PORTAL HYPERTENSION PRESENTING WITH GASTROESOPHAGEAL VARICES IN CHILDREN: CAUSES, MANAGEMENT AND OUTCOME

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ORIGINAL LITERARY WORK DECLARATION

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ABSTRACT

It has always been a challenge to manage portal hypertension presenting with gastroesophageal varices in children. The aetiologies of portal hypertension in children differs from adults, however due to a lack of paediatric data, much of current practice in children is adapted from adult guidelines. This study describes a local population of children with portal hypertension presenting with gastroesophageal varices seen in a tertiary referral centre in Malaysia. Retrospective descriptive cohort study analysing data from medical records of paediatric patients with endoscopy finding of gastroesophageal varices from 1st December 2000 to 1st December 2016 was conducted. A total of 38 patient's records were analysed.

The study population of 38 patients were made up of 18 Malay patients (47.3%), 17 Chinese patients (44.7%), 2 patients of other ethnicity and one Indian. The gender distribution was equal.

A total of 22 out of 38 patients (57.8%) had intra-hepatic aetiology of portal hypertension, which included 14 patients with biliary atresia. Seven patients (18.4%) had prehepatic aetiology of portal hypertension, of which 6 patients had portal vein thrombosis. Splenomegaly was the most common clinical finding at presentation in 35 patients (92.1%), and hematemesis was the most common presenting symptom in 19 patients (50%) in this study population.

The average age of patients at first endoscopy was 6.72 years (95% CI 5.41 years-8.47 years). Thirty out of 38 patients (78.9%) had intervention with endoscopic variceal band ligation (EVL) or endoscopic sclerosant therapy (EST) in their first endoscopy.

In the present study, most of the endoscopies performed were reactive to bleeding events. Bleeding event-driven endoscopies were done in 57.9%, 22 out of 38 patients, while in 16 out of 38 patients (42.1%) endoscopies were performed prophylactically (non-

event driven). EVL was used in 21 out of 38 patients while EST was done in 7 patients. Two patients received both EST and EVL. A total of 5 patients out of 38 patients (13.2%) encountered complications and the most frequent complication was haemorrhage in 4 patients.

Eleven patients had rebleeding after endoscopy. The average bleed-free interval was 87 days (95% CI 42 days-135 days). Shortest bleed-free period post-endoscopy was 12 days. Good bleeding control with more than 5 days interval between endoscopy and rebleeding was observed in this study.

Twelve out of 38 patients (31.6%) were still on periodical endoscopic surveillance. Five patients (13.2%) died in this study period. Four patients had liver transplant at average age of 8.46 years (95% CI 3.68 years-13.37 years).

The comparison between event-driven and non event-driven groups found higher grade varices (p=0.01) and increased intervention rate (p=0.04) in the event-driven group. There was no statistically significant difference seen in age, biochemical parameters, rebleeding events or complication rates between these two groups.

In conclusion, the population demographic and aetiology of portal hypertension that presents with gastroesophageal varices in children resembled those in literature (Ng et al., 2016). Splenomegaly and hematemesis remain the most consistent finding at presentation of those patients with gastroesophageal varices. Evaluation of endoscopic outcome by evaluation of complication, rebleeding rate and bleed-free days document safe practice and good efficacy at bleeding arrest. However further research is needed to ascertain the role of endoscopy for surveillance before bleeding event.

This study highlighted the endoscopic practises for gastroesophageal varices complicating childhood portal hypertension in University Malaya Medical Centre. This

provides a framework for future research on paediatric portal hypertension in our local population.

ABSTRAK

Hypertensi portal di kalangan kanak-kanak, dan komplikasi yang berkaitan adalah cukup mencabar untuk dirawat. Punca penyakit ini berlainan dalam golongan ini berbanding daripada orang dewasa. Akan tetapi disebabkan kekurangan data untuk kanak-kanak, kebanyakan garis panduan untuk rawatan terpaksa diadaptasi daripada garis panduan untuk orang dewasa.

Kajian ini berpandukan populasi paediatrik di Pusat Perubatan Universiti Malaya yang menghidapi hypertensi portal, berserta komplikasi pembengkakkan salur darah dalam esofagus dan perut diakibatkan penyakit ini. Data yang dianalisa adalah dari 1.12.2000 sehingga 1.12.2016.

Kajian ini mendapati bahawa kebanyakan kanak-kanak yang menghidapi hypertensi portal adalah terdiri daripada kaum Melayu (18 pesakit), dan seterusnya kaum Cina (17 pesakit). Punca utama hypertensi portal adalah daripada masalah intrahepatic, dalam 22 pesakit (57.9%) di mana 14 daripadanya mengalami penyakit bilary atresia. Punca kedua yang kerap dijumpai adalah disebabkan masalah prehepatic dalam 7 pesakit (18.4%), di mana 6 pesakit mempunyai masalah 'portal vein thrombosis'.

Umur purata pesakit sewaktu menjalani prosedur endoskopi adalah 6.72 tahun (95% CI 5.41 tahun-8.47 tahun). Kebengkakkan limpa adalah penemuan yang paling kerap pada kadar 92.1%, dan muntah darah adalah symptom yang paling kerap (50%).

Tiga puluh pesakit (78.9%) telah menjalani perawatan EST (Endoscopic sclerosant therapy) atau EVL (Endoscopic variceal band ligation) semasa endoskopi pertama mereka. Kaedah endoskopi untuk rawatan untuk salur darah yang bengkak akibat hypertensi portal di pusat perubatan ini, adalah bersifat reaktif untuk mengawal

pendarahan, membentuk 57.9% (n=22) daripada jumlah endoskopi. EVL digunakan untuk 21 pesakit (55.3%) manakala EST digunakan untuk 7 pesakit (18.4%), dan dua orang pesakit telah menjalani kedua-dua kaedah ini.

Komplikasi yang paling kerap berlaku adalah pendarahan, yang merangkumi 13.3% pesakit. Sebelas pesakit (28.9%) mengalami pendarahan semula selepas intervensi endoskopi dengan kadar purata selang waktu tanpa pendarahan 86.91 hari (95% CI 42.09 hari-135.36 hari). Jangka terpendek sebelum pendarahan semula adalah 12 hari. Oleh itu kedua-dua intervensi boleh disifatkan sebagai berkesan mengawal pendarahan.

Dua belas pesakit (31.6%) masih dipantau melalui kaedah endoskopi. Empat pesakit telah menjalani pembedahan pemindahan hati pada umur purata 8.46 tahun (95% CI 3.68 tahun-13.37 tahun).

Kajian ini merumuskan bahawa populasi yang dikaji mempunyai punca hypertensi portal seperti mana kajian lain. Juga didapati bahawa kebengkakkan limpa dan muntah darah adalah faktor utama yang dialami pesakit-pesakit ini. Perbandingan antara kumpulan pesakit yang menjalani prosedur endoskopi untuk tujuan pemberhentian pendarahan dan secara elektif mendapati kumpulan pesakit yang menjalani prosedur untuk pendarahan mempunyai gred pembengkakkan salur darah yang lebih tinggi (p=0.01) dan lebih banyak menjalani intervensi (p=0.04). Prosedur endoskopi juga adalah selamat dan efektif untuk memberhentikan pendarahan. Akan tetapi, lebih banyak kajian diperlukan sebelum memperluaskan penggunaan endoskopi untuk pesakit untuk tujuan pencegahan sebelum berlakunya pendarahan.

Kajian ini menganalisa penggunaan kaedah endoskopi di pusat perubatan ini. Kajian ini juga membuka ruang untuk lebih analisa berkenaan hypertensi portal di kalangan kanak-kanak di Malaysia.

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LIST OF SYMBOLS AND ABBREVIATION (ORDER OF APPEARANCE)

EST	Endoscopic Sclerosant Therapy
EVL	Endoscopic Variceal Band Ligation
UMMC	University Malaya Medical Centre
HIV	Human Immunodeficiency Virus
LSEC	Liver Sinusoidal Endothelial Cell
NO	Nitric Oxide
CO	Carbon Monoxide
COX	Cyclooxygenase
HSC	Hepatic Stellate Cell
VGEF	Vascular Endothelial Growth Factor
ALT	Alanine Transaminase
AST	Aspartate Transaminase
APRI	AST to Platelet Ratio Index
CT	Computed Tomography
MRI	Magnetic Resonance Imaging
HVPG	Hepatic Venous Pressure Gradient
GOV	Gastroesophageal Varices
IGV	Isolated Gastric Varices

ICU	Intensive Care Unit
USD	United States Dollars
MRED ID	Medical Research Ethics Committee Identification Number
CI	Confidence Interval
PVT	Portal Vein Thrombosis
BA	Biliary Atresia
AIH	Autoimmune Hepatitis
UVC	Umbilical Vein Catheter
TPN	Total Parenteral Nutrition
INR	International Normalized Ratio
PT	Prothrombin Time
TWC	Total White Cell
GGT	Gamma Glutamyl Transferase
HIDA	Hepatobiliary Iminodiacetic Acid
MRCP	Magnetic Resonance Cholangiopancreatography
DIVC	Disseminated Intravascular Coagulopathy
QoL	Quality of Life

LIST OF SYMBOLS AND ABBREVIATION (ALPHABETICAL ORDER)

AIH	Autoimmune Hepatitis
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APRI	AST to Platelet Ratio Index
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BA	Biliary Atresia
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CT	Computed Tomography
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LIST OF APPENDICES

CHAPTER 1 : INTRODUCTION

The paediatric gastroenterology field has evolved rapidly in the past 50 years. The introduction of endoscopic tools, laparoscopic surgeries and organ transplantation has opened up a whole new horizon for diagnostic and therapeutic options in this field.

In this field, one of the challenging conditions to manage is portal hypertension and its complication of gastroesophageal varices. Much research in the pathogenesis and management of this difficult condition has evolved over the last few years aiming to derive evidence based approach to aid early diagnosis and effective management.

Portal hypertension is a rare disease and its incidence in children is poorly reported. Portal hypertension presenting with gastroesophageal varices in children evolves from multifactorial aetiologies, largely divided into intrahepatic and extrahepatic causes. The most common aetiologies in children are intrahepatic, and includes liver cirrhosis, sinusoidal obstruction and biliary atresia. Extrahepatic causes can be either prehepatic or post hepatic, including portal vein obstruction, Budd-Chiari syndrome and veno-occlusive disease (Mileti & Rosenthal, 2011). These differ from the aetiologies commonly seen in the adult population, where viral hepatitis and alcoholic liver diseases leading to liver cirrhosis form the bulk of the cases (Lim et al., 2006).

In the paediatric age group, the common aetiology of portal hypertension is biliary atresia or portal vein thrombosis. Gastroesophageal varices is the most important and common complication of childhood portal hypertension. Gastroesophageal varices can develop early in the course of disease. In a very young child, the ensuing bleeding episodes is difficult to manage.

The diagnosis of portal hypertension itself is not straightforward. The objective measurement of hepatic venous pressure gradient (HVPG) to diagnose portal hypertension is not commonly employed by all centres (Shneider, Bosch, et al., 2012). It also comes with its own setbacks related to interpretation and technical aspects in paediatric use. Thus, the diagnosis of portal hypertension frequently falls back on clinical presentation, aided with radiological features supporting portal hypertension and endoscopy finding of gastroesophageal varices (Procopet & Berzigotti, 2017).

Gastroesophageal varices are usually quiescent until bleeding occurs. These bleeding episodes may be torrential and potentially fatal if not managed adequately (Mileti & Rosenthal, 2011). Management includes adequate resuscitation and interventional endoscopy for bleeding arrest. This can be done with endoscopic intervention via endoscopic sclerosant therapy (EST) or endoscopic variceal band ligation (EVL). There are advantages and risks associated with both interventional techniques, and they are not without complications.

Predicting bleeding gastroesophageal varices prior to a bleeding event can be employed through clinical predictive rules using spleen size, platelet count and albumin level (Gana et al., 2011). There has been much debate on the use of primary prophylaxis via medical therapy for prevention of gastroesophageal varices. Use of endoscopy for surveillance for gastroesophageal varices in selected patients, there is inadequate information to recommend its use in children for now (Shneider, Bosch, et al., 2012). The use of endoscopy for surveillance of gastroesophageal varices in children prior to bleeding is yet to be recommended in practice, though its use is established in adult guidelines (Garcia-Tsao et al., 2007; Shneider, Bosch, et al., 2012).

The mortality rate remains high for children presenting with bleeding episodes with 6-week mortality rate of almost 30% in those with severe liver disease (Mileti & Rosenthal, 2011). Early diagnosis is imperative to improve patient outcome but the finding of gastroesophageal varices at diagnosis already denotes that complication has occurred.

The available current treatment strategies for portal hypertension presenting with gastroesophageal varices in children is not ideal. A standard guideline for diagnosis and management of portal hypertension and gastroesophageal varices in children is not yet available. Much of the current practice is adapted from adult guidelines. Thus, there is an urgent need for development of evidence based clinical practice guideline for paediatric use.

CHAPTER 2 : LITERATURE REVIEW

2.1 Epidemiology and Aetiology of Portal Hypertension

The epidemiology and prevalence of portal hypertension is poorly documented worldwide, especially in paediatric population. Singapore, the country most closely representing our local population, reports biliary atresia as the most common cause of portal hypertension in 85.5% of their paediatric patients that have end stage liver disease who underwent liver transplant (Ng et al., 2016). Among the patients with end stage liver disease, Singapore also reported that 73.3% of their patients had biliary atresia, followed by 4.7% with Alagille syndrome (Lim et al., 2006). Another literature from Korea reported that 47.3% of their paediatric patients with portal hypertension had biliary atresia and 14.5% had extrahepatic aetiology of portal hypertension (Kim et al., 2013).

It is also known that the incidence of biliary atresia is higher in Asian countries as compared to European countries, from 5 per 100,000 live births in the Netherlands to 32 per 100,000 live births in French Polynesia, with a slight female preponderance (Chardot, 2006).

The multiple aetiologies of portal hypertension is classified based on the location of the pathology, intrahepatic or extrahepatic, as listed in Table 1. The intrahepatic causes are the most common aetiologies in children. Intrahepatic causes of portal hypertension frequently notes histopathology finding of liver cirrhosis or fibrosis (Ling, 2012). Extrahepatic causes can be further classified as prehepatic or posthepatic (Gugig & Rosenthal, 2012).

With the exception of posthepatic aetiologies, most of the underlying primary pathology causing portal hypertension remains unpreventable in the early stages. More often, the diagnosis is only made when the symptoms occur (Chardot, 2006).

Table 1: Causes of portal hypertension in children

Location of lesion	Diagnostic group	Examples
Intrahepatic	Cirrhosis resulting from cholestatic disease	Biliary atresia, progressive familial intrahepatic cholestasis, primary sclerosing cholangitis, cystic fibrosis liver disease, intestinal-failure associated liver disease,
	Cirrhosis resulting from hepatocellular disease	Autoimmune hepatitis, chronic viral hepatitis, alpha-1-antitrypsin deficiency, non-alcoholic fatty liver disease
	Other fibrotic liver disease	Congenital hepatic fibrosis, Caroli disease
Prehepatic	Portal vein occlusion	Portal vein thrombosis, tumour infiltration (hepatoblastoma, hepatocellular carcinoma or compression by large focal nodular hyperplasia)
	Nodular regenerative hyperplasia	Drug therapy, Turner syndrome
	Portal venopathy or portal sclerosis	Schistosomiasis, idiopathic, HIV infection, cystic fibrosis liver disease
Posthepatic	Hepatic vein obstruction	Budd-Chiari syndrome, inferior vena cava obstruction, congestive heart failure, veno-occlusive disease

HIV refers to Human Immunodeficiency Virus

Adapted from Ling (2012)

2.2 Pathophysiology of Portal Hypertension and the Mechanism of Variceal Development

The pathophysiology of development of portal hypertension is different, depending on the underlying aetiology.

The normal liver has fine regulation of hepatic blood flow. Liver sinusoidal endothelial cells (LSEC) play a major role in regulation of the hepatic vascular tone. These cells are the main source of nitric oxide (NO), which is a potent vasodilator, as well as carbon monoxide (CO) and the metabolites of the cyclooxygenase (COX) pathway.

Increased shear stress due to increased hepatic blood flow in turn causes release of these vasodilators in normal physiological states. These changes enables a narrow hepatic venous pressure gradient of 4 mmHg or less to be maintained in a normal individual. This facilitates the hemodynamic changes imposed by natural digestion process (Poisson et al., 2016). There are studies suggesting that even changes in LSECs size contributes to changes in blood flow (McCuskey, 2000).

LSECs also forms the permeable barrier with the hepatic stellate cells (HSC). In a normal liver, the HSCs are kept in an inactivated state. An inactivated HSC's function in the normal liver involves vitamin A storage and synthesis of extracellular matrix components, cytokines and growth factors. The release of the vasodilatative metabolites to HSCs from LSECs maintain a low portal pressure system (Reynaert et al., 2002).

Liver injury occurs due to oxidative stress from a variety of agents, such as drugs, viruses, bacterial endotoxins and ethanol. These results in phenotypic changes in LSECs and HSCs. LSECs dysfunction, also referred to as endothelial cell dysfunction results in the impaired vasomotor control, by increased release of vasoconstrictor metabolites and reduced vasodilators. This in turn, activates the HSCs, resulting in its transformation into myofibroblasts which express pro-inflammatory and fibrotic genes. It also becomes less contractile.

Activated HSCs are less responsive to NO and other vasodilators. These activated HSCs in turn stimulate LSECs to release angiogenic factors and vascular endothelial growth factors (VGEF) (Iwakiri, 2014). Promotion of these angiogenesis and vascular remodeling causes irregular blood flow pattern and further increase intrahepatic vascular resistance. This is the flow of events in patients with intrahepatic aetiology of portal hypertension.

Pathophysiology of the prehepatic and post hepatic causes however, needs understanding of the hepatic blood supply. The liver receives about 25% of the entire cardiac output (Treiber et al., 2005). This is delivered through a dual vascular supply, through the systemic circulation, which is a high pressure circulation system and through the portal venous flow which is a low pressure system. The systemic blood supply originates from the common hepatic artery which bifurcates into the left and right hepatic arteries to supply the left and right lobes of the liver respectively. The portal venous system comprises of few main tributaries, namely the splenic vein, hepatic vein, and both inferior and superior mesenteric arteries. Generally these veins drain the intestines, spleen, pancreas, stomach and part of the esophagus (Sharma & Rameshbabu, 2012).

Pressure within the portal circuit depends on the intrahepatic resistance and portal blood flow. Increased intrahepatic resistance or congestion of portal blood flow elevates this pressure, as occurs in portal hypertension.

In prehepatic portal hypertension, prehepatic obstruction such as portal vein thrombosis or tumour increases the pressure within the portal venous system. This congestion releases more NO as supposed to intrahepatic conditions where NO is depleted. This promotes vascular remodeling and angiogenesis.

The increased NO production in systemic and splanchnic circulation causes vasodilatation and subsequently reduced systemic vascular resistance. Due to the hyperdynamic circulation in the collateral circuit pathway, there is less effective circulating blood volume. This in turn causes release of antidiuretic hormone and activation of the renin-angiotensin-aldosterone system. This promotes sodium and water retention, contributing to overflow of fluid into the peritoneal cavity (Kim et al., 2010). This is aggravated by endothelial dysfunction and

increased permeability of the LSECs, thus plasma proteins and fluid diffuses into the hepatic lymphatic system, and later to the peritoneum causing ascites.

Hepatorenal syndrome is a serious complication secondary to reduced renal perfusion. These patients may progress into renal failure. Due to the resulting dysfunction of fluid balance hemostasis, ascites may be aggravated (Heneghan & Harrison, 2000).

The degree of blood congestion in the portal circulation in prehepatic conditions corresponds to the frequent finding of splenomegaly and gastroesophageal varices.

In posthepatic portal hypertension, the outflow of the hepatic veins are obstructed by elevated central venous pressure. This results in pooling of blood in the liver and later backflow into the portal venous circulation. Thus the severity of problems associated with hyperdynamic circulation in the collaterals and the portal venous systems might be less pronounced as compared to prehepatic causes. The obstruction of the outflow tract causes a different range of problems, namely portopulmonary hypertension and hepatopulmonary syndrome. In time the increased portal venous pressure causes intrinsic changes in the liver with perisinusoidal deposits and fibrosis and sinusoidal dilatation and liver cirrhosis develops.

The development of gastroesophageal varices is a result of elevated portal venous system pressure. Collateral circulation pathways develop to reduce the portal hypertension, by creating a conduit between the high pressure portal circulation system and the systemic venous circulation (Iwakiri, 2014). The areas drained by the tributaries of the portal venous system dilate. The dilatation of veins in the areas drained by left gastric vein and splenic vein manifest as gastroesophageal varices. This resulting hyperdynamic flow within the portal venous system and its collaterals aggravates and maintains portal hypertension.

2.3 Clinical Findings in Portal Hypertension

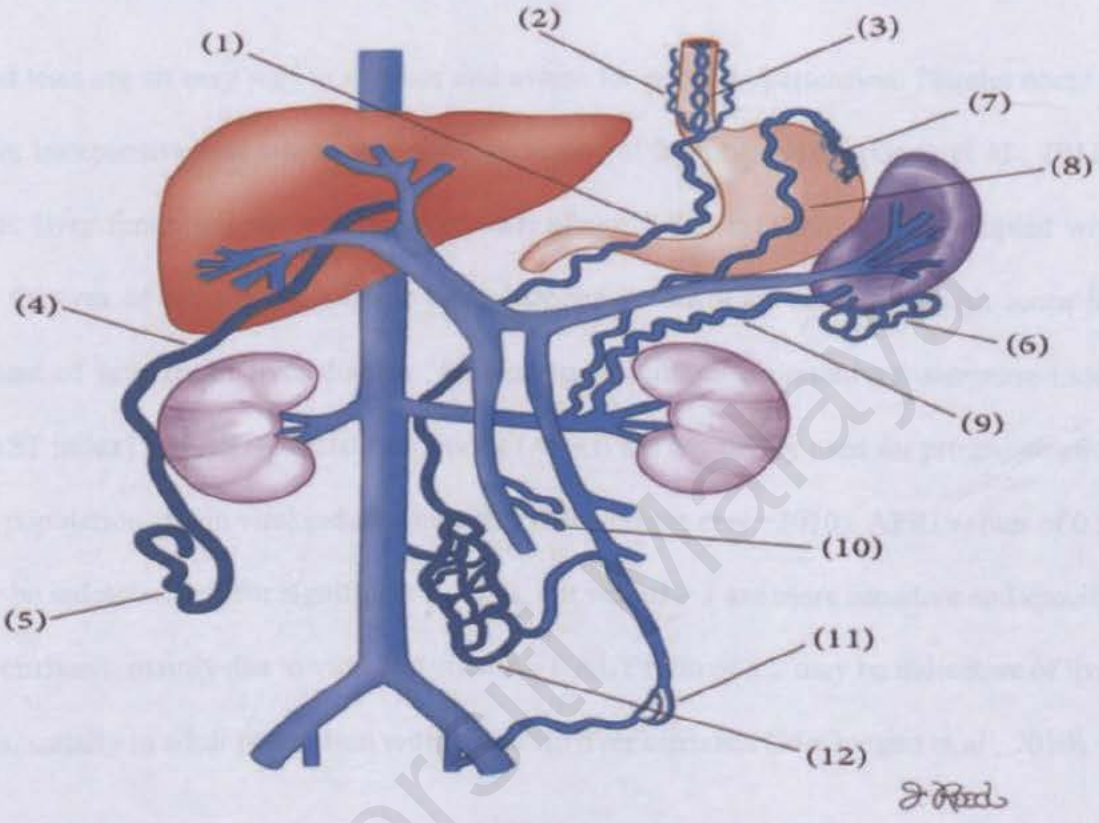
A complete history and physical examination helps to diagnose portal hypertension. Children with portal hypertension may present at any age, depending on the aetiology. When eliciting history, it is important to identify the risk factors, such as previous events causing thrombogenic states, insertion of umbilical vein catheter, hepatotoxic drugs, or severe abdominal infections (Mileti & Rosenthal, 2011).

The approach to physical examination of portal hypertension can be guided by its pathophysiology. More often the physical examination provides many clues to the underlying cause of portal hypertension.

Signs of portosystemic collaterals formation such as dilated abdominal veins (umbilical epigastric vein shunts), caput medusa (paraumbilical collateral veins), ascites and rectal hemorrhoids are more commonly seen in patients with a prehepatic cause of portal hypertension (Sharma & Rameshbabu, 2012). Children with prehepatic etiology have the most consistent finding of splenomegaly. Signs of hyperdynamic circulation is usually present in patients with collaterals, such as cardiac flow murmurs and bounding pulses.

In intrahepatic causes of portal hypertension, the patients may have more stigmata of chronic liver disease, such as jaundice, hepatomegaly and hepatic encephalopathy. The degree of ascites and splenomegaly might be lesser in these patients in the early period before cirrhosis sets in. The size of the liver may change with progression of disease, and cirrhotic livers are rarely palpable. Thus, hepatomegaly is often an inconsistent clinical finding. In biliary atresia, which is one of the common intrahepatic cause of portal hypertension, the triad of presentation includes hepatomegaly, pale stools and conjugated hyperbilirubinemia.

Manifestations of gastrointestinal bleeding due to gastroesophageal varices is the most common presenting symptom in childhood portal hypertension. Together with splenomegaly, this symptoms is always indicative of portal hypertension (Gugig & Rosenthal, 2012).



Adapted from Sangster et al. (2013)

Figure 1: Portosystemic collaterals

2.4 Diagnostic Investigations for Portal Hypertension with Gastroesophageal Varices

Diagnosis of portal hypertension is another challenge. There is no single diagnostic test for portal hypertension as it is a sequelae of the underlying primary pathology. Diagnosis of portal hypertension thus must also include the diagnosis of the underlying pathology.

Blood tests are an easy way to monitor and assess for portal hypertension. Platelet count is a simple, inexpensive test which is a good indicator of hypersplenism (Gana et al., 2011). Synthetic liver function tests, prothombin time, albumin and bilirubin levels, coupled with clinical features of ascites and hepatic encephalopathy constitute the Child Pugh score for assessment of severity of liver disease. Alanine transaminase/ aspartate transaminase index (ALT/AST index) and AST/platelet ratio index (APRI) are frequently used for prognostication in adult population and in viral induced hepatitis (McGoogan et al., 2010). APRI values of 0.5-1.5 may be indeterminate for significant fibrosis, but values > 1 are more sensitive and specific of liver cirrhosis, mainly due to viral hepatitis. AST/ALT ratio of > 2 may be indicative of liver cirrhosis, usually in adult population with alcoholic liver cirrhosis (McGoogan et al., 2010).

Most children undergo ultrasound at presentation. This is easily available, inexpensive and non-invasive, which is an added advantage in paediatric population. Ultrasound is able to demonstrate the dynamics of the portal venous flow as well as note intraluminal obstructions in cases of prehepatic portal hypertension. The liver echotexture and nodularity is a sensitive sign indicating liver cirrhosis. The pathognomonic feature to diagnose portal hypertension is finding of portosystemic collateral vessels and reversal of portal vein flow (Procopet & Berzigotti, 2017). The size of portal vein varies according to the age, height, weight and the chest circumference (Ghosh et al., 2014). More importantly is the documentation of the flow dynamics within the vessel, may give important information about the velocity and compliance of the vessel (Ghosh et al., 2014). The use of elastography relies on the principle that the healthy

liver is more elastic as compared to a fibrotic liver, which is stiffer (Procopet & Berzigotti, 2017). However, the use of ultrasound as a diagnostic tool is inter-equipment and inter-observer dependent. Bowel gas, abdominal thickness and movement can affect the result.

Computed tomography (CT) scanning and magnetic resonance imaging (MRI) can be used for full assessment of the liver, stomach and splenic structures, however it is most accurate for detection of collateral vessels. These imaging modalities are expensive and requires use of contrast media which imposes some risk to the patient (Procopet & Berzigotti, 2017).

Hepatic venous pressure gradient (HVPG) is an objective measure of the pressure gradient between the portal vein and the hepatic vein. A value of above 5mmHg is indicative of portal hypertension. Values above 12mmHg are almost always associated with development of gastroesophageal varices (Maruyama & Yokosuka, 2012). Although this measurement is feasible in children, but the challenges in interpretation and identifying normal values specific to these age group is still limiting its use (Procopet & Berzigotti, 2017). It is also not commonly used.

Liver biopsy remains the gold standard for diagnosis of portal hypertension and liver cirrhosis. Liver biopsy can be carried out from a percutaneous or a transjugular approach. The transjugular approach facilitated the measurement of HVPG in the same setting. The histologic findings provide information on the cause of liver disease and also portal hypertension (Procopet & Berzigotti, 2017).

Thus in the absence of HVPG, the diagnosis of portal hypertension is based on clinical finding of splenomegaly, aided with positive findings from ultrasound or other imaging. However the most objective indicator of the presence and severity of portal hypertension is presence of gastroesophageal varices. The diagnosis of gastroesophageal varices is through

direct visualisation during endoscopy, or signs of collateral circulation or varices seen in radioimaging (Procopet & Berzigotti, 2017). Gastroesophageal varices are asymptomatic until bleeding occurs. The severity of portal hypertension directly relates to the severity of the gastroesophageal varices (Gugig & Rosenthal, 2012).

There may be patients with evolving portal hypertension without gastroesophageal varices, however to diagnose these patients, the objective assessment with HVPG is needed. Without HVPG, the finding of gastroesophageal varices itself constitutes the diagnosis of portal hypertension, as gastroesophageal varices only occurs in association with portal hypertension (Sharma & Rameshbabu, 2012).

2.5 Grading of Gastroesophageal Varices

Grading of esophageal varices has been evolving for the past few decades. Older classifications were based on observation of the varices in phases of respiration and grading was also based on size and colour of varices. Examples of these classifications are Dagradi, Soehendra and Conn's classification (Philips & Sahney, 2016). Other classifications such as Westaby's and Calés, used observations in relation to insufflation of the esophagus and collapsibility of the varices (Philips & Sahney, 2016). The use of size for variceal grading remains debatable in children in view of the wide range of size in children. In the subsequent decades after 1980s, further development was made to include more information on colour of varices which highly predicted bleeding risk. However there is no dedicated grading for gastroesophageal varices in children (D'Antiga et al., 2015).

The World Gastroenterological Organisation now recognizes the Baveno consensus of classification to be used for grading of esophageal varices. Two classification of sizes of varices, small < 5mm and large > 5mm was used. Another classification is in relation to the area occupied by varices in the esophageal lumen, small (minimal elevation of veins above esophageal mucosa), medium (tortuous veins occupying less than 1/3 of esophageal lumen) and large (tortuous veins occupying more than 1/3 of the esophagus lumen) (World Gastroenterology Organisation, 2014).

As for gastric varices, less attention was given to its grading until the past 3 decades. The widely used classification is Sarin classification, which is based on location of the varices (Shneider, Bosch, et al., 2012). Type 1 is continuation of the esophageal varices into the lesser curvature of the stomach, type 2 is esophageal and fundal varices in continuity with the greater curvature. Isolated gastric varices type 1 is fundal varices without any esophageal varices and isolated gastric varices type 2 is fundal varices in the stomach, away from the first part of the duodenum or the cardio-fundal region (Philips & Sahney, 2016).

Table 2: Sarin's classification of gastroesophageal varices

Location	Type	Characteristics
Gastro-esophageal varices	Type 1 (GOV1)	Continuation of esophageal varices into the lesser curvature (GOV1)
Gastro-esophageal varices	Type 2 (GOV2)	Esophageal and fundal varices are present in continuity with the greater curvature (GOV2).
Isolated gastric varices	Type 1 (IGV1)	Fundal varices are present in the cardia in the absence of esophageal varices (IGV1)
Isolated gastric varices	Type 2 (IGV2)	Fundal varices present in the stomach outside of cardio-fundal region or first part of duodenum (IGV2).

Adapted from Philips and Sahney (2016)

In this study, the grading that was used was Calés classification for esophageal varices in view of clinician's preference, to facilitate the standardization of data set.

Table 3: Calés classification of esophageal varices

Grade of varices	Characteristics
Grade 1	Varices flattened by insufflations.
Grade 2	Varices not flattened by insufflations and separated by areas of normal mucosa.
Grade 3	Confluent esophageal varices not flattened by insufflations

Adapted from Philips and Sahney (2016)

2.6 Therapeutic Endoscopy in Portal Hypertension presenting with Gastroesophageal Varices

In clinical practice guidelines for adult portal hypertension, endoscopic surveillance for varices is recommended once the diagnosis of liver cirrhosis is made. In children however, other factors need to be duly considered in view of the risks and benefits incurred to the patient

by undertaking endoscopic surveillance at the outset itself. Often the children are young, and the technical aspect of performing the endoscopy itself is demanding.

These gastroesophageal varices are the major sites of bleeding in portal hypertension. Gastroesophageal varices is seen in up to 70% of children with biliary atresia and portal vein thrombosis. It is found that 75% of children under 2 years of age with biliary atresia would have had gastrointestinal bleeding. This is regardless of the outcome post Kasai procedure-hepatoportoenterostomy (Duché et al., 2010).

Endoscopic variceal band ligation (EVL) is performed via a multiband ligator device which is already loaded with latex rubber bands. This device is triggered by a trigger cord passed through the biopsy channel of the endoscopy unit (Zargar et al., 2002). Multiple bands can be applied at the same setting. However due to the size and angle of the endoscopy device, smaller canals may be difficult to manoeuvre through and target for banding (Kim & Kim, 2013).

Endoscopic sclerosant therapy (EST) uses a free-hand technique, with introduction of a small gauge injector, which injects sclerosant at a specified dose into the varices. This device is easier to manage in smaller children, especially infants.

Endoscopic treatment of gastroesophageal varices are not without complications. Administration of anaesthesia itself has its own sets of complications. Furthermore, some children do have other co-morbid conditions, such as congenital heart disease, respiratory problems and such. These factors, in addition to possible unstable hemodynamic condition due to bleeding prior and during endoscopic procedure, increases the risk imposed on the patient. Often, one has to attain a more hemodynamically stable condition prior to endoscopy, and at the same time keep a very close watch on the patient during the procedure. Although both

interventions are both performed for bleeding control and to reduce varices, there is always risk of acute haemorrhage during procedure. Blood products need to be readily available for resuscitation. In certain patients with co-morbid conditions or a poor clinical status prior to endoscopy, a backup bed at Intensive Care Unit (ICU) is a must.

As the endoscopy involves intubation of the patient and introduction of tools into the patient's body, infection post procedure well known complication. Some centres practice prophylactic antibiotics before procedure to reduce the risk of infection. Often poor lung compliance post anaesthesia poses an increased risk of developing pneumonia. Perforation of the esophagus could also occur, especially in EST, whereby the lungs may manifest chemical pneumonitis (Zargar et al., 2002).

Repeated endoscopy poses a whole new set of problems. Ulceration of the thin mucosa of the esophagus may occur after repeated EST or EVL, and this itself may be a point of haemorrhage. Reduced compliance and scarring post repeated EST or EVL can cause esophageal stricture. If a stricture has developed, further intervention by endoscopic method will be extremely difficult or in some cases, not an option.

In adult guidelines, only band ligation is currently recommended as a method of primary prophylaxis as there is adverse effects on use of sclerotherapy for primary prophylaxis (Shneider, Abel, et al., 2012). Most undergo surveillance endoscopy for the first time only when signs of complications, such as unexplained anemia or bleeding manifestations are present.

Table 4: Complications of endoscopic variceal band ligation and sclerosant therapy

Mode of endoscopic intervention	Associated complications
Endoscopic Variceal Band Ligation (EVL)	Hemorrhage Esophageal ulceration Bacteremia Motility disorders Esophageal stricture
Endoscopic Sclerosant therapy (EST)	Hemorrhage Pneumonia and pleural effusion Pericarditis Intramural hematoma Esophageal ulceration Esophageal stricture Esophageal perforation Motility disorders Bacteremia

Adapted from Zargar et al. (2002)

Worldwide literature reports complication rate post endoscopic intervention as 12.1% in France (Duché et al., 2013). In Korea, patients post EVL had complication rate of 10.3% and 18.8% post EST (Kim et al., 2013). In India, complication rate is reported as 4% post EVL and 25% post EST (Zargar et al., 2002). The literature from Singapore did not report their complication rate post endoscopic intervention (Ng et al., 2016).

2.7 Acute Management of Variceal Bleeding Episodes

The treatment guidelines in the event of acute variceal hemorrhagic episode are aimed at maintaining hemodynamic circulation to allow adequate tissue perfusion. Physiologic compensatory mechanism should be monitored, such as changes in heart rate. A good indicator of circulating volume is central venous saturation and pressure. Biochemical marker such as

venous lactate is useful to predict tissue perfusion. Adequate volume should be reinstituted to the patient for this purpose.

The blood product recommended for use is packed red blood cells, with adequate platelet and fresh frozen plasma. The aim of transfusion should be only to maintain tissue perfusion, as abnormalities in clotting time and thrombocytopenia often are already pre-existing or refractory, and this does not warrant aggressive correction (Costaguta & Alvarez, 2012). Detrimental effects to the other organs are frequently observed as a result of unwarranted aggressive resuscitation and excessive use of blood products which cause fluid overload.

Antibiotic therapy should be instituted whenever there is a risk of infection. Endoscopic evaluation and intervention is recommended to be done within 24 hours post admission after stabilization of hemodynamic status. Use of vasoactive drugs in combination with endoscopy is recommended, and is advised to be continued for up to 5 days after bleeding event (Shneider, Bosch, et al., 2012).

Balloon tamponade is used in massive bleeding events, especially in adults, where it is helps to control the bleeding temporarily before patient is stable enough for endoscopic intervention. It is only to be used by trained staff in intensive care setting in paediatric age group.

2.8 Rebleeding

The outcome indicator of an endoscopy is bleeding arrest at the outset and prevention of further bleeding episodes. Both EVL and EST are effective in bleeding control. It is estimated that at least about one third of patient who undergo EST may have recurrent bleeding episodes. However this may be centre dependent (Maksoud-Filho et al., 2009). A minimum bleed-free

period of 5 days documents effective endoscopy (Shneider, Bosch, et al., 2012). It is recommended for surveillance interval between 2-4 weeks to maintain the bleed- free period, post initial intervention with EVL (Shneider, Bosch, et al., 2012).

2.9 Role of Primary Prophylaxis

Primary prophylaxis via medical therapy, such as the use of non-selective beta blocker is also not proven to be effective in children (Shneider, Bosch, et al., 2012). The therapeutic dose, safety profile and efficacy is still not evidenced by research (Shneider, Bosch, et al., 2012). It is deemed detrimental as it may hinder the physiological compensatory mechanism of the body in the event of a bleeding episode (Kim et al., 2013). However, continued treatment of the cause of portal hypertension may reduce or delay its clinical complications.

2.10 Role of Liver Transplant and Shunt Surgery

A shunt system created surgically is aimed at restoring flow into the portal veins and thereby reducing the portal system pressure. There are two types of portosystemic shunts (PSS). Selective type is a splenorenal shunt which shunts the flow from the gastroesophageal varices through the short gastric veins, spleen and splenic veins to the left renal vein. However the superior mesenteric vein flow to the liver is maintained. The non-selective type of shunt decompresses all portal hypertension (Emre et al., 2009).

A Meso-rex procedure connects the mesenteric vein and the portal vein, with an autologous vein graft, typically harvested from the internal jugular vein. Both these procedures are used in patient with refractory gastroesophageal varices and those with relatively normal livers. It may serve an alternative to liver transplant in cases where liver transplantation is not an option.

Liver transplant is the definitive treatment for portal hypertension. The factors limiting this option is the resources and expertise, cost, availability of suitable donor liver, the risks incurred during surgery and post-transplant therapy. In Malaysia, liver transplantation is only just available and the first successful adult to adult liver transplant was done in University Malaya Medical Centre (UMMC) in year 2017.

The expenditure incurred for liver transplantation relates closely to the cost of living of the country. It is estimated that the cost of liver transplant in the Unites States of America starts at $300,000 USD and $140,000 USD in the United Kingdom. Malaysian patients tend to seek transplant services from China, Taiwan or Singapore in view of more readily available cadaveric donors (Wong & Musa, 2012). The cost ranges from RM 180,000 to RM 1,000,000 for the transplant alone in these countries (Wong & Musa, 2012). This is not inclusive of the travel expenses incurred for follow up, medications post-transplant and such.

Some centres report up to 95% 1 year survival rate post liver transplantation for biliary atresia (Kelly & Davenport, 2007). Literature from Singapore reports mortality rate post liver transplantation at 15% (Lim et al., 2006). Liver transplantation is not without its own set of problems, namely graft rejection and late onset portal vein thrombosis (de Goyet et al., 1996). However as a definitive management to portal hypertension, this option must always be considered and donor screening done whenever available.

CHAPTER 3 : STUDY OBJECTIVES

3.1 Rationale of Study

In portal hypertension presenting with gastroesophageal varices in children, making the diagnosis itself poses a huge challenge to the clinicians. The most objective diagnostic tool, HVPG, is not routinely done in most centres. As gastroesophageal varices only occur in patients with portal hypertension, this is also an objective diagnostic criteria for this condition (Garcia-Tsao et al., 2007). However, the pathophysiology of portal hypertension notes gastroesophageal varices as a sequelae of increasing portal venous pressure, and gastroesophageal varices relates directly to the severity of portal hypertension. Thus, this also means that portal hypertension is diagnosed late, and denotes lost opportunities for early intervention.

There is also no accepted clinical predictive risk assessment for bleeding for portal hypertension presenting with gastroesophageal varices (Shneider, Bosch, et al., 2012). These children often only have their first endoscopic evaluation and intervention after a bleeding episode. In children, there is no accepted consensus on primary prophylaxis with medical therapy or the use of routine endoscopic evaluation of varices (S. C. Ling et al., 2011). Factors limiting the adoption of these treatment in children include lack of supportive data, limitation of resources, risks of general anaesthesia and associated procedural complications which are more difficult to manage in this age group as compared to adults (Dar & Shah, 2010; Shneider, Bosch, et al., 2012).

Thus, paediatric portal hypertension presenting with gastroesophageal varices remain an area requiring research and specific management guidelines. Similarly there is lack of data involving the local population. This study hopes to give more insight into these areas. These

information will help to build the framework for further research in this field, in this centre. The outcome analysis also will give insight on the areas requiring improvement.

3.2 Study Objectives

The objectives of this study are as follows:

1. To outline the demographics, causes, risk factors and clinical features of children with gastroesophageal varices complicating portal hypertension in local setting.
2. To describe the endoscopic practices in management of gastroesophageal varices in paediatric patients in University Malaya Medical Centre (UMMC).
3. To analyse the outcome post endoscopy treatment.

3.3 Expected Outcome

This study is conducted in University Malaya Medical Centre (UMMC), which is one of the main referral centres for paediatric gastroenterology disorders in Malaysia. Through this study, we hope to ascertain the prevalence and demographic information on children with portal hypertension and gastroesophageal varices. Most literature on paediatric portal hypertension involving Asian population is done in the East Asian countries such as Japan and Korea.

Although the commonest cause for portal hypertension in children is as a sequelae of biliary atresia, other causes are not well described in literature (Ling, 2012). A better understanding of the common causes in local setting will enable a more focused approach for clinicians to diagnose portal hypertension before development of complications.

Risk factor analysis will help to determine the subset of patients who need more stringent screening to allow earlier diagnosis and possibly prevent the first bleeding episode. This is made more relevant as primary prophylaxis for bleeding prevention these children is not recommended.

This will also be an audit study for the gastroenterology team in UMMC on the practice of endoscopic management for gastroesophageal varices and evaluate the outcome, in terms of complications, rebleeding, mortality and liver transplants.

CHAPTER 4 : METHODOLOGY

4.1 Study Design and Protocols

This was a retrospective descriptive cohort study of paediatric patients from University Malaya Medical Centre (UMMC), Kuala Lumpur. Data for the study period was taken from 1st December 2000 till 1st December 2016 over a period of 16 years. Study protocol was approved by Medical Research Ethics Committee of University Malaya Medical Centre, MREC ID No: 2017727-5440.

Prior to starting data collection, the inclusion and exclusion criteria for the patients were set. Considering the lack of objective methods to diagnose portal hypertension other than the endoscopic finding of gastroesophageal varices, this became the main criteria to include patients for the study. All patients fulfilling inclusion and exclusion criteria irrespective of bleeding events were listed for the study.

The inclusion criteria was as follows:

- First endoscopy within the study period
- Age less than 18 years at first endoscopy
- Positive finding of gastroesophageal varices
- At least 6 months duration of follow up post first endoscopy
- Medical records are available

The exclusion criteria was as follows:

- First endoscopy outside of study period
- Age more than 18 years at first endoscopy
- No gastroesophageal varices

- Less than 6 months follow up
- Medical records are not available

Two routes were used to enlist patients for the study to minimize missing samples. Firstly, all available endoscopic records from the endoscopy room was examined. These records contained information on patient's basic details and information on endoscopy finding. The records that were available in the endoscopy unit started from year 2010 to year 2016. Unfortunately, the records from the years before that, have already been redistributed into patient's individual records folders and are not available in endoscopy unit. However this records enlisted both the patients who had their first endoscopy and also who were having repeated surveillance endoscopies within that time period. Thus, a preliminary list was made comprising of all patients with positive findings of gastroesophageal varices through this route.

This list was then crosschecked with Gastro Database UMMC, an electronic database listing all paediatric patients with gastroenterological disorders. The information available in this database is basic patient information as well as their diagnosis. Though the database provided basic information from patients dating back to year 2000, but only records from the past 5 years were updated. At the time that the study population was listed, there were 1491 patients names entered in this database. All the patients with possible aetiologies that may give rise to portal hypertension (please refer to Table 1, page 21) was listed. This shortlisted 110 patients, whose medical records were then traced. These patient's endoscopy notes in their medical records were checked for positive finding of gastroesophageal varices.

Thus, 44 patients were listed through the endoscopy records review, and 51 patients were listed through the Gastro Database UMMC records review. There was an overlap of the same 44 patients who were already listed through the endoscopy records with those listed from Gastro Database UMMC when the list was cross-checked.

All 51 patient's records were further analyzed for exclusion and inclusion criteria. Four patients were not eligible for the study as they were either aged more than 18 years or did not have follow up. Another 9 patient's records were not able to be traced despite multiple attempts.

A total of 38 patients, 31 patients from the endoscopy records and an additional 7 patients from the Gastro Database records were eligible for the study. Data from these 38 patients was then transcribed into a data collection form, which was designed before embarking on this study. The flow chart in Figure 2 summarizes the case ascertainment and patient enlisting process as explained here.

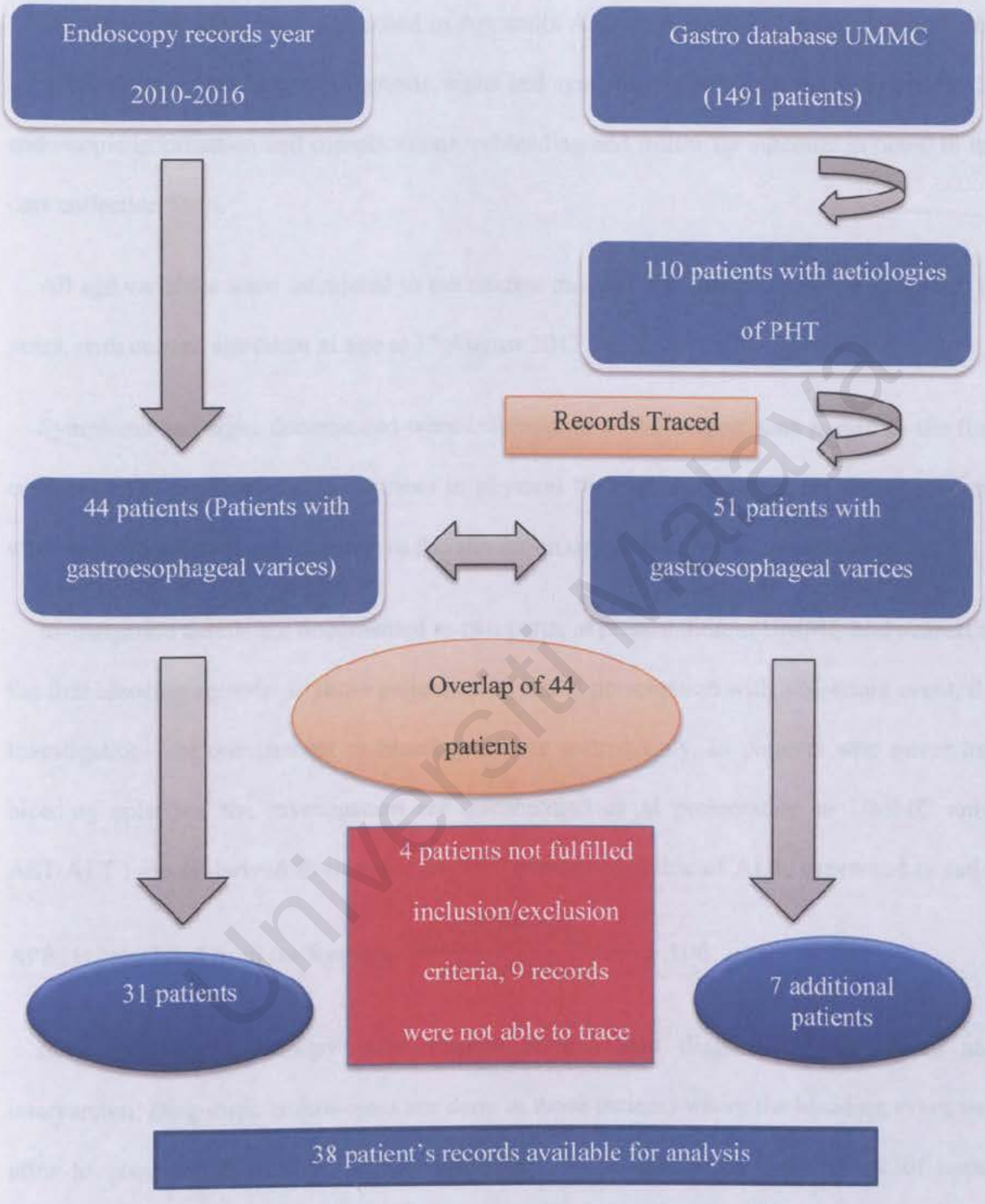


Figure 2 : Flow chart of patients enlisting process and case ascertainment from endoscopy records UMMC and Gastro database UMMC

4.2 Description of Variables

The data collection form is attached in Appendix A. Data collected included demographic data, birth history, underlying diagnosis, signs and symptoms, investigations, final diagnosis, endoscopic information and complications, rebleeding and follow up outcome as noted in the data collection form.

All age variables were calculated to the nearest month from date of birth and presented in years, with current age taken as age at 1st August 2017.

Symptoms and signs documented were information at the nearest time period to the first endoscopy. In the event that differences in physical findings were noted, the findings of the most senior medical doctor, nearest to the admission day, was taken for documentation.

Investigation details are documented in two parts, at presentation to UMMC and nearest to the first bleeding episode. In those patients with initial presentation with a bleeding event, the investigations are documented at bleeding events section only. In patients who never had bleeding episodes, the investigation are documented as at presentation to UMMC only. AST/ALT ratio is derived from value of AST divided by value of ALT, expressed in ratio. APRI is calculated from the formula $\frac{\frac{AST(Patient)}{AST(Upper\ Normal\ Limit:50)}}{Platelet(10\text{^}9/L)} \times 100$.

Indications for endoscopy were mainly divided into diagnostic, surveillance and intervention. Diagnostic endoscopies are done in those patients where the bleeding event was prior to presentation to the hospital, with the aim of investigating the cause of upper gastrointestinal bleeding. Surveillance endoscopies are performed when there is presence of risk factors and clinical suspicion of portal hypertension by the medical doctor to perform an endoscopic surveillance before any bleeding event. Interventional endoscopy was defined as endoscopy done in patients presenting with acute bleeding event, with aim of arresting the

bleeding. As for patients who presented with a bleeding event, the rebleeding section documents information on their progress in terms of rebleeding after this first endoscopy and the interval between this rebleeding and the second endoscopy.

The patients were regrouped based on the indication of the endoscopy to facilitate analysis for the comparison of two groups. The diagnostic and surveillance endoscopies are regrouped as non-event-driven group. The intervention endoscopies were grouped as event-driven group.

The follow up section documented the status of patients after the first endoscopy until 1st August 2017 or in the duration of at least 6 months post first endoscopy. Importantly the information of liver transplantation was documented, and also surveillance interval, transfer of care or defaults as well as mortality.

4.3 Statistical Analysis

Data was entered and analyzed using Microsoft Excel (Microsoft Corp., Redmond, WA, USA). Statistical analysis was done using the IBM SPSS Statistics Version 21 (IBM Corporation, Armonk, NY, USA) statistical package.

Descriptive analysis of the demographics, clinical characteristics of patients, etiologies, endoscopic practices and complications and follow up outcome of portal hypertension was performed. Results are predominantly consisting of means, medians, standard error of the mean, ranges and proportions. Relevant continuous variables were bootstrapped with 10,000 repetitions to generate a 95% confidence interval (Campbell & Torgerson, 1999). The results were depicted in tables, figures and charts.

The study population was also grouped as two groups, event-driven and non-event driven endoscopies. Comparison of relevant variables between these groups was performed.

Appropriate significance testing tools were utilized in accordance to the assumptions met by variables examined using Mann-Whitney U test, student T-test or Fischer's exact test.

CHAPTER 5 : RESULTS

5.1 Demographic Data and Patient Characteristics

Of the study population consisting of 38 patients, there was equal number of males (n=19) and females (n=19). Portal hypertension presenting with gastroesophageal varices was almost equally distributed in the Malays (n=18) and Chinese (n=17) population. There was only one Indian (n=1). One patient was a Sabahan and the other was an Orang Asli. The average age at presentation was 4.87 years (95% CI 3.58 years - 6.22 years). A majority of patients, 27 patients out of 38 patients (71.1%) were born at term. Thirty patients, 78.9% were delivered via spontaneous vaginal delivery.

Table 5: Patient characteristics of study population (N=38)

Parameter	Frequency (N=38)
Gender, n	
• Male	19 (50.0%)
Ethnicity n	
• Malay	18 (47.3%)
• Chinese	17 (44.7%)
• Indian	1 (2.6%)
• Others	2 (5.2%)
Gestation, mean in weeks	36.45 (95% CI 35.45 -37.37)
Birth weight, mean in kg	2.64 (95% CI 2.37-2.89)
Pre-existing comorbid condition, n	19 (50%)
Age at first endoscopy, mean in years	6.72 (95% CI 5.41-8.47)
Event-driven endoscopy, n	22 (57.9%)
Intervention done, n	30 (78.9%)
• EVL	21 (70.0%)
• EST	7 (23.3%)
• Both	2 (6.7%)
Complication, n	5 (13.1%)
Liver transplant, n	4 (10.5%)
Mortality, n	5 (13.1%)

Kg: kilogram

Out of the 38 patients, a majority of the patients were referred from other institutions at diagnosis, comprising of 21 patients (55.3%) from government hospitals and 6 patients (15.8%) from private institutions. The remaining 11 patients (28.9%) presented to UMMC at the outset itself.

5.2 Patient Risk Factors and Aetiology

Table 7 shows the cause of portal hypertension in 38 patients. Out of the 38 patients, the commonest underlying aetiology for portal hypertension presenting with gastroesophageal varices was biliary atresia (BA) in 14 patients (36.8%), followed by idiopathic portal hypertension in 8 patients (21.1%), portal vein thrombosis (PVT) in 6 patients (15.7%) and autoimmune hepatitis (AIH) in 5 patients (13.2%). The full list of aetiologies divided by location of pathology is depicted in the table below.

Table 6: Causes of portal hypertension in study population (N=38)

Location	Aetiology	n (%)	Total n (%)
Intrahepatic	Biliary atresia	14 (36.8)	22 (57.9)
	Autoimmune hepatitis	5 (13.2)	
	Caroli's syndrome	1 (2.6)	
	Congenital hepatic fibrosis	1 (2.6)	
	Primary sclerosing cholangitis	1 (2.6)	
Prehepatic	Portal vein thrombosis	6 (15.7)	7 (18.4)
	Hepatocellular carcinoma	1 (2.6)	
Posthepatic	Severe veno-occlusive disease	1 (2.6)	1 (2.6)
Unknown	Idiopathic portal hypertension	8 (21.1)	8 (21.1)

Out of the 38 patients, 22 patients (58%) had intrahepatic aetiologies of portal hypertension. Biliary atresia was the most common aetiology in the intrahepatic group, made up of 14 patients out of 38 patients (36.8%). Eleven of these 14 patients with biliary atresia were of Chinese ethnicity, and the other 3 patients were of Malay ethnicity. Autoimmune hepatitis was the

second most common among the intrahepatic aetiologies, comprised of 3 Malay patients, one Chinese patient and one Sabahan girl.

Out of the 38 patients, 7 patients had prehepatic aetiology of portal hypertension. Among these 7 patients, 6 patients had portal vein thrombosis, making this the most common prehepatic aetiology of portal hypertension presenting with gastroesophageal varices in this study population. Five of these 6 patients with portal vein thrombosis, were of Malay ethnicity.

Eight patients out of 38 patients (21.1%) had idiopathic portal hypertension. Out of these eight patients, 4 patients were of Malay ethnicity, 2 patients were of Chinese ethnicity, and also one Indian patient and one Orang Asli patient.

Among the 18 Malay patients, the most common aetiology was portal vein thrombosis in 5 patients, followed by autoimmune hepatitis and idiopathic portal hypertension at 3 patients each, and 2 patients with biliary atresia followed by other aetiologies.

Three patients had umbilical vein catheterization (UVC) of which the duration of cannulation was not documented. Two of these patients were born at term and had sepsis in the neonatal period. They both later had portal hypertension secondary to portal vein thrombosis.

Only 5 patients had documented use of total parenteral nutrition (TPN) for a range of 3-30 days. Of these 5 patients, 4 patients had sepsis and 1 had birth asphyxia in the neonatal period. Four of them were also premature at birth. This subset included the two patients described above, 2 patients with biliary atresia and one patient with congenital hepatic fibrosis.

Six patients had portal vein thrombosis, including the 2 patients described above. Of the remaining 4 patients, 3 were referred from other centre, and 2 of them were born prematurely. They first presented to UMMC at age 7-10 years, and the information on UVC and TPN use was not documented in their records.

Half of the patients (n=19) had pre-existing comorbid conditions, as listed in the Table 7 below. Some conditions were directly related to liver disease, such as autosomal polycystic kidney disease. This patient had congenital hepatic fibrosis, a known association of fibropolycystic diseases. There were no patients with positive family history of liver disorders.

Table 7: List of comorbid conditions (n=19)

Type	Comorbid condition	Frequency
Syndromic children	Down Syndrome	1
	Dysmorphism (unspecified diagnosis)	3
Learning difficulty	Slow Learner	1
	Autism Spectrum Disorder	1
	Global Developmental Delay	1
Renal	Renal Microlithiasis	1
	Autosomal Dominant Polycystic Kidney Disease	1
	Nephritic syndrome	1
Malignancy	Acute Lymphoblastic Leukemia	1
	Suprasellar Germinoma	1
	Neuroblastoma	1
Respiratory	Bronchial Asthma	1
	Pulmonary tuberculosis	1
Gastrointestinal	Peptic Ulcer Disease	1
Miscellaneous	Alpha Thalassemia Trait	1
	Prematurity	2

5.3 Investigations

Table 8: Biochemical parameters of study population at presentation (n=27)

Parameter	Normal range	Mean	95% confidence interval	
			Lower limit	*Upper limit*
Platelet (10^9/L)	200-500	96.7	59.43	152.14
APRI	NA	2.1	1.12	3.31
TWC (10^9/L)	6-16	9.37	5.41	14.61
PT (s)	9.4-12.6	14.5	12.03	17.49
INR	1-1.2	1.3	1.16	1.66
Albumin (g/L)	32-48	34.7	29.71	39.14
T.Bilirubin (umol/L)	< 17	71.0	13.57	171.43
C.Bilirubin (umol/L)	NA	58.6	5.86	149.28
AST (U/L)	<34	95.7	45.14	158.57
ALT (U/L)	10-49	93.4	38.57	155.86
AST/ALT ratio	NA	1.1	0.89	1.48
GGT (U/L)	< 73	168.1	36.43	364.71

T.Bilirubin refers to total bilirubin; C.Bilirubin refers to conjugated bilirubin; GGT refers to gamma glutamyl transferase; PT refers to prothrombin time; INR refers to international standardized ratio; APRI refers to AST to platelet ratio index; TWC refers to total white cells, NA denotes Not Applicable

Investigations taken at presentation before a bleeding event noted a low average platelet count, with normal white cell count (TWC) and albumin level. Mean International Normalized ratio (INR) and prothrombin time (PT) was slightly higher than the reference range. As expected in portal hypertension related disorders, transaminases were raised. Average gamma glutamyl transferase (GGT) level was high. Also important to note was that the APRI was more than 2, suggesting liver cirrhosis (McGoogan et al., 2010).

Table 9: Biochemical parameters of study population at bleeding event (n=26)

Parameter	Normal range	Mean	95% confidence interval	
			Lower limit	*Upper limit*
Hemoglobin (g/dL)	11-14	9.5	8.50	10.71
Platelet (10^9/L)	200-500	89.8	68.67	110.89
APRI	NA	2.4	1.06	4.11
TWC (10^9/L)	6-16	5.4	3.68	7.34
PT (s)	9.4-12.6	13.6	11.70	15.91
INR	1-1.2	1.20	1.11	1.51
Albumin (g/L)	32-48	31.3	27.67	35.0
T.Bilirubin (umol/L)	< 17	104.4	21.67	237.56
C.Bilirubin (umol/L)	NA	82.6	15.00	191.55
AST (U/L)	<34	101.00	51.11	165.89
ALT (U/L)	10-49	86.11	39.89	148.22
AST/ALT ratio	NA	1.29	0.86	1.78
GGT (U/L)	< 73	64.22	39.00	89.78

T.Bilirubin refers to total bilirubin; C.Bilirubin refers to conjugated bilirubin; GGT refers to gamma glutamyl transferase; PT refers to prothrombin time; INR refers to international standardized ratio; APRI refers to AST to platelet ratio index; TWC refers to total white cells, NA denoted Not Applicable

At bleeding event, both mean TWC and platelet count was low. Coagulation profile was slightly higher compared to reference range. Mean albumin level was low and transaminases are raised. Mean GGT value had normalized. The APRI value still more than 2 and was higher than at presentation.

A total of 36 out of 38 patients (94.7%) underwent ultrasound of hepatobiliary system at clinical presentation, however only eight patients (22.2%) have documentation of the portal vein size, with mean of 6.75mm (95% CI 5.00mm-8.50mm). The size of portal vein was not able to be interpret in view of relevant parameters such as height, weight and chest circumference for comparison with normogram was not available. Six patients with portal vein thrombosis did have ultrasound done, but only 2 out of these 6 patients (33.3%) had documentation of portal vein size and flow.

Eighteen patients out of 38 patients (47.3%) underwent contrasted imaging studies. The most common investigation was computed tomography of the abdomen, followed by Hepatobiliary Iminodiacetic Acid (HIDA) and Magnetic Resonance Cholangiopancreatography (MRCP) scans. These investigations were more directed to ascertain the aetiology of the primary aetiology of liver disease instead of assessment for portal hypertension.

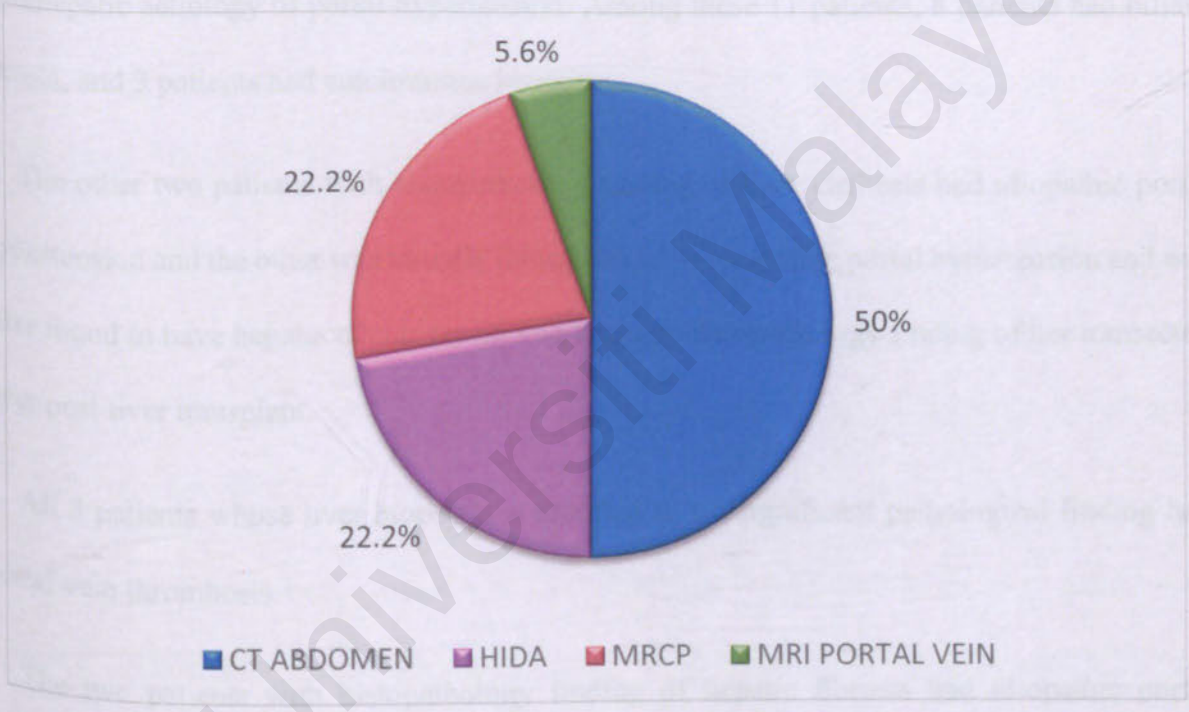


Figure 3: Contrast study type at presentation for study population (n=18)

A total of 71.1% (27/38) of patients had liver biopsy. Five out of these 27 patients did not have documentation of biopsy results as it was done at another centre. Listed below are the histopathology findings of the liver biopsy for the remaining 22 patients.

Table 10: Histopathology findings of liver biopsy (n=22)

Liver histopathology finding	Frequency	Percentage (%)
Liver cirrhosis	13	59.1
No specific pathology	3	13.6
Hepatic fibrosis	2	9.1
Chronic inflammation	1	4.5
Primary sclerosing cholangitis	1	4.5
Autoimmune hepatitis	1	4.5
Possible metabolic disorder	1	4.5

Eleven out of the 13 patients who had histopathology finding of liver cirrhosis, had intrahepatic aetiology of portal hypertension. Among these 11 patients, 8 patients had biliary atresia, and 3 patients had autoimmune hepatitis.

The other two patients with histopathology finding of liver cirrhosis had idiopathic portal hypertension and the other was initially thought to have idiopathic portal hypertension and was later found to have hepatocellular carcinoma through histopathology finding of her transected liver post liver transplant.

All 3 patients whose liver biopsy was reported as no significant pathological finding had portal vein thrombosis.

The two patients with histopathology finding of hepatic fibrosis had idiopathic portal hypertension and congenital hepatic fibrosis. One patient's biopsy was described as possibly indicative of metabolic disorder, but later was diagnosed to have autoimmune hepatitis. The patient with Caroli's syndrome did not have documentation of liver biopsy at our centre.

Of the 8 patients who had idiopathic portal hypertension, only 2 had biopsy results, one reported hepatic fibrosis and the other reported liver cirrhosis.

5.4 Clinical Characteristics of Patients at First Endoscopy

The average age of patient at first endoscopy was 6.72 years (95% CI 5.41 years-8.47 years). The most frequent physical finding was splenomegaly, which was found in 35 patients out of 3 patients (92.1%). The mean size of splenomegaly was 5.2 cm (95% CI 4.00 cm -6.64 cm) in this study population. A total of 23 patients out of 38 patients (60.5%) had hepatomegaly with average size of liver of 3.8 cm (95% CI 3.00 cm -4.68 cm).

Out of the 38 patients, only 12 patients (31.5%) had jaundice, and 11patients (28.9%) had ascites at presentation. The most common presenting symptom was hematemesis, in 19 patients (50%), followed by malaena in 18 patients (26.3%). Other symptoms included abdominal distension (n=15), abdominal pain (n=9) and anorexia (n=9).

When analyzed the 22 patients with intrahepatic aetiology of portal hypertension, the average age at their first endoscopy was 6.83 years (5.04 years -8.62 years). All of them had splenomegaly, with mean size of 6.41 cm (95% CI 5.05 cm-7.82 cm). Six patients (27.3%) did not have hepatomegaly.

Further analysis of the 6 patients who had portal vein thrombosis found the average age at their first endoscopy was 7.19 years (4.64 years -9.33 years). All of them had splenomegaly with average size of 6 cm (95% CI 4.00 cm-7.80 cm). Only 50% of them had hepatomegaly.

5.5 Endoscopic Findings

Of the 38 patients who underwent endoscopy, 57.9% (n=22) had endoscopy done for interventional purpose. A total of 36.8% (14/38) patients had endoscopy done for diagnostic purposes and 2 patients (5.3%) had endoscopy done for surveillance purposes. The two patients

who had endoscopy done for surveillance had autoimmune hepatitis, with spleen size of 9 cm and 11 cm respectively.

A total of 37 patients had esophageal varices. Of these patients, the most commonly seen was the most severe grade 3 (n=23), followed by grade 2 (n=8) and then grade 1 (n=6). Four patients had both gastric and esophageal varices, and one patient had only gastric varices. The common type of gastric varices was type 1 (GOV) seen in 4 patients and type 2 (GOV), which was seen in one patient. There were five cases in which a cherry red spot was seen, and three of them were in the esophagus.

Among the study population, 78.9% patients (30/38) underwent intervention for varices. A total of 21 of these 38 patients underwent EVL only, and a total of 7 out of 38 patients underwent EST only. Two patients underwent both EST and EVL in the same setting. Patients who underwent EVL commonly had 2 ligations done (n=9), whereas patient who underwent EST commonly had 3 or 4 injections given (n=3).

There were 5 out of 38 patients (13.1%) who developed complications post endoscopy. One patient had stricture, and two patients had hemorrhage post endoscopy. Two other patients had a combination of acute hemorrhage and ulceration and acute hemorrhage with infection. There was no event of perforation or anaesthetic complications. Of these 5 patients who had complications, 2 patients had underwent EST and 3 patients had underwent ligation. Thus 28.5%, 2 out of 7 patients who underwent EST had encountered complications, as compared to 14.3%, 3 out of 21 of patients who underwent EVL.

Eleven out of 38 patients (28.9%) had rebleeding after endoscopy. The mean period of bleed free days was 86.91 days (95% CI 42.09 days-135.36 days). It was noted that in 36.3% of the

patients (n=4), the bleed occurred within the first 30 days post endoscopy. Shortest bleed-free period post endoscopy was 12 days.

From the total of 11 patients that had rebleeding post endoscopy, ten patients (91.1%) had a second endoscopy performed, with a mean interval of 3.2 days (95% CI 1.70 days-4.90 days). One patient did not have a repeat endoscopy as child was too unstable for the procedure in the same setting. After stabilization via medical therapy in that admission, patient was planned for elective endoscopy but was lost to follow up.

5.6 Outcome

Of the 38 patients, only 4 patients (10.52%) underwent liver transplant in the duration of follow up. The average age at transplant was 8.46 years (95% CI 3.68 years-13.37 years). All 4 patients had end stage liver disease due to different causes. One patient had autoimmune hepatitis, another patient had Caroli syndrome, and two others had idiopathic portal hypertension, one of which had been diagnosed with hepatocellular carcinoma after correlating with the liver histopathology of the transected liver. Three out of these 4 patients who had liver transplantation had continued follow up at the transplant centre, whereas the one patient who had autoimmune hepatitis was on joint follow up under both UMMC and the transplant centre.

Five patients out of the 38 patients (13.2%) died in the course of follow up. In four patients, the cause of death was due to the underlying end stage liver disease and portal hypertension complicated by bleeding disorders. This included one patient who had underlying high risk acute lymphoblastic leukemia and had bone marrow transplant. This patient had severe veno-occlusive disease with gastrointestinal bleeding, for which he underwent first endoscopy at age 10 years. This endoscopy was complicated with acute hemorrhage and this child passed away

in the same admission due to uncontrolled variceal bleeding. Two other patients that died both had underlying biliary atresia, and had complication of rebleeding after their first endoscopy. Both these patients were young, aged 1.3 years and 0.91 years respectively at time of their first endoscopy. They both died due to multiorgan failure secondary to decompensated liver disease and disseminated intravascular coagulopathy (DIVC), at 2.5 years and 1.12 years respectively. Another patient had underlying autoimmune hepatitis, underwent first endoscopy at age 13.5 years without any complications. She had non traumatic intracranial hemorrhage secondary to coagulopathy end stage liver disease. She died of multiorgan failure and DIVC at age 14.5 years.

The last patient's death was not directly due to bleeding complications due to gastroesophageal varices. She had idiopathic portal hypertension and underwent first endoscopy at age 16 years with no complications. She died at age 19 years due to complications of septicaemic shock, and did not have any coagulopathy.

Twelve patients (12/38) were still under ongoing surveillance, of which only one patient was undergoing surveillance at less than 6 monthly intervals. This particular patient had a recent variceal bleed, thus was on short interval monitoring.

Five patients had been transferred to other hospitals and were not on follow up with UMMC, and 8 patients had defaulted follow up. The average age of patients still under follow up in UMMC is 13.10 years (95% CI 11.43 years-13.78 years). The oldest patient still under follow up was 19.5 years old as of 1st August 2017. There were no patients transferred to adult team. A total of 20 patients (52.6%) were still under regular follow up in UMMC.

The documented mortality rate of this study population was 13.2% (5/38) but in view of the lack of information on the patients who have defaulted (8/38) and those who have since

transferred to other hospital (5/8), it is assumed that the highest mortality rate could be up to 47.3% (18/38) in this sample of 38 patients.

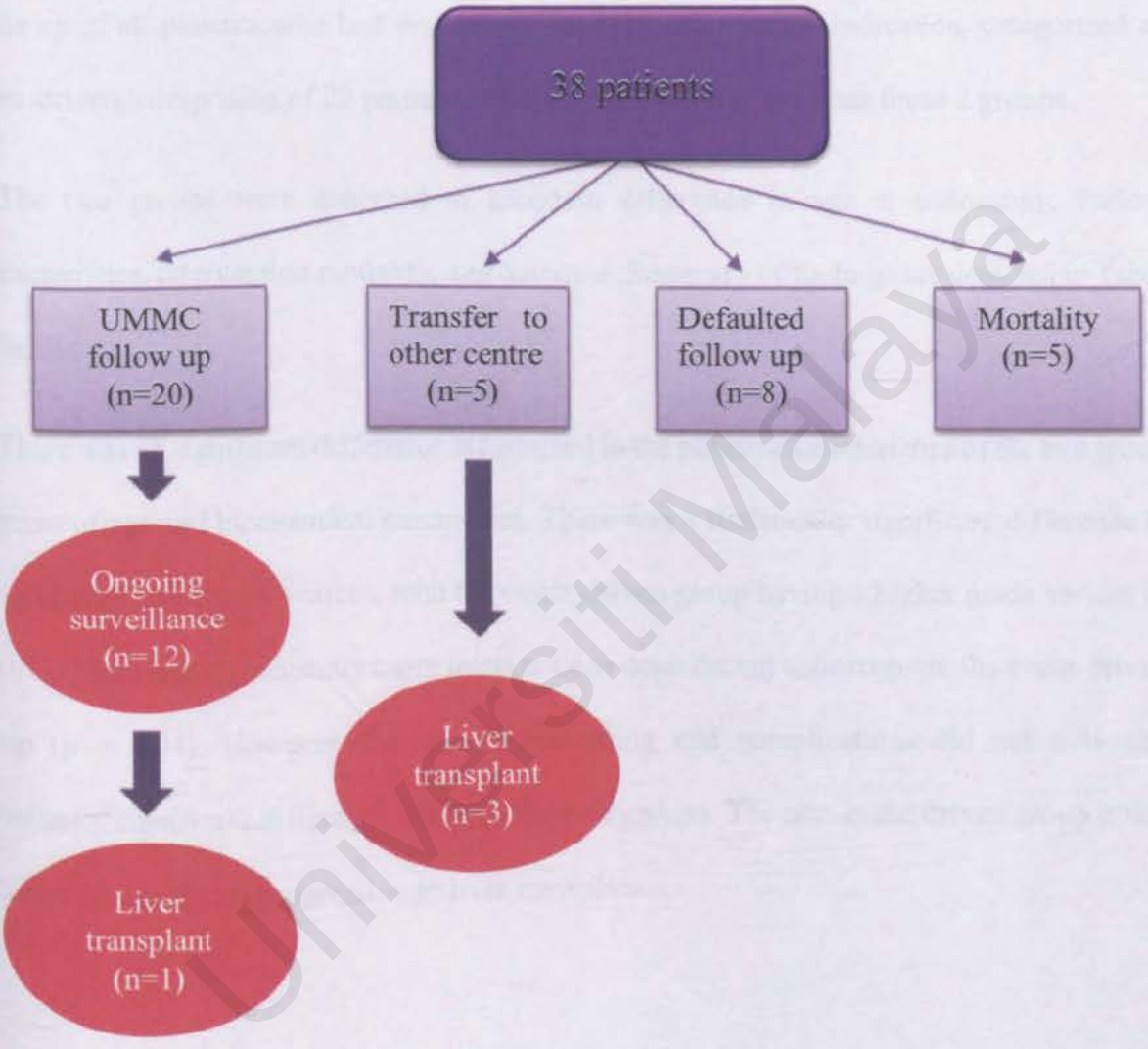


Figure 4: Outcome of study population (N=38)

5.7 Comparison Between The Non-Event Driven And Event-Driven Endoscopy Groups

Those patients who underwent endoscopies were grouped again for comparison according to the indication of their initial endoscopy. Both diagnostic and surveillance indications were categorized as non-event-driven group which comprised of 16 patients. Another group was made up of all patients who had endoscopy done for intervention indication, categorized as event-driven, comprising of 22 patients. There was no overlap between these 2 groups.

The two groups were analyzed to ascertain difference in age at endoscopy, varices characteristics, intervention modality, and outcome. Summary of findings are depicted in Table 11 below.

There was no significant difference ascertained in the patient characteristics of the two group in terms of age and biochemical parameters. There was a statistically significant difference in the grades of esophageal varices, with the event-driven group having a higher grade varices ($p = 0.01$). There was significantly more interventions done during endoscopy in the event-driven group ($p = 0.04$). However the rate of rebleeding and complications did not note any statistically significant difference between the two groups. The non-event driven group noted statistically significant progression to liver transplant.

Table 11: Comparison between non-event driven and event driven endoscopies

Parameter	Non-event driven	Event-driven	p-value
Number of patients (n)	16	22	NA
Age in years (mean)	7.20 (95% CI 5.54-8.85)	6.38 (95% CI 4.48-8.29)	0.543[§]
Grade of esophageal varices	15 (93.8%)	22 (100%)	NA
• Grade E1	6 (40.0%)	0	0.010[†]
• Grade E2	3 (20.0%)	6 (27.3%)	
• Grade E3	6 (40.0%)	16 (72.7%)	
Grade of gastric varices	2 (12.5%)	3 (13.6%)	NA
• Grade GOV1	2 (100.0%)	2 (66.7%)	0.94[†]
• Grade GOV2	0	1 (33.3%)	
Intervention performed	9 (56.3%)	21 (95.5%)	0.005[α]
Type of intervention	NA	NA	NA
• EVL	6 (66.7%)	14 (66.7%)	0.52[†]
• EST	2 (22.2%)	6 (28.5%)	
• Both	1 (11.1%)	1 (4.8%)	
Occurrence of rebleed	2 (22.2%)	9 (42.9%)	0.15[α]
Rebleeding, n days (mean)	182.5 (95% CI 182.00-183.00)	52.0 (95% CI 26.33-91.50)	0.07[†]
Complication	2 (22.2%)	3 (14.3%)	0.99[α]
Blood investigations	NA	NA	NA
• Total White Count (10^9/L)	7.89 (95% CI 5.41-10.91)	9.18 (95% CI 7.07-11.40)	0.34[†]
• Platelet Count (10^9/L)	140.38 (95% CI 84.75-209.87)	105.73 (95% CI 86.23-126.18)	0.94[†]
• Serum albumin (g/L)	33.94 (95% CI 30.94-36.75)	33.19 (95% CI 31.00-35.43)	0.802[§]
Liver transplant	4 (25.0%)	0	0.025[α]
Mortality	1 (6.3%)	4 (18.2%)	0.374[α]

Endoscopic Variceal Ligation (EVL); Endoscopic Sclerosant Therapy (EST)

[§]T-test; [†]Mann-Whitney U test; [α]Fischer's exact test

NA denotes Not Applicable

CHAPTER 6: DISCUSSION

This study shows that portal hypertension presenting with gastroesophageal varices in children was equally distributed, as compared to a slight female preponderance noted in literature in our neighbouring country, Singapore (Ng et al., 2016).

Peninsular Malaysia is unique in its diverse ethnicity distribution. The peninsular region has few major groups of ethnicity namely the Malays, Chinese and the Indians. The 2010 Malaysian national census reported the distribution of ethnicity of Malays to be 67.4%, the Chinese as 24.6% and the Indians as 7.3% (Department of Statistics Malaysia, 2011). The prevalence of portal hypertension in this study did not follow the ethnic distribution in the country. The study found more percentage of Chinese patients (44.7%), which was almost a two fold increase, when compared to the distribution on Chinese population in this country. The probable reason could be, that this difference could be representative of the patient population distribution in UMMC itself but this information is not available. This discrepancy could also be due to the finding in the study that a majority of patients seen in UMMC for portal hypertension presenting with gastroesophageal varices (71%) were referred from other centres all over Malaysia, including Sabah and Sarawak. Another possibility is that this result depicts the actual prevalence of this condition in the Chinese ethnicity. This is made more difficult as the ethnic diversity of our nation is not represented by any other countries to be used for meaningful comparison.

The most common aetiology for portal hypertension presenting with gastroesophageal varices in this study population was of intrahepatic origin in 22 patients out of 38 patients. This was similar to literature (Ling, 2012). The most common aetiology among that group was biliary atresia. It was noted that a majority of patients with biliary atresia in this study population were of Chinese ethnicity, 11 out of 14 patients. It was also noted in this study that

among the Malay patients, the most common aetiology was portal vein thrombosis. This could be a true representation of the actual ethnic preponderance to the underlying disease, however larger studies need to be done in the targeted aetiology groups, biliary atresia and portal vein thrombosis to derive more information.

Risk factors associated with the development of portal hypertension was of low incidence as a whole in this study population. However umbilical vein catheterization and TPN use was frequently seen in specific aetiologies of portal vein thrombosis and congenital hepatic fibrosis. Neonatal events of birth asphyxia and sepsis also were frequently seen in portal vein thrombosis, possibly as these are usually the subset of patients who do receive TPN through umbilical vein catheter. It is also likely that more patients could have had these risk factors but due to poor documentation, we were not able to establish any link between them. A prospective study to follow up patients with these risk factors to development of portal hypertension later may help to support this risk factors association with portal hypertension.

As per literature (Gana et al., 2011), the common presenting symptom was hematemesis and clinical finding of splenomegaly, which was consistent in this study population. This reinforces the positive association between these parameters to diagnose portal hypertension in this study population. The use of biochemical values such as use of APRI and AST/ALT ratios for prediction of bleeding risk was not established in this study, but elevated mean APRI value at first endoscopy suggested that patients had liver dysfunction at presentation itself.

Ultrasound of the hepatobiliary system has been observed as the commonest form of imaging investigative tool employed in this study population. However, due to poor documentation records, no meaningful information regarding the diameter of portal vein and the reporting of its flow dynamics were obtained in this study, even in the subset of patients with portal vein thrombosis where this information was imperative to diagnosis. The

documentation of parameters, such as height, weight, and chest circumference to aid analysis of the size of portal vein needs to be documented well (Ghosh et al., 2014). Improvement in documentation of imaging reports will help in future analysis of ultrasound usage for the purpose of early detection and diagnosis of portal hypertension. Effective communication between the clinicians and the radiology team also may help for targeted screening of portal hypertension related signs such as collateral vessels and liver elasticity (Procopet & Berzigotti, 2017). These improvements could help in establishing ultrasound as a monitoring tool for portal hypertension in children as it is a cheap, effective and non-invasive imaging modality.

This study noted the lower frequency of surveillance and diagnostic endoscopic procedures (16 out of 38 patients) among the study population as compared to interventional endoscopic procedure (22 out of 38 patients). There is less preponderance to utilize endoscopic procedure for the purpose of surveillance and routine diagnostics in this centre. In the absence of a concrete modality for bleeding risk prediction and no recommendation for medical primary prophylaxis, preemptive surveillance endoscopy may need to be considered in patients with splenomegaly as is being offered in other centres (Duché et al., 2013; Ng et al., 2016). In the centres that do employ surveillance endoscopies, they have reported promising results. This is supported by the finding of no increased rate of adverse events in the event-driven versus non-event-driven groups. However more studies is needed in this area to strongly support this statement.

In the overall analysis of the study population, there was increased prevalence of grade 3 esophageal varices in 23 out of 38 patients during the first endoscopic procedure itself. The comparison analysis also found that higher grades of varices were seen in the event-driven endoscopy group of patients. This consolidates the argument that the severity of esophageal

varices is related to occurrence of bleeding event. This also shows that the diagnosis of portal hypertension presenting with gastroesophageal varices is late.

Among the variceal bleed preventive measures, EVL was commonly used compared to EST. EVL which is technically a challenging procedure to perform is commonly practiced among older children and ESTs were only performed in very young children. Such observation among the study population could be influenced by the clinician's preferential mode of intervention or to the type of equipment used by them. This could have contributed to the small cohort of patients who underwent EST having a higher complication rate compared to those who underwent EVL (Kim et al., 2013; Zargar et al., 2002). This similar discrepancy is also seen in other literature in other regions. Irrespective of the choice of intervention, the uncommon occurrence of a rebleeding episode among patients in study population must be taken into note. It suggests good efficacy of endoscopic based intervention to control bleeding events. A bleed-free period of at least five days is defined as efficacious in endoscopic based intervention (Shneider, Bosch, et al., 2012) and this was positively observed among this study population in all 11 patients out of 38 patients with rebleeding. In the course of follow up, only one patient had underwent endoscopic surveillance frequency of less than 6 monthly intervals thus suggesting that endoscopic intervention were stable, safe and effective to eradicate varices. The relative safety of this procedure paired together with the finding of higher grade of esophageal varices in the event-driven group, further promotes the adaptation of surveillance endoscopy as form of bleed preventive measure.

Liver transplantation procedure was uncommon among the study population. Among the 4 patients out of 38 patients who had liver transplant, all were done overseas, namely Taiwan, China and Singapore. This study did not focus on liver transplantation, but lack of liver transplant done in the study population is possibly attributed to the high financial expenditures

incurred with the procedure which form a heavy cost burden to the families (de Villa et al., 2003). Other factors that could contribute such as the availability of suitable and compatible donor liver and the health stability of the affected patients to withstand the stress of travel to the nearest transplant centre (Lim et al., 2006). Singapore quotes that 47.51% of their paediatric patients with end stage liver disease manage to have liver transplant. However, there is only limited availability of expertise and transplant centres in Malaysia. In view of the increasing prevalence of the disease, it is worthwhile to further invest in the training and development of organ transplantation expertise and resources in UMMC, Kuala Lumpur.

Although the mortality in patients with portal hypertension in this study population was low (13.1%), 5 out of 38 patients, significant morbidity due to the disease is undeniable. This can be further quantified through a Quality of Life (QoL) assessment in future research exercise among the study population.

The development of an electronic database dedicated for portal hypertension will facilitate future research. In this database, including details on spleen size on follow up, detailed ultrasound findings, serial endoscopy information and follow up details will help future research. This can also aid to monitor complications of portal hypertension in these patients. However the challenges in diagnosing portal hypertension itself remains to be addressed.

6.1 Limitation of Study

The secondary data obtained for this study is from patient's physical and electronic records. Poor, incomplete documentation and illegible handwriting by medical staffs were found to be prevalent during the data mining process. Hence, many forms of data types were deemed as incomplete, missing or simply could not be legibly interpreted. Some of the identified patient's

medical records could not be found at all despite multiple attempts to locate them by the Records Office staff. Due to the lower prevalence of disease, a long study period gained more records, but most were from the latest electronic records, and physical medical records were still not available for use. These factors limited the study sample considerably.

This study was purely descriptive and exploratory in nature. This aids to gain information in Malaysian setting in respect to paediatric portal hypertension. The data acquired and discussed in this study will function as a pilot project for subsequent research in this field. It also serves as a clinical audit of the endoscopy practices in UMMC, Kuala Lumpur. It is hoped that further research questions may be prompted by this study to motivate more work in this area to benefit children with portal hypertension presenting with gastroesophageal varices.

This study focused more on the endoscopy practices in the study population as a diagnostic and therapeutic modality in portal hypertension presenting with gastroesophageal varices in children. As the focus was more towards establishment of the diagnosis and endoscopy use, information on medical prophylaxis therapies instituted, condition of patient and needs for resuscitation were not included. A comprehensive study which includes all these parameters are probably more ideal and representative management of portal hypertension, which may be done using this study as a framework.

The information recorded was at the time of presentation with liver disease, then at first endoscopy and again at the end of study period or at the last follow up. The period in between may have had information which were not used and might cause bias. Lastly the comparison analysis done between the two groups of patient was limited by the study design and size of study population, thus yielded little statistically significant information.

CHAPTER 7: CONCLUSIONS

In conclusion, our study population demographics closely resembled other East Asian countries such as Singapore in researches on portal hypertension in terms of gender and ethnic distribution.

Presence of hematemesis and splenomegaly are useful clinical markers to denote presence of portal hypertension and gastroesophageal varices. Though biochemical markers for prediction of bleeding risk was not useful in this study population, continued research in this area is imperative to facilitate early diagnosis of portal hypertension in children.

Ultrasound is a valuable imaging modality but its efficacy in diagnosis in this study was limited by poor documentation. Improved communication, focused documentation and more exposure to radiological signs of portal hypertension is needed to establish its use in this area.

The use of endoscopy for bleeding control was effective, the endoscopic intervention in this centre was event-driven and not as a screening tool. There is an urgent need for research to isolate predictive factors for development of gastroesophageal varices in portal hypertension to facilitate early diagnosis and prevention of bleeding event and possibly increase the scope of endoscopy use to partake preventive option with surveillance endoscopy.

Liver transplant is the definitive treatment for portal hypertension. It was not common in this study population, possibly due to limiting factors such as limited availability of liver transplant in local setting and the high expenditure incurred for this treatment overseas. Thus, patients with documented gastroesophageal varices are only monitored via surveillance endoscopies. This reinforces the need for more research to upgrade the endoscopy services and staff training and establishment of transplant units.

This study provides the framework for more directed research related to childhood portal hypertension and its complication of gastroesophageal varices. This study in overall highlighted the function of UMMC as a tertiary referral centre for gastroenterology disorders in children with safe endoscopic practices and good outcome.

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