring

system. Other scoring systems that are used are Ranson score, SIRS, Glasgow and APACHE II score.

However, all these scoring cannot be applied in the pediatric group because adult based metric and biochemistry values. There is no validated scoring for organ failure in pediatric. The scoring is important to predict the severity of acute pancreatitis.

The 2015 consensus from NASPGHAN (North American Society for Pediatric Gastroenterology Hepatology and Nutrition) pancreatic committee suggests that there should be a scoring to define organ failure in pediatric group. The study propose the scoring criteria for organ failure in pediatrics which is derived from the definitions accepted in the International Pediatric Sepsis consensus(Maissam et al 2017). Furthermore, Japanese (JPN) Guidelines 2015 has been widely used as a scoring system for organ failure in pediatric patients.

JPN Guidelines 2015 scoring system include eight parameters which are : 1) base excess – 3 mEq or shock (systolic BP cutoffs according to the age group); 2) PaO2 < 60 mmHg(room air) or respiratory failure 3) Blood urea nitrogen > 40 mg/dL or creatinine > 2 mg/dL or oliguria (< 0.5mls/kg/hour) 4) Lactate Dehydrogenase(LDH) > 2 times the value of the upper limit 5)Platelet count < 1X 10^5/mm3 6) Calcium < 7.5mg/dL 7) C-reactive protein > 15 mg/dL 8) Number of positive measures in pediatric systemic inflammatory response syndrome(SIRS) score > 3 and 9) Age < 7 years old/weight < 23 kg. If the patients fulfill three or more parameters, they may indicate a severe outcome(Masamichi et al 2015, Dabirian 2016).

Table 3: Severity classification of acute pancreatitis in children

Severity	Definition
Mild AP	• No presence of organ failure or local/systemic complications
Moderately severe AP	• Presence of either transient organ failure which lasted less than 48 hours or local/systemic complications
Severe AP	• Presence of persistent organ failure which is more than 48 hours

Goh and Maonmen et al did not look at the severity of acute pancreatitis in children. However, Werlin et al and Henedina et al reported that most of acute pancreatitis are mild and self-limiting and require brief hospitalization. Both studies classified severity according to Revised Atlanta 2012 Classification but with some modification. For the purpose of the study, both studies classified into mild and severe. Severe cases include children with moderately severe and severe. All children with moderately severe were considered as severe cases since the most severe case resolve organ failure within 48 hours. The median hospital stay range between 6- 12 days (Goh et al 2003, Maonmen et al 2004, Ibrahim et al 2011, Henedina et al 2014).

2.5 Management of Pediatric Acute Pancreatitis

Treatment of acute pancreatitis is determined by the etiological factors(Pancreatology 2013). There is not much difference in managing adult and pediatric patient. Acute pancreatitis can be treated conservatively or surgically. Majority of acute pancreatitis are mild and most resolve spontaneously. The initial treatment for acute pancreatitis is to withhold oral and fluid intake so as to allow the pancreas to rest (prevent stimulation of pancreatic exocrine secretion). Most mild to moderate AP will settle after keeping patient fasting for a few days. The resumption of enteral nutrition is usually after

complete resolution of abdominal pain and preferably after normalization of the serum enzymes levels(Abdelbasit 2012). The other supportive treatment include fluid and electrolytes supplementation and pain management(Mitsuyoshi et al 2014). Pain control is the most important management in acute pancreatitis. In general, narcotic analgesics for example morphine are preferred in children. However, there is concern that it would cause further exacerbation of the acute pancreatitis as morphine may cause spasm of sphincter of oddi(John et al 2015). Parenteral nutrition is required who had prolonged course of illness (Steven et al 2003).

ERCP or surgical approaches are rarely used in pediatric AP. ERCP is indicated within 24 hours in gallstones pancreatitis and within 72 hours if there is high suspicion of common bile duct stone(John et al 2015). In children, cholecystectomy can be done at a later stage when the patient's condition is favorable. Surgical intervention in pediatric patient with acute pancreatitis should be restricted to patients with complications such as severe necrotizing pancreatitis requiring debridement or in patients with other complications such pancreatic ascites, pancreatic abscess collections not amenable for percutaneous drainage and pancreatic pseudocyst(Abdelbasit 2012). Even in traumatic pancreatitis, most children can be treated conservatively without surgical intervention.

2.6 Complication of Pediatric Acute Pancreatitis

2.6.1 Early and late complication

Complication of acute pancreatitis in children can be divided into early onset, late onset and long term complication. It occurs less than 2 weeks from initial presentation whereas for late onset occurs after 2 weeks of initial presentation (Carlos et al 2011). Early onset complications include multi-organ dysfunction or shock. Two major organs

involved are the lung and kidney. Patients can develop acute respiratory distress syndrome, pleural effusion, pneumonia or renal failure. Late onset complications are mainly pancreatic necrosis or pseudocyst. Pancreatic necrosis can be either infected or non infected. Both late onset complications can be managed conservatively. Harrison et al reported that, the size of the pseudocyst is not a prognostic factor because even large pseudocyst may resolve spontaneously and percutaneous drainage has higher mortality (16%). The most reported complication in children in previous studies were pleural effusion followed by pancreatic pseudocyst (Henedina et al 2014, Ibrahim et al 2011). Ibrahim et al reported that the other common complication is hyperglycemia.

Table 4: Early and late onset complication in acute pancreatitis in children (Carlos et al 2011)

Early complication	Late complication
Shock	Edema
Pleural effusion	Fat necrosis
Acute renal failure	Coagulopathy
Pancreatic necrosis	Pancreatic pseudocyst
Rupture or pancreatic duct stricture	Bacteremia
Sepsis	Multisystem organ failure
Haemorrhage	Hypermetabolic state
Hyperglyacemia	Abscess
Vascular loss	Peritonitis

2.6.2 Long term complication

Acute recurrent pancreatitis and chronic pancreatitis are the long term complication of acute pancreatitis. Approximately about 10% of children with AP can develop ARP or CP. Acute recurrent pancreatitis (ARP) is defined as more than two episodes of AP without any evidence of chronic pancreatitis. Based on Kedia et al, ARP usually occurs in the idiopathic group. Ibrahim et al reported that the most common long term complication is acute recurrent pancreatitis.

Table 5: Common cause of acute recurrent pancreatitis in children (Kedia et al 2014)

Mechanical	Toxic Metabolite
Gallstone	Hypertriglyceridemia
Sphincter of oddi dysfunction	Hypercalcaemia
Pancreas divisum	Drugs
Congenital biliary anomalies	Miscellaneous • Vascular • Hereditary • Genetic mutation • Chronic Pancreatitis
Pancreatobiliary tumour	
Trauma	
Parasitic Infections	

Chronic pancreatitis (CP) is a progressive inflammatory disease leading to irreversible damage of the pancreas with resultant exocrine and endocrine insufficiency. Recurrent or chronic abdominal pain is one the most common distressing symptoms of CP. Diagnosis of CP are based on the presence of typical clinical presentation (abdominal pain) and abnormal imaging (pancreatic calcification, atrophy or ductal dilatation) (Chowdury et al 2013).CP is rare in children. Trauma and hereditary pancreatitis are the

two known causes of pediatric CP. Long term follow up is needed for patients with ARP or CP. Exocrine and endocrine complication are rare in children with ARP and CP (Ibrahim et al 2011). There were 2 cases reported in Ibrahim et al, one patient complicated with endocrine complication in which child has Diabetes Mellitus and one patient has exocrine complication. No reported cases in other studies.

CHAPTER 3: OBJECTIVES

- To describe the clinical manifestation, etiology, diagnosis, management, outcome and follow up of acute pancreatitis in children in University Malaya Medical Centre from 1st January 2007 till 31st July 2017.

CHAPTER 4: METHODOLOGY

4.1 Study Center

This study was done in University Malaya Medical Center (UMMC). UMMC which was formerly known as University Hospital is a government-funded medical institution located in Pantai Dalam, southwest corner of Kuala Lumpur. It was established by statute in September 1962 and is part of University of Malaya (UM). It is also a teaching hospital, catering for the educational and training needs of undergraduate and postgraduate student of UM. Currently, UMMC has approximately 1300 beds and 44 wards; the medical center serves population of 1,782,375 in the district of Petaling.

4.2 Study Design

This is a single center, retrospective cohort study conducted at University Malaya Medical Center (UMMC). Ethical approval was obtained from institution's ethics committee. (Ethics committee/MEDIC. No.201762-5304)

4.3 Study Period

The study period is between 1st January 2007 until 31st July 2017.

4.4 Study Population

Patients were diagnosed with acute pancreatitis in University Malaya Medical Centre from 1st January 2007 till 31st July 2017.

a) Inclusion Criteria

1) All children and adolescent who were less than 18 years old
2) All patients diagnosed with acute pancreatitis who presented to University Malaya Medical Centre for the first time

b) Exclusion Criteria

1) Patients who were more than 18 years old

4.5 DATA COLLECTION

The patients were recruited by searching DSM-ICD-10 code for acute pancreatitis (K85.9) from UMMC medical record from 1st January 2007 until 31st July 2017.

Collection data includes (Appendix A: Data collection form):

1) Age of presentation
2) Year of presentation
3) Gender
4) Race
5) Comorbidity (Yes or No)
6) Duration of hospital stay
7) Diagnosis

- Clinical manifestation
- Biochemical level on admission includes:
  - Serum amylase (30-118 U/L)
  - Urine amylase (0-650 U/L)
- Radiological finding

8) Severity (Revised Atlanta 2012 Classification)

- Mild (mild)
- Severe(moderately severe and severe)

9) Outcome

- Early and late onset complication
- Long term complication
  - Acute recurrent pancreatitis
  - Chronic pancreatitis
  - Endocrine complication

- Exocrine complication

- Follow up
  - Defaulted
  - Death

10) Management
  - Medical
  - Surgical

4.6 Data Description

Data described includes clinical presentation, etiology, severity, diagnosis, management, outcome and follow up of acute pancreatitis. Outcome measures were complications of acute pancreatitis, morbidity and mortality.

4.7 Ethical Approval

Ethical approval for this study was obtained from the Ethical Review Committee of UMMC (MECID No: 201762-5304) – Appendix B

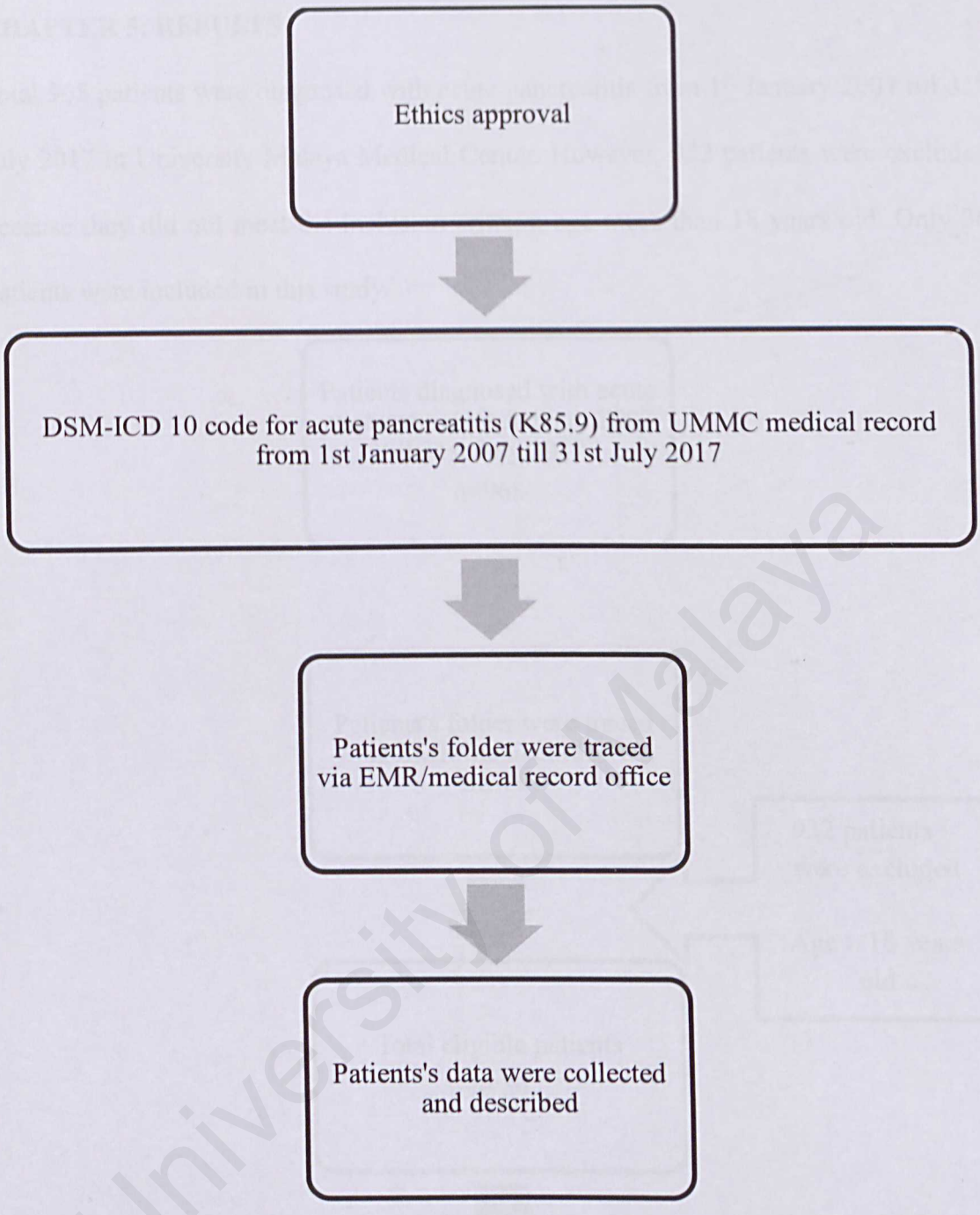
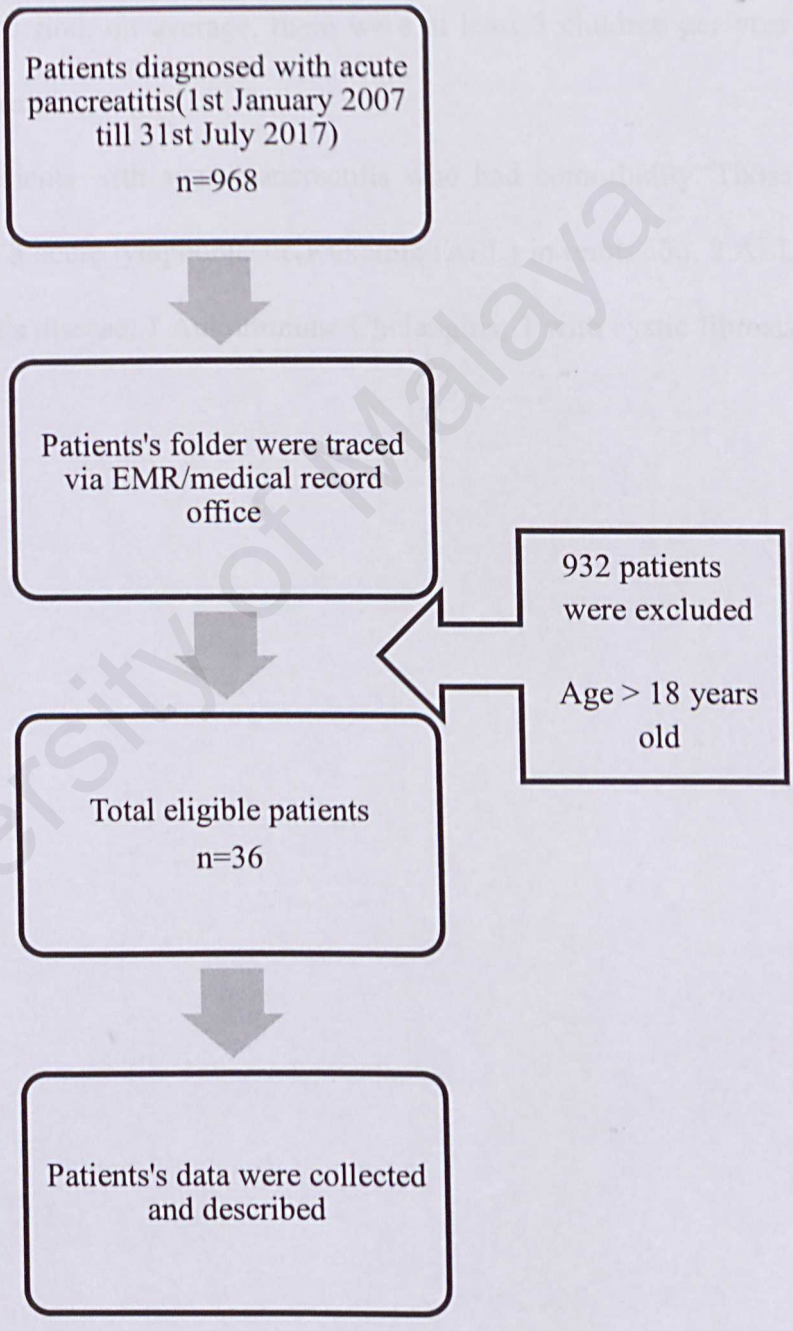


Figure 1: Study flow chart

CHAPTER 5: RESULTS

Total 968 patients were diagnosed with acute pancreatitis from 1st January 2007 till 31st July 2017 in University Malaya Medical Center. However, 932 patients were excluded because they did not meet the inclusion criteria: age more than 18 years old. Only 36 patients were included in this study.



EMR: Electronic medical record

AP: Acute pancreatitis

Figure 2: Flow chart for patient's recruitment

5.1 Demographic Data

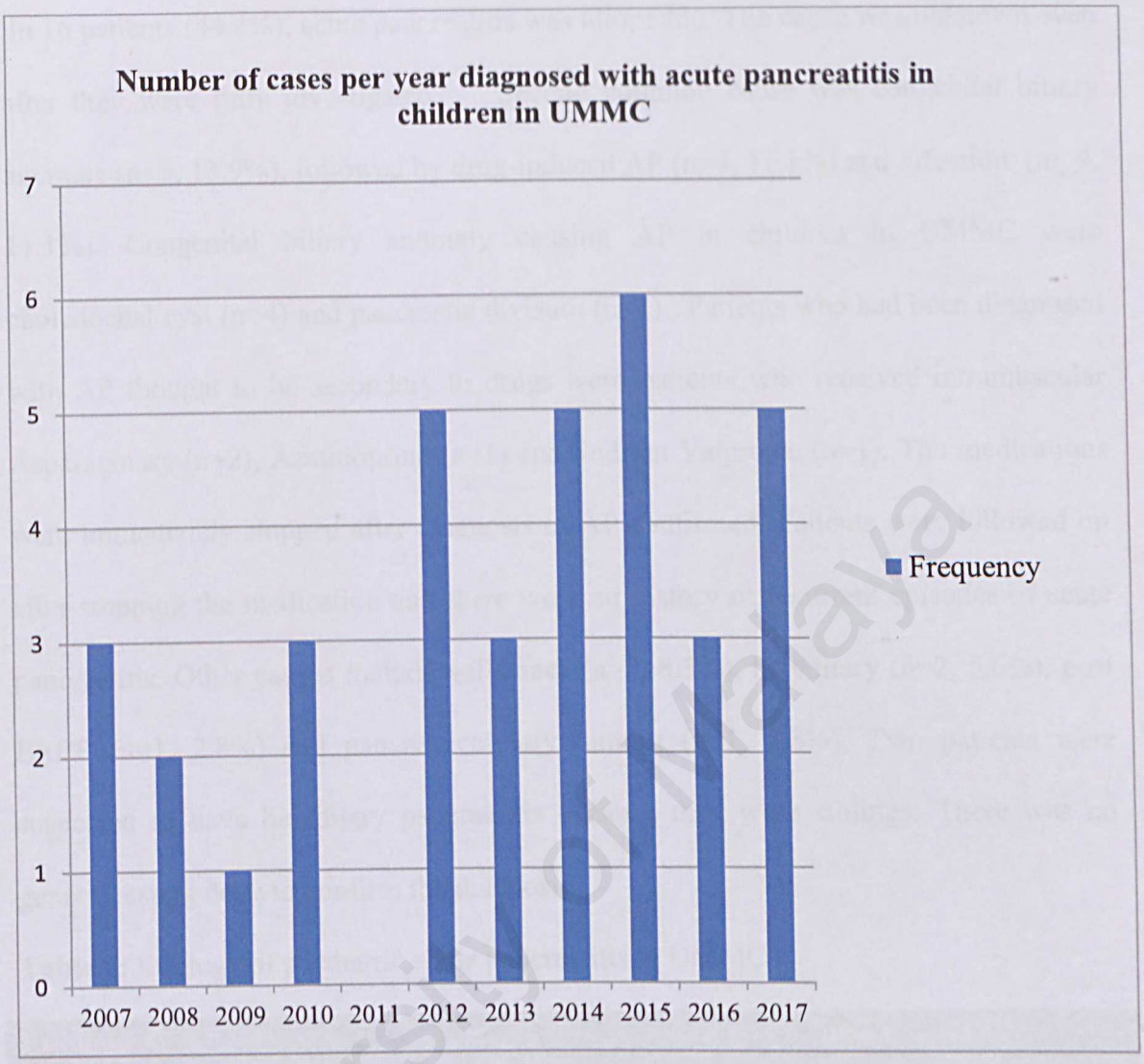
Demographic data of all patients are shown in table 6. The median age of patients with acute pancreatitis was 10.50 (age range 2 to 18 years old). There were more female (n=20) than male (n-16) in this study. Most patients diagnosed with acute pancreatitis were Malay (n=20, 55.6%), followed by Chinese (n=9, 25.0%) and Indian (n= 7, 19.4%). During this study period, on average, there were at least 3 children per year diagnosed with acute pancreatitis.

There were 10 (22.8%) patients with acute pancreatitis who had comorbidity. Those who had comorbidity were 3 acute lymphoblastic leukemia (ALL) in remission, 2 ALL on treatment, 2 with Crohn's disease, 1 Autoimmune Cholangitis, 1 with cystic fibrosis and 1 with epilepsy.

Table 6: Demographic data of children with acute pancreatitis in UMMC

Characteristic	n(%)	Median
Age		
2- 18 years old	36(100.0)	10.50
Gender		
2) Male	16(44.4)	
3) Female	20(55.6)	
Race		
4) Malay	20(55.6)	
5) Chinese	9(25.0)	
6) Indian	7(19.4)	
Comorbidity		
7) No	26 (72.2.)	
8) Yes	10 (22.8)	
- **ALL(remission)**	3	
- **ALL(treatment)**	2	
- **Crohn's disease**	2	
- **Autoimmune cholangitis**	1	
- **Cystic fibrosis**	1	
- **Epilepsy**	1	

SD: Standard deviation ALL: Acute lymphoblastic leukemia



AP: acute pancreatitis

Figure 3: Distribution of acute pancreatitis cases in children per year

5.2 Etiology of Pediatric Acute Pancreatitis in UMMC

In 16 patients (44.4%), acute pancreatitis was idiopathic. The cause was unknown even after they were fully investigated. Second common cause was congenital biliary anomaly (n=5, 13.9%), followed by drug-induced AP (n=4, 11.1%) and infection. (n= 4, 11.1%). Congenital biliary anomaly causing AP in children in UMMC were choledochal cyst (n=4) and pancreatic divisum (n=1). Patients who had been diagnosed with AP thought to be secondary to drugs were patients who received intramuscular Asparaginase (n=2), Azathioprine (n=1) and Sodium Valproate (n=1). The medications were immediately stopped after diagnosis of AP confirmed. Patients were followed up after stopping the medication and there were no history of recurrent episodes of acute pancreatitis. Other causes include gallstones (n=3, 8.3%), hereditary (n=2, 5.6%), post ERCP (n=1, 2.8%) and pancreaticobilary tumour (n=1, 2.8%), Two patients were suspected to have hereditary pancreatitis because they were siblings. There was no genetic testing done to confirm the diagnosis.

Table 7: Etiology of paediatric acute pancreatitis in UMMC

Etiology	n(%)
Idiopathic	16(44.4)
Congenital biliary anomalies	5(13.9)
Drug-induced	4(11.1)
Infection	4(11.1)
Gallstones	3(8.3)
Hereditary	2(5.6)
Pancreaticobiliary tumour	1(2.8)
Post ERCP with underlying autoimmune cholangitis	1(2.8)

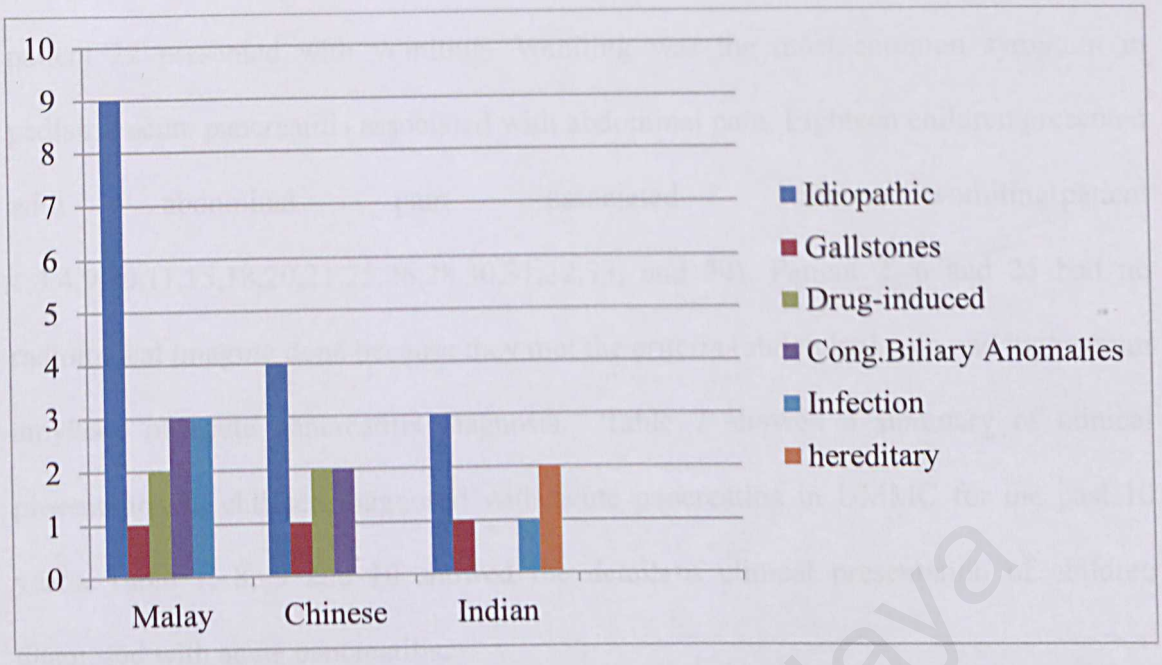


Figure 4: Etiology of acute pancreatitis in children according to ethnic group in UMMC

5.3 Diagnosis of Pediatric Acute Pancreatitis in UMMC

Diagnosis of acute pancreatitis in UMMC was based on clinical manifestation, biochemical level and radiological imaging. In INSPPIRE criteria, patients should meet 2 out 3 criteria which include:

1) Abdominal pain compatible to AP
2) Serum amylase 3 times higher than normal limit
3) Radiological imaging compatible to AP

Urine amylase has been included as one of diagnostic criteria for acute pancreatitis in UMMC. Out of 36 children diagnosed with acute pancreatitis, thirty-four children fulfilled the INSPPIRE criteria. The other 2 children (patient 10 and 32) had only met one criteria which was abdominal pain. Both of these two patients who did not meet the criteria had high urine amylase level. Their clinical presentations were different. All children diagnosed with acute pancreatitis except patient 22. 23 and 24 presented with

non abdominal pain symptoms. Patient 23 and 24 presented with hematemesis whereas patient 22 presented with vomiting. Vomiting was the most common symptom in pediatric acute pancreatitis associated with abdominal pain. Eighteen children presented with abdominal pain associated with vomiting(patient 1.3,4,9,10,11,15,18,20,21,25,26,28,30,31,32,33, and 34). Patient 2, 6 and 25 had no radiological imaging done because they met the criteria (abdominal pain and high serum amylase) of acute pancreatitis diagnosis. Table 7 showed a summary of clinical presentation in children diagnosed with acute pancreatitis in UMMC for the past 10 years. Table 7, 8, 9 and 10 showed the detail of clinical presentation of children diagnosed with acute pancreatitis.

Table 8: Summaries of clinical presentation in children diagnosed with acute pancreatitis in UMMC

Patient	Age	Clinical manifestation	Amylase level	Radiological findings
1	9	Epigastric pain & vomiting	High serum	Abnormal
2	13	Left hypochondriac pain	High serum & urine	Not done
3	9	Left hypochondriac pain & vomiting	High serum & urine	Abnormal
4	5	Non specific abdominal pain& vomiting	High urine	Abnormal
5	2	Vomiting & diarrhea	High urine	Abnormal
6	15	Right hypochondriac pain	High serum	Not done
7	11	Epigastric pain	High urine	Abnormal
8	11	Non-specific abdominal pain	High serum	Abnormal
9	10	Epigastric pain & vomiting	High urine	Abnormal
10	8	Epigastric pain & vomiting	High urine	Normal
11	14	Epigastric pain & vomiting	High serum	Normal
12	9	Right hypochondriac pain	High serum & urine	Normal
13	10	Non-specific abdominal pain	Normal	Abnormal
14	7	Epigastric pain	Normal	Abnormal
15	16	Epigastric pain & vomiting	High urine	Abnormal
16	18	Typical abdominal pain	High serum & urine	Abnormal
17	5	Epigastric pain & vomiting	High urine	Abnormal
18	12	Typical abdominal pain, vomiting & diarrhea	High serum	Abnormal
19	11	Periumbilical pain & vomiting	High serum & urine	Abnormal
20	10	Epigatsric pain, vomiting & fever	High serum & urine	Normal
21	10	Epigastric pain, vomiting & fever	High serum & urine	Abnormal
22	8	Vomiting	High serum	Normal
23	14	Hematemesis	High serum	Abnormal
24	12	Hematemesis	High serum & urine	Abnormal
25	4	Epigastric pain, vomiting & diarrhea	High serum & urine	Not done
26	18	Epigastric pain & vomiting	High serum & urine	Abnormal
27	13	Epigastric pain	High serum & urine	Abnormal
28	18	Epigatsric pain, vomiting & diarrhea	High serum	Abnormal
29	9	Epigastric pain & fever	Normal	Abnormal
30	9	Typical abdominal pain & vomiting	High serum & urine	Abnormal
31	11	Epigastric pain, vomiting & diarrhea	High serum & urine	Abnormal
32	12	Typical abdominal pain & vomiting	High urine	Normal
33	9	Epigastric pain & vomiting	High serum	Normal
34	12	Epigastric pain, vomiting & diarrhea	High serum & urine	Abnormal
35	16	Epigastric pain	High serum & urine	Abnormal
36	4	Epigastric pain	Normal	Abnormal

5.3.1 Clinical manifestation

Table 9 showed a list of patients diagnosed with acute pancreatitis and their clinical manifestation during the initial presentation. Majority of patients presented with abdominal pain (n= 33, 91.6%) followed by vomiting (n=18, 50.0%). The other clinical manifestations which present in children with AP were fever (n=5), diarrhoea (n=3), and hematemesis (n=2) (Table 9). Abdominal pain was mostly epigastric pain (n=25, 75.8%) and it can occur at other abdominal region such as right hypochondriac pain (n=2, 6.1%), left hypochondriac pain (n=2, 6.1%) and periumbilcal pain (n=1, 3.0%) (Table 10). Non-specific abdominal pain present in a small number of patients (n=3, 9.1%). Only 4 patients had typical abdominal pain similar as adult patients in which they presented with epigastric pain with radiation to the back.

Table 9: Clinical manifestations of acute pancreatitis in children in UMMC

Clinical Manifestation	n(%)
Abdominal pain	33(91.6)
Vomiting	18(50.0)
Fever	5(13.8)
Diarrhoea	3(8.3)
Hematemesis	2(5.5)

Table 10: Site of abdominal pain in pediatric acute pancreatitis in UMMC

Site of Abdominal Pain	n(%)
Epigastric	25(75.8)
9) Non radiating	21(84.0)
10) Radiating to the back	4(16.0)
Right hypochondriac	2(6.1)
Left hypochondriac	2(6.1)
Periumbilical	1(3.0)
Non-specific	3(9.1)

5.3.2 Biochemistry level

For biochemistry parameters, serum amylase and urine amylase are used to diagnose acute pancreatitis in paediatric patients in UMMC. All children diagnosed with AP in this study had serum amylase and 27 patients had both serum and urine amylase done. Serum amylase was high in 29 patients (>118 U/L) and 23 of them had serum amylase 3 times the upper limit of normal (>350 U/L). The median serum amylase was 573 U/L (range 77-3507 U/L). Twenty-three patients had high urine amylase level (>650 U/L) and the median urine amylase level was 1126 U/L (range 35-58573 U/L). Nineteen patients had both high serum and urine amylase level.

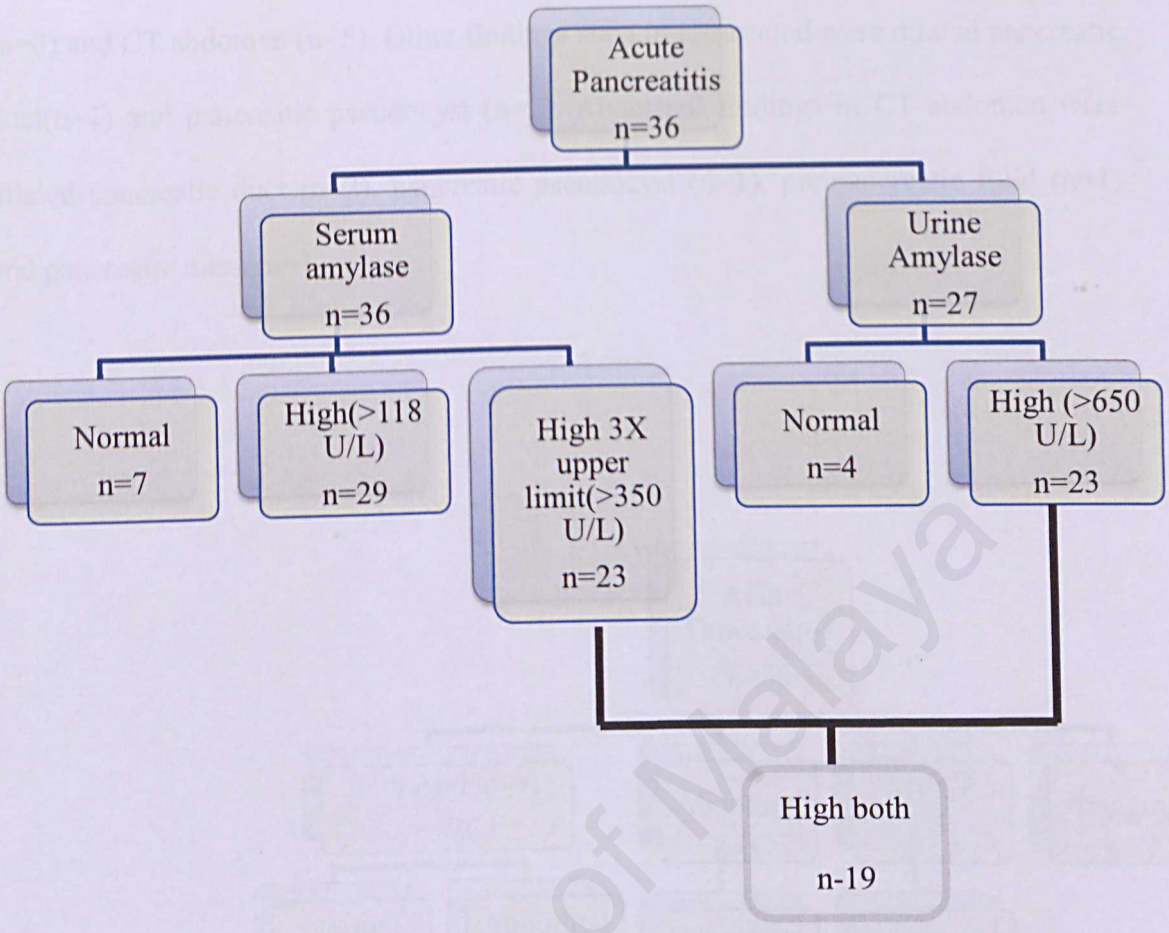


Figure 5: Serum and urine amylase level in acute pancreatitis in children in UMMC

5.3.3 Abnormal Radiological Imaging

Radiological imaging is part of diagnostic tools for acute pancreatitis. In UMMC, there are 3 radiological modalities that are used to diagnose acute pancreatitis which are transabdominal ultrasound, CT abdomen with contrast and MRCP.

Radiological imaging was done to look for evidence and cause of AP in children, who had persistent abdominal pain and normal biochemistry level. Transabdominal ultrasounds were performed in 26 patients, CT abdomen in 5 and MRCP in 2 patients (Table 10). Eleven patients had abnormal findings from ultrasound, 10 from CT abdomen and 2 from MRCP (Table 11). CT abdomen was performed in 6 patients with normal findings in ultrasound in which 1 patient had normal CT findings and 5 patients

with abnormal CT findings. Pancreatic enlargement was commonly seen in ultrasound (n=8) and CT abdomen (n=5). Other findings seen in ultrasound were dilated pancreatic duct(n=1) and pancreatic pseudocyst (n=2). Abnormal findings in CT abdomen were dilated pancreatic duct (n=2), pancreatic pseudocyst (n=1), peripancreatic fluid (n=1) and pancreatic mass (n=1).

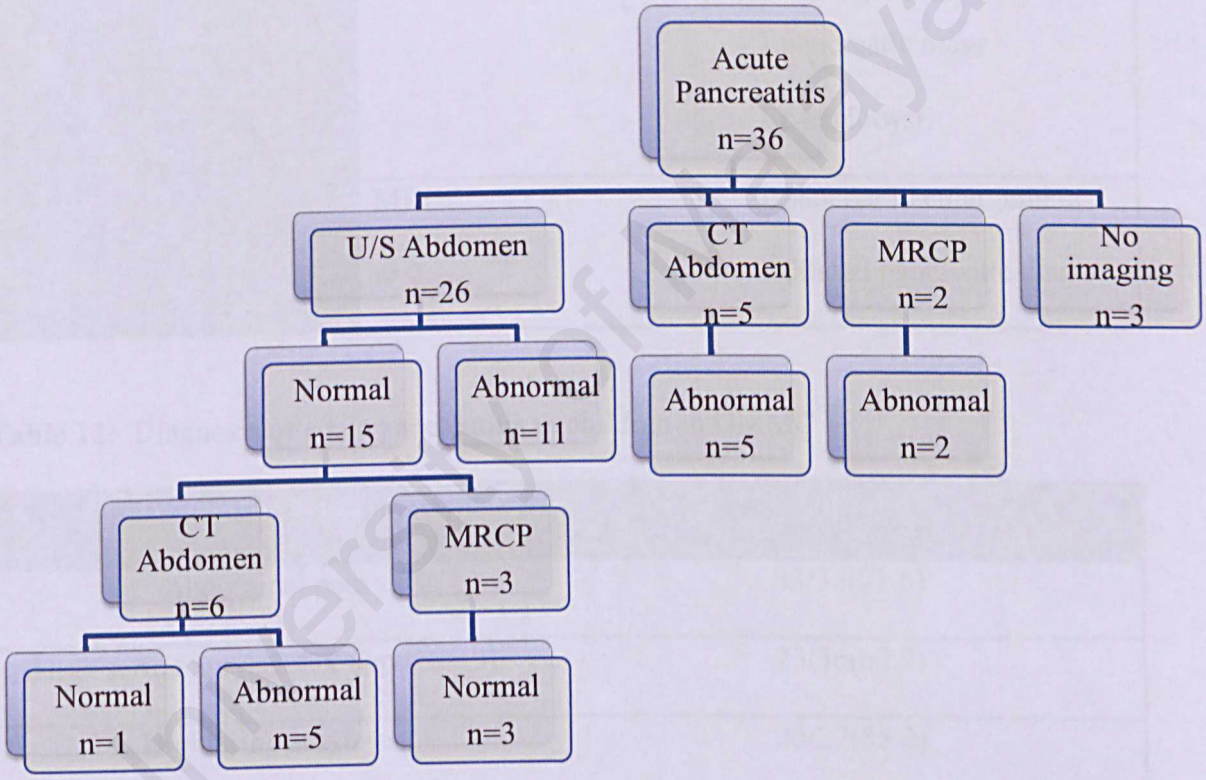


Figure 6: Radiological imaging in acute pancreatitis in children in UMMC

Table 11: Imaging finding in pediatric acute pancreatitis in UMMC

Acute Pancreatitis	Imaging	Finding
n=36	U/S Abdomen n=11	8 pancreatic enlargement 1 dilated pancreatic duct 2 pseudocyst
	CT Abdomen n=10	5 pancreatic enlargement 2 dilated pancreatic duct 1 peripancreatic fluid 1 pancreatic mass 1 pseudocyst
	MRCP n=2	1 pancreatic enlargement 1 dilated pancreatic duct

Table 12: Diagnosis of acute pancreatitis in children in UMMC

Diagnostic criteria	n(%)
Abdominal pain	33/36(91.6)
High serum amylase(3x upper limit)	23/36(63.9)
High urine amylase	23/27(85.2)
High serum and urine amylase	19/27(70.4)
Abnormal ultrasound	11/26(42.3)
Abnormal CT	10/11(90.9)
Abnormal MRCP	2/5(40.0)

CT: Computed tomography
MRCP: Magnetic resonance cholangiopancreatography

5.4 Severity of Pediatric Acute Pancreatitis In UMMC

Revised Atlanta 2012 classification classified acute pancreatitis into mild, moderately severe and severe. For the purpose of this study, we classified the severity into mild and severe group. All children with moderately severe were grouped as severe . Thirty-three patients (91.7%) with acute pancreatitis were mild disease and only 3 patients (8.3%) with severe disease. In the mild group patients, 14 were idiopathic, 5 congenital biliary anomalies, 4 drugs induced, 4 infection, 2 gallstones, 2 hereditary, 1 pancreaticobiliary tumour and 1 post ERCP. In the severe group, 2 children were idiopathic and 1 with gallstones.

Table 13: Severity of pediatric acute pancreatitis in UMMC

Severity	n(%)
Mild	33(91.7)
Severe	3(8.3)

Table 14: Etiology according to severity of pediatric acute pancreatitis in UMMC

Etiology	Mild(n)	Severe(n)
Idiopathic	14	2
Congenital biliary anomalies	5	-
Drug-induced	4	-
Infection	4	-
Gallstones	2	1
Hereditary	2	-
Pancreaticobiliary tumour	1	-
Post ERCP with underlying autoimmune cholangitis	1	-

5.5 Management of Pediatric Acute Pancreatitis in UMMC

The median duration of hospital stay for children with AP in UMMC was 7 days (range between 3 to 120 days). Twenty nine patients with acute pancreatitis were treated with medical treatment. Twenty seven patients received medical treatment were from mild AP group. All patients with mild acute pancreatitis were kept fasting and most cases(n=35) were given intravenous fluids. Twenty two patients received opioids analgesics as pain control. Twelve patients received antibiotics, for treatment for known or suspected associated infection. One patient with severe disease received octreotide. Table 16 shows summary of treatment received according to severity of pediatric AP. Four patients with choledochal cyst and 3 patients with gallstones were treated surgically. One pseudocyst was drained surgically because the patient had worsening abdominal distension with peritonitis and another 2 resolved spontaneously.

.**Table 15:** Management in pediatric acute pancreatitis in UMMC

Treatment	Mild(n)	Severe(n)	Total n(%)
Medical	26	2	28(77.8)
Surgical	7	1	8(22.2)

Table 16: Medical management in pediatric acute pancreatitis in UMMC

Treatment	Mild(n)	Severe(n)	Total(n)
IV fluids	33	3	36
Opioids analgesic	19	3	22
Antibiotic	9	3	12
Octreotide	-	1	1

IV: Intravenous infusion

5.6 Outcome of acute pancreatitis in children UMMC

5.6.1 Early and late onset complication

Complications can be divided into early and late onset. For early onset complications, there were 2 patients with pleural effusion, one with hyperglycaemia and one with systemic hypotension. All these complications resolved within 48 hours. For late onset complications, 3 patients had pancreatic pseudocyst and only 1 patient had peritonitis.

One patient with severe disease had multiple complications. She was a 10 year old girl, who was initially referred to paediatric gastroenterology team from tertiary hospital in East Coast for further management of acute pancreatitis. She presented with 5 days history of epigastric pain associated with vomiting and fever. The diagnosis was based on the typical abdominal pain, high serum and urine amylase level and ultrasound abdomen which showed enlargement of pancreas. She had persistent abdominal pain in which she required intravenous fluids, intravenous morphine infusion, antibiotic and octeriotide. Her disease was complicated with pleural effusion and systemic hypotension. Symptoms persist for almost a month and due to persistent abdominal pain, a CT abdomen was done and it showed pancreatic pseudocyst. She also had peritonitis and worsening abdominal distension needing pseudocyst drainage. Due to her prolong illness, she was started on total parenteral nutrition (TPN). However, due to prolonged hospitalization, her parents decided to bring her home without completed treatment. Even after thorough investigation done, the cause of acute pancreatitis was still unknown.

Table 17: Acute complication in pediatric acute pancreatitis in UMMC

Acute Complication	
Early onset(n)	**Late onset(n)**
Pleural effusion n=2	Pancreatic pseudocyst n=3
Hypergylcemia n=1	Peritonitis n=1
Hypotension n=1	

5.6.2 Long term complication

Out of 33 patients with mild disease 18 resolved spontaneously, 8 progressed to acute recurrent pancreatitis (ARP) and 7 progressed to chronic pancreatitis (CP).Two patients with severe disease had CP and 1 patient defaulted treatment. Diagnoses of chronic pancreatitis were confirmed in 9 patients based on the radiological evidence of pancreatic calcification. Besides pancreatic calcification, 1 of them had diabetes mellitus and 1 had malabsorption.

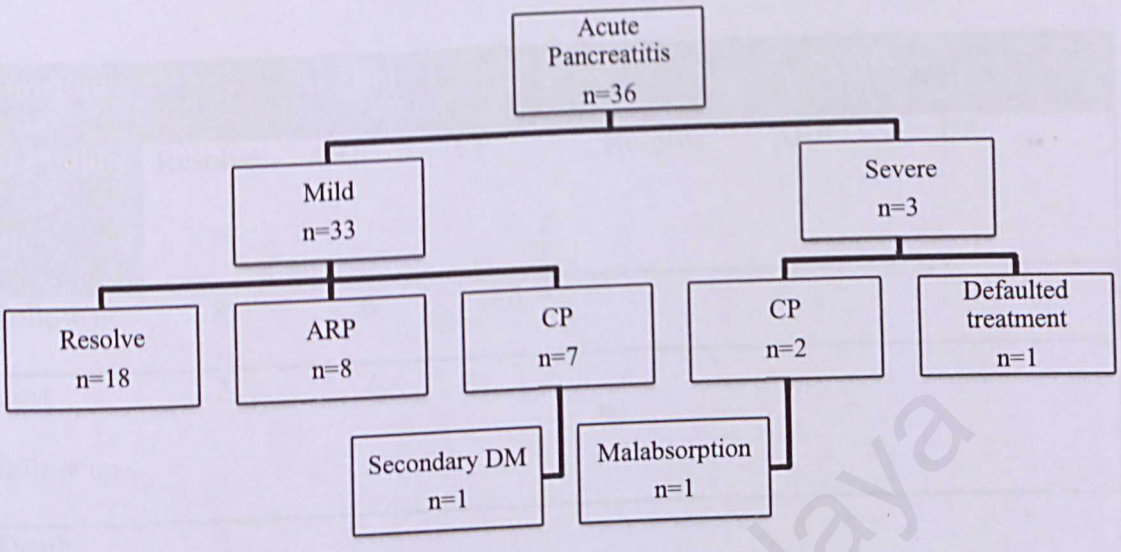


Figure 7: Long term complication in pediatric acute pancreatitis in UMMC

5.6.3 Follow up

Seventeen patients with mild acute pancreatitis are still continuing their follow up with gastroenterology, oncology and surgical team. However, thirteen patients have lost to follow up. Three patients died during the follow up, 2 patients died because of relapse acute lymphoblastic leukaemia and 1 patient died due to hypovolemic shock after choledochal cyst resection. Two patients with severe acute pancreatitis are still continuing their follow up. Four patients are under adult gastroenterology follow up. Patients who are still under follow up, were seen at least 3 monthly in clinic and the median duration of follow up is 4 monthly (2-6 months). The eldest patient who is still under follow up is 19 years old.

Table 18: Follow up in pediatric acute pancreatitis in UMMC

Outcome of follow up	Mild			Severe		
	Resolve	ARP	CP	Resolve	ARP	CP
Follow up	8	6	4	-	-	2
Lost follow up	7	2	3		-	
Death	3	-		-	-	-
Total	18	8	7	-	-	2

ARP: acute recurrent pancreatitis CP: chronic pancreatitis

*1 discharge at own risk

5.6.4 Cases with rare long term complication of Pediatric Acute Pancreatitis

There were 2 cases reported in children who were previously diagnosed with acute pancreatitis in UMMC who developed rare long term complications of acute pancreatitis. Both of the patients initially progressed to chronic pancreatitis.

Case 1 : A 9 year-old girl with underlying acute lymphoblastic leukaemia 5 years in remission. She initially presented with typical abdominal pain and vomiting for 2 days. Biochemistry investigations showed high serum and urine amylase. Diagnosis of acute pancreatitis was confirmed with ultrasound abdomen which showed dilatation of the pancreatic duct. She was managed medically. The cause of acute pancreatitis was unknown even after a thorough blood investigations and ultrasound abdomen. After 3 years of follow up, she had recurrent epigastric pain, polyuria and polydipsia. MRCP showed evidence of chronic pancreatitis (pancreatic calcification). Diagnosis of

diabetes mellitus was confirmed based on abnormal HbA1c 9.7%. She also had symptomatic polyuria, polydipsia with HbA1c was 9.7%. She was diagnosed with diabetes mellitus secondary to chronic pancreatitis. Subsequently she was started on basal bolus insulin injection. She had to undergo Whipple procedure to prevent recurrent abdominal pain and other complication of chronic pancreatitis. Currently, she is still under follow up with gastroenterology, surgical and endocrine team 7 years after her first presentation. Currently, she has no further history of recurrent epigastric pain and her blood sugar is well controlled.

Case 2: A 9 year-old boy presented with 1 week history of epigastric pain and fever. Serum amylase level was not high to suggest acute pancreatitis. Diagnosis of acute pancreatitis was confirmed by transabdominal ultrasound which showed pancreatic pseudocyst and gallstones. He was given a supportive treatment. However, a month after his first presentation, reassessment with MRCP is suggestive of chronic pancreatitis. His condition was also complicated with malabsorption in which he had steatorhea 1 year after his initial presentation. MRCP reassessment showed an atrophic pancreas. Stool for fat globules was positive. He was subsequently started on pancreatic enzymes replacement therapy and still continues follow up with gastroenterology team. During his last visit in gastroenterology clinic in October 2017, he still had recurrent abdominal pain but there was no history of steatorhea.

These 2 cases demonstrate endocrine and exocrine complication may occur as a long term complication in acute pancreatitis.

CHAPTER 6: DISCUSSION

6.1 Discussion

Acute pancreatitis is common in adults but was previously considered to be rare in paediatric patients. In UMMC, on average at least 3 cases per year diagnose patient with acute pancreatitis over the past 10 years, which suggest that the disease is uncommon in UMMC, similar with findings from other centres described in literature. Compared to other Asian countries, our patients mean age are higher. There were more female than male in this study similar reported by Goh et al. Acute pancreatitis has variable etiology. Goh et al, Henedina et al and Maonmen et al reported that trauma is common etiology. The other common etiology reported are congenital biliary anomalies and idiopathic (Henedina et al 2014, Werlin et al 2011, Anca Savu et al 2009). Many cases in our study is idiopathic and it is similar as reported by Ibrahim et al study. Trauma is not in our list of causes for acute pancreatitis in children in UMMC. When we went through the notes of patients diagnosed with acute pancreatitis, most of the notes did not document whether patient had history of trauma. Based on our experience in managing children with non accidental injury (NAI), there were no children diagnosed with acute pancreatitis secondary to NAI. In previous study done by Goh et al, home accidents and child abuse contributed to cases of acute pancreatitis. The study suggests a need for the clinician to be mindful of the possibility of non-accidental injury when handling children presenting with abdominal discomfort or pain. Two patients with hereditary causes were siblings but no documented genetic testing was done. Among patients with idiopathic pancreatitis, a hereditary cause for acute pancreatitis may be possible. If further genetic testing are done in patients with idiopathic pancreatitis, probably at least 50% of these patients, may have an identifiable cause. In this study, about 50% of patients diagnosed with acute pancreatitis with comorbidity had underlying acute

lymphoblastic leukemia (ALL) and all of them received asparaginase as chemotherapy medication. Approximately 60% of them were ALL in remission. However, there was no reported study about delayed asparaginase effect associated with acute pancreatitis. Majority of cases in this study are Malay. However, this does not represent the major ethnic group for pediatric acute pancreatitis in Malaysia as this is a single centre study.

INSPPIRE criteria can be used as a guideline in diagnosing acute pancreatitis. INSPPIRE criteria is used to diagnose acute pancreatitis in previous study done by Goh et al, Henedina et al, Maonmen et al, Werlin et al and Ibrahim et al. Ninety five per cent children diagnosed with acute pancreatitis in UMMC fulfilled INSPPIRE criteria. Diagnosis of acute pancreatitis in children requires high index of suspicion especially in children presented with abdominal pain. There is no doubt that abdominal pain is the most common manifestation for acute pancreatitis and it is similar to the other studies(Ibrahim et al 2011, Henedina et al 2014, Werlin et al 2013). We found epigastric area is the commonest site of abdominal pain and non specific abdominal are commonly reported in the younger patients. This study includes urine amylase as one of diagnostic criteria and it shows that urine amylase can be used as an alternative to serum amylase. In this study, 80% patients with high serum amylase also have high urine amylase level. Mumtaz et al showed that urine amylase had the best correlation with serum amylase. Therefore, urine amylase can be used as an alternative to serum amylase because the levels remain high for several days after serum amylase level have returned to normal. Urine amylase is better because it is non-invasive and we can easily monitor the progression of acute pancreatitis. Transabdominal ultrasound is used as the first choice for radiological imaging in UMMC but majority of abnormal findings are seen in CT abdomen. Other studies show most diagnosis of acute pancreatitis were

made from abnormal findings in CT abdomen. (Goh et al 2003, Moanmen et al, Werlin et al 2013, Henedina et al 2014)

Majority of acute pancreatitis are mild and most of them are treated medically in which the patients are given supportive treatment. The treatment is basically supportive and there is no difference in our treatment of acute pancreatitis compared to previous studies.

Majority of cases are spontaneously resolved. Complications of acute pancreatitis are not common as been described in this study and other studies include Ibrahim et al and Henedina et al. A few patients had either early or late onset and the most common is pancreatic pseudocyst and pulmonary complication. Acute recurrent pancreatitis has been described as the commonest long term complication in acute pancreatitis in children and it is reported similarly in Ibrahim et al and Henedina et al. Rarely reported are cases of acute pancreatitis with either endocrine or exocrine complication. Endocrine and exocrine complications are rare in UMMC, similarly reported by Ibrahim et al. Ibrahim et al reported diabetes as a complication in patients with idiopathic pancreatitis and recurrent abdominal pain. In this study, there were 2 patients with chronic pancreatitis who had secondary diabetes and malabsorption. Delay presentation and idiopathic pancreatitis were seen in these 2 cases with endocrine and exocrine complication. Similarities in both cases were, both patients had recurrent abdominal pain and the complications were picked up during clinic follow up. Even though, complications rarely occur, it is important to follow up the patients with acute pancreatitis. During follow up, we should focus more in looking for long term complications. In this study, death is not related to acute pancreatitis. Patient died because of the underlying comorbidities and due to post operative complication. There

were no reported death in previous studies ((Ibrahim et al 2011, Henedina et al 2014, Werlin et al 2013). Maonmen et al reported 1 death due to underlying disease in ALL patient who had chemotherapy.

6.2 Conclusion

Paediatric pancreatitis is rare in our population. Most acute pancreatitis in children are mild and resolved spontaneously with medical and supportive treatment. Approximately 5% of patients with acute recurrent and chronic pancreatitis may develop complications. Proper monitoring and follow up is important in patient with acute pancreatitis.

6.3 Limitation

The main limitation in this study is because it is a retrospective study. There is possibility of missing data. We cannot describe any association between obesity and acute pancreatitis due to lack of documentation of the weight of the patient during presentation. Besides that, patients were not classified according to severity and there were no proper listed investigations documented. The other limitation is small sample size because acute pancreatitis is a rare disease in children.

6.4 Recommendation

A database for acute pancreatitis for children which includes severity classification should be created to aid management and prognostication for patients. It is important to remind patients regarding follow up. Strict follow up of patients with acute pancreatitis as they are at risk of developing long term complications.

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APPENDIX A

DATA COLLECTION FORM:
Acute Pancreatitis in Children in University Malaya Medical Centre: A Retrospective Study

RN	
Name	
Year of presentation	
Age during presentation	
Gender	
Race	
Comorbidity	○ No ○ Yes ----------
Etiology	
Clinical presentations	
Diagnostic criteria	○ Typical abdominal pain • Epigastric pain –radiated or not • RIF • LIF • Periumbilical pain • Non specific abdominal pain ○ Serum amylase > 350 U/L (_____) ○ Urine amylase > 650 U/L (_____) ○ Abnormal both urine and serum amylase ○ Abnormal imaging compatible with AP • US • CT • MRCP • ERCP
Severity	○ Mild ○ Moderately severe • Organ failure < 48 hours • Local complication • Systemic complication ○ Severe • Organ failure > 48 hours • Local complication • Systemic complication
Sequelae	○ Resolved ○ Acute recurrent pancreatitis ○ Chronic pancreatitis ▪ Imaging findings ▪ Exocrine complication ▪ Endocrine complication ○ AOR ○ Defaulted ○ Death

Duration of follow up	
Treatment	○ Conservative • Fluid management • TPN • Pain controlled—analgesics_____ • Duration NBM ○ Surgery ----------
Duration of hospital stay	

APPENDIX B

UNIVERSITY OF MALAYA MEDICAL CENTRE

MEDICAL RESEARCH ETHICS COMMITTEE
(Formerly known as Medical Ethics Committee)
UNIVERSITY OF MALAYA MEDICAL CENTRE
ADDRESS : LEMBAH PANTAI, 59100 KUALA LUMPUR, MALAYSIA
TELEPHONE : 03-79493209/2251 FAXIMILE : 03-79492030

NAME OF ETHICS COMMITTEE/IRB Medical Research Ethics Committee, University Malaya Medical Centre	**MREC ID NO**: 201762-5304
ADDRESS : LEMBAH PANTAI, 59100 KUALA LUMPUR, MALAYSIA	
PROTOCOL NO(if applicable) :	
TITLE: THE INCIDENCE AND CLINICAL PRESENTATION OF PAEDIATRIC ACUTE PANCREATITIS IN UMMC:A-10 YEAR-RETROSPECTIVE STUDY	
PRINCIPAL INVESTIGATOR : DOCTOR FARAH SYUHADA BINTI MOHD RADZI	**SPONSOR** -

The following item [✓] have been received and reviewed in connection with the above study to conducted by the above investigator.

[✓] Application to Conduct Research Project(form)	Ver.No :	Ver.Date : 02-06-2017
[✓] Study Protocol	Ver.No : 1	Ver.Date : 01-06-2017
[ ] Patient Information Sheet	Ver.No :	Ver.Date :
[ ] Consent Form	Ver.No :	Ver.Date :
[ ] Questionnaire	Ver.No :	Ver.Date :
[✓] Investigator's CV / GCP (DOCTOR FARAH SYUHADA BINTI MOHD RADZI,christopher Boey Chion Meng.)	Ver.No :	Ver.Date :
[ ] Insurance certificate	Ver.No :	Ver.Date :
[✓] Other documents		

and the decision is [✓]

[ ] Approved (Full Board)
[✓] Approved (Expedited)
[ ] Rejected(reasons specified below or in accompanying letter)

Comments:

Retrospective study

The Investigators are required to:

1) *follow instructions, guidelines and requirements of the Medical Research Ethics Committee.*
2) *report any protocol deviations/violations to Medical Research Ethics Committee.*
3) *provide annual and closure report to the Medical Research Ethics Committee.*
4) *comply with International Conference on Harmonization – Guidelines for Good Clinical Practice (ICH-GCP) and Declaration of Helsinki.*
5) *obtain a permission from the Director of UMMC to start research that involves recruitment of UMMC patient.*
6) *ensure that if the research is sponsored, the usage of consumable items and laboratory tests from UMMC services are not charged in the patient's hospital bills but are borne by research grant.*
7) *note that he/she can appeal to the Chairman of Medical Research Ethics Committee for studies that are rejected.*
8) *note that Medical Research Ethics Committee may audit the approved study.*
9) *ensure that the study does not take precedence over the safety of subjects.*

Date of expedited approval : 13-07-2017

This is a computer generated letter. No signature required.