Sohag University
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Study of the Small-Bowel Lesions in Patients with Liver Cirrhosis Using Capsule Endoscopy

Thesis
Submitted for Partial Fulfillment of the M.D. Degree in Internal Medicine

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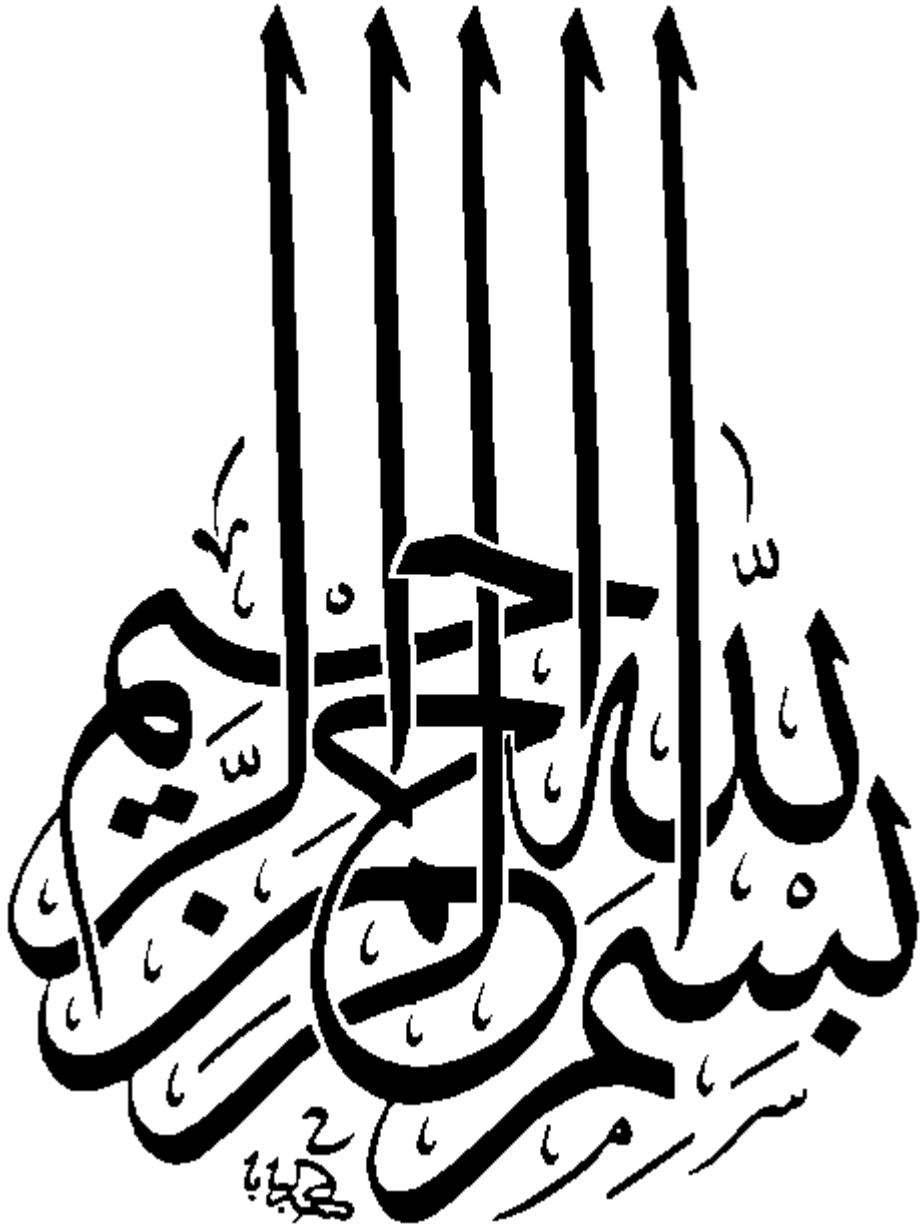
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Signature

Usama M Abdel-aal

List of Abbreviations

(Arranged alphabetically)

AUROC; area under receiver operating characteristics curve.
BB; β-blockers.
BMI; body mass index.
BSG; British society of gastroenterology.
CHF; congestive heart failure.
COPD; chronic obstructive pulmonary disease.
CPT; Child-Pugh-Turcotte.
CS; colonoscopy.
CSPHT; clinically significant portal hypertension.
CT, computed tomography.
DBE; double balloon endoscopy.
DD, differential diagnosis.
ECM; extracellular matrix.
EGD; esophagogastroduodenoscopy.
EIS; endoscopic injection sclerotherapy.
ELP; enhanced liver fibrosis.
eNOS; endothelial nitric oxide synthetase.
EV; esophageal varices.
EVL; endoscopic variceal ligation.
FDA; food and drug agency.
FHVP; free hepatic vein pressure.
FPI; fibrosis probability index.
GAVE; gastric antral vascular ectasia.
GEV; esophagogastric varices.
GV; gastric varices.
HCV; hepatitis C virus.
HE; hepatic encephalopathy.
HRS; hepatorenal syndrome.
HVPG; hepatic vein pressure gradient.
IBD; inflammatory bowel diseases.
ICC; intra-class correlation coefficient.
kPa; kilopascal.
LVP; large volume paracentesis.
MCTE; multidetector computed tomography esophagography.
MRI, magnetic resonance imaging.
NASH; non-alcoholic steatohepatitis.

NNT; number needed to treat.
NO; nitric oxide.
NSAIDs; non-steroidal anti-inflammatory drugs.
OGIB; obscure gastrointestinal bleeding.
OLT; orthotropic liver transplantation.
PC; personal computer.
PEG; polyethylene glycol.
PHD; portal hypertensive duodenopathy.
PHG, portal hypertensive gastropathy.
PHIV; portal hypertensive intestinal vasculopathy.
P**H**T; portal hypertension.
Pts; patients.
SAAG; serum ascitic albumin gradient.
SB; small-bowel.
SBET; small-bowel follow through.
SBP; spontaneous bacterial peritonitis.
TE; transient elastography.
TIPS; transjugular intrahepatic portasystemic shunts.
VCE; video capsule endoscopy.
VEGF; vascular endothelial growth factor.
WHVP; wedged hepatic vein pressure.

INTRODUCTION AND AIM OF THE WORK

INTRODUCTION

Patients with liver cirrhosis (LC) exhibit portal hypertension (PHT), which causes various pathological changes in the entire gastrointestinal tract (from esophagus to anus) **(N. Higaki et al. 2008)**. During the past decates, the term of portal hypertensive intestinal vasculopathy (PHIV) have been described to explain the effects of PHT on the entire bowel and includes portal hypertensive gastropathy (PHG), enteropathy (PHE), and colopathy (PHC) **(Ricardo et al. 2005**) . Among these pathological lesions , esophageal varices (EV), PHG, and PHC represent common sources of bleeding. These lesions are usually diagnosed and treated by esogaphagogastroduodenoscopy (EGD) and colonoscopy (CS) **(N. Higaki et al. 2008)**.

Portal hypertensive gastropathy is a well-established cause of bleeding in cirrhotic patients, present in up to 98% of patients with PHT **(Burk et al. 2003)** and accounting for 25.8% of acute bleeding episodes **(Primignani et al. 2000**) . Changes in the gastric mucosa of patients with PHT were first described by McCormack et al. (**P. Figueiredo et al. 2008)** but the mechanisms implicated in its pathogenesis are not yet fully understood. Portal hypertensive gastropathy is graded by its endoscopic appearance from mild to severe. A mosaic characterizes mild or a “snakeskin” pattern of erythema in the gastric mucosa, whereas, severe gastropathy is characterized by a variety of morphologic changes, including bright red puctate mucosal erythema; diffuse hemorrhagic lesions; and black or brown spots, which indicate submucosal hemorrhages **(P. Figueiredo et al. 2008)** .

Similarly, PHC has been known and described **(Bresci et al. 2006)**. The sepctrum of lesions categorized as PHC includes findings resembling colitis (edema, diffuce hyperemia, friability, granularity, and/or spotaneous bleeding) and vascular lesions (cherry red spots, telangiectasias, or angiodysplasia like lesions) **(Bini et al. 2000)**. Although PHC is found in up to 70% of patients with PHT and is more frequent in patients with evidence of EV or PHG **(Ricardo et al. 2005**), it seems to be rare cause of bleeding **(Mirsa et al. 2005)**.

The recognized existence of PHG and PHC suggests that the small intestine might also show endoscopic changes related to PHT which is called PHE. In fact, in 1989, Thiruvengadam and Gostout reported three patients, presenting with blood loss, who had diffuse erythema and scattered petechiain the stomach, but also in the duodenum and jejunum **(P. Figueiredo et al. 2008)**.

The small Bowel (SB) constitutes the largest part of the gut. However, little is known about the endoscopic features of the small intestine in different diseases . Also, almost nothing is known about these features in patients with LC. Our limited knowledge about SBis attributed to the limitations of convential endoscopy, because only small parts of it can be examined by EGD or CS **(N. Higaki et al. 2008)**. Recently, new endoscopic methods, capsule endoscopy (CE) and double balloon edoscopy (DBE), have been developed for the examination of entire SB **(Iddan et al. 2000, Yamamoto et al.2001)**. Capsule endoscopy permits direct easy, painless, and direct visualization of the SB mucosa **(M. Kodama et al. 2008).**

To our knowlegde, there is limited prospective studies in which CE was used to assess the frequency and the features of the PHE that are present in cirrhotic patients with PHT.

Measurement of hepatic venous pressure gradient (HVPG) currently is considered the golden standard for evaluation of PHT **(Burroughs et al. 2005)**. Nevertheless, HVPG measurement is invasive, relatively expensive, difficult, time comsuming, and available only in major centers, indicating the need to develop reliable, non-invasive, and widely available methods **(Vizzutti et al. 2007).** Transient elastography (TE) has been introduced as a rapid and non-invasive technique that measure liver tissue stiffness **(Sandrin et al. 2002)**. Many recent studies proposed the use of liver stiffness meaurement (LSM) using TE for detection cirrhosis, and prediction of related complications including presence of EV, and variceal bleeding **(Foucher et al. 2006, Kazemi et al. 2006)**. Vizzutte ET et al. (2007) proposed LSM by using TE may represent non invasive, rapid, cheap, and easy method for prediction of clinically significant and severe PHT (with a cutoff values of LSM $\geq$ 13.6 kPa, and $\geq$ 17.6 kPa respectively).

To our knowledge, there is no prospective trial studied the association between TE score and the presence of PHE in cirrhotic patients, to decide the ability of TE to predict presence and severity of PHE in liver cirrhosis especially if it is accompanied by unexplained anemia.

Aims of the work

The purpose of this study was to better identify the mucosal abnormalities of PHE using CE, and its frequency in cirrhotic and non cirrhotic patients. Also , to determine wether these findings are associated with the severity of liver disease, and the clinical and endoscopic parameters of PHT. Moreover, we aimed to create reliable scorring system for the mucosal findings of PHE diagnosed by CE.

REVIEW OF LITERARURE

LIVER CIRRHOSIS

Definition

Cirrhosis is defined as the histological development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury, which leads to portal hypertension and end-stage liver disease.

The major clinical consequences of cirrhosis are impaired hepatocyte (liver) function, an increased intra-hepatic resistance (portal hypertension), and the development of hepatocellular carcinoma (**Wanless IR et al. 2000, Desmet VJ et al. 2004**).

Epidemiology

The exact prevalence of cirrhosis worldwide is unknown. It was estimated at 0.15% or 400,000 in the USA, which accounted for more than 25,000 deaths and 373,000 hospital discharges in 1998.

Causes of cirrhosis

Causes of cirrhosis can usually be identified by the patient's history combined with serological and histological investigation (**Erlinger S et al. 1991, Tangerman A et al. 1994**) (**Table 1**).

Alcoholic liver disease and hepatitis C are the most common causes in developed countries, whereas hepatitis B is the prevailing cause in most parts of Asia and sub-Saharan Africa. After the identification of hepatitis C virus in 1989 and of non-alcoholic steatohepatitis in obese patients with diabetes, the diagnosis of cirrhosis without an apparent cause (cryptogenic cirrhosis) is rarely made. The causes of cirrhosis can predict complications and direct treatment decisions.

	Description	Cause
Jaundice	Yellow discoloration of skin, cornea, and mucous membranes	Compromised hepatocyte excretory function, occurs when serum bilirubin >20 mg/L
Spider angiomata	Central arteriole with tiny radiating vessels, mainly on trunk and face	Raised oestradiol, decreased oestradiol degradation in liver
Nodular liver	Irregular, hard surface on palpation	Fibrosis, irregular regeneration
Splenomegaly	Enlarged on palpation or in ultrasound	Portal hypertension, splenic congestion
Ascites	Proteinaceous fluid in abdominal cavity, clinically detected when ≥1.5 L	Portal hypertension
Caput medusae	Prominent veins radiating from umbilicus	Portal hypertension, reopening of umbilical vein that shunts blood from portal vein
Palmar erythema	Erythema sparing central portion of the palm	Increased oestradiol, decreased oestradiol degradation in liver
White nails	Horizontal white bands or proximal white nail plate	Hypo-albuminemia
Hypertrophic osteoarthropathy/ finger clubbing	Painful proliferative osteoarthropathy of long bones	Hypoxemia due to right-to-left shunting, Porto-pulmonary hypertension
Dupuytren's contracture	Fibrosis and contraction of palmar fascia	Enhanced oxidative stress, increased inosine (alcohol exposure or diabetes)
Gynecomastia, loss of male hair pattern	Benign proliferation of glandular male breast tissue	Enhanced conversion of androstenedione to oestrone and oestradiol, reduced oestradiol degradation in liver
Flapping tremor (asterixis)	Asynchronous flapping motions of dorsiflexed hands	Hepatic encephalopathy, disinhibition of motor neurons
Foetor hepaticus	Sweet, pungent smell	Volatile dimethylsulfide, especially in Porto-systemic shunting and liver failure

Table 1. Clinical features of cirrhosis

Knowledge of the cause also allows the discussion of preventive measures, for example, with family members of patients with alcoholic cirrhosis or chronic viral hepatitis, and consideration of (genetic) testing and preventive advice for relatives of patients with genetic diseases, such as hemochromatosis or Wilson's disease.

Clinical presentation

Cirrhosis is often indolent, asymptomatic, and unsuspected until complications of liver disease are present (**Conn H et al. 1993**). Diagnosis of asymptomatic cirrhosis is usually made when incidental screening tests such as liver transaminases or radiological findings suggest liver disease, and patients undergo further assessment and liver biopsy (**Peck-Radosavljevic M et al. 2000, Groszmann RJ et al. 2005**) (**Table 2**).

Imaging of cirrhosis

Ultrasonography, CT, and MRI are not sensitive enough to detect cirrhosis, and final diagnosis still relies on histology. Ultrasonography provides important information about hepatic architecture, is inexpensive, and is widely available. Nodularity and increased echogenicity of the liver are often found in cirrhosis but are also present in steatosis. Atrophy of the right lobe and hypertrophy of the left and especially caudate lobes are typical signs (**Tchelepi H et al. 2002, Awaya H et al. 2002**).

Ultrasonography and doppler ultrasonography of portal-vein and central-vein diameters and velocities are useful screening tests for portal hypertension and vessel patency. Contrast ultrasonography examines the

	Description	Cause
AST, ALT	Often normal or moderately raised	Leakage from damaged hepatocytes; AST to ALT ratio often >1, especially in alcoholic cirrhosis (relative vitamin B6 deficiency)
ALP	Increased by less than three-fold, apart from PBC and PSC	Cholestasis
γ -GT	More specific for liver than ALP, high concentrations in active alcoholics	Cholestasis
Bilirubin	Raised later than γ -GT and ALP, important predictor of mortality	Cholestasis, decreased hepatocyte and renal excretory function (exacerbated by systemic inflammation)
Albumin	Decreased in advanced cirrhosis	Decreased hepatic production, sequestration into ascites and interstitium (exacerbated in systemic inflammation); DD: malnutrition, protein losing enteropathy
Prothrombin time	Decreased in advanced cirrhosis	Decreased hepatic production of factor V/VII (while thrombin production is maintained); DD: vitamin K deficiency (e.g., due to mechanical biliary obstruction)
Immunoglobulins	Increased (mainly IgG)	Shunting of portal venous blood carrying (intestinal) antigens to lymph tissues with resultant stimulation of plasma cells
Sodium imbalance	Hyponatraemia	Inability to excrete free water via kidneys due to increased activity of antidiuretic hormone (vasopressin 2 receptor effect)
Anemia	Macrocytic, normocytic, or microcytic anemia	Folate deficiency, hypersplenism, direct toxicity (alcohol), gastrointestinal blood loss (e.g., via esophageal varices)
Thrombocytes and leucocytes	Thrombocytopenia (leucopenia)	Hypersplenism, dysfibronogenemia, reduced hepatic thrombopoietin production

Table 2: Laboratory tests and findings in cirrhosis

appearance of echogenic micro-bubbles in the hepatic vein **(Blomley MJ et al. 2003).**

Ultrasonography is the first imaging method for suspected hepatocellular carcinoma, but its sensitivity and specificity to detect hepatocellular cancer is lower than that of CT or MRI (**Kim CK et al. 2001**), and the malignant potential of nodular lesions should be confirmed by helical CT or MRI. Contrast ultrasonography, harmonic imaging, and power Doppler improve detection of hepatoceullar carcinoma via sensitive visualization of abnormal vessels but are not yet generally available (**Lencioni R et al. 2002**).

Conventional CT and MRI can be used to define the severity of cirrhosis—e.g., by determining spleen size, ascites, and vascular collaterals (**Ito K et al. 1999**)—but helical CT and MRI with contrast are preferred if hepatocellular carcinoma or vascular lesions are suspected (**Choi D et al. 2001**). In a comparison, MRI was found to be better than helical CT at detecting small hepatocellular cancers (1–2 cm size) (**Burrel M et al. 2003**).

Liver biopsy

Biopsy is considered the gold standard for diagnosis of cirrhosis, and sequential histological grading of inflammation and staging of fibrosis can assess risk of progression. Furthermore, biopsy is important for establishing the cause of cirrhosis in up to 20% of patients with previous unknown cause (**Ratziu V et al. 2005**) (**Table 3**). The staging of fibrosis in hepatitis C by use of the METAVIR system (which is simple and uses only five stages, with stage four indicating cirrhosis) showed that a third of scores differed by at least one stage when a biopsy sample from the left liver lobe was

compared with that from the right lobe, with similar results for inflammation grading (**Regev A et al. 2002**).

	Specific physical associations	Diagnostic (laboratory) variables	Value of liver biopsy (identifiable features)
HBV	Arthritis	HBsAg, HBeAg, HBc-antibodies, HBV DNA	+
HCV	**……**	HBsAg, HDV antibodies, HDV RNA	++ (HDAg)
Alcoholic	**……**	AST:ALT ratio ≥2, increased CDT and γ−GT	++ (Mallory bodies, steatosis, granulocytes > hepatocyte ballooning)
Non-alcoholic steatohepatitis	Overweight/obesity ,metabolic syndrome, type 2 diabetes	Uric acid, fasting glucose/insulin/triglycerides	++ (Mallory bodies, steatosis, hepatocyte ballooning>granulocytes)
Autoimmune	**……**	Autoantibodies (ANA, LKM antibodies, SLA antibodies), increased γ-globulins	+++ (bridging necrosis)
Primary biliary cirrhosis	Sicca syndrome, xanthelasma	AMA; increased ALP, γ GT, and cholesterol	++ (cholangitis, paucity of bile ducts, granuloma, ductopenia)
Primary sclerosing cholangitis	Ulcerative colitis (90%)	pANCA antibodies (70%), increased ALP and γ GT, imaging: beaded intra-hepatic and extra-hepatic bile ducts	+++ (concentric peribile ductular fibrosis, ductopenia)
Haemochromatsis	Arthritis, myocarditis, diabetes	Fasting transferrin saturation >60% (men), >50% (women); increased ferritin, HFE mutation	++ (periportal iron-loaded hepatocytes, quantification of liver iron)
Wilson's disease	Neurological	Increased oeruloplasmin, and copper in 24 h urine; slit-lamp: corneal copper deposits	+++ (quantification of liver copper)
α 1-antitrypsin	Pulmonary fibrosis	Reduced α 1-antitrypsin; α 1-antitrypsin sub typing	+++ (α 1-antitrypsin-loaded hepatocytes)
Congenital disease	**……**	**……**	+++ (e.g., bile ductular plate malformations)

Table 3: Diagnostic tests in chronic liver disease, according to cause

HbcAg; hepatitis B core antigen ***Hbe;*** hepatitis B envelope antigen ***HbsAg;*** hepatitis B surface antigen ***HBV;*** viral hepatitis B ***HCV;*** viral hepatitis C ***HDAg;*** hepatitis D antigen ***HDV;*** viral hepatitis D ***AMA;*** antimitochondrial antibodies ***CDT;*** carbohydrate-deficient transferring ***γ-GT;*** γ-glutamyl transpeptidase ***HFE;*** haemochromatosis C282Y mutation ***LKM;*** liver kidney membrane ***SLA;*** soluble liver antigen ***pANCA;*** perinuclear neutrophil cytoplasmic antigen.

A liver biopsy sample is obtained by either a (radiographically-guided) percutaneous, transjugular, or laparoscopical route. An increased risk of bleeding after biopsy has been seen with large-diameter needles (<1.4 mm) (**Bravo AA et al. 2001**).

Natural history and prognosis

The natural history of cirrhosis depends on both the cause and treatment of the underlying cause. Yearly rates of decompensation are 4% for viral hepatitis C and 10% for viral hepatitis B, and incidence of hepatocellular carcinoma is 2–7% per year. Decompensation in alcoholic cirrhosis with continued alcohol use is even more rapid and often associated with alcoholic hepatitis on a background of cirrhosis. Once decompensation has occurred in all types of liver disease, mortality without transplantation is as high as 85% over 5 years. Child-Pugh-Turcotte (CPT) classification is widely used (**Pugh, RN et al. 1973**) (**Table 4**). One year survival rates for patients with CPT class A, B, and C cirrhosis are 100%, 80%, and 45%, respectively (**Infante-Rivard C et al. 1987**). CPT class predicts the development of complications, such as variceal hemorrhage and the response of patients to surgical interventions (**Wiesner RH 2005**).

Treatment and Reversibility of Cirrhosis

Elimination of the triggers leading to cirrhosis will probably delay progression to a higher CPT class and reduce the occurrence of hepatocellular carcinoma. Patients with alcoholic cirrhosis should not continue alcohol consumption because it drives hepatitis, which favors hepatic fibrogenesis and decompensation (**Runyon, BA 1997**).

Patients with compensated cirrhosis and with replicating hepatitis C virus benefit from interferon-based antiviral treatment. Viral eradication and a consequently lowered risk of hepatic decompensation and hepatocellular carcinoma can be achieved in up to 40% of patients with genotype 1 and in 70% of patients with genotypes 2 or 3 (**Everson GT 2005**).

	1 point	2 points	3 points
Encephalopathy	Absent	Medically controlled	Poorly controlled
Ascites	Absent	Controlled medically	Poorly controlled
Bilirubin (mg/L)	< 20	20−30	> 30
Albumin (g/L)	< 35	28−35	< 28
INR	<1.7	1.7−2.2	>2.2

Table 4. Child Pugh Turcotte (CPT) classification

CPTA (5−6 points), **CPTB** (7−9 points), and **CPTC** (10−15 points) predict a life expectancy of 15−20, 4−14, and 1−3 years, respectively, and a perioperative mortality (abdominal surgery) of 10%, 30%, and 80%, respectively.
INR: international normalized ratio.

Long-term treatment with oral nucleoside and nucleotide inhibitors of hepatitis B virus DNA polymerase might not only retard or reverse cirrhosis, but also have been shown to prevent complications of end-stage liver disease (**Dienstag JL et al. 2003**).

The data for reversibility and stabilization of other causes of cirrhosis are less well established. Cohort studies have shown that some patients with cirrhosis who also had autoimmune hepatitis showed regression after long-term treatment with corticosteroids (**Dufour JF et al. 1997**), and venesection of patients with hereditary hemochromatosis could reduce the development of complications of portal hypertension (**Fracanzani, AL et al. 1995**).

	Prevention	Treatment
Variceal bleeding	Non selective B-Blockers* Variceal band ligation	① **Acute:** Resuscitation Vasocontrictors† Sclerotherapy Band ligation TIPS Surgical shunts ② **Chronic:** Variceal obliteration TIPS Surgical shunts
Ascites	Low sodium diet	Low sodium diet Diuretics Large volume paracentesis TIPSS (LeVeen/Denver shunts)
Renal failure	Avoid hypovolaemia	Discontinue diuretics Rehydration Albumin infusion Hepatorenal syndrome: add terlipressin or midodrine (noradrenaline) and somatostatin (octreotide)
Encephalopathy	Avoid precipitants	**Treat precipitating factors:** Infection Bleeding Electrolyte imbalance Sedatives High protein intake Lactulose Neomycin, metronidazole, rifaximin
Spontaneous bacterial peritonitis	Treat ascites	Early diagnostic paracentesis: >250 neutrophils per mL, intravenous antibiotics (plus albumin) Secondary prophylaxis with oral antibiotics such as levofloxacin

Table 5. Prevention and treatment for complications of cirrhosis

TIPSS; transjugular intrahepatic Porto systemic shunt.
*Nadolol, propranolol.
†Vasopressin, octreotide/somatostatin, terlipressin.

Complications of cirrhosis

Major advances have been made in recent years to both prevent and treat the common complications of cirrhosis such as variceal bleeding, ascites, spontaneous bacterial peritonitis, and encephalopathy (**de Franchis**

R et al. 2004, Gines P et al. 2004) (**Table 5**)**.** However, bacterial infections are common, especially in decompensated cirrhosis, which exacerbates hepatic dysfunction, encephalopathy, and portal hypertension, and underlines the need for vigilance and rigorous antibiotic treatment.

Circulatory and cardiac abnormalities in cirrhosis should be noted, which can preclude transplantation eligibility. Hepatopulmonary syndrome, which occurs in 15–20% of patients with cirrhosis, is due to overproduction of nitric oxide and over expression of the endothelin B receptor, with consequent pulmonary arteriolar vasodilatation, shunting, and hypoxaemia (**Fallon MB 2005**). The disorder is largely reversible after transplantation. Portopulmonary hypertension is rare, but occurs in up to 16–20% of patients with refractory ascites. Cirrhotic cardiomyopathy is characterized by a blunted stress response of the heart, combined with hypertrophy (**Gaskari SA et al. 2006**).

Recent advances and future directions

Molecular pathology of hepatic fibrosis and cirrhosis

The scar tissue in cirrhosis is composed of a complex assembly of different extracellular matrix molecules (ECM), consisting of: the fibril-forming interstitial collagens type I and III; basement membrane collagen type IV; non-collagenous glycoproteins such as fibronectin and laminin; elastic fibres; and glycosaminoglycans and proteoglycans, among others **(Schuppan D et al. 2001)**. Toxins, viruses, cholestasis, or hypoxia can trigger a wound healing reaction termed fibrogenesis—i.e., the excess synthesis and deposition of ECM. Initially, fibrogenesis is counterbalanced by removal of excess ECM by proteolytic enzymes, such as specific matrix

metalloproteinases (MMPs). Chronic damage usually favours fibrogenesis over fibrolysis, with an up regulation of tissue inhibitors of MMPs (TIMPs) **(Benyon RC et al. 2001)**. The major hepatic ECM-producing cells are myofibroblasts that either derives from activated hepatic stellate cells or perivascular fibroblasts **(Friedman SL 2000, Schuppan D et al. 2003)**. Myofibroblast activation is mainly driven via fibrogenic cytokines and growth factors that are released by activated macrophages (Kupffer cells), other inflammatory cells, and bile duct epithelia. The most prominent profibrogenic cytokine is TGF-β, which suppresses inflammation but drives fibrogenic gene expression in these myofibroblasts (**Schuppan D et al. 2003, Bissell DM et al. 2001**).

Genetic predisposition for cirrhosis

Recently, a growing number of functional genetic polymorphisms that probably increase the risk of fibrosis progression have been described. Implicated genes encode cytokines or chemokines and their receptors (**Muhlbauer M et al. 2003**), molecules involved in fibrogenesis or fibrolysis (**Satsangi J et al. 2001**), blood coagulation (**Wright M et al. 2003**), antigen presentation (**Yoshizawa K et al. 2003**), iron uptake (**Erhardt A et al. 2003**), oxidative and antioxidative metabolism (**Silvestri L et al. 2003**), detoxification (**Stickel F et al. 2005**), and polygenetic traits linked to the metabolic syndrome and non-alcoholic steatohepatitis. In a gene association study, 1609 of 24 882 single nucleotide polymorphisms (SNPs) were found to be associated with fibrosis progression in chronic hepatitis C, with the DDX5 gene having a high positive predictive value (**Huang H, et al. 2006**). With established extrinsic risk factors such as excess alcohol consumption,

obesity, or advanced age, these SNPs will allow the establishment of risk profiles for individual patients (**Bataller R et al. 2003**).

Feasibility of pharmacological reversal of cirrhosis

The rapid progress in the understanding of molecular mechanisms leading to cirrhosis or its reversal has spawned the development of antifibrotic drugs. We can classify the therapeutic approaches to reversal of fibrosis as primary and secondary. Primary approaches focus on treatment of the underlying disease such as hepatitis B and C that have been shown to result in regression of (compensated) cirrhosis (**Poynard T et al. 2002, Dienstag JL et al. 2003**). The secondary approach is to develop intrinsic antifibrotic drugs that specifically target the mechanism of fibrogenesis, irrespective of the cause of the liver disease. The major obstacle to antifibrotic drug development has been the difficulty in defining validated endpoints for clinical trials.

Non-invasive markers of fibrogenesis and fibrolysis

Non-invasive serological markers to cross-sectionally stage liver fibrosis (**Patel K et al. 2004, Kelleher TB et al. 2005**) have been extensively reviewed (**Parkes J et al. 2006, Pinzani M et al. 2008**). Although showing potential, especially for the diagnosis of cirrhosis, none meets the criteria for an ideal surrogate fibrosis marker.

A problem is the heterogeneity of liver diseases, with different stages being present in different areas of the liver, particularly between stages 1 and 3. These markers either indicate hepatic function (**Berg T et al. 2004**) or turnover of ECM (**Patel K et al. 2004, Kelleher TB et al. 2005**) (**Table 6**).

	N	Cause	AUROC(SD)	% classified
Fibrotest*	352	HCV	0.76(0.03)	46%
Fibrotest	209	HBV	0.78(0.04)	….
Forns index†	476	HCV	0.78	49%
APRI‡	192	HCV	0.80(0.06)	51%
APRI	484	HCV	0.74	57%
HA, TIMP-1, α2M	696	HCV	0.831	….
HA, PIIINP, TIMP-1, age121	921	All liver diseases	0.804 (0.02)	….
HA, albumin, AST	137	HCV/HIV	0.87	….
Comparisons:				
APRI *vs* Fibrotest	323	HCV	0.74 (0.03) 0.83(0.02)	….
APRI *vs* AST:ALT ratio	239	HCV	0.773 0.820	….
Fibroscan plus fibrotset	183	HCV	0.88	….

Table 6. Differentiation of fibrosis stage F0−1 from F2−4 by serum markers and Fibroscan

Performance of tests is better for differentiating F3–4 (4=cirrhosis) from F0–1 than vice versa. ***AUROC***; area under receiver operator curve ***HBV***; viral hepatitis B ***HCV***; viral hepatitis C ***α2M***; α2-macroglobulin.

Matrix-derived markers: hyaluronic acid (HA), aminoterminal propeptide of procollagen III (PIIINP), tissue inhibitor of matrix metalloproteinase 1 (TIMP-1). Test combinations are: *Algorithm of bilirubin,δ-glutamyl transpeptidase (GT), δ-globulin, haptoglobin, α2-macroglobulin, age;†algorithm of g-GT, cholesterol, platelets, age; AST to platelet ratio index (APRI):AST (upper limit of normal) divided by platelets (109/ L), either ≤ 0・5 (for F0–1) or > 1・5 (for F2–4).

Combinations have been developed, since no single biomarker has the adequate sensitivity and specificity. Unfortunately, current ECM-derived serum markers correlate mainly with fibrosis stage, and only to a lesser degree with fibrogenesis. We regard the performance of most of these biomarkers to be similar with a diagnostic accuracy approaching 80% for the differentiation between mild fibrosis (Metavir F0–1) and moderate to severe

fibrosis (F2–4). However, the performance is consistently improved at both spectrums of disease from no fibrosis to cirrhosis, and importantly, for the prediction of cirrhosis. Hepatic elasticity measurement (Fibroscan) (**Ziol M et al. 2005, Colletta C et al. 2005**) in combination with these serum indices could yield a better prediction of histological fibrosis than could either test alone (**Castera L et al. 2005**), and Fibroscan has been shown to be more effective than has Fibrotest in patients with hepatitis C and persistently normal or low transaminases (**Colletta C et al. 2005**).

Pharmacological and cellular reversal of hepatic fibrosis and cirrhosis

Many drugs with proven direct and indirect antifibrotic effects in experimental animals would merit clinical testing (**Rockey DC et al. 2005**), and efficient reversal treatments probably need antifibrotic drug combinations.

First following three boxes provide examples of drugs that have shown convincing antifibrotic activity on hepatic stellate cells in vitro, or more importantly, in suitable animal models of liver fibrosis or even in patients in vivo (**Schuppan D et al. 2003, Friedman SL. 2004**). Most of these drugs suppress hepatic stellate cell activation directly; others prevent hepatocyte damage or loss, or halt proliferation of bile duct epithelial cells that, via release of profibrogenic factors, drive fibrogenesis. Drug effects can vary greatly between lobular and biliary fibrosis, which makes their preclinical testing in suitable animal models of lobular and biliary fibrosis obligatory.

Inhibition of profibrogenic activation of hepatic stellate cells

① Cytokines/cytokine antagonists

- Recombinant interferon-α/β/γ
- TGF-β and TGF-β-signalling antagonists (TGF-β antisense oligonucleotides, TGF-β receptor blocking peptidominetics, soluble TGF-β decoy receptors)
- Inhibition of TGF-β activation: integrin αvβ6 antagonists (EM405270)

② Phosphodiesterase-inhibitors

- Pentoxifylline, phosphodiesterase-3/4-inhibitors (rolipram)*

③ MMP-inducers

- Halofuginone

④ Prostanoids

- Prostaglandin E2

⑤ Vasoactive modulators

- Endothelin-A-receptor antagonists
- Angiotensin system inhibitors (captopril, enalapril, pirindopril, losartan, irbesartan)*
- Nitric oxide donors (pyrro-nitric-oxide)

⑥ Histone deacetylase inhibitors

- Trichostatin A, MS-275

PPAR-α agonists

- Fibrates (bezafibrate, fenofi brate)

PPAR-γ agonists

- Glitazones (pioglitazone, rosiglitazone, troglitazone)*

⑦ Plant-derived drugs (mainly antioxidants)*

- Apigenin, compound 861, FuZhengHuaYu, glycyrrhicin, inchin-ko-to (TJ135), quercetin, resveratrol, rooibus, salvia miltiorrhiza, sho-saiko-to (TJ9), silymarin

Farnesoid-X-receptor agonists

- 6-ethyl-chenodeoxycholic acid

Inhibition of migration/proliferation of hepatic stellate cells

① HMG-CoA-reductase inhibitors
- Statins

② Diuretics
- Aldosterone (spironolactone); sodium/hydrogen ion exchanger (cariporide)

③ Immunosuppressants
- Mycophenolate mofetil, rapamycin

④ Angiogenesis inhibitors
- VEGF-receptor 1 and 2 antagonists (PTK787)
- Integrin αvβ3 antagonists (cilengitide, EMD409915)

⑤ Other kinase inhibitors
- PDGF-β-receptor antagonists (imatinib [SU9518])

Hepatocyte maintenance/protection

- Hepatocyte growth factor
- Insulin-like growth factor I

*Drugs that are or have been used in clinical trials aiming at inhibition of disease progression. ***Integrin***; receptor for matrix proteins or cell-adhesion molecules ***MMP***; matrix metalloproteinase ***PDGF;*** platelet-derived growth factor ***PPAR***; peroxosome-proliferator- activated receptor ***VEGF***; vascular-endothelial growth factor ***HMG-CoA;*** hydroxymethyl-glutaryl-coenzyme A.

Once an ant fibrotic effect has been proven in human beings (which largely depends on the development of better non-invasive markers or imaging of fibrosis progression or regression), these agents are likely to be used as combinations, either for long-term or interval therapy. Many potential antifibrotic drugs possess a reasonable safety profile, whereas their long-term safety in patients with cirrhosis has to be proven.

To achieve quick restitution of the functional parenchymal mass combined with reversal of cirrhosis, the combination of antifibrotic

treatment and hepatocyte renewal is attractive (**Fausto N. 2004**). Thus, hepatocyte transplantation has improved liver function (**Kobayashi N et al. 2000, Ahmad TA et al. 2002**) and ameliorated or even reversed advanced fibrosis (**Nagata H et al. 2003**). Hepatocyte engraftment was increased by oxidative preconditioning and activation of hepatic stellate cells (**Benten D et al. 2005**), and infusion of hepatocyte growth factor (a potent hepatocyte mitogen) improved liver function (**Matsuno Y et al. 2003**).

PORTAL HYPERTENSION

Portal hypertension (PHT) is a clinical syndrome defined by a portal venous pressure gradient exceeding 5 mm Hg. Cirrhosis is the most common cause of PHT in the Western world (**Garcia-Pagan JC et al. 2005**).

Pathogenesis; Hemodynamic Factors

The hallmark of PHT is a pathologic increase in the pressure gradient between the portal vein and the inferior vena cava, which is measured by the hepatic venous pressure gradient (HVPG) (**Garcia-Pagan JC et al. 2005).** Briefly, the wedged hepatic vein pressure (WHVP), a marker of sinusoidal pressure, and the free hepatic vein pressure (FHVP) are measured with radiologic assistance. HVPG is calculated by the following formula (**Wongcharatrawee S et al. 2000**):

$$HVPG = WHVP - FHVP \qquad (1)$$

The FHVP is subtracted from the WHVP to correct for intra-abdominal pressure to provide an accurate measure of the portal vein pressure. As in any other vessel, the pressure within the portal vein is determined by the product of blood flow and resistance to its egress, as defined by Ohm's law (**Figure 1**):

$$P \text{ (pressure)} = Q \text{ (blood flow)} \times R \text{ (resistance)} \qquad (2)$$

PHT is initiated by increased outflow resistance; this can occur at a presinusoidal (intra- or extra hepatic), sinusoidal, or post sinusoidal level. As the condition progresses, there is a rise in portal blood flow, a combination that maintains and worsens the PHT (**Sanyal et al. 2008**).

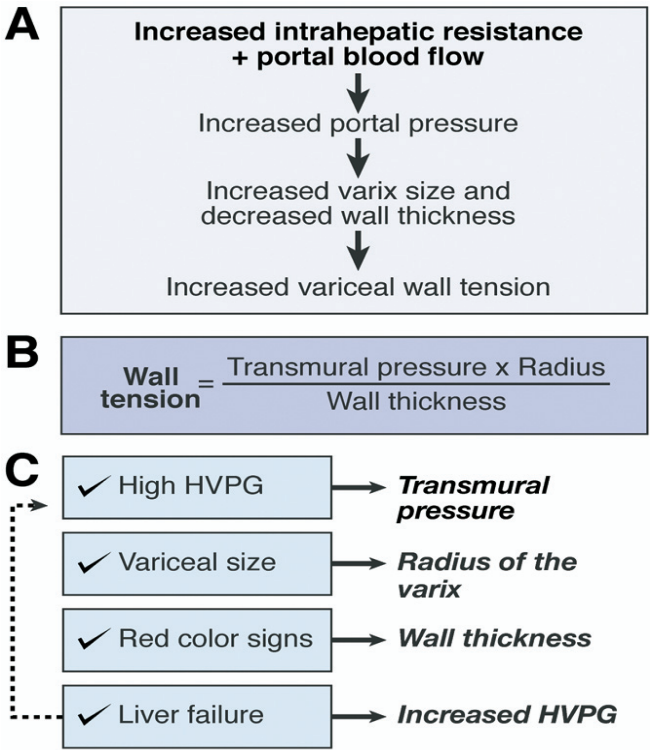


Figure 1: Pathophysiology of variceal bleeding. Bleeding occurs when the tension exerted by the thin wall of the varices exceeds the rupture point. This is facilitated by the progressive increase in the size of the varices and decreased wall thickness (*A*). These factors are mathematically interrelated in Laplace's law (*B*) and explain why an increased HVPG, the endoscopic appearance of the varices, and the degree of liver failure are associated with increased risk of variceal bleeding (*C*).

A) Increased Hepatic Vascular Resistance;
Structural and Dynamic Components

In cirrhosis, the principal site of increased resistance to outflow of portal venous blood is within the liver itself. These results from two factors: (1) mechanical obstruction to flow because of fibrotic disruption of architecture and (2) a dynamic component produced by active contraction of vascular smooth muscle cells and activated stellate cells (**Bataller et al. 2000, Bataller R et al. 2003**). Although the former is not acutely modifiable, disease stabilization and improvement, e.g., after successful treatment of hepatitis C or abstinence from alcohol, can improve fibrosis and the mechanical component (**Rincon D et al. 2006**). The dynamic component

accounts for approximately 30% of the intrahepatic resistance in cirrhosis and is an important target for future therapy (**Sanyal et al. 2008**).

- **Mechanism of Increased Hepatic Vascular Tone; Intrahepatic Endothelial Dysfunction**

Cirrhosis is associated with evidence of endothelial dysfunction, both in the systemic circulation and within the liver (**Gupta TK et al. 1998**). The net effect in the liver is intrahepatic vasoconstriction. This is mediated by decreased endothelial nitric oxide synthetase (eNOS) activity and NO production (**Shah V et al. 1998**). Hepatic eNOS activity is decreased because of impaired Akt-mediated eNOS phosphorylation (which is partially reversible by statins) and increased caveolin expression (particularly if folate deficiency exists) (**Morales-Ruiz M et al. 2003, Matei V et al. 2006**). Other factors that contribute to intrahepatic vasoconstriction include decreased NO availability because of its utilization for nitrosylation reactions secondary to oxidative stress (**Loureiro-Silva MR et al. 2006**) and vasoconstriction mediated by endothelin, angiotensinogen, and eicosanoids (**Moore K et al. 2004**). The role of several other vasoactive mediators such as carbon monoxide, adrenergic tone, endotoxemia, and inflammatory cytokines are currently under investigation.

B) Increased Portal Venous Inflow

Mesenteric arterial vasodilatation is a hallmark of cirrhosis and contributes to both increased portal venous inflow and a systemic hyperdynamic circulatory state (low systemic vascular resistance and mean arterial pressure with high cardiac output) (**Iwakiri Y et al. 2006)**. Increased NO production because of increased eNOS activity in the systemic circulation is a major driver of arterial vasodilatation (**Pizcueta MP et al. 1992**). Shear stress, increased vascular endothelial growth factor (VEGF),

and tumor necrosis factor-α are causes of increased splanchnic NO production in cirrhosis (**Abraldes JG et al. 2006, Fernandez-Martinez E et al. 2006**). Increased heme-oxygenase activity and CO production may also contribute to the hemodynamic disturbances (**Fernandez M et al. 1999**). Bacteremia can increase vasodilatation by stimulating tumor necrosis factor-α production and activation of endocannabinoids, which are potent vasodilators (**Batkai S et al. 2001**). Blockade of VEGF signaling attenuates the increase in portal venous inflow seen in cirrhosis (**Fernandez M et al. 2004**).

Diagnosis; clinically significant portal hypertension (CSPTH)

Portal pressure can only be measured by invasive methods; the most widely used method is based on the catheterization of a hepatic vein via the femoral or jugular route. A balloon-tipped catheter is used. The pressure is first measured with the deflated balloon (FHVP), and then with the balloon inflated to occlude the hepatic vein (WHVP). By calculating the difference between these two pressures, HVPG can be obtained, which is an indirect but precise measure of portal pressure (**Groszmann RJ et al. 2004**). The upper limit of normal for the HVPG is 5mmHg (**Bosch J et al. 1999**). Any value in excess of this limit marks the existence of PHT.

Portal hypertension is defined as clinically significant (CSPTH) when the level of portal pressure is such that the patient is at risk of developing complications: patients with CSPTH should undergo treatment to prevent such complications. Recently, the definition of CSPTH has been given at an international consensus development workshop on PHT (**de Franchis R 2000**): “CSPH is defined by the increase of the HVPG above a threshold value of about 10 mmHg. The presence of esophago-gastric varices, of

variceal bleeding and/or ascites indicates the presence of CSPTH". Hence, the strategy of identifying and surveying the patients with PHT should be mainly focused on patients with CSPTH.

Evaluation of patients to identify CSPTH

HVPG measurement is an accurate and reproducible method: when it is done correctly**.** However, at present, HVPG measurement cannot be done routinely, and therefore, alternative methods must be used.

(A) Endoscopy:

Complete endoscopic examination of the esophagus, stomach and duodenum, which is far more widely available than HVPG measurement, is an appropriate method, since the size of varices is clearly related to the risk of bleeding (**North-Italian Endoscopic Club 1988**): by this technique, a good degree of interobserver agreement for the assessment of variceal size can be achieved (**Sanyal et al. 2008**), together with a good accuracy for the diagnosis of cirrhosis (**D'Amico G et al. 2000**). In addition, endoscopy allows the identification of other potentially bleeding lesions related to portal hypertension, such as portal hypertensive gastropathy (PHG) and gastric antral vascular ectasia (GAVE).

Knowledge of the rate of development and growth of varices would be important, since it would help defining the optimal intervals for surveillance endoscopy, with the aim of identifying varices at risk of bleeding before they bleed, in order to start a prophylactic treatment. The annual rate of development of "new" varices is about 5–10% (**Merli M et al. 2003**); the rate of growth of varices from small to large is 5–30% in different studies (**Merkel C et al. 2004, de Franchis R et al. 2003**). Accordingly,

practice guidelines (**Grace ND et al. 1998, Jalan R et al. 200**) for the treatment of PHT recommend that all patients should undergo endoscopic screening for varices at the time when cirrhosis is diagnosed. After screening endoscopy, patients with medium or large varices should be treated to prevent bleeding, while all other patients should undergo periodic surveillance endoscopy. The recommended intervals are 2–3 years for patients with compensated disease and no varices, 1–2 years for those with small (**D'Amico G et al. 2000**) and 1 year for those with decompensated disease, with or without varices (**Grace ND et al. 1998)**.

(B) Possible alternatives to endoscopy:

Predicting the presence of esophageal varices by noninvasive means would restrict the performance of endoscopy to those patients with a high probability of having varices. Several studies (**Thabut D et al. 2006, de Franchis R et al. 2007, Kim SH et al. 2007**) have addressed the issue of identifying patients with varices by non-invasive or minimally invasive means, with the aim of avoiding endoscopy in those at low risk of having varices. These studies have assessed the potential of biochemical, clinical and ultrasound parameters, blood markers of fibrosis, transient elastography (TE), multidetector CT esophagography and video capsule endoscopy (VCE).

(C) Biochemical and ultrasound parameters:

Several biochemical and ultrasound parameters have been found to be related to the presence of varices. They include a low platelet count, splenomegaly, a portal vein diameter on ultrasound scan of ≥13 mm, advanced Child–Pugh class, low prothrombin activity and the presence of telangectasias. Differences in the populations examined (i.e. the disease

spectrum) probably account for the fact that different predictors of varices have been identified in different studies.

This underlines the difficulty of developing a widely applicable predictive model. For example, when considering platelet count, the discriminating threshold for the presence of varices ranges between 68,000 and 160,000/mm^3. In addition, when a prognostic model (**Schepis F et al. 2001**) based on a platelet count of <100,000/mm3, a portal vein diameter >13mm and a prothrombin activity of <70% was tested in an independent patients series (**Riggio O et al. 2002**), the results were disappointing, since 42% of the patients classified by the model as having the highest risk had no varices, and 34% of those classified as having the lowest risk had varices. Based on these data, the conclusions of the Baveno IV Consensus Workshop on Portal Hypertension (**de Franchis R 2005**) were that, while further studies are awaited, endoscopic screening is still the best practice to detect varices.

Giannini et al. (**2003**) proposed to use the platelet count/spleen diameter ratio as a non-invasive tool to predict the presence of varices. This ratio, which is calculated by dividing the platelet number/mm^3 by the maximum spleen bipolar diameter in mm as estimated by abdominal ultrasound, is higher in patients without than in those with varices. Using a cut-off value of 909 of the platelet count/spleen diameter ratio, Giannini et al. found that the AUROC (area under the receiver operating characteristics curve) was 0.981, corresponding to positive and negative predictive values for the presence of varices of 96 and 100%, respectively.

(D) Blood markers of liver fibrosis:

Several diagnostic indexes based on panels of blood markers of fibrosis have been recently proposed: they are non-invasive and suitable for

repeated testing, thus allow monitoring the evolution of liver disease. One study in particular (**Thabut D et al. 2006**) addressed the issue of identifying patients with large varices by means of the Fibrotest, which is a combination of several blood markers. In 99 patients with cirrhosis, the ability of the Fibrotest to detect large varices was compared with that of platelet count and Child–Pugh score. The Fibrotest performed better than the other two tests, with an AUROC of 0.77. It appears thus that the Fibrotest is not an adequate means of reliably identifying patients at risk of having large varices in a non-invasive manner.

(E) Multidetector CT esophagography :

Multidetector computer tomographic esophagography (MCTE) allows the examination of hollow viscera both in two-dimensional images and in 3D reconstruction. A recent study (**Kim SH et al. 2007**) has examined the potential of this technique in detecting esophageal varices and discriminating between large and small varices in 90 patients with cirrhosis. Conventional endoscopy served as the gold standard. The AUROC for the differentiation between small and large varices ranged between 0.931 and 0.958, with sensitivity ranging between 90 and 93.3% and specificity between 81.7 and 96.6%. The authors also showed that the patients largely preferred MCTE over unsedated esophagogastroduodenoscopy (EGD). Nevertheless, if the data from this study are confirmed, MCTE might prove to be a suitable tool for the diagnosis of high-risk varices.

(F) Transient elastography
(G) Video capsule endoscopy

Will be discussed in details.

Management of PHT related complications

Variceal Hemorrhage

1- Management of the subject who has never bled from varices

● *Assessment of bleeding risk and identification of those who need intervention:*

The risk of bleeding from esophageal varices depends on the HVPG (> 12 mm Hg), variceal diameter, endoscopic "red signs," and liver failure (**de Franchis R et al. 2003**). Subjects with medium to large varices as well as those with Child–Pugh class B or C cirrhosis and varices of any size are considered to be at high risk of bleeding (**de Franchis R et al. 1997**).

● *Primary prophylaxis of variceal hemorrhage:*

An algorithm for the primary prophylaxis of variceal hemorrhage is shown in **Figure 2**.

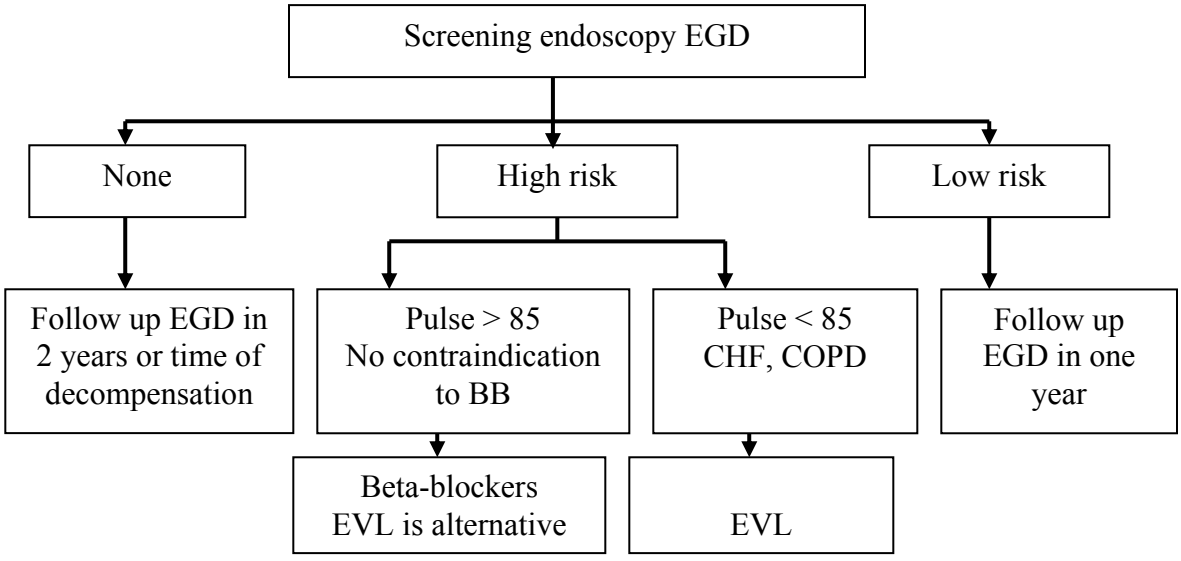


Figure 2: An algorithm for the primary prophylaxis of variceal hemorrhage.

2- Management of active hemorrhage

(A) General measures:

1- Airway protection:

Endotracheal intubation if altered mental status or unconscious

2- Gastric aspiration

3- Hemodynamic resuscitation:

Crystalloids and blood transfusion

Correction of coagulopathy and thrombocytopenia

4- Antibiotic prophylaxis for spontaneous bacterial peritonitis:

Blood cultures and diagnostic paracentesis if ascites present

Third-generation cephalosporin intravenously and switch to oral quinolone when patients stable and GI tract is functional

5- Renal support:

Urine output above 50 mL per hour

Avoid nephrotoxic drugs

6- Metabolic support:

Injectable thiamine when indicated

Monitoring and treating delirium tremens

Monitoring and treating acid base and electrolyte disturbances

Monitoring blood glucose level

7- Neurologic support:

Monitor mental state

Avoid sedation

(B) Control of bleeding.

An algorithm for the management of variceal hemorrhage is shown in **Figure 3**. Initial treatment is with endoscopic and pharmacologic treatment.

Continued bleeding or severe early rebleeding can be managed with TIPS. Those who respond to first-line treatment should receive band ligation and β -blockers. A transplant evaluation should be initiated based on the standard of care locally. Varices should be ligated to obliteration, and suitable patients should undergo transplantation when an organ is available. TIPS is used as a salvage treatment for recurrent bleeding. Liver transplantation remains the only treatment that corrects both the portal hypertension and the underlying liver disease and is the definitive treatment of choice in the long-term for appropriate candidates.

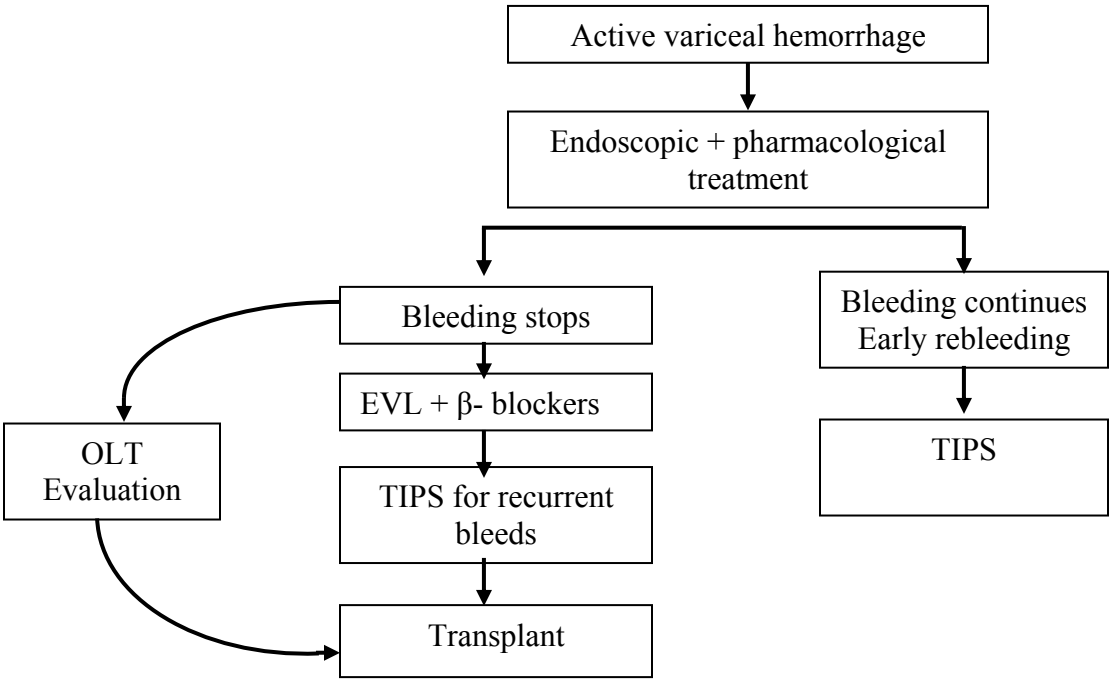


Figure 3. An algorithm for the management of variceal hemorrhage.

3- Prevention of recurrent bleeding :

EVL reduces the relative risk (*vs* sclerotherapy) of rebleeding by 37% and the absolute risk by 13% (number needed to treat (NNT), 8) (**Laine L et al. 1995**). Nonselective β-blockers reduce the relative risk of bleeding by 33% with an NNT of 4.76 (**D'amico G et al. 1999**). Combination therapy of

EVL and β -blockers is superior to EVL alone (**Lo GH et al. 2000**). Although the use of nonselective β-blockers (with or without nitrates) vs sclerotherapy or in combination with sclerotherapy has been studied, (**Villanueva C et al. 2001, Patch D et al. 2002**) their use has been supplanted by EVL+β-blockers. TIPS provide an effective salvage therapy for those who experience recurrent bleeding despite EVL+β-blockers (**Meddi P et al. 1999**). Liver transplantation should be considered if bleeding recurs despite a patent TIPS. TIPS patency is substantially superior with coated stents, which should be used whenever possible.

4- Gastric varices :

Gastric varices (GV) are classified as gastroesophageal varices (GEV) or isolated GV. Esophageal varices (EV) that extend along the lesser and greater curves are called GEV1 and GEV2, respectively. GEV1 can be treated like EV. GEV2 bleed more often than GEV1 and have a higher mortality as well (**Sarin SK et al. 1992**). Isolated gastric varices commonly exist in the fundus and are often associated with spontaneous splenorenal collaterals. They bleed at lower HVPG than EV and bleed more severely (**Sarin SK et al. 1992**). There is no consensus on primary prophylaxis of bleeding for isolated gastric varices. Once bleeding occurs, both cyanoacrylate EIS and TIPS have been used effectively to establish hemostasis and prevent rebleeding (**Lo GH et al. 2001**).

Management of Ascites

1- Uncomplicated ascites:

The initial diagnostic evaluation of ascites should always include a paracentesis. A serum to ascites albumin gradient (SAAG) >1.1 establishes the presence of PHT-related ascites. A neutrophil count >250/mm3 is diagnostic of spontaneous bacterial peritonitis (SBP) (**Runyon BA 2004**). The severity of ascites may vary from that only detectable by imaging studies (grade 1) to that which is clinically obvious but not tense (grade 2) and tense ascites (grade 3) (**Moore KP et al. 2003**).

Goals: A) symptoms relief

B) Create a negative Na balance

C) Prevent complications of ascites

Na restriction is an important component of the treatment strategy. A low Na diet (60–90 mEq/day), equivalent to 1.5–2 g of salt/day, should be prescribed along with adequate calorie and protein intake to maintain the nutritional status of the patient.

Spironolactone inhibits distal tubular Na reabsorption by antagonizing aldosterone. Spironolactone inhibits distal tubular Na reabsorption by antagonizing aldosterone. Spironolactone has a synergistic effect with furosemide, a loop-acting diuretic that is less effective than spironolactone as a single agent for cirrhotic ascites. Therapy is usually started with 100 mg/day spironolactone and 40 mg furosemide and doses modified based on either adverse effects or lack of response (<1.5 kg weight loss/week).

Large volume paracentesis (>5 L removed at a single sitting) (LVP) is used mainly for symptom relief and rapid mobilization of tense ascites. LVP is sometimes associated with postparacentesis circulatory dysfunction, characterized by worsened vasodilatation, hyponatremia, increased renin,

and norepinephrine activity (**Ruiz-Del-Arbol L et al. 1997**). Intravenous administration of albumin (6 –8 g/L ascites removed) reduces the risk of postparacentesis circulatory dysfunction, which has been associated with an increased mortality risk (**Gines A et al. 1996**).

2- Refractory ascites:

Definition (**Salerno F et al. 2007**):

A) Diuretic resistant ascites: Ascites that is difficult to mobilize, as defined by a failure to lose at least 1.5 kg/week of fluid weight, despite maximal diuretic therapy with spironolactone (400 mg/day) and furosemide (160 mg/day) or an equivalent dose of a distal-acting and loop-acting diuretic, respectively

B) Diuretic intractable ascites: Ascites that is difficult to mobilize, as defined above, because of the inability to provide effective doses of diuretics because of diuretic-induced adverse effects, e.g., azotemia, hyponatremia, and others.

Repeated LVP or total paracentesis are the most commonly used modalities for refractory ascites. TIPS are superior to LVP for long-term control of ascites (**Saab S et al. 2004, Albillos A et al. 2005**). However, both of them do not improve survival.

Management of hepatorenal syndrome

Definition (**Salerno F et al. 2007**):

- Presence of cirrhosis with ascites
- Presence of renal failure (creatinine level >1.5 mg/dL or 133 mol/L)

- Lack of improvement in serum creatinine after 48 hours of diuretic withdrawal and volume expansion with intravenous albumin administration (1 g/kg/day up to 100 g/day)
- Absence of shock
- Use of nephrotoxic drugs, eg, aminoglycosides
- Parenchymal renal disease (urine protein >500 mg/day, granular or red cell casts, hematuria, urinary obstruction by sonography)

The initial approach to the evaluation of sudden worsening of renal function in a subject with cirrhosis includes (1) exclusion of iatrogenic or other causes of renal failure, (2) aggressive evaluation for and treatment of sepsis, and (3) excluding volume depletion by clinical assessment and a therapeutic challenge with albumin (1g/kg or up to 100 g) given intravenously.

Type 2 HRS (slowly progressive type) usually occurs in the setting of refractory ascites and is managed as refractory ascites. The Type 1 HRS (rapidly progressive type) ads to the value of the Model for End-Stage Liver Disease score to predict mortality with medical treatment (**Alessandria C et al. 2005**). Liver transplantation is the only definitive treatment of HRS, and the outcomes depend on successful treatment of HRS prior to transplantation (**Restuccia T et al. 2004**).

Other ascites-related complications

Dilutional hyponatremia is a marker of poor outcome and predicts the development of HRS (**Heuman DM et al. 2004**). The initial management includes volume restriction to 1500 cc/day. For serum Na levels<125 mEq/L, more severe volume restriction is recommended.

Hepatic hydrothorax results from movement of ascites across diaphragmatic fenestrae into the pleural cavity. It is initially managed by Na restriction, diuretics, and intermittent thoracentesis. TIPS have been used effectively in some patients with refractory hydrothorax (**Boyer TD et al. 2005**).

Management of hepatic encephalopathy (HE)

1- *Removal of the precipitating factor*: Volume depletion and azotemia are important precipitants of HE. Diuretic-induced HE may also arise from the effects of hypokalemia and from urea-fueled ammoniagenesis. Hydration is the key therapeutic approach. In one study, albumin was more efficacious than saline in reversing diuretic-induced HE (**Jalan R et al. 2004**).

2- Reducing nitrogen and ammonia load: Prescription of low-protein diets for patients with HE should be abandoned. Branched-chain amino acid supplementation on a composite outcome of time to decompensation and death (**Marchesini G et al. 2003, Ghanta RK et al. 2005**).

3- Nonabsorbable disaccharides: The mechanisms of action include acidification of the colon and a reduction in cerebral water content (**Shawcross D et al. 2005**).

4-Antibiotics: Neomycin, metronidazole, and rifaximin, which have widely different antimicrobial spectra, have been used to treat HE.

5-Probiotics: a term that includes a wide range of nonpathogenic microorganisms, have been used in a wide range of digestive disorders (**Liu Q et al. 2004, Jenkins B et al. 2005**). Colonization with nonurease containing lactobacilli would result in a reduction in colonic

ammoniagenesis. Indeed, in a human study in which a probiotic preparation was combined with fiber in patients with cirrhosis, (**Liu Q et al. 2004)** a reduction in circulating ammonia levels was seen.

6-Agents that increase ureagenesis: Na phenylbutyrate eliminates 2 nitrogen atoms by forming phenylacetylglutamine, and Na benzoate binds to glycine (1 nitrogen atom) and is excreted by the kidneys as hippuric acid (**Batshaw ML et al. 2001**). Zinc supplementation has also been used to increase ureagenesis. Ornithine-aspartate provides substrate for both urea and glutamine synthesis. It accelerates the recovery from grade 2 encephalopathy.

7- Agents that work directly on the brain: Flumazenil, a benzodiazepine receptor antagonist, indicated a beneficial effect on short-term awakening from deeper stages of encephalopathy (**Als-Nielsen B et al. 2004**); the drug is, however, not available for chronic administration.

TRANSIENT ELASTOGRAPHY;
Non-invasive Assessment of Liver Fibrosis and Portal Hypertension

Hepatic fibrosis is the result of a wide variety of types of liver injury. Fibrosis is a wound healing response, which is similar mechanistically to that observed in essentially all organs (**Wynn TA 2007**). One of the most remarkable aspects of the wounding response in the liver (and in all tissues) is enhanced extracellular matrix production, or fibrogenesis. Injury-induced fibrogenesis is characterized by a multifold increase in interstitial collagens such as type I and type III, and many other extracellular matrix constituents. Hepatic wounding is an integrated response, involving many cellular, biochemical, and molecular events. A critical feature is the transformation of resident stellate cells (also lipocytes, Ito cells, or perisinusoidal cells) from the quiescent to the activated state (**Friedman SL et al. 2007**). Among the most prominent functional changes associated with activation is a striking increase in secretion of extracellular matrix proteins (**Maher JJ et al. 1990**), presumably responsible for the overall fibrogenic response. Several other cell types, including bone marrow derived precursors, portal fibroblasts, and perhaps others, may play a role in fibrogenesis.

Relationship of fibrosis and PHT: Pathophysiology

Elevated portal pressure resulting from liver injury has been postulated to include elements of increased intrahepatic resistance as well as increased flow through the splanchnic system (e.g., a hyperdynamic circulation). Increased intrahepatic resistance is an early and consistent feature of liver injury; potential causes include impaired blood flow owing to regenerative nodules, intrahepatic shunts, hepatocyte swelling, extinction of

typical vascular units after cycles of injury/repair, and perisinusoidal constriction. The latter mechanism has been proposed to be due to stellate cells, which also morphologically resemble tissue pericytes, a smooth muscle–like cell that regulates blood flow via pericapillary constriction (**Sims DE. 1991**).

An additional feature of stellate cell activation is the de novo expression of smooth muscle–specific proteins, including smooth muscle α actin,5 presumably imparting an exaggerated contractile phenotype on stellate cells (**Rockey DC et al. 1993**), consistent with enhanced perisinusoidal constriction and increased intrahepatic resistance (**Bauer M et al. 1995)**. Furthermore, stellate cells respond to a number of "vasoactive peptides" (**Rockey DC. 2003**). Therefore, stellate cell activation leads to both fibrosis and contractility, raising the possibility that the processes may be linked. Furthermore, in the context of emerging data emphasizing endothelial dysfunction after liver injury, there is a compelling pathophysiologic basis for increased intrahepatic resistance typical of early forms of liver injury (**Liu S et al. 2005**)

Why is quantitation of fibrosis important?

Precise measurement of the fibrotic lesion is important for several reasons. First, progressive fibrosis is believed to predict progression to cirrhosis in patients with hepatitis C virus (HCV) infection (**Poynard T et al. 1997**), and other diseases (**Friedman SL et al. 2007**). Additionally, the fibrosis stage may predict the likelihood of response to interferon-based antiviral therapy in patients with HCV; for example, patients with F3 or F4 fibrosis typically have a lower response rate to therapy (**Dienstag JL et al.**

2006). Finally, therapy may be intentionally withheld in patients with minimal fibrosis or slow progression.

Test	Examples	Advantages	Disadvantages	Comments
Physical exam	Spider angiomata, splenomegaly	Very simple and readily available, inexpensive	Indirect, low sensitivity and specificity	Limited usefulness
Simple blood tests	Platelet count, AST	Very simple and readily available, inexpensive	Indirect, low sensitivity and specificity	Limited usefulness
Serum makers	Hyaluronic acid Type I collagen Fibronectin	Simple, quantitative	Indirect, low sensitivity and specificity, availability limited	Limited usefulness
Imaging	Ultrasound MRI CT	Simple, readily available, large previous experience	Low sensitivity and specificity, generally costly, radiation with CT	May be helpful as a tip off to PHT
Marker panels	"ELF" "FPI" "Fibrotest" "Fibrospect"	Enhanced sensitivity and specificity, quantitative	Indirect, availability limited, some are costly	May also be useful for tracking a change in fibrosis status

Table 7. Noninvasive methods to assess liver fibrosis

N.B; An ideal noninvasive diagnostic test for hepatic fibrosis would be simple, readily available, inexpensive, and accurate. Unfortunately, at the current time, neither individual tests nor a combination of tests meets these criteria.

Data suggesting a relationship between fibrosis and outcome are emerging. In 116 patients with HCV infection undergoing liver biopsy (and HVPG measurement) after liver transplantation, a METAVIR fibrosis score of >F2 predicted clinical decompensation (AUC: 0.80) (**Blasco A et al. 2006**). In a long-term cohort study of 160 patients with primary biliary cirrhosis, for every stage increase of fibrosis identified (on a 1- to 4-point fibrosis scale) on initial liver biopsy, there was a 2-fold increase in future

complications or death (relative risk, 2.4; 95% confidence interval [CI], 1.6 –3.6) (**Mayo M et al. 2006**). Finally, patients with fibrosis regression may be protected from developing clinical complications (**Colletta C et al. 2007**).

Tools used to quantitate fibrosis

The historical "gold standard" for assessment of fibrosis is histologic assessment of the liver (liver biopsy). However, liver biopsy is invasive and is associated with serious potential complications, requires substantial training and skill, makes both patients and physicians anxious, and can be associated with substantial sampling error. As a result, there has been great interest in noninvasive measurement of fibrosis; many methods have been proposed (**Table 7**).

Transient Elastography

TE is a novel, ultrasound based technology that involves acquisition of pulse-echo ultrasound signals to measure liver stiffness (**Sandrin L et al. 2003**) (**Figure 4**). In brief, the tip of an ultrasound transducer probe is placed between ribs over the right lobe of the liver. The probe transmits a low-amplitude (vibration and frequency) signal to the liver, which in turn induces an elastic shear wave that propagates through liver tissue. The pulse-echo ultrasound allows measurement of wave velocity, expressed in kilopascals, a measure of liver stiffness. Normal liver stiffness is reported to be in the range of 4–6 kPa, whereas cirrhosis is generally present at levels>12–14 kPa (**Ziol M et al. 2005, Castera L et al. 2006, Fraquelli M et al. 2007**).

TE is associated with attractive features beyond the fact that it is noninvasive. Most important, it assesses a relatively large sample-across an area of 1–2 cm of the liver, estimated to be some 100 times greater than a liver biopsy specimen. Additionally, TE allows multiple readings to be taken (from slightly different areas, thereby providing data on an even larger sample). This is critical because sampling error associated with liver biopsy (**Ratziu V et al. 2005**) is likely due to the small portion of the liver sampled (**Bedossa P et al. 2003**).

Transient elastography and fibrosis

The pathophysiologic basis of liver stiffness, and the degree to which fibrosis correlates with liver stiffness, is an area of active investigation.

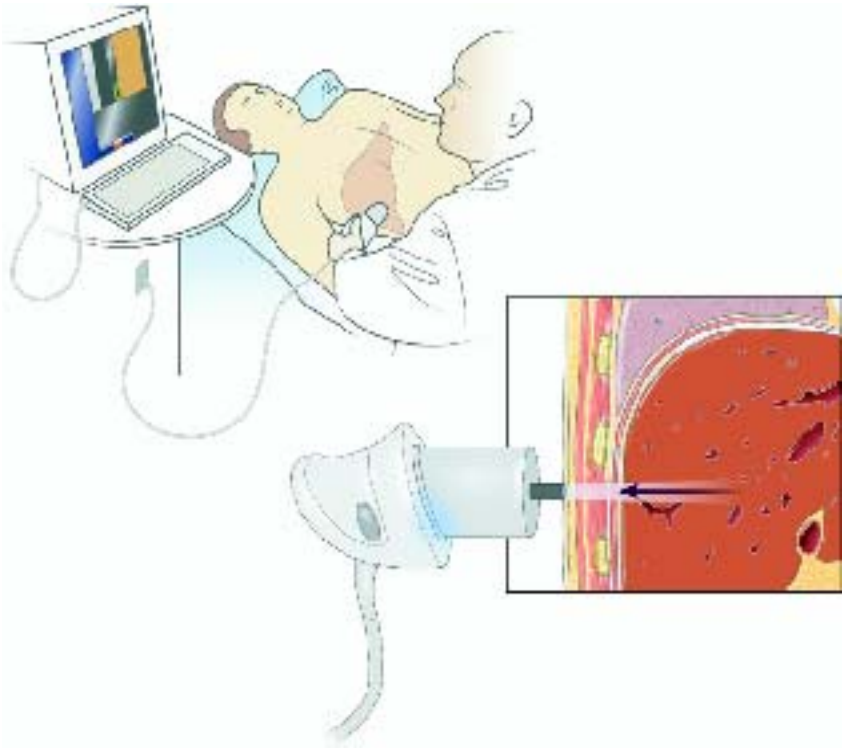


Figure 4: The figure depicts an overview of the technique. Briefly, a pulse-echo ultrasound signal is obtained by placing a transducer probe between ribs over the right lobe of the liver. The low amplitude signal transmitted to the liver induces an elastic shear wave that propagates through liver tissue. The pulse-echo ultrasound allows measurement of wave velocity obtained provides a measure of liver stiffness.

Indeed, the relationship of fibrosis to the "mechanical" or "physical" state of the liver is not well understood, although it has long been appreciated that the cirrhotic liver is stiff. Indeed, Rene Laennec, wrote many years ago (1826): "The liver, reduced to a third of its ordinary size . . ., one could not mash but a small portion: the rest gave to the touch the sensation of a piece of soft leather." Investigation over the last 2 decades has more precisely evaluated tissue elasticity, typically using ultrasound technology (**Erkamp RQ et al. 1998, Yeh WC et al. 2002**). One study evaluated the consistency of the liver as a change in a resonance frequency (**Kusaka K et al. 2000**). In patients undergoing hepatic resections for various indications, liver stiffness was measured intraoperatively and correlated with both liver function and liver fibrosis.

It is further known that the injured liver itself is contractile (and thus has elastic properties), presumably as a result of cellular elements within the liver such as myofibroblasts. Liver fibrosis appears to be characterized by elements of reversible and irreversible fibrosis; the irreversible component may be made up of relatively acellular bands of cross-linked collagen, (**Issa R et al. 2004**) the latter possibly associated with reduced elasticity. Thus, a fundamental pathophysiologic question is this: Do elements at the cellular level play a role in determining tissue elasticity?

This is highly likely; in fact, it was suggested that liver stiffness precedes fibrosis and stellate cell activation, raising the possibility even that fibrosis and liver stiffness may not be linked (**Georges PC et al. 2007**). We know that liver fibrosis is a result of activation of effector cells (stellate cells, fibroblasts, fibrocytes) with subsequent fibrogenesis. Additionally, liver stiffness may be increased in the setting of hepatic inflammation; thus,

a "cellular" contribution to liver stiffness is attractive. Nonetheless, further investigation is clearly required to test this possibility.

Given this background, it is clear that there are many issues surrounding the use of TE for quantitation of liver fibrosis including several highlighted below.

1. How accurate is TE and can it differentiate no fibrosis from very early fibrosis stages?

   Will measurement of liver stiffness allow longitudinal quantitation of fibrosis as the patient transitions from F1 to F2 to F3?
2. How reproducible and reliable is it?
3. How much training is required?
4. Are differences in gender important?
5. What is the cost? Is it cost effective?
6. What are the limitations of TE?
7. How might TE be used in clinical practice?

Accuracy

TE has been shown to have a reasonably high sensitivity and specificity for fibrosis at both ends of the spectrum. TE appears to be able to tell us that the liver is either normal or cirrhotic. For example, in a prospective multicenter study of 327 chronic HCV patients, the AUROC for METAVIR stage ≥F2 and cirrhosis (F4) were 0.79 and 0.97, respectively (**Ziol M et al. 2005**). Many other studies have yielded similar results (**Masaki N et al. 2006, Friedrich-Rust M et al. 2007**). Liver stiffness measurements have been shown to correlate with fibrosis in a variety of liver

diseases, including primary biliary cirrhosis, primary sclerosing cholangitis, NASH, (**Corpechot C et al. 2006**) and others (**Foucher J et al. 2006**).

It is likely that TE can be used in combination with other (noninvasive) tests to more accurately assess fibrosis stage. In a prospective analysis comparing transient elastography, serum markers, and the APRI in a cohort of 183 chronic HCV patients with evenly matched F1–F4 disease, the performance of the various noninvasive tests was similar (the AUROC for transient elastography, serum tests, and APRI were 0.83, 0.85, and 0.78, respectively, for METAVIR F≥2) (**Castera L et al. 2005**). However, the best overall performance was obtained by combining TE and serum markers (AUROC of 0.88 for F≥2, 0.95 for F≥3, and 0.95 for F=4).

Although the "global" accuracy of TE is high, it is imprecise in quantitating intermediate levels of fibrosis (as is the case with serum markers). Thus, it is difficult to differentiate the normal liver from METAVIR stage F1, stage F1 from F2 disease or even stage F2 from F3 disease. To the degree that this degree of differentiation may be important from a clinical management standpoint, the use of TE will be limited.

Reproducibility and Reliability

TE is reported to have good reproducibility with low variability. Intraobserver and interobserver agreement were analyzed using the intraclass correlation coefficient (ICC) and correlated with different patient-related and liver disease-related covariates, in one study (**Fraquelli M et al. 2007**). In 800 examinations (in 200 patients), the overall interobserver agreement ICC was 0.98 (95% CI, 0.977– 0.987). Increased body mass

index (BMI, .25 kg/m^2), steatosis, and low staging grades (<F2) were significantly associated with reduced ICC (P <0.05).

Training

Certain clinical features may be associated with acceptable performance and success of TE (**Kettaneh A et al. 2007**). The success rate of "shots" (i.e., a valid measurement) decreased with age, and was lower in obese than in those with lower BMIs (**Kettaneh A et al. 2007**). Operators who had performed ≥50 prior examinations had a higher success rate. Additionally, reproducibility was significantly reduced in patients with steatosis, increased BMI, and lower degrees of hepatic fibrosis. In another study (**Foucher J et al. 2006**), the only factor associated with technical failure of the study was BMI >28.

Gender

There may be differences in liver stiffness among men and women. In a cohort of normal individuals, the median liver stiffness value was 4.8 kPa (range, 2.5– 6.9) and did not correlate with age, body weight, or height, but it was significantly higher in men than in women (5.2 ± 0.7 *vs* 4.5 ± 1.0; P <0.01); other variables did not differ among the genders (**Corpechot C et al. 2006**). These data suggest an intrinsic difference in fibrogenesis in men and women. Experimental data support the possibility that female hormones protect against fibrosis (**Yasuda M et al. 1999**). Larger studies of normal individuals are required to more robustly assess this issue.

Limitations

In addition to the issues related to accuracy and extension of its use in populations other than those with known liver disease, several important technical limitations merit comment. First, to obtain a high-quality pulsed signal, there must be a direct and relatively short path to the liver. The depth of signal penetration is limited, so it is difficult to perform TE in obese patients or those with ascites. In addition, ribs may obscure the pulsed signal. It is likely that newer transducers will overcome at least some of these issues.

An important limitation to date is that TE has been performed largely in patients with known liver disease. Because the experience with general populations is limited, it is unknown whether TE will be useful as a widely applicable screening tool. For example, because liver fibrosis likely varies with age (**Choy-Smith C et al. 2002**), better standards among normals are required.

An inherent limitation of the published literature is that liver histology obtained by biopsy has been used as a "gold standard," and it, although considered the best measure of fibrosis, is associated with sampling error (**Regev A et al. 2002, Bedossa P et al. 2003**), not surprising given that liver biopsy samples a small fraction of the liver. Therefore, because liver biopsy itself may not be truly reliable, it is difficult to accurately assess tests compared to it.

Use in Practice

Perhaps the greatest clinical utility of TE will be its ability to determine whether the patient has cirrhosis. The specificity of TE in patients

with known liver disease has been reproducibly in the 90%–95% range (**Friedrich-Rust M et al. In press**). Thus, a measurement in the 8–9 kPa range would suggest less severe fibrosis, perhaps at a METAVIR F2 level, and unlikely histologic cirrhosis (i.e., a false positive for cirrhosis). Thus, TE appears to be best at excluding cirrhosis (with a liver stiffness threshold of ≈14 kPa). False negatives appear to be attributable largely to inactive or macro nodular cirrhosis (**Ganne-Carrie N et al. 2006**). If the clinician believes it is important to know the precise (particularly, intermediate) stage of fibrosis, then TE is unlikely to be definitive.

An attractive area for TE is that it may assist clinicians in ascertaining the severity of liver disease at the bedside. In one study (**Nahon P et al. 2006**), physicians were asked to predict the stage of fibrosis using clinical data alone and then again after addition of TE data. Interestingly, the clinician's ability to predict cirrhosis was significantly improved, although improvement in prediction of other stages was less pronounced.

Transient Elastography and PHT/Varices

Although the pathophysiologic basis for use of TE as a surrogate for fibrosis seems relatively straightforward, the basis for its correlation with PHT remains poorly defined. In virtually all forms of intrahepatic liver disease, PHT initially develops as the result of an increase in intrahepatic resistance. However, as PHT advances, increased portal pressure appears to be perpetuated largely by (increased) flow derangement in the splanchnic circulation (**Bosch J et al. 2000**). Thus, it might be predicted that TE could predict changes in intrahepatic vascular resistance resulting from effector cell activation at the level of the sinusoid (i.e., early in the disease process).

Notwithstanding, it would be predicted that TE should not be able to measure complex hemodynamic (especially flow) abnormalities typical of advanced PHT.

Liver stiffness appears to correlate with HVPG measurements. In a study of 61 consecutive patients with HCV (**Vizzutti F et al. 2007**), the correlation was excellent in patients with HVPG <10, but was less optimal for HVPG values >10 mm Hg. The AUROC for prediction of HVPG >10 and >12 mm Hg were 0.99 and 0.92, respectively, and at liver stiffness cutoff values of 13.6 kPa and 17.6 kPa, sensitivity was 97% and 94%, respectively. There was also good correlation between liver stiffness and the presence of EV but not between liver stiffness and variceal size. Other studies have demonstrated a correlation between increasing liver stiffness and variceal size (**Kazemi F et al. 2006**). Because the degree of fibrosis appears to correlate with PHT (**Blasco A et al. 2006**), the fact that liver stiffness measured by TE also correlates with PHT suggests that fibrosis and PHT are linked, either directly or indirectly.

In conclusion; TE appears to be capable of providing reliable and reproducible quantitative measurements of liver stiffness, which in turn can be correlated with fibrosis. This provides further evidence that the practice of hepatology may shift toward use of noninvasive tools to assess disease. Perhaps one of the greatest potential uses for measurement of liver stiffness with TE is in prediction of PHT (and EV). This is likely because TE appears to accurately measure advanced fibrosis, which appears to correlate with portal hypertension. Unfortunately, TE does not appear to be robust at discriminating between intermediate grades of fibrosis, and is really not helpful in assessing early fibrosis. To the extent that these data may be

important in clinical management, TE alone will be limited in clinical practice (**Don C. Rockey et al. 2008**).

Future

Notwithstanding the enthusiasm for transient elastography, many questions remain. Could MR elastography provide a better global assessment of the liver?

Can TE be used as a screening tool in patients without known liver disease (i.e., to screen obese patients for the presence of nonalcoholic fatty liver disease or NASH)?

What will it cost and will it be cost effective compared with other noninvasive tests or liver biopsy?

Most important, it will be essential for us to learn whether TE can be combined with other clinical data or other noninvasive tests to provide a more accurate measure of fibrosis. As with all diagnostic tests that strive to assess liver fibrosis, we need more natural history data, we must understand how well the diagnostic test informs us about long-term outcomes.

CAPSULE ENDOSCOPY

Capsule endoscopy of the small bowel

Brief history

The first CE model in the world, called M2A (meaning "mouth to anus"), was manufactured by Given Imaging (**Iddan et al. 2004**). After clinical use and evaluation (**Appleyard et al. 2001, Ell et al. 2002, Lewis et al. 2002**), M2A was approved for general clinical use in Europe in May 2001, and by the U.S. Food and Drug Administration (FDA) in August 2001. M2A was renamed PillCam SB (meaning "small bowel"; **Figure 5**) after the advent of esophageal CE (PillCam ESO; **Figure 5**), also developed by Given Imaging (**Eliakim et al. 2004**).

In Japan, the first clinical CE trial for small-bowel (SB) disease, including Crohn's disease, was carried out at Dokkyo Medical University (Tochigi) and Social Insurance Central Hospital (Tokyo) in 2003 (**Nakamura et al. 2004**). PillCam SB was approved by the Ministry of Health, Labour and Welfare of Japan in April 2007, and finally reimbursement for CE costs was approved by Social Insurance Agency of Japan in October 2007. Another type of CE for the SB has been developed by Olympus (EndoCapsule EC type 1) **(Gheorghe et al. 2007)** and is already approved in Europe but not yet in Japan. More than 600,000 PillCam SB capsules have been used worldwide since 2001.

PillCam SB system

The PillCam SB system has three components: a capsule endoscope body, an external receiving antenna consisting of eight sensor arrays with

attached portable hard disc drive (data recorder), and a customized PC workstation (RAPID: reading and processing images and data) with dedicated software for review and interpretation of images (**Cave DR 2004**).

Figure 5: Capsule endoscopy devices from Given Imaging: PillCam SB2 for small intestine, PillCam COLON for large bowel, and PillCam ESO for esophagus.

The PillCam SB capsule (11 mm × 26 mm, 3.64 g) consists of metal oxide silicon (CMOS) chip imager, a short focal lens, six white light-emitting diode illumination sources, two watch batteries, and a UHF band radio telemetry transmitter. Image features include a 140° field of view, 1: 8 magnifications, 1- to 30- mm depth of view, and a minimum size of detection of about 0.1 mm. The activated PillCam SB capsule provides images at a frequency of 2 frames per second until the battery expires, after about 8 h, which enables the device to take up to 55000 still images (JPEG format) (**Figures 5, 6**) (**Lewis B. 2004**).

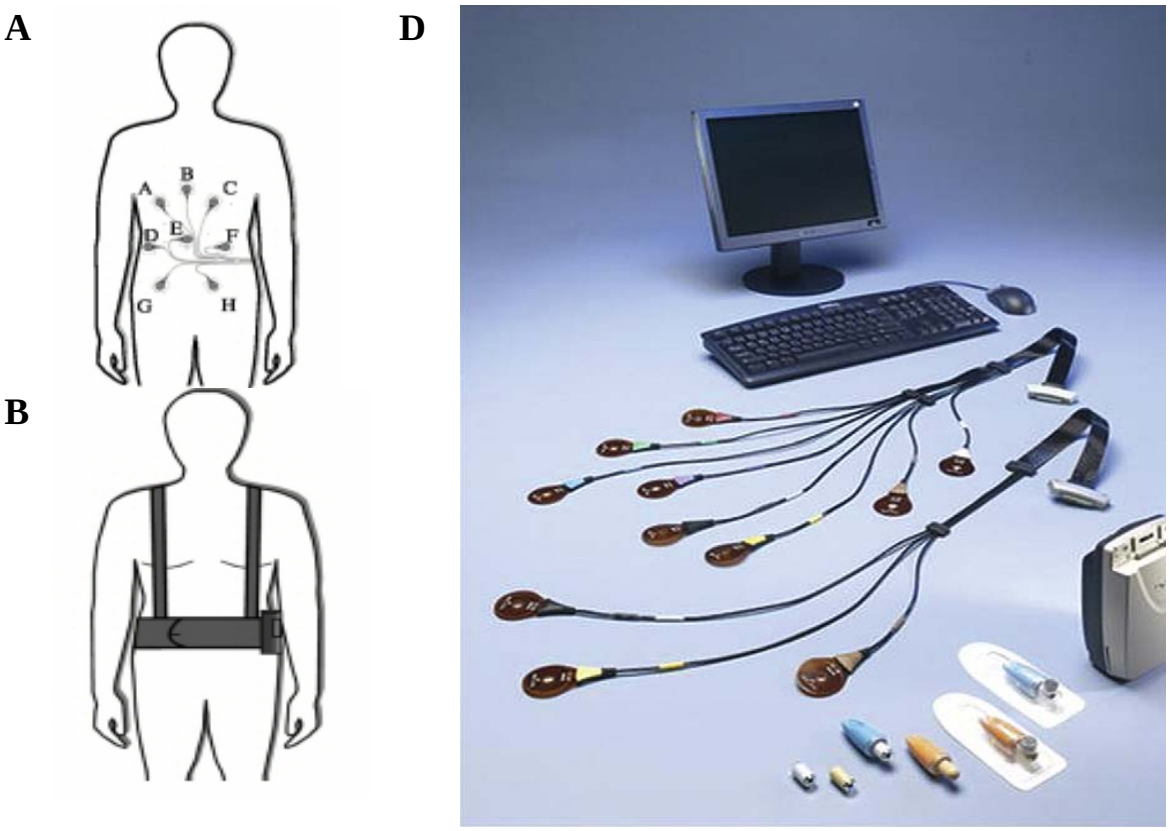


Figure 6: A- Small Bowel Sensor Placement of the sensor array, B- Recorder Belt attached to patient, C- Non-Adhesive Tab, D- Capsule endoscope, PillCam, sensing system with sensing pads and data recorder/battery pack, PC workstation

Guidelines on Capsule Endoscopy (Sidhu et al. 2008)

Formulation of guidelines

These guidelines were commissioned by the Clinical Services and Standards Committee of the British Society of Gastroenterology (BSG) and have been produced by the SB and endoscopy sections of the BSG. The guidelines have been produced to conform to the North of England evidence based guidelines development project (**Grimshaw et al.1995, Eccles et al.**

1996). They have been drawn up from a Medline, Embase and Ovid literature search using term ‘‘capsule endoscopy’’. The literature search for CE includes 100 peer review studies, 51 review articles, 74 case studies and letters, 21 editorials, 4-pooled analyses and 2 sets of guidelines: American and European on CE (**Mishkin et al. 2006, Rey et al. 2004, Rey et al. 2006**).

Grading of recommendations

Grade A—requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation (evidence categories Ia and Ib).

Grade B—requires the availability of clinical studies without randomisation on the topic of consideration (evidence categories IIa, IIb and III).

Grade C—requires evidence from expert committee reports or opinions or clinical experience of respected authorities, in the absence of directly applicable clinical studies of good quality (evidence category IV).

Indications for capsule endoscopy

(1) Obscure gastrointestinal bleeding (OGIB)

(2) Small bowel Crohn’s disease

(3) Assessment of coeliac disease

(4) Screening and surveillance for polyps in familial polyposis syndromes

(1) **Obscure overt and occult gastrointestinal bleeding**

Capsule endoscopy (CE) now has an established role in patients with persistent OGIB who have had a negative gastroscopy and colonoscopy. Most studies using CE in patients with OGIB have been in comparison to other modalities of investigation of the small bowel. Prospective studies have consistently revealed a superior diagnostic yield for CE compared to push enteroscopy in patients with OGIB **(Figure 9-A)** (**Costamagna et al. 2002, Hopper et al. 2005, Sidhu et al. 2006**). A recent meta-analysis (of 14 studies on patients with OGIB) reported yields of 63% for CE and 28% for PE (**Triester et al. 2005**). The yield of CE has also been shown to be superior to barium follow through and CT enteroclysis in the context of OGIB (**Marmo et al. 2005, Nakamura et al. 2006**). The second meta-analysis of 17 studies (526 patients) supports these findings: the rate difference (i.e., the absolute pooled difference in the rate of positive findings) between CE and other investigative modalities for OGIB was 37% (95% CI, 29.6 to 44.1) (**Marmo et al. 2005**).

The rate of rebleeding in patients with OGIB and negative CE is significantly lower compared to those with a positive CE (48% *vs* 4.6% respectively) (**Lai et al. 2006**). In patients with a negative CE and cessation of bleeding, a conservative approach may be adopted (**Lai et al. 2006**). In the subgroup of patients with negative results on initial CE and persistent bleeding, a second look CE may be considered, as small studies have shown an additional yield of 35–75% (**Bar-Meir et al. 2004, Jones et al. 2005**). (*Recommendation grade C*).

When comparing more invasive forms of endoscopy (DBE) with CE, diagnostic rates are similar. Studies comparing DBE and CE have shown diagnostic yields of between 42.9–60% (for DBE) and 59.4–80% (for CE)

(**Nakamura et al. 2006, Hadithi et al. 2006**). Complete SB examination was achieved more frequently by CE (**Nakamura et al. 2006, Hadithi et al. 2006**) (90.6% compared to 62.5%, respectively; $p < 0.05$).

Historically, intra-operative endoscopy has been considered the gold standard in patients with OGIB and negative standard endoscopic evaluation. When compared to intraoperative endoscopy, CE had sensitivity, specificity, positive and negative predictive values of 95%, 75%, 95% and 86%, respectively (**Hartmann et al. 2005**). An algorithm for investigation of patients with OGB is suggested in **Figure 7**. (**Sidhu et al. 2006**). (*Recommendation grade B*)

(2) **Crohn's disease**

The SB is commonly affected by Crohn's disease. Endoscopically, however, the SB is relatively inaccessible. In addition, ileal intubation is not always achieved at colonoscopy (CS). Small bowel contrast studies have variable success rates in diagnosing active Crohn's disease (**Eliakim et al. 2003, Eliakim et al. 2004, Hara et al. 2006**). Whilst CT may be effective in diagnosing SB thickening and complications of Crohn's disease, its accuracy in determining the presence of mucosal disease is unknown. This difficulty partly explains a mean delay of between 1 and 7 years from onset of symptoms to diagnosis (**Timmer et al. 1999, Pimentel et 2000**).

A number of studies have now addressed the question of how best to investigate patients in whom conventional tests have failed to confirm a diagnosis of active Crohn's disease. These include patients with symptoms of pain, diarrhea, weight loss, or investigational findings including iron deficient anemia and an acute phase response (**Kornbluth et al. 2005**). Which combination of these features accurately predicts a diagnosis of

Crohn's disease is not known, but a consensus group has suggested that further investigation using CE might be considered in patients with two or more of these criteria (**Kornbluth et al. 2005**). (*Recommendation grade C*)

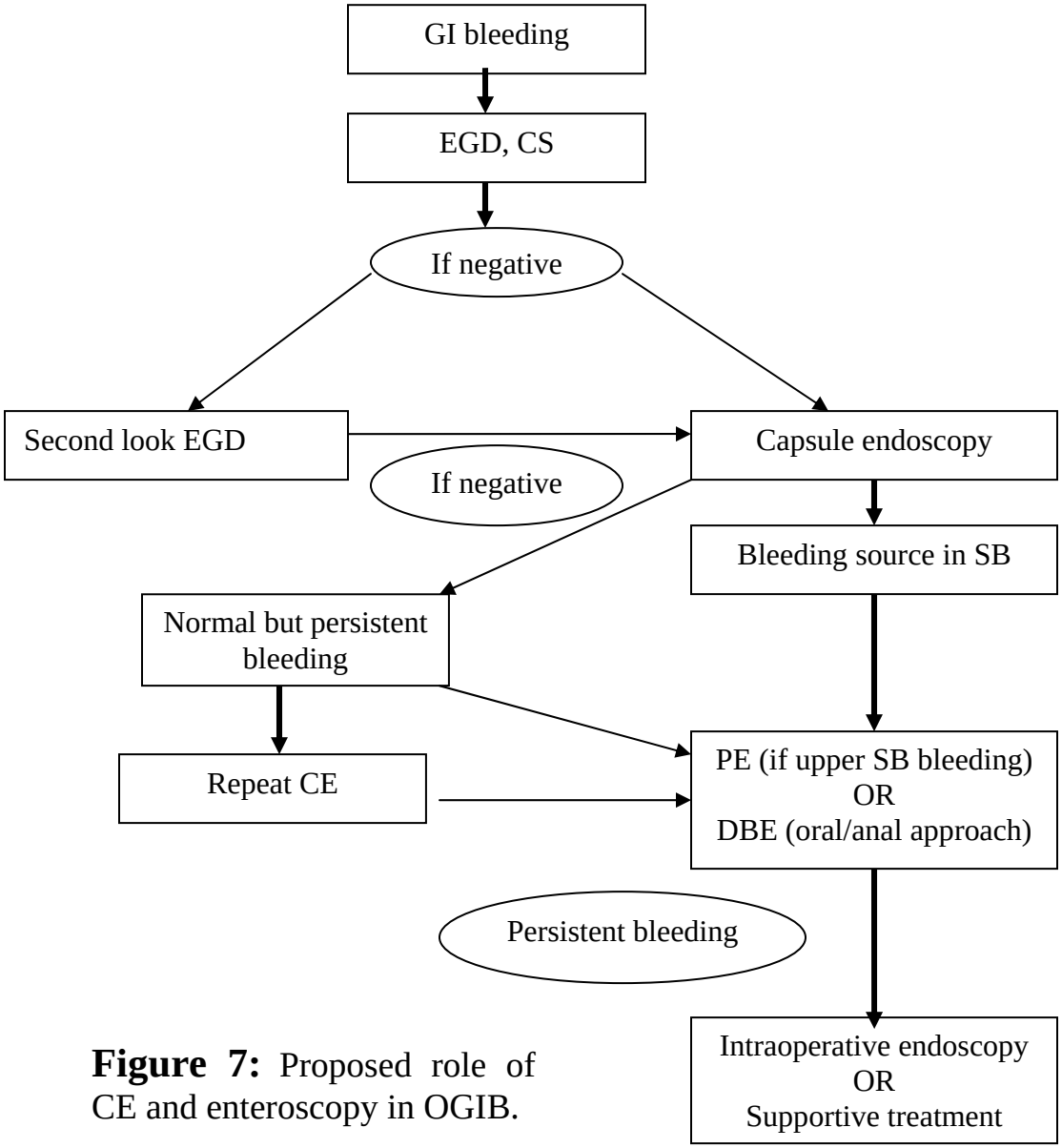


Figure 7: Proposed role of CE and enteroscopy in OGIB.

A number of studies performed have compared CE with CS and ileoscopy, small bowel follow through (SBFT), CT enteroclysis and MRI (**Fireman et al. 2003, Mow et al. 2004, Chong et al. 2005**). In addition to confirming suspected Crohn's disease and assessing disease extent, CE has

also been used in the context of recurrence of disease post-operatively (**Bourreille et al. 2006**).

Capsule endoscopy versus endoscopy

Evidence of Crohn's disease was found by CE in 43–71% of patients typically suspected of having Crohn's disease in which CS (and small bowel radiography) had previously been normal (**Herrerias et al. 2003, Ge et al. 2004**). An analysis of four prospective comparative studies (total of 115 patients) showed a diagnostic yield of 61% for CE compared to 46% for ileocolonoscopy in the detection of small bowel Crohn's (p=0.02; 95% CI, 2 to 27) (**Kornbluth et al. 2005**). CE was also able to identify the extent of disease proximal to the terminal ileum. CE has been found to have a greater diagnostic yield when compared to PE in patients known to have established Crohn's disease perhaps reflecting the greater extent of SB mucosa visualized during CE **(Figure 9-B)** (**Toth et al. 2004, Chong et al. 2005**).

The use of CE for recognition of disease recurrence within 6 months of ileo-colonic resection had a reported sensitivity of between 62 and 76% compared to 90% for ileo-colonoscopy (**Bourreille et al. 2006**). However, CE did identify lesions outside the reach of an ileocolonoscope. This data does not necessarily represent that of routine clinical practice: capsules entered the colon in all cases (compared to a reported incomplete examination in 10–25% of other series) and all patients had successful ileo-colonoscopy (compared to an average UK rate of 57% for caecal intubation) (**Bowles et al. 2004**). Ileo-colonoscopy has a higher yield in the detection of recurrent disease compared to CE in patients post ileo-colonic resection. (Recommendation grade C)

Capsule endoscopy versus small bowel radiology

In patients with suspected new or recurrent Crohn's disease, CE was more likely to identify active disease than small bowel barium imaging (**Dubcenco et al. 2005, Marmo et al. 2005, Triester et al. 2006**). Studies comparing CT enteroclysis with CE also showed a higher yield of SB ulceration for CE (**Voderholzer et al. 2003, Eliakim et al. 2004, Voderholzer et al. 2005**). The two studies comparing CE and MR enteroclysis showed either comparable or better yield for CE (**Albert et al. 2005, Golder et al. 2006**). An important observation from most radiological versus CE studies is that radiological examination was able to delineate the presence of strictures which precluded the use of CE in a significant number of patients (**Voderholzer et al. 2005, Buchman et al. 2004**).

A recent meta-analysis made a comparison of CE versus other modalities in established and suspected Crohn's disease (**Triester et al. 2006**). In the evaluation of recurrence, CE is superior to both barium studies and ileo-colonoscopy in established non-stricturing Crohn's disease. (Recommendation grade B)

However, despite a higher yield of CE in comparison to other modalities in the suspected Crohn's group, the sub-analysis did not show a statistically significant difference in favor of CE in this group (**Triester et al. 2006**). Larger studies are needed to better establish the role of CE in the diagnosis of suspected Crohn's disease. (Recommendation grade C)

Capsule retention remains a risk in patients with Crohn's disease even in the presence of radiological investigations that do not show significant strictures. In the studies referred to, with predominantly Crohn's patients, retention occurred in 0–6.7% of cases (**Herrerias et al. 2003, Chong et al. 2005, Albert et al. 2005**) and capsules passed either after medical treatment

of Crohn's disease, (**Albert et al. 2005**) endoscopic removal (**Voderholzer et al. 2005)** or surgery (**Mow et al. 2004, Buchman et al. 2004).** The risk is greater in patients with established Crohn's disease compared to patients suspected to have Crohn's disease (**Cave et al. 2005**).

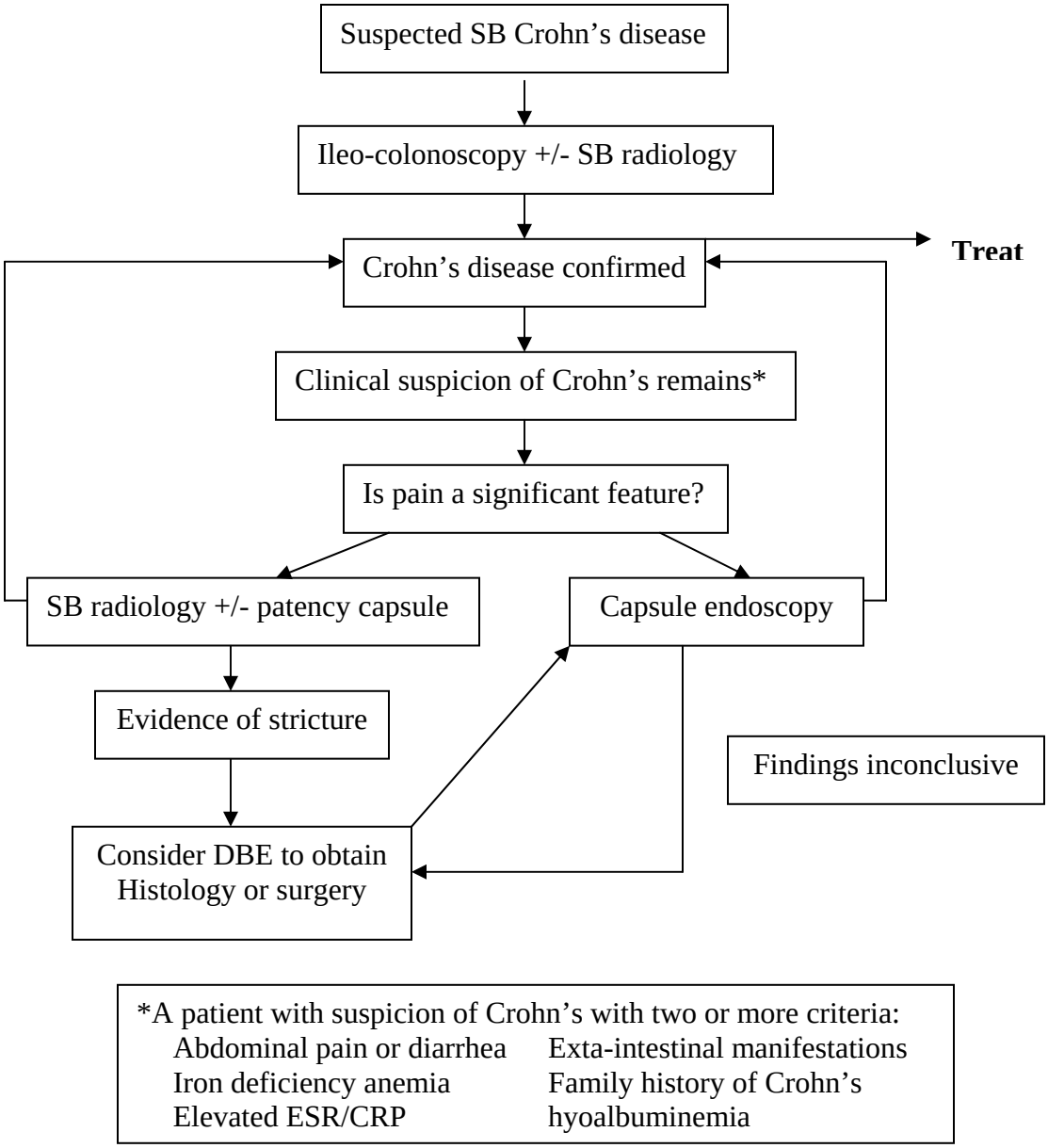


Figure 8: the use of CE and DBE in investigation of Crohn's disease

CE should be considered in patients with a high suspicion of small bowel Crohn's disease undetected by conventional means. These patients should have radiological imaging to exclude strictures prior to CE. (Recommendation grade C)

An algorithm for the investigation of patients suspected of having Crohn's disease using CE is suggested in **Figure 8**. (Recommendation grade C)

A **B**

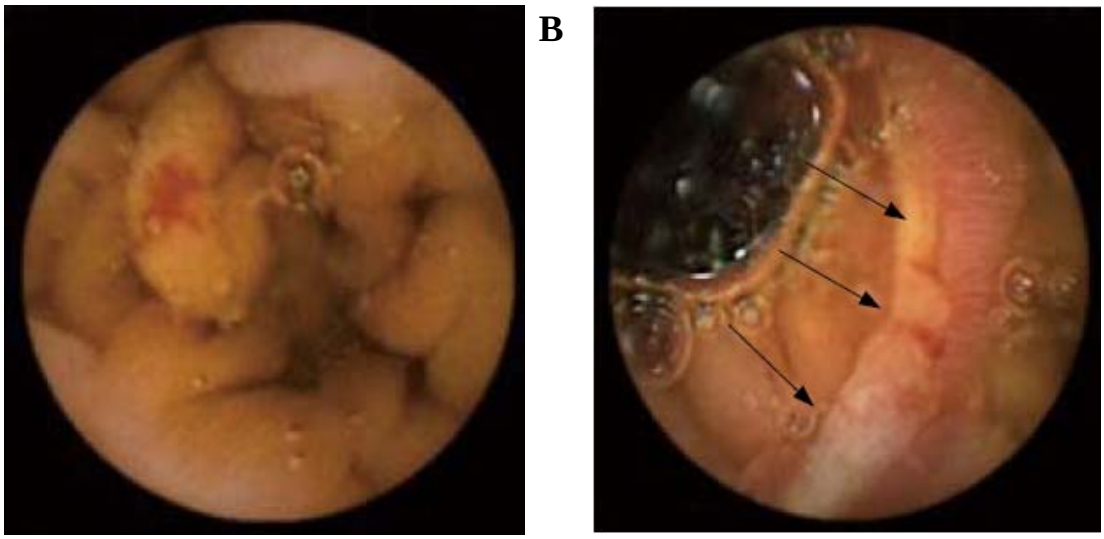


Figure 9: A- Artero-Venous Malformation (AVM) of the distal duodenum in a patient undergoing CE for OGIB, **B-** Jejunal ulcers in a patient with Crohn's disease

(3) **Celiac disease**

There have been two reported roles for the use of CE in celiac disease. Firstly, typical mucosal changes of celiac disease has been recognized at CE including a mosaic pattern, scalloping, ''octopus leg'' appearance, loss of mucosal folds and atrophy (**Petroniene et al. 2005, Hopper et al. 2007**). As a result there have been small studies using CE as virtual histology in conjunction with positive celiac serology, as the mucosal changes seen on CE is comparable to the macroscopic appearance at endoscopy. The

sensitivity, specificity, positive and negative predictive values of CE for celiac disease has been reported as 70%, 100%, 100% and 77%, respectively (**Petroniene et al. 2005**). At present, duodenal biopsy remains the gold standard and there is insufficient evidence for CE for the routine diagnosis of celiac disease. (Recommendation grade C)

The second group of patients who would benefit from CE is those with known celiac disease established on a gluten free diet but with ongoing symptoms or those who develop alarm symptoms. These patients often undergo extensive radiological and sometimes surgical evaluation to look for possible complications of ulcerative jejunitis and small bowel lymphoma (**Apostolopoulos et al. 2004, Culliford et al. 2005, Joyce et al. 2005**). A reported study showed a yield of 60% in detection of celiac related complications including ulcerated mucosa, stricture and malignancy (**Culliford et al. 2005**).

CE might be indicated in the diagnosis of complications of celiac disease. (Recommendation grade C)

(4) Familial polyposis syndromes

There are a small number of studies looking at the use of CE in surveillance of polyposis syndromes (familial adenomatous polyposis and Peutz–Jegher's syndrome) (**Schulmann et al. 2005, Barkay et al. 2005, Mata et al. 2005**). CE is more accurate in detection of polyps than SBFT and it can also detect smaller polyps in comparison to MRI (**Caspari et al. 2004**). Given the limited number of studies, the routine use of CE in patients with polyposis syndromes is currently not advocated. The effect of CE on the change of management in this group of patients also needs further clarification. (Recommendation grade C)

(5) **Other indications (outside the guidelines)**

A- NSAIDs induced damage:

Surprisingly two (**Gomez et al. 2006, Goldstein et al. 2005**) of eight randomized controlled studies published on CE evaluated the role of this technique in assessing SB lesions due to NSAIDs consumption. This probably derived from the fact that these widely used drugs can induce small, spotty and superficial mucosal lesions (i.e. mucosal breaks) difficult to identify with other techniques (**Figure 10**).

Nevertheless, the most important information in this field is the demonstration that small mucosal inflammatory lesions (such as mucosal breaks, small isolated erosion or superficial ulcers) have been detected in about 10%-13% of healthy subjects (**Goldstein et al. 2005**). Although the clinical implications of these findings remain unclear, the occurrence of these lesions in young healthy subjects, define a new benchmark that must be considered in any further clinical study about CE.

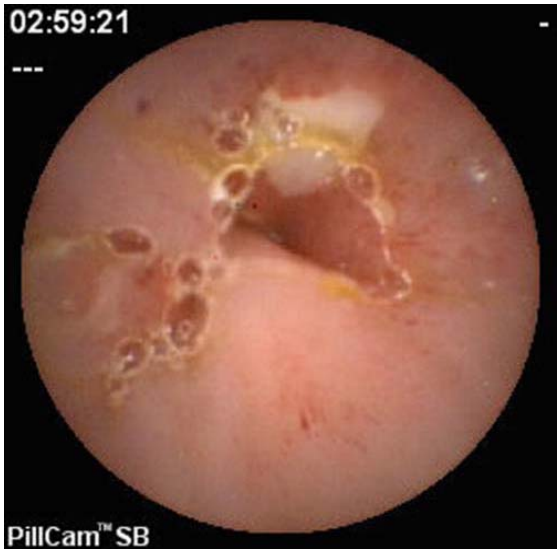


Figure 10: Typical CE image of a mucosal break with ulceration at center and surrounding erythema in NSAIDs induced injury.

B- Small bowel tumors:

Small bowel tumors are still considered, particularly when compared with gastric or colonic neoplasms, a rare disease accounting for 1% to 3 %

of all primary GI tumors (**Di Sarjo et al. 1994**), however, since the introduction of CE in clinical practice, some small studies have been published reporting a frequency of SB tumors ranging between 6% and 9% (**Cobrin et al. 2006, Bailey et al. 2006)**. These studies, including a series of patients undergoing CE in which this tool was able to identify the presence of SB tumors, showed a higher than expected frequency of these tumors (Figure 11). All published series concluded that the main clinical indication for CE in the field of SB tumors is OGIB.

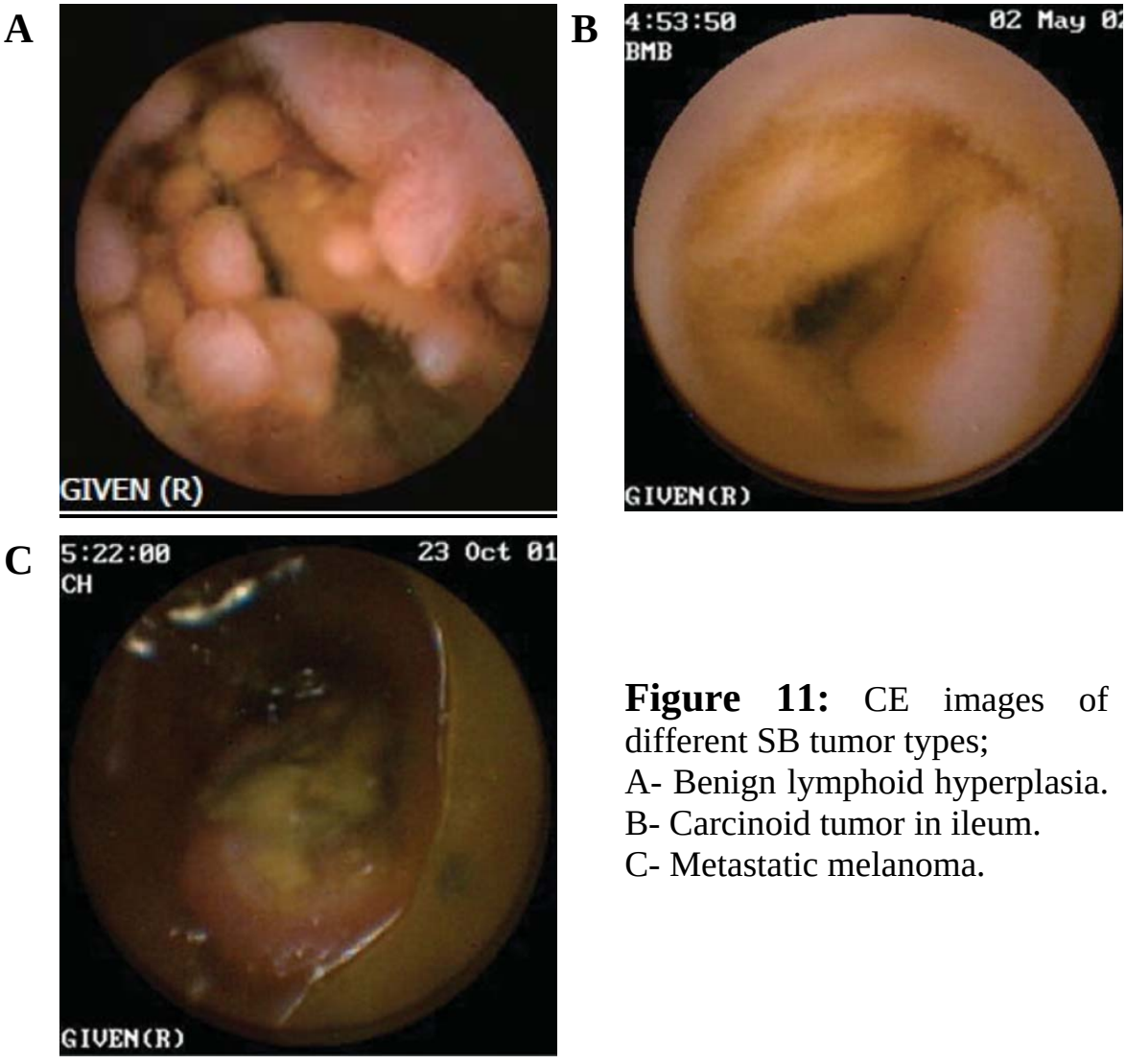


Figure 11: CE images of different SB tumor types;
A- Benign lymphoid hyperplasia.
B- Carcinoid tumor in ileum.
C- Metastatic melanoma.

C-Abdominal pain:

May et al (**2007**) clearly demonstrated that when chronic abdominal pain is associated with other signs or symptoms (weight loss > 10% of body weight, inflammation shown by laboratory tests, chronic anemia, or suspected GI bleeding) relevant, or potentially relevant, findings are diagnosed by CE in about 60% of cases.

D- Others:

CE has also been used , with promising results, in other rare clinical conditions such as indeterminate colitis (**Viazis et al. 2007, Maunoury et al. 2007**), SB transplantation (**de Franchis et al. 2003**), graft versus host disease (**Neumann et al. 2007**), protein losing entheropathy (**Pungpapong et al. 2007**), primitive lymphangectasia (**Vignes et al. 2007)** (mostly in the pediatric population), Whipple disease (**Fritscher-Ravens et al. 2004**) and irritable bowel syndrome (with clinical suspicion of celiac disease) (**Adler et al. 2006**).

Complications of capsule endoscopy

The main risk of CE is capsule retention. CE is contraindicated in patients with known strictures or swallowing disorders. Patients with extensive small bowel Crohn's (discussed before) chronic usage of non-steroidal anti-inflammatory drugs (NSAIDs) and abdominal radiation injury are at higher risk. Patients should be fully informed about the risk of retention before consent for CE is undertaken. It should be highlighted that further intervention including surgery may be required if passage of the capsule is impeded by a stricture. Capsule retention has been defined by the International Conference on Capsule Endoscopy (ICCE) working group, as

the capsule remaining in the digestive tract for 2 weeks or more requiring directed medical, endoscopic or surgical intervention (**Cave et al. 2005**). A large study (937 patients) reported an incidence of 0.75% of patients worldwide who required surgical intervention to remove a retained capsule (**Barkin et al. 2002**). An alternative imaging modality should be considered prior to CE in patients with obstructive symptoms. (Recommendation grade B)

The absence of strictures on a barium study however does not entirely preclude the capsule being safely passed, as retention is known to occur despite normal barium or enteroclysis study (**Buchman et al. 2004, Mow et al. 2004, Pennazio et al. 2004**). In certain situations, however, CE may be used to diagnose an obstructing lesion not identified by other techniques and the capsule removed at surgery.(Recommendation grade C)

A plain abdominal radiograph should be obtained to confirm excretion of capsule if the video fails to show that it enters the colon. Patients should not undergo magnetic resonance imaging after CE until they have safely passed the capsule. Occasionally the capsule may be retained in the stomach due to gastroparesis. In these cases, specifically designed ‘‘capsule delivery systems’’ are recommended for delivery of the capsule directly into the SB (**Leung et al. 2004, Toth et al. 2004, Carey et al. 2004**). (Recommendation grade C)

There is theoretical potential for interference between the radiofrequency of the capsule, data recorder and permanent pacemakers (PPM) and implantable cardiac defibrillators (ICD). The manufacturers of CE have listed them as a relative contraindication for use of CE. Small studies have tested the use of CE in patients with these devices and have

shown it to be safe without adverse events or interference of capsule images (**Rey et al. 2004, Payeras et al. 2005, Leighton et al. 2005**).

Larger studies are required to verify its safe use. Either advice should also be obtained from the manufacturers of the cardiac device or the cardiologists to ensure that the capsule does not affect function of the cardiac device (Swain et al. 2005, Boivin et al. 2005). (Recommendation grade C)

Limitations (outside the guidelines)

A- Missing rate

Lewis et al (**2005**) analyzing a master database, provided by Given Imaging Ltd (Yoqneam, Israel), found that the global miss rate of CE is about 11% ranging between 0.5% for ulcerative disease and 18.9% for neoplastic disease. Despite the estimated miss rate, CE is significantly lower than that of conventional examinations (global miss rate: 73.3%, miss rate for ulcerative lesions and neoplastic disease: 78.7% and 63.2% respectively) these percentages, in some selected subgroups of patients (i.e. patients with SB tumor) are alarming.

Unfortunately there are no conclusive explanations for false negative capsule endoscopies but several factors such as the *incompleteness of examination* (that can occur in 15%-20% of cases), *technical limitations* (battery life duration, field of view) and the *suboptimal cleanliness of the SB* (mostly in distal segments) can play a role (**Rondonotti et al. 2005**).

At present, although all published papers strongly underlined that SB cleanliness is a key point to ensure a complete and accurate examination, and several papers aimed at evaluating factors (dietary restrictions and/or

laxatives and/or prokinetic and/or postural tricks) potentially affecting SB cleanliness (**Dai et al. 2005, Ben-Soussan et al. 2005, Niv et al. 2005**) have been published, there are still no recommendations about SB preparation for CE.

B- Decreased specificity of the findings

The absence of a remote control and of the capability of taking biopsies significantly decrease the specificity of CE findings, since the diagnosis can be based only on the endoscopic appearance (Rondonotti et al. 2007).

C- Incapability for sizing and locating lesions

In fact, the size and the location of the lesions are a key point to define, ultimately, the clinical significance of CE findings and to direct further management. This problem, mainly highlighted in studies performed in patients with SB hereditary polyposis syndromes (**Brown et al. 2006, Schulmann et al. 2005**).

D- Cost effectiveness

Although recently published studies confirmed that this examination is cost-effective in patients with OGIB (**Marmo et al. 2007**), the cost of the procedure can prevent the use of this potentially helpful device in everyday clinical practice. To partially reduce costs of the procedure a possible “two steps” strategy (first step; revision of the video by the nurse and second validation of results by a physician) has been proposed (**Bossa et al 2006**).

Patency capsule

The M2A patency capsule was designed to overcome the potential hazard of capsule retention in high risk patients. This capsule is identical to the video capsule in size and shape. It is filled with lactose and protected by a plug with a specifically sized hole that allows the influx of intestinal fluid

if impacted in stenosed bowel, which in turn dissolves the lactose in a predetermined time of approximately 40 h (**Boivin et al. 2005**). The patency capsule also has a transmitter which allows it to be detected by a hand-held scanner placed close to the anterior abdominal wall. Small studies have recommended its safe use in patients with known SB strictures (**Spada et al. 2005**) whilst one study showed that it can precipitate symptomatic intestinal occlusion (**Delvaux et al. 2005**). The occlusion may have occurred because the lactose plug requires fluid to dissolve and the distal side of an obstructed stricture may be relatively dry.

More recently, the agile patency capsule (Given Imaging, Yoqneam, Israel) which has dissolvable plugs at both ends has been devised to improve its use as a non-invasive tool in the assessment of functional patency of intestinal strictures (**Koslowsky et al. 2006, Cauned-Alvarez et al. 2006**). Larger studies are needed before the patency capsule can be recommended for routine use in the high risk group. (Recommendation grade C)

Summary and recommendations

- If there is a high suspicion of bleeding from an upper GI source, a second look endoscopy should be undertaken prior to CE to ensure no pathology has been missed. (*grade B*)
- Patients presenting with obscure gastrointestinal bleeding with a negative gastroscopy and colonoscopy should undergo capsule endoscopy if no contraindications exist. (*grade B*)
- All patients undergoing CE for any indication should be appropriately counselled on the risks of capsule retention. (*grade C*)

- Non-passage of a capsule may occur in the presence of a normal radiological contrast study. (*grade B*)
- Those patients with pathology/bleeding sites identified on CE should subsequently undergo either a PE or DBE (oral/anal route) depending on location/site of bleeding. (*grade B*)
- In patients with a negative CE and persistent OGB, a second look capsule endoscopy may be considered. If this is negative, they should be referred for DBE. (*grade* C)
- CE should be considered in patients with a high suspicion of small bowel Crohn's disease based on the clinical history and inflammatory markers undetected by conventional means. Patients with abdominal pain as a significant feature should have radiological imaging to exclude a stricture prior to CE. (*grade* C)
- CE should be considered in patients with refractory celiac disease to look for celiac associated complications. (*grade C*)

Service provision and training

The demand for CE has risen since its introduction in the United Kingdom. This is reflected by the increase in the number of centers, which offer this service. In addition to developing a role in the investigation pathway of OGIB and IBD, the use of CE is cost effective by preventing unnecessary cycles of investigations in patients (**Sidhu et al. 2006, Lewis et al. 2005, Goldfarb et al. 2004**).

The reading of CE videos remains a time consuming exercise for gastroenterologists. Few studies have compared the inter-observer variability between an experienced gastroenterology or endoscopy nurse against a physician (**Niv et al. 2005, Bossa et al. 2006, Sidhu et al. 2007**). Other investigators have also made comparisons between physicians of different

levels of experience (endoscopy fellows or juniors endoscopists versus experienced physicians) (**De Leusse et al. 2005**). These studies have shown that trainees were able to interpret CE images and reach the correct diagnosis in all clinically relevant cases. Specialist registrars and nurse specialists who have an interest in the small bowel may wish to take up this role. Incorporation of a section on capsule endoscopy into the generic curriculum would help to formalize the training in this field.

Despite the expansion of the service of CE, DBE is likely to remain as a regional service. A DBE users group has recently been established to help promote standards, uniformity of practice and training across the UK. Like CE, formal training and perhaps, in addition, a basic skills course should be mandatory for all wishing to practice DBE. Regular audit of the service should be carried out at appropriate intervals. (Recommendation grade C)

Other types of capsule endoscope, and the future of capsule endoscopy

(1) EndoCapsule EC type 1

EndoCapsule EC type 1 is another type of small-bowel CE, developed by Olympus. There are two differences between the Olympus CE and PillCam SB systems. The Olympus capsule has a high-resolution CCD and an external real-time image viewer (External Viewer) monitor (**Gheorghe et al. 2007**). However, a recent randomized study comparing these two types of CE reported a statistically non significant rend for the EndoCapsule to detect more bleeding sources in patients with suspected SB bleeding than the PillCam SB (**Hartmann et al. 2007**).

(2) PillCam ESO

Introduced in 2004, the Pill Cam ESO is a video capsule that is specifically designed to view the inner lining of the esophagus. The capsule is equipped with miniature cameras on both ends and is about the size of a multivitamin, which can be easily swallowed. The PillCam ESO travels through the esophagus by normal peristaltic waves, flashing 14 times per second, each time capturing images of the inner lining of the esophagus. As it continues down the esophagus, the captured images may identify potential abnormalities, such as reflux esophagitis, Barrett's esophagus, and esophageal varices (**Eliakim et al. 2004, Eisen et al. 2006**). The benefits over traditional endoscopy are that there is little discomfort and it does not require sedation, thereby eliminating potential sedation-related cardiopulmonary complications (**Figure 12**).

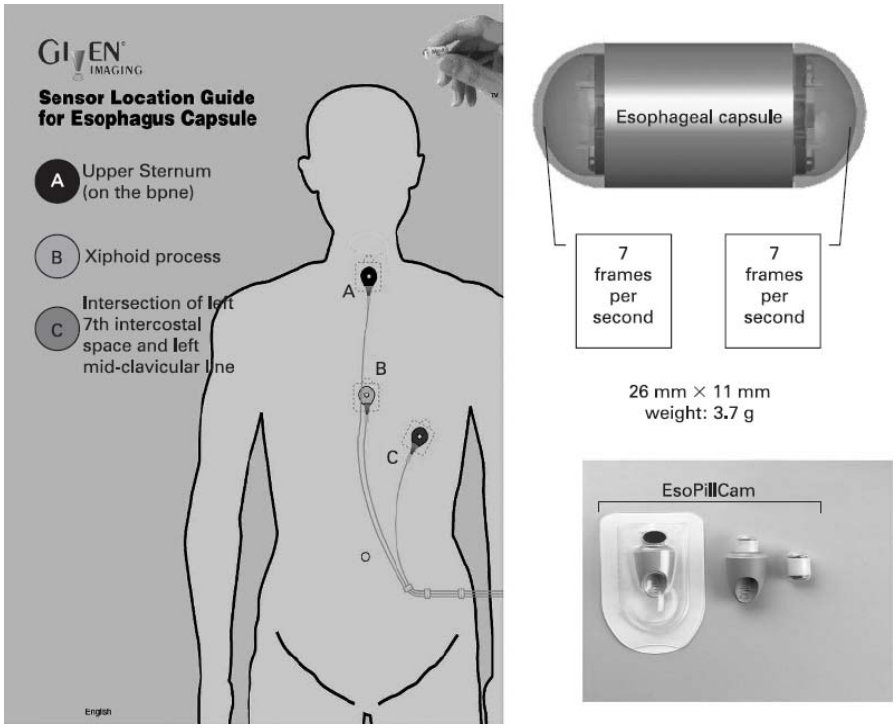


Figure 12: Schematic representation of the EsoPillCam technology developed by Given Imaging for esophageal endoscopy. Note the dual camera (proximal and distal optics) and the location of sensors.

(3) PillCam COLON

PillCam COLON (11 × 31 mm) was recently developed by Given Imaging to detect colonic neoplasia. Two pilot trials with PillCam COLON have been conducted (**Eliakim et al. 2006, Schoofs et al. 2006**), and a large prospective multicenter trial is now underway. Interestingly, some polyps can be detected by PillCam COLON that is missed by a traditional colonoscopy, according to this interim analysis (**Saurin et al. 2007**).

(4) Patency capsule

Discussed before.

The future of capsule endoscopy

Therapeutic interventions using a CE, such as delivery of medication to specific disease sites and the possibility of using lasers, are also being discussed, according to updated CE guidelines of the European Society of Gastrointestinal Endoscopy (**Rey et al. 2006**).

PORTAL HYPERTENSIVE INTESTINAL VASCULOPATHY (PHIV)

Awareness of the association between portal hypertension (PHT) and intestinal mucosal changes has increased over the past decade. Even though "congestive gastropathy" has emerged as distinct nosological entity (**Cales P et al. 1991**), there is confusion regarding the diagnostic criteria and clinical significance of this condition. With regard to the information reported to date, several problems exit. These are 1) uncertainty of the general clinical significance, 2) confusion in terminology, 3) lack of uniformity in the endoscopic descriptions, 4) absence of distinctive histopathological features, and 5) the ill-defined spectrum of the more extensive involvement of the gut distal to the stomach.

Many factors hamper efforts to correlate the endoscopic and histologic appearances of the gastrointestinal mucosa in patients with PHT. Endoscopic reports are often vague and do not clearly describe the location, extent, or specific nature of the mucosal appearances. Some of the endoscopic findings are transient, whereas others are progressive, and differences in endoscopic appearances may represent various stages in these conditions. Observer variability may also contribute to the reported differences in endoscopic appearances (**Cales P et al. 1990, and Cles P et al. 1991**). Endoscopists have been reluctant to biopsy patients who present with impaired coagulation and/or recent hemorrhage. Even when obtained, endoscopic biopsies are small, superficial, and subject to considerable sampling error. Despite the fact that most pathologist reserve the term ectasia for a more severe degree of vessel dilatation, the

terms dilatation and ectasia have been used interchangeably, without precise definitions of either. It should be noted the mucosal changes that resemble "congestion" may be caused by the pinch-avulsion technique of most commonly used biopsy forceps (**Weinstein W et al. 1987**).

We chosen the term "portal hypertensive intestinal vasculopathy" (PHIV) to describe the intestinal changes of longstanding PHT generically. This term encompasses other previously used terms (*i.e.,* congestive gastropathy, congestive gastroenteropathy, portal colopathy, etc.), and can then be geographically referenced to a more specific location in the gut, *i.e.,* stomach, small bowel, and colon. This term also describes the fundamental structural changes in the intestine-a vasculopathy (**Sarfeh J et al. 1987**) resulting from changes in the intestinal microcirculation that are probably secondary to PHT. There is evidence that suggests that other physiologic alterations may be important in the development of the vascular abnormalities.

Portal Hypertensive Gastropathy (PHG)

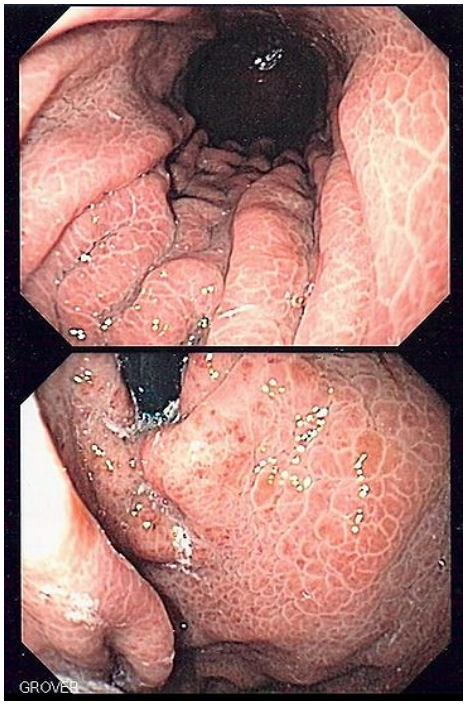
Brief History

In 1945, Wangensteen et al., reported four patients with gastric hemorrhage and PHT, and questioned whether PHT rendered the gastric mucosa more susceptible to injury. In 1957, Palmer et al. found dilatation of mucosal and submucosal veins in the stomach after portal vein ligation in rats. Similar changes in gastric mucosa were observed in patients with PHT (**Sandblom P et al. 1975**). Several endoscopic studies reported a 30 -40% incidence of bleeding from gastritis in patients with PHT and esophageal varices (**Lebrec D et al. 1980**). Bleeding gastritis was

thought to be a manifestation of severe PHT associated with advanced live disease (**Teres J et al. 1977**) or large **EV Lebrec D et al. 1980**). Some reports disputed the association of gastritis with cirrhosis (**Brown R et al. 1981**), or attributed the presence of gastritis to alcohol ingestion only by patients with alcoholic cirrhosis (**Naparstek Y et al. 1980**).

In 1981, Sarfeh et al. reported high rates of bleeding, rebleeding, and death in patients with liver disease in whom EV and hemorrhagic gastritis coexisted. Subsequently, S**arfeh et al.** (**1982**) reported that gastric resection was associated with a high rate of recurrent bleeding, and that portal decompression reduced the risk of hemorrhage from gastritis. He concluded that hemorrhagic gastritis in patients with EV should be viewed as portal hypertensive bleeding, and that treatment should be directed at reducing portal pressures.

A



B

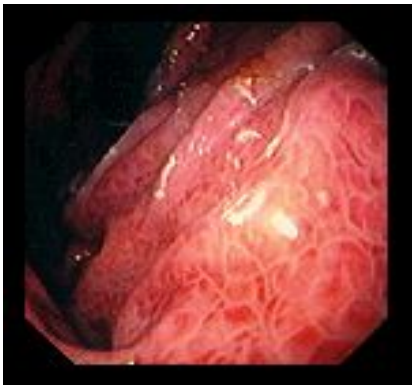


Figure 13.
A- mosaic appearance ,
B- cherry red spots of PHG

Term Description

In 1985, McCormack et al. described clinical, endoscopic, and histologic findings in 127 patients with PHT. Endoscopy indicated that 65 (51%) patients had gastritis, classified into two major types, according to the description by **Taor et al. (1975)** (**Table 8**). Mild gastritis was often transient and infrequently associated with bleeding (two of 37 patients). Severe gastritis was persistent (lasting 8 wk), and invariably was associated with clinically significant bleeding. There was no correlation between the presence and severity of gastritis with the severity of liver disease as assessed by Child's classification.

Table 8. Endoscopic Classification of Gastritis

Mild gastritis
1) A fine pink speckling or "scarlatina" rash. 2) Superficial erythema on the surface of rugae giving a striped appearance. 3) Mosaic pattern-a fine while reticular pattern separating areas of erythematous edematous mucosa resembling "snake skin". (Figure 13-A)
Severe gastritis
1) Discrete cherry-red spots. (Figure 13-B) 2) Diffuse hemorrhagic gastritis.

Endoscopic Appearances

As the endoscopic appearances of the Taor classification of gastritis later adopted by McCormack and others, the endoscopic findings of erythema appear to have much less significance than red spots, scarlatina rash, or mosaic pattern (**Vigneri S et al. 1991**). The mosaic pattern is most commonly found and is highly specific (**Table 9**) for PHG (**Sarin SK et al. 1988, Misra SP et al. 1990, and Lin W et al. 1991**).

The variable frequency with which the mosaic pattern has been found may be explained by differences in ethnic groups examined, observer variability, differences in endoscopic technique, or other unidentified factors. It should be noted that observers who report a high frequency of mosaic pattern have localized it more commonly to the proximal stomach (**Tiger D et al. 1989, and Papazian A et al. 1986**). Whether erosions can be explained by PHG or are a manifestation of the resultant mucosal susceptibility to injury is uncertain at this time.

Author	Sensitivity%	Specificity%	Positive Predictive value %	Negative Predictive value %	Overall Diagnostic accuracy %
Papazian	94	99	98	99.6	98.2
Sarin	7.4	98.6	66.7	74.1	73.9
Lin	41	100	100	63	71
Misra	14	99	37	97	96

Table 9. Diagnostic accuracy of the mosaic pattern

Are there other ways to evaluate the problem?

Although there appears to be minimal risk of bleeding, the role od endoscopic biopsies in assessing PHG is not clear, and other noninvasive methods seem promising. **Saverymuttu et al. (1990**) evaluated the transabdominal ultrasound measurements of the stomach in patients with and without PHT and found a significant difference in the mean thickness of the antrum and body of the stomach in portal hypertensive patients. **Saveryiiuttu et al. (1990**) also reported a thickened gallbladder wall (> 4 mm) in patients with PHT and without hypoalbuminemia. These findings resolved with treatment for PHT.

Relationship to Sclerotherapy

D'Amico et al. (**1990**) reported the prevalence and incidence of PHG in cirrhosis and its relationship to sclerotherapy. PHG was significantly more common in patients treated with sclerotherapy; however, it is not clear which exact endoscopic findings (i.e., mosaic vs. erythema) were found. A multivariate regression analysis confirmed that sclerotherapy and the presence of large EV significantly increased the risk of PHG. Thus, PHG is observed more frequently after sclerotherapy; however, it is also commonly observed in patients without sclerotherapy (**Table 10**).

Athor	% of patients with PHG	
	Pre-sclerotherapy	Post-sclerotherapy
Sarin	2.9	13.8
Lin et al. (1991)	38	64
D'Amico et al. (1990)	50	83
Kotzampassi	47.3	92.1

Table 10.

Clinical Significance

1- The presence of PHG doesn't correlate with the severity of PHT as assessed by endoscopic estimates of the size of EV (**Misra SP et al. 1990, and Lin W et al. 1991**) or clinical estimates of severity of liver disease as determined by Child-Pugh classifications (**McCormack TT et al. 1985**).

2- There is some evidence that gastropathy occurs more often in cirrhotic vs. noncirrhotic causes of PHT (**Sarin SK et al. 1988**), suggesting that mechanisms other than PHT alone are important in producing PHG.

3- The presence of gastropathy has been observed more frequently after sclerotherapy, (**McCormack TT et al. 1985, Sarin SK et al. 1988,** and **Papazian A et al. 1986**). However, it has also often been observed in patients without sclerotherapy.

4- The risk of bleeding does not correlate with endoscopic appearance of mild gastropathy (**McCormack TT et al. 1985, and Papazian A et al. 1986**), endoscopic size of varices (**Misra SP et al. 1990**), or Child-Pugh classifications of severity of liver disease (**McCormack TT et al. 1985)**.

5- Most important, the risk of bleeding in patients with PHG does correlate with endoscopic appearances of severe gastropathy (**Perez-Ayuso R et al. 1991**).

In the study by **D'Amico et al. (1990**), multivariate analysis showed that PHG was a predictive factor for both chronic and overt bleeding.

Response to Treatment

Hosking et al. (1987) reported groups of bleeding and nonbleeding patients with PHG who were treated with propranolol. Bleeding was observed only in patients with severe PHG (red spots or diffuse gastritis), and 13 of 14 patients (93%) stopped bleeding on propranolol. In nine of these 14 patients, the gastric cherry-red spots became less obvious. In the nonbleeding group, nine of 22 patients had improvement in the endoscopic grading of PHG.

Perez-Ayuso et al. (1991) also reported significant higher percentages of patients free of acute bleeding from PHG among propranolol-treated patients than among untreated controls, at both 12

(65% *vs.* 38%) and 30 months of follow up (52% *vs.* 7%). Multivariate analysis also showed that the absence of propranolol treatment was the only predictive variable for acute rebleeding from PHG. However, there were no significant differences in the percentages of patients free of chronic bleeding in the control and propranolol-treated groups. Surgical portal decompression has prevented both acute and chronic rebleeding, and has shown reversibility of the endoscopic and histologic findings of PHG.

Overlap with watermelon stomach

Several cases with an endoscopic appearance of watermelon stomach (gastric antral vascular ectasia GAVE) (**Jabbari M et al. 1984**) have been reported in patients with cirrhosis. However, GAVE and PHG represent two separate entities. GAVE occurs more often in the absence of PHT, and has a distinctive endoscopic appearance without the proximal mucosal appearances commonly encountered in PHG (Figure 14). Moreover, histologicaly both entities have different structure. Both the mucosal abnormalities predictably respond to endoscopic coagulation. In contrast, PHG responds best to medical or surgical portal decompression.

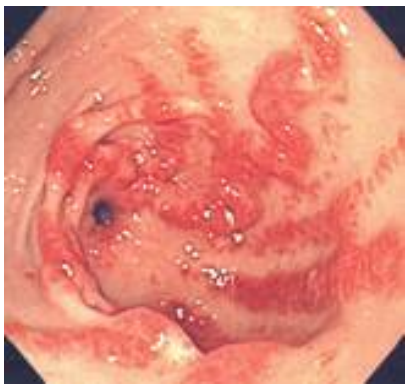


Figure 14: Endoscopic appearance of water melon stomach (GAVE)

Portal Hypertensive Colonopathy (PHC)

Colorectal lesions in patients with liver cirrhosis are referred to as PHC. Changes described in the colon include hemorrhoids, anorectal varices, and mucosal changes similar to those of portal hypertensive gastropathy: diffuse hyperemia and edema resembling chronic colitis, angiodysplasia-like lesions, patchy hyperemic lesions, and a severe acute colitis like appearance with spontaneous bleeding from the mucosa (**Ganguly et al. 1995, Tam et al. 1995, Eleftheriadis et al. 1997) (Figure 15).**

A **B**

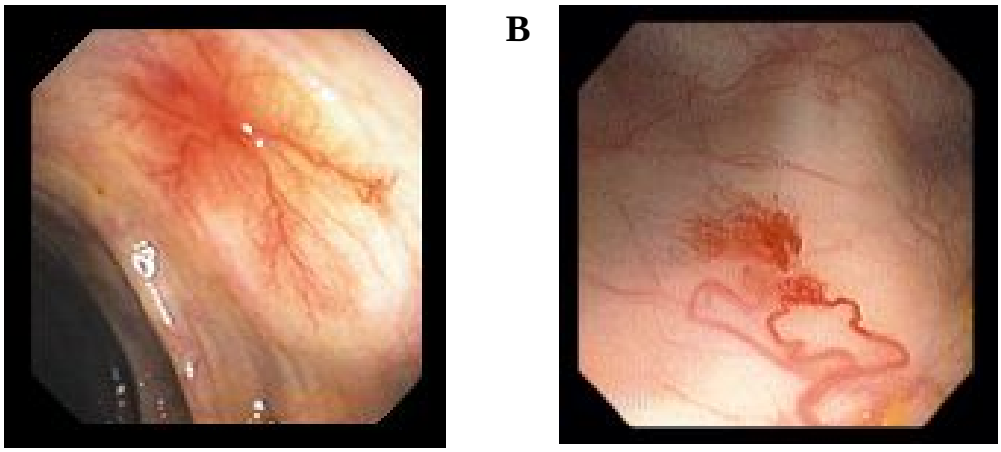


Figure 15: colonoscopic picture of PHC. A-Spider angioectasia B- Congested colonic vasculature.

The prevalence of hemorrhoids in patients with PHT varies greatly (from 20 to 60%) but seems to be comparable with that observed in agematched controls. On the other hand, anorectal varices are identified more frequently in patients with portal hypertension (0% to 89.3% of cases), but their prevalence was significantly different from that of controls only in the paper by (**Ghoshal et al. 2001).**

Several reports (Hosking SW et al. 1989) have emphasized the importance of differentiating hemorrhoids from anorectal varices.

Hemorrhoids are prolapsed normal anal vascular cushions that are not found more frequently in patients with PHT. Hemorrhoids rarely cause massive bleesing, and respond well to injection, banding, cryosurgery, infrared cautery, or excision. Anorectal varices, however, are portosystemic collaterals that develop in many patients with PHT. Massive bleeding can occur from anorectal varices and it usually des not respond to measures to treat hemorrhoids. There some reports of bleeding after endoscopic sclerotherapy of EV (**Foutch PG et al. 1984**).

All studies highlight the high prevalence of PHC in patients with PHT (**Table 11**), but they do not clarify whether there is a relationship between these abnormalities and clinically relevant parameters such as etiology of liver disease, Child-Pugh class, and history of variceal bleeding, platelet count, or presence of portal hypertensive gastropathy.

Author	**Prevalence of PHC in control population**	**Prevalence of PHC in cirrhotic patients**	***P***
Misra et al. 1996	3%	48.5%	< 0.001
Ghoshal et al. 2005	0%	36.6%	< 0.001
Misra et al. 2004	0%	52.3%	< 0.001
Kozarek et al. 1991	—	70.0%	—
Ito et al. 2005	—	66.0%	—
Eleftheriadis et al. 1993	—	93.0%	—

Table 11. Prevalence of portal hypertensive colopathy

Kozarek et al. (1991) reported 20 patients with PHT who underwent colonoscopy. The presenting symptoms were hematochezia in 10 patients, occult-positive stools and anemia in nine patients, and a polyp in one patient. Fourteen of 20 patients (70%) had multiple vascular-appearing lesions (10 cherry-red spots, six spider telangectasias,

and three angiodysplasia-like lesions). Four of the 14 patients with telangectasias had coexisting chronic cololitis. There is no correlation between the severity of hepatic dysfunction and the presence of vascular ectasia- like lesions. Fifty percent of patients had coexistent PHG, and 60% had previously undergone variceal sclerotherapy.

Although colonic vascular lesions could represent a potentially important cause of lower GI hemorrhage (**Misra et al. 2004**), their true clinical importance remains to be established because of the heterogeneity of patients and controls included in different studies.

Portal Hypertensive Enteropathy (PHE)

Most of the studies that focused on the involvement of the gastric and colonic mucosa in PHT suggest that other parts of the GI tract such as the duodenum and jejunum could undergo mucosal changes because of PHT. Thus, it has been suggested that the entire GI tract, which drains into the portal venous system, might undergo PHT-related changes (**Tiruvengadam et al. 1989).**

Anecdotal reports suggest that in patients who have cirrhosis, the SB mucosa is a potential source of bleeding (M**isra et al. 1997, Desai et al. 2004)**; however, until recently, the SB was relatively inaccessible. Therefore, only a limited number of studies were performed using enteroscopes to evaluate the jejunal mucosa (**Desai et al. 2004)** or colonoscopes to intubate the terminal ileum (**Misra et al. 2004**). In these studies, the reported prevalence of SB involvement ranged between 15% and 25%, and varices were identified in the terminal ileum in about 18% of cases (**Misra et al. 2004, Desai et al. 2004**). The changes located in the proximal SB or terminal ileum, described in these studies, were

similar to those identified in the colon and stomach, such as diffuse hyperemia and edema, spider angiomata, patchy hyperemia, and severe acute inflammation with spontaneous bleeding from the mucosa. In these studies, the presence/absence of SB varices also was reported.

Since its introduction in clinical practice, CE demonstrated a superior diagnostic yield in comparison with push enteroscopy and ileoscopy in many clinical conditions, such as obscure GI bleeding. This is probably because of the ability of CE to evaluate the entire SB and to provide high-quality endoscopic images.

Based on these considerations, CE could be considered as a promising diagnostic tool to assess SB mucosal abnormalities in patients with PHT (**Misra et al. 2004, Tang et al. 2004)**. CE findings suggestive of portal hypertensive enteropathy (PHE) are similar to those described with traditional endoscopy (**Figure 16**). As of today, very few studies (**De Palma et al. 2005, Repici et al. 2005, Jacob et al. 2005)**, only one of which has been published in full (**De Palma et al. 2005)**, have explored the potential of CE for diagnosing SB involvement in patients who have PHT.

The available data on the use of CE in patients who have cirrhosis and PHT are inadequate to reach a firm conclusion about the usefulness of this diagnostic tool in this patient population. (**Rondonotti et al 2006**). It appears that in patients with PHT, the SB frequently shows mucosal abnormalities, however, the clinical significance of these findings remains undefined, however, especially in view of the fact that SB lesions also have been found in about 10% of patients with arthritis not taking NSAIDs and in 13.8% of healthy subjects (**Graham et al. 2005, Goldstein et al. 2005**).

Therefore, large prospective studies are needed to evaluate the prevalence and clinical significance of SB mucosal changes in patients who have cirrhosis. Such studies should compare patients who have cirrhosis with healthy subjects (**Rondonotti et al 2006**).

A **B**

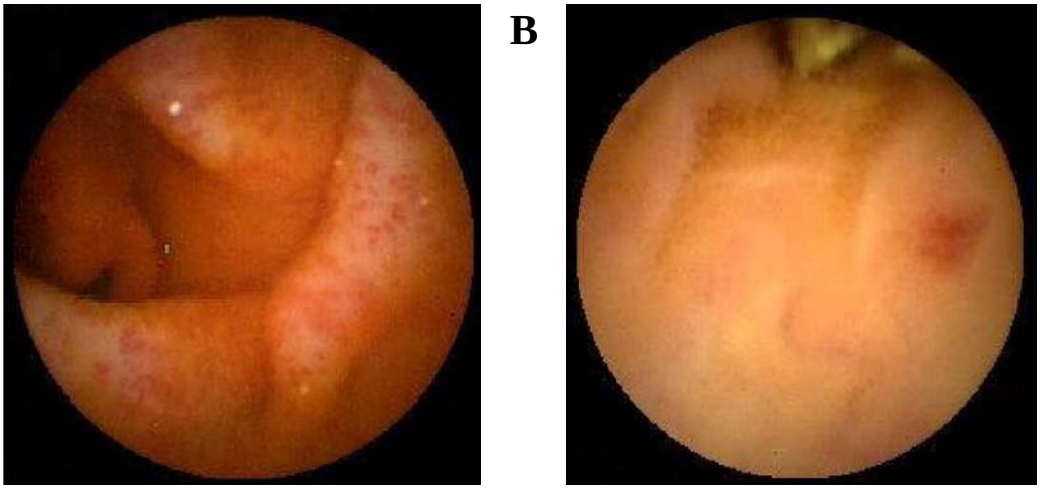


Figure 16: A- Portal hypertensive jejunopathy, B- Angiodysplasia-like lesion.

PATIENTS AND METHODS

PATIENTS AND METHODS

Patients

This is a non-randomized, controlled, prospective study of a cohort of 31 consecutive patients with documented cirrhosis with PHT who underwent CE. The indication of CE in all of them was clinical trial for imaging the small-bowel in liver cirrhosis complicated with PHT. They were admitted in the hepatology department of our hospital from June 2008 to February 2010. The Japanese Institional Review Board and Ethics Committee of our hospital approved the study. Written informed consent was obtained from all the patients after the nature and purpose of our study was precisely explained.

Inclusion criteria were:

Evidence of liver cirrhosis and PHT. Patients with prior history of endoscopic variceal injection sclerotherapy (EIS) or ligation (EVL) were also included.

Exclusion criteria were:

1- History of recent or current intake of medications which affect the degree of PHT e.g. diuretics, and B-blockers.
2- History of recent or current intake of medications that affect the intestinal mucosa such as NSAIDs.
3- Presence of advanced renal or cardiac impairment.
4- Patients with enteritis for another e.g. Crohn's disease.
5- Conditions associated with technique difficulty in TE measurement such as BMI $\geq$ 30 k/m^2 and/or massive ascites.

6- Patients with risk of CE retention e.g. prior history of intestinal obstruction, and major abdominal surgery.

The control group consisted of 29 patients, age and gender matched, who were selected randomly from our outpatient clinic. They previously assessed by EGD, colonoscopy, abdominal ultrasound, liver biochemistry, and prothrombin time, that showed no evidence of cirrhosis or PHT. Control patient were all presented by obscure gastrointestinal bleeding (OGIB) that was already diagnosed as bleeding colonic diverticulosis. We thought to perform CE for them to exclude any other bleeding points might be in the small-bowel.

Cirrhosis was confirmed by histology or by compatible physical findings, laboratory tests, and typical radiological features. Severity of cirrhosis was graded by using Child-Pugh classification **(Pugh et al. 1973).** A high Child Pugh score was considered if it was more than grade 6.

Either endoscopic evidence of esophagal and/or gastric varices, or TE score ≥ 13.6 kPa (**Vizzutti et al. 2007**) diagnosed portal hypertension**.**

Endoscopic findings:

Esophageal and gastric varices were graded using criteria of criteria proposed by the Japanese Society for Portal Hypertension (Idezuki Y 1995). The form (F) of EV was classified as straight small-calibered varices (F1), moderately enlarged, beady varices (F2), or markedly enlarged, nodular, or tumor shaped varices (F3). F2 with signs of impending bleeding as red color sign or telangiectasia and F3 were considered large EV.

Portal hypertensive gastropathy (PHG) was diagnosed following the recognition of elementary lesions, such as a mosaic like pattern, red point

lesions, cherry red spots, or black brown spots **(Rondonotti et al. 2006)**. It was classified as absent or present.

Transient elastography

Transient elastography was performed using the FibroScan® apparatus (Echosens, Paris, France). The operator was a staff physician who had previously performed at least 100 determinations in patients with chronic liver disease. The median value of 10 successful acquisitions, expressed in kilopascal (kPa), was kept as representative of TE score of the patients.

Capsule endoscopy procedure and scoring system

Capsule endoscopy was performed within two weeks after the EGD. A Pill Cam SB (Given Imaging, Yoqneam, Israel) video capsule was used. To improve small-bowel visualization, patients began a fasting period, which started 12 hours before the procedure. After that, they drank 2 L polyethylene glycol-electrolyte (PEG) solution for better bowel preparation. Each patient drank a solution that contained simethicone just before swallowing the capsule. Thereafter, they were not permitted to take anything by mouth for 4 hours and were observed for 8 hours at the study site. After 8 hours, the sensor array and the recording device were removed. The digital video image steams of the examinations were downloaded to the RAPID system. After completetion of the imaging study, patients were permitted to return home.

The CE digital image stream was reviewed and interpreted by two staff endoscopists blinded to the clinical and endoscopic data of cirrhotic and

control patients. Rapid Reader software, version 5 was used for interpretation of CE images.

For every CE procedure, we first assessed the classical landmarks (first gastric image, first duodenal image, and first cecal image). The small-bowel passage (transit time; time needed for the capsule to pass all small-bowel) time in hours was determined. Next, we equally divided transit time; ileum was considered the first half, and jejunum was considered the second half.

Esophageal varices and PHG images (as detected with CE) were not considered in this study.

Portal hypertensive enteropathy was defined (**De Palma et al. 2005**) as:

(1)-Mucosal inflammatory like lesions: edema, erythema, granularity, and/or friability.

(2)-Vascular lesions: cherry red spots, angioectasias, and SB varices.

As a result, PHE lesions divided into four main subcategories;

1- Red spots. 2- Angioectasisas.

3- Inflammatory like lesions. 4- SB varices.

Each of these four lesion worthy two points if it was multiple (more than two lesions), and only one if it was not multiple. We calculated the positive points for every patient to make a final PHE score out of a maximum of eight points.

Study Design:

Patients of both groups were subjected to:

1) Laboratory tests:
   - Complete blood picture.

- Complete liver functions
- Routine tests like renal functions, and random blood sugar.

2) Transient elastography to determine the TE score of every patient.
3) Imaging procedures: Abdominal ultrasonography and/or Abdominal CT.
4) Capsule endoscopy.

Patients of liver cirrhosis group were additionally subjected EGD; to detect the presence of esophagogastric varices, their degree, and PHG.

NB: Patients of control group were already performed EGD to diagnose the source of OGIB, but the results was not applicable for our study.

Data collected on each patient of cirrhotic patients included:

Age, and gender, underlying hepatic pathology, Child-Pugh class and grade, hemoglobin concentration, hemocrit value, platelets count, history of EIS/EVL and/ or Gl bleeding, liver function tests, TE score, EGD and CE findings.

Data collected on each patient of control groups included:

Age and gender, TE score, and CE findings

- We compared the prevalence and characteristics of small-bowel lesions between cirrhotic and control patients.
- Cirrhotic patients with and those without PHE were compared to determine whether these findings were associated with the severity of liver disease, EV and/or gastric varices, PHG, TE score , and other clinical characteristics.
- Using our scoring, we compare the PHE score of cirrhotic patients with all clinical, laboratory, and endoscopic parameters of liver disease, and PHT, including TE score.

Statistical analysis :

Statistical analysis was performed by using statistical software, (SPSS, version 16; SPSS Inc, Chicago, III). The data are shown as their means ±SD. Comparisons were performed using the student t test and the chi-square test, with or without Yates correction. Differences were considered statistically significant when the P value was equal or less than 0.05.

RESULTS

RESULTS

A total 31 cirrhotic patients with PHT (19 females, and 12 males, mean age of all patients was 70.8±8 years) fulfilled the inclusion criteria during the study period. The control group consisted of 29 patients (9 females, and 20 males, mean age of all patients was 68.9±11 years).

The most common underlying hepatic pathology was hepatocellular carcinoma (in 20 patients, 64.5%), followed by hepatitis C viral infection (in eight patients, 25.8%), and other pathologies (in three patients, 9.7%) at last. The dominant gender was female (61.3%). Twenty-six patients (83.9%) had esophageal varices; eight of them (32.3% of total) had large varices (F2 +RC, and/or +TE, or F3), and fourteen of them (45.2% of total) had additional gastric varices; combined esophageal and gastric varices). Eight patients (25.8%) received sclerotherapy (EIS), or band ligation (EVL). Five patients (5.1%) experienced variceal bleeding. portal hypertensive gastropathy was evident in 20 patients (54.6%).

A Child-Pugh score was attributed to all patients; Class A was the most common, found in 20 (64.5%) patients, followed by Class B, detected in 10 (32.3%) patients, then Class C detected in only one (3.2%) patient.

The control group consisted of 29 patients, age and gender-matched, consecutively admitted to our outpatient clinic to undergo CE due to obscure gastrointestinal bleeding (OGIB).

The demographic characteristics of cirrhotic and control patients are listed in **Table 12**.

Mean small-bowel transit time (in hours) of capsule endoscopy was 5.54±1.5 for cirrhotic patients and 4.04±2.1 for control patients. All patients

completed the CE procedure uneventfully. No technical problems or complications occurred during the examinations, and all patients naturally excreted the capsule.

Almost all the laboratory data are significantly different between both groups including serum levels of albumin ($p < 0.001$), Bilirubin ($p < 0.001$), alanine transaminase ($p < 0.001$), and platelet count ($p < 0.004$). Transient elastography score was significantly different between cirrhotic patients and control patients ($p < 0.001$).

Capsule Endoscopic Findings

The mucosal findings detected by the CE in both cirrhotic and control patients are listed in Table 13. Twenty-one of the cirrhotic patients (67.7%) were found to have CE signs of PHE; nineteen patients (61.3%) of them had diffused PHE, and twenty patients (64.5%) had more than one lesion. The jejunum and ileum were equally involved. Active bleeding was seen during endoscopic examination in only one case (3.2%) and was submitted to double balloon endoscopy.

The pattern of small-bowel mucosal changes included vascular, and inflammatory like lesions. The vascular lesions (**Figure 17**) included red spots (17 patients, 54.8%), angioectasisas (16 patients, 51.6%), and small-bowel varices (5 patients, 16.1%). Inflammatory like lesions (**Figure 18**) that included erythema, edematous villi, and erosions, were in 13 patients (41.9%).

On the other side, the mucosal findings were present only in two of the control patients (67.7% *vs.* 6.9%, $p < 0.001$). None of these patients revealed diffuse lesions (61.3% *vs.* 0, $p < 0.001$), and none of them had more than one lesion (64.5% *vs.* 0, $p < 0.001$).

Other lesions , that might not related to PHE, were detected in cirrhotic patients included small-bowel polyps in three cases, exanthemata in four cases, sub-mucosal tumors in one case, and SB ulcer in one case. In the control group, two cases had SB polyps, two cases had xanthomata, two cases had sub-mucosal tumors, and one case had small-bowel ulcers (**Figure 19**).

The Association between Portal Hypertensive Enteropathy (PHE) and the Clinical Characteristics

A comparison of cirrhotic patients with and those without PHE is shown in **Table 14**. There presence of PHE was significantly related the platelets count ($p < 0.02$), serum albumin level ($p < 0.02$), and serum bilirubin level ($p < 0.04$). Cirrhotic patients with high Child-Pugh score, more than grade 6 ($p = 0.041$), large esophageal varices ($P = 0.023$), PHG ($P = 0.049$), and prior history of endoscopic variceal treatment ($P = 0.023$) were significantly associated with presence of PHE.

Additionally, patients with high TE score were significantly associated with presence of PHE ($p = 0.018$).

However, there was no difference between these two groups of patients with regard to ALT level, hemoglobin level, hematocrit value, underlying hepatic pathology, and prior history of variceal bleeding.

The Association between PHE Score and Clinical Characteristics of the Patients

Using our scoring system, we sought to evaluate the relationship between the scores of small-bowel mucosal lesions of PHE detected by CE, and the clinical data of cirrhotic patients to determine whether PHE score

was associated with liver disease severity (Child-Pugh score), and the endoscopic findings of EGD (**Tables 15, 16**).

Cirrhotic patients with high PHE score were significantly correlated to the serum level of Albumin (negative correlation, r = -0.415, p < 0.02), the serum Bilirubin level (***r*** = – 0.485, $p < 0.005$), and TE score ($p < 0.004$). However, there was no correlation with age, platelets count, and ALT level. In addition, we found that cirrhotic patients with a high Child-Pugh score ($p = 0.011$), large EV ($p= 0.006$), and prior EIS/EVL ($p = 0.006$) were significantly associated with a higher PHE score (severe PHE). Surprisingly, patients with a higher TE score were significantly related with the PHE score (***r*** = 0.561, $p= 0.004$) (**Figure 20**).

In the other hand, we found no association between high PHE score and serum level of ALT, platelet count, presence of gastric varices, and PHG.

Table 12. Demographic, Clinical, and Endoscopic Characteristics of Cirrhotic and Control Patients

Characteristic	Cirrhotic Patients (*n* = 31)	Control Patients (*n*= 29)	*P* value
Age, years (mean± SD)	**70.8±8**	**68.9±11**	**0.019***
Female/Male, *n* (%)	**19 (61.3%)/12(38.7%)**	**20 (69%)/ 9 (31%)**	
Prior GI bleeding, *n* (%)	**5 (16.1%)**	**NA**	
Prior EIS or EVL, *n* (%)	**8 (25.8%)**	**NA**	
Hepatic pathology, n (%):			
HCV	**8 (25.8%)**	**NA**	
HCC	**20 (64.5%)**		
Others	**3 (9.7%)**		
Child-Pugh class, n (%)			
A	**20 (64.5%)**	**NA**	
B	**10 (32.3%)**		
C	**1 (3.2%)**		
Laboratory findings, (mean±SD)			
S. Albumin, g/dl	**3.4±0.7**	**4.4± 0.3**	**< 0.001***
S. Bilirubin, mg/dl	**1.2± 1.4**	**0.7± 0.1**	**< 0.001***
ALT, IU/l	**49.3 ± 36.9**	**16.3 ± 5.8**	**< 0.001***
Plateletes, $10\times^3$ /mm^3	**98.3 ±38**	**229.6 ±387**	**0.004***
EGD findings, n (%)			
● EV,			
Presence	**26 (83.9%)**	**NA**	
Large EV	**8 (25.8%)**		
● Gastric varices	**16 (51.6%)**		
● EGV	**14 (45.2%)**		
● PHG	**20 (64.5%)**		
TE Score, kPa, (mean±SD)	**26 ± 12.4**	**6.8 ±1.4**	**< 0.001***

***** ***P*** < 0.05 was considered statistically significant.

EIS, endoscopic injection sclerotherapy **EVL**, endoscopic variceal ligation **EV**, esophageal varices **EGV**, combined esophagogastric varices **PHG**, portal hypertensive gastropathy **EGD**, esophagogastroduodenoscopy **ALT**, Alanine transaminase **TE**, Transient Elastography **kPa**, kilopascal

Table 13. Small-Bowel Mucosal Findings Detected by Capsule Endoscopy among the two Groups

Mucosal Findings	Cirrhotic Patients (*n*=31)	Control Patients (*n*= 29)	*P* value
Prevalence	21 (67.7%)	2 (6.9%)	< 0.001*
Diffuse type*	19 (61.3%)	0	< 0.001*
More than one lesion	20 (64.5%)	0	< 0.001*
Active bleeding	1 (3.2%)	0	NS
Mucosal lesions, *n (%)*			
① Red spot	17 (54.8%)	1 (3.4%)	< 0.001*
② Angioectasia	16 (51.6%)	0	< 0.001*
③ Inflammatory like	13 (41.9%)	1 (3.4%)	< 0.001*
④ Varices	5 (16.1%)	0	0.024*

***** ***P*** < 0.05 was considered statistically significant.

*** Diffuse**, involves both ileum and jejunum.

Table 14. Comparison of Cirrhotic Patients with and those without Portal Hypertensive Enteropathy

Variable	with PHE (*n* =21)	without PHE (*n* =10)	*P* value
Age, years (mean± SD)	70.6±7.7	68.3±13.8	NS
Female/Male, *n* (%)	12 (57.1%)/ 9(42.9%)	7 (7%) / 3 (3%)	NS
Laboratory findings, (mean ±SD)			
S. Albumin, g/dl	3.2 ±0.7	3.7 ±0.5	< 0.02*
S. Bilirubin, mg/dl	1.5 ±1.6	0.7 ±0.2	< 0..04*
ALT, IU/l	43.6 ±33.6	60.1 ±42.2	NS
Plateletes, 10×3 /mm3	87.6 ±33.5	120.7 ±38.7	< 0.02*
Haemoglobin, g/dl	11.2 ±2.1	11.1 ±1.1	NS
Haematocrite value, %	32.6 ±5.3	29.4 ± 10.6	NS
High Child-Pugh score, n (%)	10 (46.6%)	1 (10%)	0.041*
TE score, kPa; (mean± SD)	29 ±12.6	18 ±7.8	0.018*
EGD findings, n (%)			
Large EV	8 (38.1%)	0	0.023*
Gastric varices	11 (52.4%)	5 (50 %)	NS
PHG	16 (76.2%)	4 (40%)	0.049*
Prior GI bleeding, n (%)	5 (23.8%)	0	NS
Prior EIS or EVL, n (%)	8 (38.1 %)	0	0.023*

P < 0.05 was considered statistically significant.

PHE, portal hypertensive enteropathy; **TE**, transient elastography; **kPa**, kilopascal; **EV**, esophageal varices; **PHG**, portal hypertensive gastropathy; **GI**, gastrointestinal; **EIS**, endoscopic injection sclerotherapy***;*** **EVL**, endoscopic variceal ligation.

Table 15. Correlation between PHE Score and Some Clinical Variables

Variable	Correlation Coefficient	*P* value
Laboratory findings, (mean ±SD)		
S. Albumin, g/dl	**- 0.415**	**< 0.02***
S. Bilirubin, mg/dl	**0.485**	**0.005***
ALT, IU/l	**- 0.099**	**NS**
Plateletes, 10×3 /mm3	**- 0.264**	**NS**
TE score	**0.561**	**0.004***

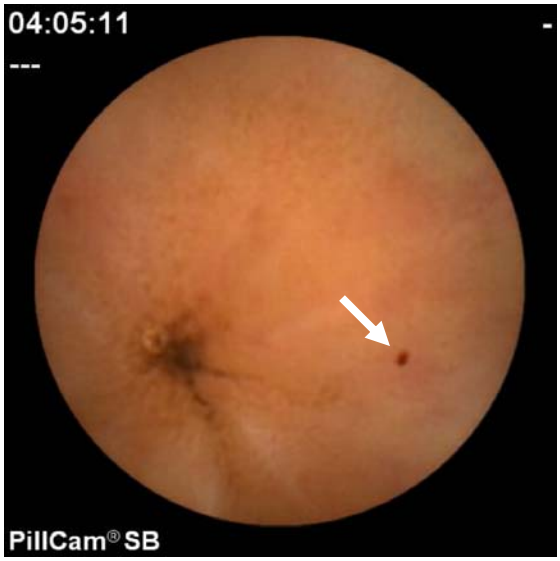
***P** < 0.05 was considered statistically significant, TE, transient elastography.

Table 16. Relation between PHE Score and other Clinical Variables

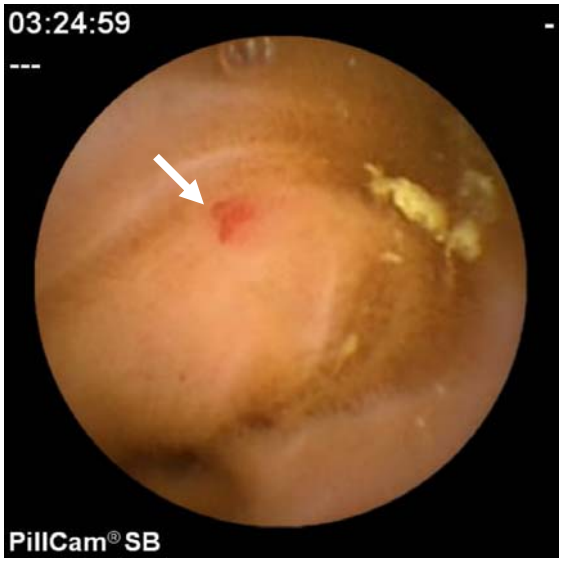
Variable		PHE score, (mean ± SD)	*P* value
High Child-Pugh score	*Yes	**3.4 ±1.9**	**0.011**
	*No	**1.8 ±1.6**	
Large EV	Yes	**3.7± 1.4**	**0.006**
	No	**1.7 ±1.8**	
Gastric Varices	Yes	**2.1 ±1.7**	**NS**
	No	**2.4 ± 2.1**	
PHG	Yes	**2.8 ±1.6**	**NS**
	No	**1.7 ±2.1**	
Prior EIS/ EVL	Yes	**3.8 ±1.4**	**0.006**
	No	**1.9 ±1.8**	
Prior GI bleeding	Yes	**3.4 ±1.7**	**NS**
	No	**2 ±1.9**	

*** P** < 0.05 was considered statistically significant

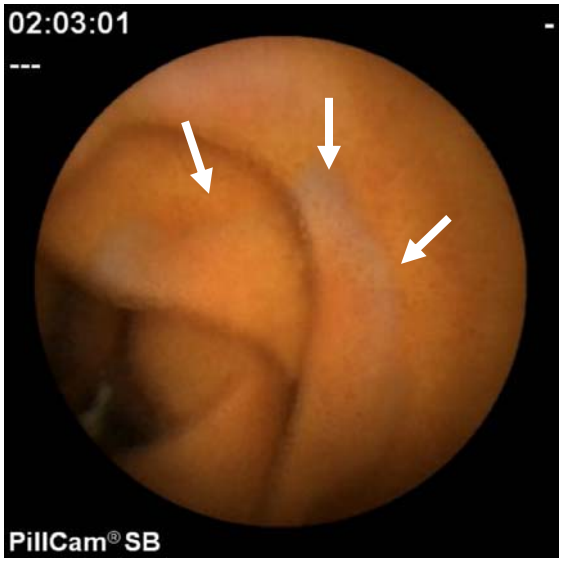
Yes, presence of the variable; **No**, absence of the variable



A. Red Spot

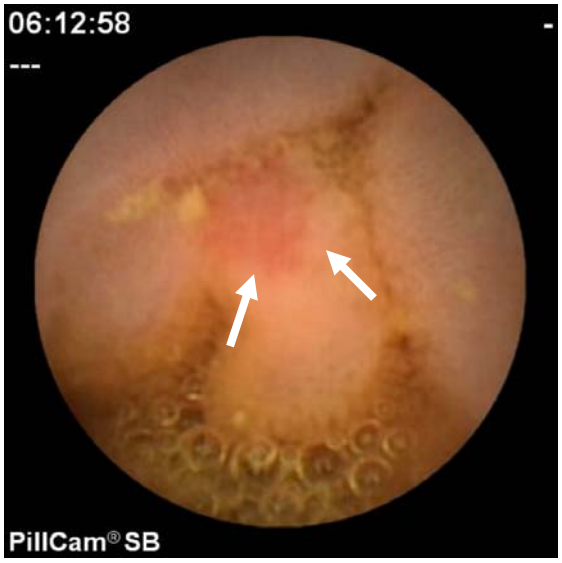


B. Angioctasia

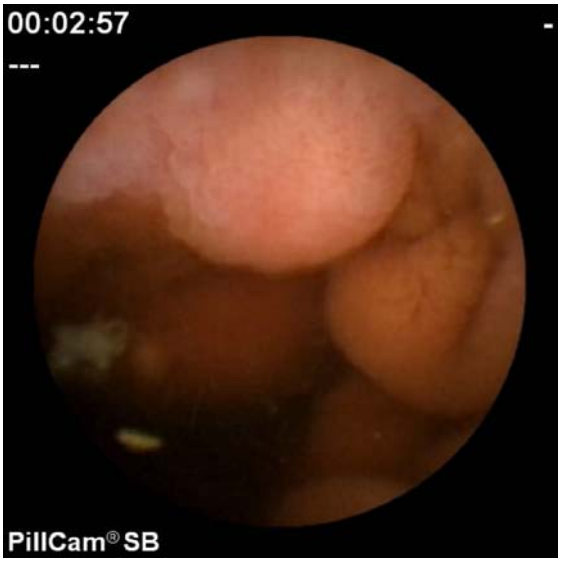


C. Small-bowel serpiginous varix

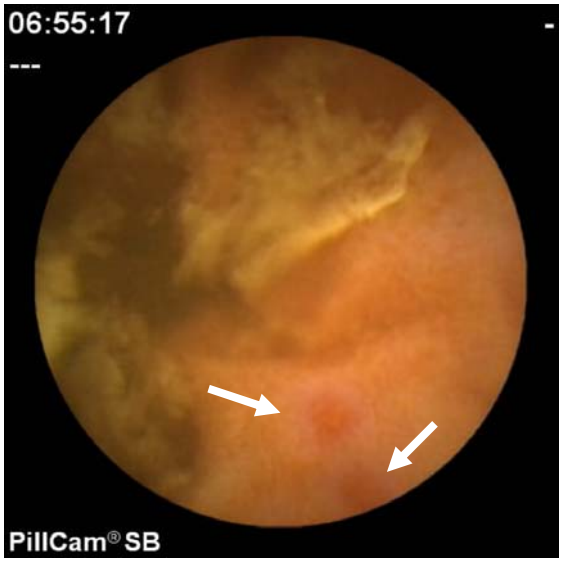
Figure 17: Capsule Endoscopic Views on the Vascular Lesions of Portal Hypertensive Enteropathy



A. Erythema

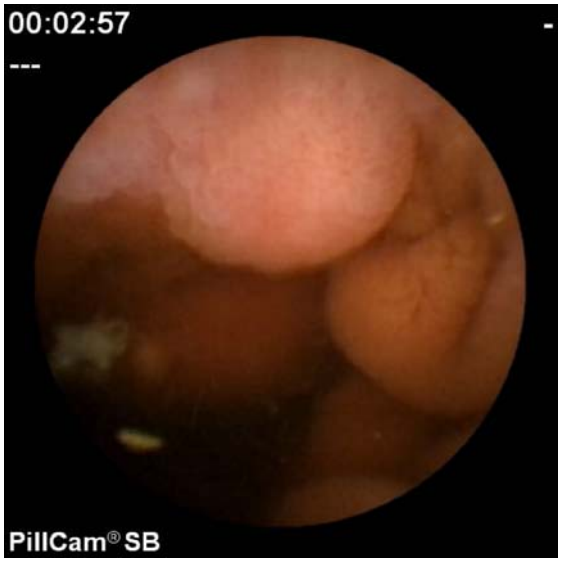


B. Edematous villi

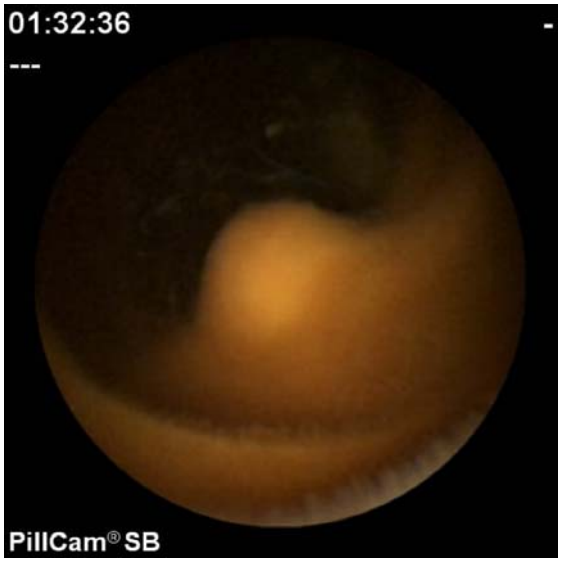


C. Erosions

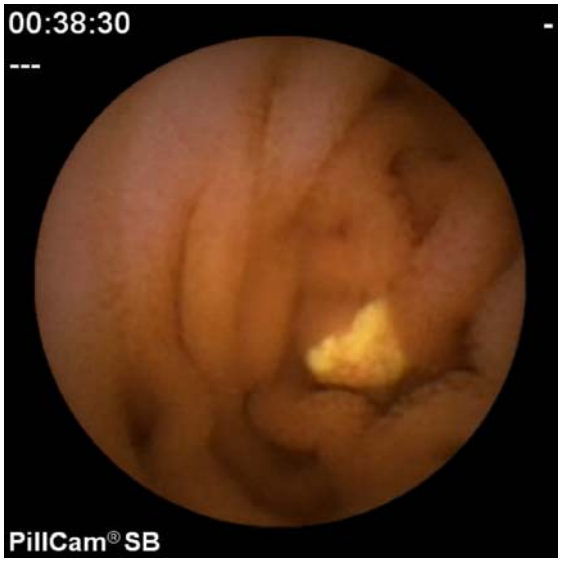
Figure 18: Capsule Endoscopy Views of the Inflammatory Like Lesions of Portal Hypertensive Enteropathy



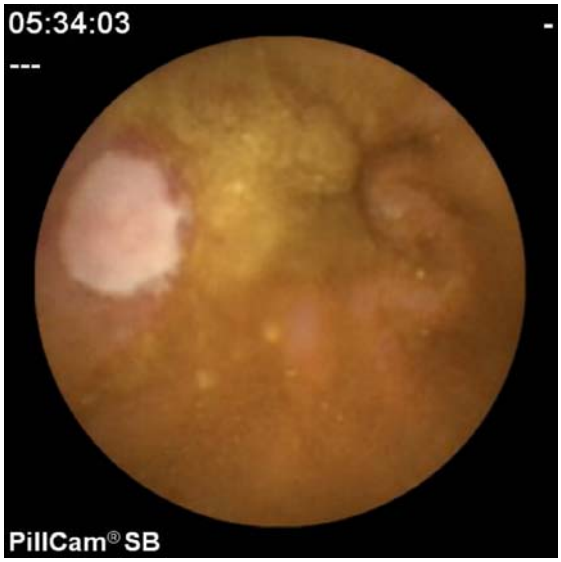
A. Duodenal polyp



B. Sub-mucosal tumor



C. Xanthoma



D. Small-bowel ulcer

Figure 19: Other Lesions Detected in Cirrhotic Patients that might Not Related to Portal Hypertensive Enteropathy

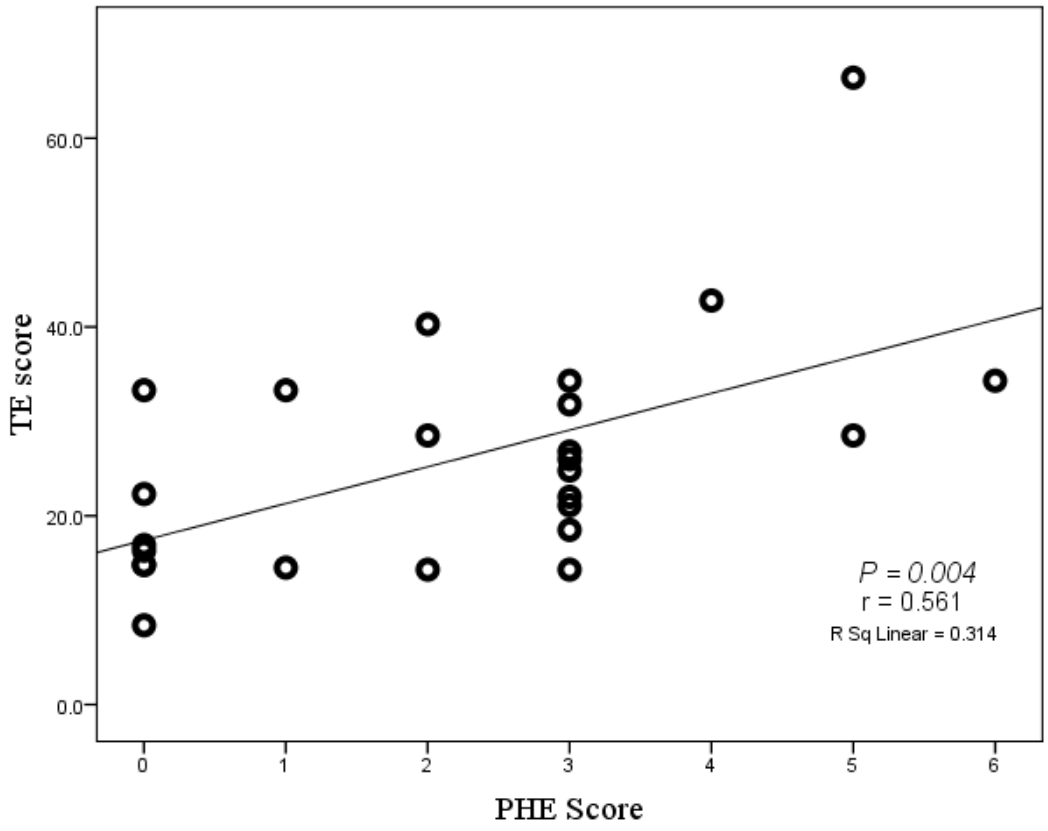


Figure 20: Linear Distribution of TE Scores According to PHE Scores ($p = 0.04$, $r = 0.561$)

DISCUSSION

DISCUSSION

Cirrhosis is a progressive chronic liver disease, and its clinical features are dependent on the disease duration and the nature of the etiological factors (**Higaki N et al. 2008**). Cirrhosis is the most cause of portal hypertension (PHT) through increased resistance to portal blood flow (**Garcia-Pagan JC et al. 2005, Goulas S et al. 2008).** The term PHT was first introduced by Gilbert and Carnot in 1902 for patients with ascites, splenomegaly, and esophageal hemorrhage **(Goulas S et al. 2008**).

Portal hypertension is by a portal pressure increase above the normal values, which rang from 3 to 6 mmHg. Clinically significant PHT is defined by a pressure increase above 10mmHg (**Nietsch HH et al. 2005**). Portal hypertension in cirrhosis is determined by an increase in intrahepatic vascular resistance and portal venous flow. The former is caused by the architectural distortion of the liver secondary to fibrosis and by increased sinusoidal tone. The latter results from a combination of a hyper-dynamic circulatory state and increased plasma volume (**Pinzani M et al. 200, Reynaert H et al. 2002**).

The increased intrahepatic resistance leads to development of collateral vessels, which divert portal flow away from the liver into the systemic circulation. The development of collaterals does not lead to normalization of portal pressure, which is maintained at high levels by the increased splanchnic blood inflow mediated by nitric oxide (NO), carbon monoxide, gut-derived vasoactive hormones such as glucagons and vasoactive polypeptides, and other less well-defined factors (**Rockey DC et al. 2004, Lubel JS et al. 2005, Garcia-Tsao G. 2005**).

The most life threatening complication of PTH is the overt bleeding especially acute variceal bleeding, which, despite recent progress, carries a mortality in the order of 20% (**D'Amico G et al. 2003, Chalasani N et al. 200**3). Prospective studies show that more than 90% of cirrhotic patients will develop esophageal varices in their lifetime (**Grace ND. 1997, The North Italian Endoscopic Club Study. 1988**). De novo variceal formation is estimated at about 6% per year in compensated cirrhosis (**Merli M et al. 2003**). In patients with varices, the 2- year rate of bleeding is about 30% (**Grace ND. 1997, The North Italian Endoscopic Club Study. 1988**).

In fact, PHT causes various changes in the entire GI tract (from esophagus to anus) (**Sarfeh IJ et at. 1987**). As a result, the term portal hypertensive intestinal vasculopathy (PHIV) has been used to explain the effects of PHT on the entire bowel, and includes portal hypertensive gastropathy (**PHG**), enteropathy (**PHE**), and colonopathy (**PHC**) (**Viggiano TR et al. 1992**). Among these pathological lesions, esophageal varices (EV), PHG, and PHC represent common sources of bleeding, and they are diagnosed and treated by esophagogastroduodenoscopy (EGD), and colonoscopy (CS) (**Kozarek RA et al. 1991, Viggiano TR et al. 1992**).

Changes in the gastric mucosa of patients with PHT first were described by McCormack in 1985 (**Mc Cormack TT et al. 1985**). These changes are referred to as portal hypertensive (or congestive) gastropathy and they have been attributed to alterations in the gastric microcirculation (**Sarfeh IJ et al. 1987, Tarnawski A et al. 1988**). PHG has been graded endoscopically into mild, moderate, and severe forms (McCormick PA et al. 1991). The classification of PHG is based on the recognition of elementary lesions such as the mosaic-like pattern (presence of small, polygonal areas surrounded by whitish-yellow depressed border), red-point lesions (small,

flat, red point-like areas less than 1 mm in diameter), cherry-red spots (round, slightly protruding red lesions greater than 2 mm in diameter), and black-brown spots (**Mc Cormack TT et al. 1985)**. The prevalence of PHG ranges between 7% and 98% and seems to be correlated with the duration of liver disease. A higher prevalence of PHG is observed among patients with large varices and those with ongoing or previous variceal sclerotherapy (**Primignani M et al. 2000**).

The proportion of bleeds than be attributed to PHG ranges between 4% and 40%, and the probability of bleeding even from mild forms of PHG ranges between 0% and 15% (**Primignani M et al. 2000**). Bleeding is either slow and insidious or severe and fatal (**Nagral AS et al. 1993**).

Colorectal lesions in patients with cirrhosis are referred to as PHC. Changes described in the colon include hemorrhoids, anorectal varices, and mucosal changes similar to those of PHG: diffuse hyperemia and edema resembling colonic colitis, angiodysplasia-like lesions, patchy hyperemic lesions, and a severe acute colitis-like appearance with spontaneous bleeding from the mucosa (**Ghoshal UC, et al. 2001**). All studies highlight the high prevalence of PHC in patients with PHT (ranges between 36.3% and 66%), but they do not clarify whether there is a relationship between these abnormalities and clinically relevant parameters such as etiology of live disease, Child-Pugh class, history of variceal bleeding, platelet count, or presence of PHG (**Ghoshal UC, et al. 2001, Misra SP et al. 2004, Ito k et al. 2005**). As in PHG, the colonic vascular lesions are not solely detected in the presence of cirrhosis, but can also be found in cases of extra-hepatic portal vein obstruction. PHC seems to be a rare cause of GI bleeding (**Misra SP et al. 2005, Bresci G et al. 2006**).

Most of the studies that focused on the involvement of the gastric and colonic mucosa in PHT suggest that other parts of the GI tract such as the duodenum and jejunum could undergo mucosal changes because PHT. Thus, it has been suggested that the entire GI tract, which drains into the portal venous system, might undergo PHT-related changes. In fact, Thiruvengadam and Gostout the first reported three patients, presenting with blood loss, who had diffuse erythema and scattered petechia in the stomach, but also in the duodenum and the jejunum (**Thiruvengadam R et al. 1989**).

Anecdotal reports suggest that in patients who have cirrhosis, the small-bowel mucosa is a potential source of bleeding (**Misra V et al. 1997, Desai N et al. 2004**); however, most of the studies on portal hypertensive enteropathy (PHE) found in literature were obtained by EGD (**Menchén L et al. 2006, Barakat M, et al. 2007**), by push enteroscpy (**Desai N et al. 2004**), or by retrograde ileoscopy at colonoscopy (**Misra SP et al. 2004, Rana SS et al. 2006**), and only include the duodenum, proximal jejunum, and terminal ileum.

Two studies that used retrograde ileoscopy at colonoscopy reported the prevalence of ileal involvement (ileopathy) was around 25%, and that of ileal varices ranged between 18% and 21% in patients with cirrhosis and PHT (**Misra SP et al. 2004, Rana SS et al. 2006)**. However, they reported failure of ileal intubation ranged between 7% and 12%. There was significant relationship between ileopathy and only PHC, and PHG from all the clinical data of the patients. Ileopathy was reported in non cirrhotic portal hypertensive patients, but it was not reported in patients have no evidence of cirrhosis or PHT (**Misra SP et al. 2004**). The small-bowel lesions of ileopathy were described to be akin to those of portal hypertensive colonopathy such as spider angiomata, patchy erythematous lesions, cherry

red spots, and ileal varices. The use of retrograde ileoscopy at colonoscopy might underestimate the true prevalence of ileopathy as only short segment of ileum be examined by that technique. **Misra SP et al. (2004)** suggested that use of CE in future might reveal the true extent of small-bowel involvement in cirrhotic patients with PHT, and may be useful for detection of bleeding and non-bleeding of ectopic varices.

Bleeding from ileal varices is reported (**Ohtani T et al. 1999, Kobayashi K et al. 2000, Varanasi RV et al. 2000**), and massive lower GI bleeding attributed to ileopathy is reported in two cases (**Santoro GA et al. 1997**). However, the clinical significance of ileopathy was unclear in those two studies.

Studies that used EGD to reveal the duodenal lesions in cirrhotic patients with PHT reported very great difference in prevalence of portal hypertensive duodenopathy (PHD) ranging between 8.4% (**Menchén L et al. 2006**), and 60% (**Boron-Kaczmarzka A et al. 1990**). Lesions of PHD were being reported as congestive vascular pattern only not included erosions or ulcer (**Menchén L et al. 2006**). However, **Barakat M et al (2007)** state that PHD might include patchy erythema, diffuse erythema, erosions, ulcers, telangiectasia, and villious edema. Some data showed a significant relation between PHD and overt or occult GI bleeding especially from the erosive lesions (**Barakat M, et al. 2007),** but other didn't show that **(Menchén L et al. 2006).** An interesting data was reported by **Menchén L et al. (2006)** that PHD might be reversible as the authors discovered improvement of PHD after liver transplantation, authors attributed that to the reduction in PHT degree.

None of those both studies showed any data about duodenal involvement in non-cirrhotic non-portal hypertensive patients.

One article (**Desai N et al. 2004**) using push enteroscopy, showed that congestive jejunopathy was significantly higher in patients with cirrhosis and PHT than normal patients (15% vs. 0%). Its prevalence was 15%. Jejunopathy was associated with PHG, and PHD. Lesions included erythemata and cherry red spots.

Recently, new endoscopic methods, CE and DBE, have been developed for examination of the entire small-bowel (**Iddan G et al 2000, Yamamoto H et al 2001**). DBE allows clinicians to obtain tissue samples and to make interventional procedures **(Sun B et al 2006, Kodama M et al. 2008**). However, DBE is invasive, time consuming, and required very experienced physicians. Moreover, **Kodama M et al. 2008** and others concluded that the post procedure fever was more common in patients with PHT than those without. This complication might be associated with bacterial translocation which typically occurs in patients with liver cirrhosis **(Cirera I et al. 2001, Francés R et al. 2005).** As a result, studies using DBE that studied the small-bowel involvement in cirrhotic patients with PHT are scare and include small number of cirrhotic patients.

There are two article published as full text used DBE to study the lesions compatible with PHE in cirrhotic patients, performed in Japan (**Kodama M et al. 2008, Higaki N et al. 2008)**. We will discuss and compare their results in details with ours later.

Since its introduction in clinical practice, CE demonstrated a superior diagnostic yield in comparison with conventional endoscopic methods (**Rondonotti E, et al. 2006**). An important feature, CE procedure is non-invasive that might be used in advanced cirrhosis without worrying about complications. As a result, a little bit published studies were performed using CE compared with DBE, although CE is a relatively expensive.

In our study, the prevalence of the mucosal lesions in small-bowel compatible with PHE was 67.7% among the cirrhotic patients. This prevalence is almost in accordance with most mentioned in literature (67.5%, 69%, 63.1%, and 65.7%) for **De Palma et al. 2005, Figueiredo P et al. 2008, Canlas KR, et al. 2008,** and **Goulas S et al. 2008** respectively. However, **Repici A et al. 2005**, and **Urbain D et al. 2008** reported a higher prevalence of PHE (82%, and 80% respectively) among cirrhotic patients although small number of subjects included in their studies. This is explained by different selection criteria of cirrhotic group. According to **Urbain D et al. 2008**, 25 cirrhotic patients were included, and the majority was towards Child class B, and C (15 pts of total 25 pts.), while in ours, most of cirrhotic groups are Child A (20 pts of total 31 pts.).

Author	Population		Prevalence of Abnormalities	Prevalence of SB varices
	Cirrhotic	Control		
1-De Palma et al. 2005	**37**	**34**	67.5% vs. 0%	8.1% vs. 0%
2- Repici A et al. 2005	**29**	**29**	82% vs. 48%	10.3% vs. 0%
3- Jacob P et al. 2005	**21**	**0**	48%	4.8% vs. 0%
4-Figueiredo P et al.2008	**25**	**11**	69% vs. 3%	27.8% vs. 3.3%
5-Canlas KR, et al. 2008	**19**	**0**	63.10%	15.80%
6-Urbain D et al. 2008	**25**	**17**	80% vs. 24%	20% vs. 0%
7- Goulas S et al. 2008	**35**	**70**	65.7% vs. 15.7%	25.7% vs. 0%

Table 17. Prevalence of Small-Bowel Lesions due to PHT and Small-Bowel Varices Detected by CE in Different Studies

Moreover, hepatocellular carcinoma was excluded, but in our study was not. According to **Repici A et al. 2005**, only abstract is published, so the details of patients' selection were not mentioned. On the other side,

Jacob P et al. 2005 mentioned the lowest prevalence (48%) for PHE among cirrhotic patients. All cirrhotic patients had unexplained bleeding at the time of CE procedure, and small number of patients, might explained the lower prevalence of PHE compared with other studies.

We reported mucosal lesions in small-bowel of the non-cirrhotic group of a prevalence of 6.9%. That was a matter of controversy between previous studies. **Figueiredo P et al. 2008, and Goulas S et al. 2008** reported same as ours (3% and 15.7% respectively). **Urbain D et al. 2008, and Repici A et al. 2005** reported highest prevalence (24%, and 48% respectively). However, **De Palma et al. 2005** reported absence of such mucosal lesions in small-bowel of the control group. We thought that discrepancy is attributed to difference in choosing criteria and size of the control group.

Small-bowel varices were diagnosed as tortuous enlarged veins with serpiginous or nodular shape (**Tag S et al. 2004**). Their prevalence among cirrhotic patients was a little bit variable in all studies including ours (ranged between 4.8% and 27.8%, **(Table 17)**. For us, small-bowel varies were found in 16.1% of cirrhotic patients. Small-bowel varices were not found among non-cirrhotic non-portal hypertensive patients in all studies. However, there is only study reported in one patient of control group (3.3%) (**Figueiredo P et al. 2008).** Although, the selection criteria of control patients were definitively variable between all studies. However**, Figueiredo P et al. 2008** didn't give any explanation for the presence of varices in the control patients.

As a result, we concluded that the overall prevalence of mucosal lesions compatible with PHE detected by CE was significantly higher than that of mucosal lesions detected by the conventional endoscopy (EGD,

colonoscopy, and push enteroscopy). This emphasizes that CE has an important clinical impact for visualization the entire small-bowel.

The prevalence of PHE was very heterogeneous between **Kodama M et al. 2008, and Higaki N et al. 2008,** who used DBE to explore small-bowel in cirrhotic patients. **Kodama M et al. 2008,** included 15 cirrhotic with 49 control patients, and reported the prevalence of villous and vascular abnormalities as 93%, and 100% respectively among the cirrhotic patients while in control group was 0%. However, **Higaki N et al. 2008** included 21 cirrhotic patients and didn't include control group. He reported a prevalence of erythema, angioectasia, and edemous villi as 24%, 5%, and 38% respectively. **Kodama M et al. 2008** included patients with extra hepatic portal vein obstruction in the cirrhotic group. He suggested that high prevalence of PHE in his study likely correlates with the finding that 13 of 15 patients with PHT had evidence of OGIB with negative findings on EGD and colonoscopy. However, **Higaki N et al. 2008** didn't give any explanation of his low prevalence of PHE.

Lesions attributable to PHE are present equally in ileum and jejunum in 28 patients (out of total 31 patients), ileal prominent in one patient, and jejunal prominent in one patient. Generally, we reported that jejunum as well as the ileum are equally involved. This is in accordance with results mentioned by **De Palma et al. 2005**, and **Goulas S et al. 2008.** Other authors didn't study this point in their literature.

Capsule endoscopic findings suggestive of PHE are similar to those described with conventional endoscopy (**Rondonotti E et al. 2006**). However, we found a little bit difference between authors' definition of PHE from the CE view.

In our study, we divided the mucosal lesions of PHE into vascular, and inflammatory like elements. The vascular lesions included red spots, angioectasia, and small-bowel varices. While the inflammatory like elements were erythema, villous edema, and erosions. The most common lesion was red spots that found in 54.8% of cirrhotic patients. Red spots was either non-bleeding, or bleeding ones. Bleeding red spots are of minute leakage not overt bleeding. The second common lesion was the angioectasias that found in 51.6% of patients. The third one was the inflammatory like lesions that found in 41.9% of patients. Small-bowel varices came at last with 16.1% prevalence. Our results regarding the individual lesion prevalence, and description of PHE were in accordance with those of **De Palma et al. 2005.** However**, De Palma et al. 2005** described the inflammatory like lesions as erythema, edema, granularity, and friability, and the authors didn't give any information about granularity and friability items of the inflammatory lesions. Additionally**, De Palma et al. 2005** didn't include erosions.

Figueiredo P et al. 2008 described PHE lesions as small-bowel varices, angioectasias, ulcerations/erosions, and mucosal reticular pattern. This study mentioned two new data; involvement of ulcerations, and the introduction of mucosal reticular pattern. Although, current or recent intake of NSAIDs was not definitely included in the exclusion criteria of his study, but the au didn't explain his opinion in adding ulcerations to his definition of PHE. Mucosal reticular pattern mostly meant the combination of villous edema, and congestion. In the other side, **Goulas S et al. 2008** excluded ulcers and erosions from PHE lesions, although the au excluded NSAIDs intake from study patients. Surprisingly**, Goulas S et al. 2008** didn't mention the red spots in the vascular lesions of PHE. Small-bowel erosions and ulcers are also excluded from **Canlas KR, et al. 2008** definition of PHE.

We diagnosed the villous edema by increasing the width of the villi to be equal or more than the length. **Higaki N et al. 2008** in a study using DBE gave a very interesting and new term to the villous edema, which is herring roe appearance. The microscopic changes of the mucosa having herring roe appearance were not evident in the mucosa not having it. As a result, **Higaki N et al. 2008** gave a big attention to this finding and considered it characteristic to PHE.

Kodama M et al. 2008 using DBE, described the PHE to be divided intro three categories, villous, vascular abnormalities, and small-bowel varices. The villous abnormalities included erythema, edema, and villous atrophy. Vascular ones included red spots, angioectasia, lymphoid follicles with dilated vessels, and congested mucosal vessels. The authors excluded the erosions, ulcerations, added villous atrophy, lymphoid follicles, and congested vessels.

Two studies (**Misra SP et al. 2004, Barakat M et al. 2007**) mentioned the mosaic appearance in their description of PHE that has been reported as a common feature of PHG (**Spina GP et al. 1994)**.

Erosions were documented by **Shudo R et al. 2002** as a common and distinctive feature of portal hypertensive duodenopathy.

Generally, gastrointestinal angioectasias may be encountered in an idiopathic form or in association with some hereditary and non-hereditary diseases (**Fiorella ML et al. 2004**). However, they may develop as characteristic lesions of PHT (**Vigneri S et al 1991**), and the potential of bleeding from such lesions can not be overlooked (**Barakat M et al. 2007**).

The varying lesions imply that none might be specific for PHE. In our opinion, there are a lot in common between all previous studies regarding the individual lesions description of PHE. We recommend that an

international consensus is needed to standardize the definition of mucosal lesions compatible with PHE.

Our data demonstrated that the prevalence of PHE increased with worsening Child-Pugh class. A comparison of cirrhotic patients with and those without PHE showed that large sized esophageal varices, PHG, high Child-Pugh score, platelets count, and prior history of EIS/EVL were all significantly associated with PHE. However, there were no differences between these two groups of patients with regard to the underlying hepatic pathology, history of GI bleeding, age, gender, gastric varices, haemoglobin concentration and hemocrite value. These data almost in accordance with those of **De Palma et al. 2005.** However, **De Palma et al. 2005** didn't find any relation between PHE, and prior history of EIS/EVL.

We think that the presence of PHE is quite related to the parameters of liver disease severity (Child-Pugh score), and PHT degree (large esophageal varices, PHG, prior history of EIS/EVL, platelets count). Our previously mentioned data was variably not accordance with those of **Goulas S et al. 2008, Figueiredo P et al. 2008, Repici A et al. 2005, Urbain D et al. 2008,** and **Higaki N et al. 2008.**

Goulas S et al. 2008 reported absence of relation between PHE and all the clinical characteristics of cirrhotic patients except severe PHG. The authors were so surprised from the absence of such relation between PHE and Child-Pugh class, although the same results were reported by **Repici A et al. 2005, Urbain D et al. 2008, Figueiredo P et al. 2008.** However, none of them offered an explanation of that. In the other side, the absence of linear relationship between the severity of liver disease and prevalence of PHG was reported by **Primignani M et al. 2000.** Moreover, the presence of PHC in the absence of cirrhosis is also observed by **Ganguly S et al. 1995** in

a similar frequency in cirrhotic and non-cirrhotic patients. This implies that the presence of cirrhosis is not a sine qua non condition for occurrence of PHG and/or PHC (**Goulas S et al. 2008**).

Increase the prevalence of PHG and ectopic variceal formation after obliteration of esophageal varices by sclerotherapy or ligation is well known (**Sarin SK et al. 1997, Primignani M et al. 2000, Mirsa SP et al. 1999).** However, such inverse relation could be demonstrated by **De Palma et al. 2005** and **Goulas S et al. 2008** for PHE**.** This was not in accordance with ours, as we reported significant inverse relation between PHE and prior EIS/EVL. **De Palma et al. 2005** recommended that larger studies or pooled data from future studies might define a relation between these two entities. In addition the effect of beta-blockers on enteropathy also should be investigated (**Sezai S et al. 1998**). However, only one published study showed no relationship between PHE and prior beta-blockers intake (**Figueiredo P et al. 2008**).

Our data proves that PHE, and PHG may not be distinct entities, instead, may be regional manifestations of PHE. Furthermore, they may share similar mechanisms with regard to pathogenesis. This was completely matched with results of **De Palma et al. 2005.** Additionally the former author reported the significant relation between PHE, and portal hypertensive colonopathy.

The concept of portal hypertensive vasculopathy which includes PHG, PHE, and PHC, was selected by Viggiano and Gostout to describe the effects of PHT in the gut (**Viggiano TR et al. 1992**). The association between PHG and PHC is well documented by **Bini et al. 2000** for large series of cirrhotic patients. However, **Repici A et al. 2005,** and **Figueiredo P et al. 2008** didn't find any relation between these two entities with PHE.

Barakat M et al. 2007 in his study on the portal hypertensive duodenopathy (PHD) on 105 cirrhotic patients, reported that PHD don't related to the size of esophageal varies or prior GI bleeding , but it was related to PHG. However, the authors emphasized very interesting data, that determining factor for development of PHD is not the high portal pressure itself but the point at which this high pressure starts to produce congestive changes. When this point is reached and the congestive state gives spreading severe gastric lesions then the process tends to be more generalized also affecting intestinal segments. Our data disagree with the conclusion of **Barakat M et al. 2007,** for many reasons. The first we reported the significant relation between PHE and PHG. Second, his study visualized very small part of the small-bowel; duodenum, so it's not logic to reach such this emphasis from the theoretical point of view. Third, measurement of portal pressure was not included in his study.

In our study, PHE has a significant relation with Child-Pugh score and PHT parameters. However, our data was not agreement with those of **Menchén L et al. 2006**. Since, they didn't find any statistical difference between Child score, and PHD, but there is a relation between it and PHG, esophageal varices, and higher values of hepatic venous pressure gradient (HVPG). As a result the authors support the idea of; PHT not the liver function seems to be the main factor for PHD development. Moreover, increase the prevalence of PHD in patients with prior EVL, is not attributed to EVL itself, instead, the higher portal pressure, as it is well known that EVL has no effect on portal pressure (**Pereira-Lima JC et al. 2003**).

In our study, we were the first who studied the relation between liver stiffness measurement through TE score and the prevalence of PHE. We reported a significant statistical relation between high TE scores and

presence of PHE. Liver stiffness appears to correlate with HVPG measurements (**Vizzutti F et al. 2007**). Moreover, there was also good correlation between liver stiffness and the presence and size of EV (**Kazemi F et al. 2006, Vizzutti F et al. 2007).** Upon all these previous data, we add more supportive and new data for the theory of; PHE might strongly relate to degree of PHT.

Portal hypertensive gastropathy is a well-established cause of bleeding in cirrhotic patients (**Primignani M et al. 2000**), and PHC seems to be a rare cause of bleeding (**Bresci G et al. 2006**). Nevertheless, the question of whether the mucosal lesions compatible with PHE can be a cause of overt or occult bleeding in cirrhotic patients remains unanswered. In our study, we found one patients (3.2%) with active bleeding who submitted to DBE and the responsible lesion was not in small-bowel. Most important, we didn't find any significant relation between the presence of PHE and haemoglobin concentration and haemocrite value. Our data was in accordance with those of **De Palma et al. 2005.** The former reported active bleeding in 10.8% of their patients who diagnosed as angioectasias. Nevertheless, angioectasia should not be considered a small-bowel manifestation of PHE, as it was reported with the same frequency between cirrhotic and non-cirrhotic patients (**Figueiredo P et al. 2008).** The assumption that PHE lesions are implicated in GI bleeding is based on reports of bleeding small-bowel varices and other PHE lesions (**Ohtani T et al. 1999, Lewis P et al 1990, Guth E et al. 1996, Tang SJ et al. 2004**). Portal hypertensive was documented to be the cause of overt or occult bleeding from erosions and/or ulcers, the episodes of overt bleeding were self-limited and not severe (**Barakat M et al. 2007**).

Some case reports described bleeding from other lesions as erythematous duodenopathy (**Thiruvengadam R et al 1989**), while others presented cases of massive hemorrhage that forced an emergency shunting procedure (**Santoro GA et al. 1997**).

Among all CE studies, only one study that reported significant association between PHE and low hemoglobin levels (**Repici A et al. 2005**). The authors proposed that PHE could be a source of bleeding in cirrhotic patients with anemia.

Our data suggest that cirrhotic patients with worsening Child-Pugh score, larger esophageal varices, PHG, prior EIS/EVL and higher TE scores are candidates for the clinical use of CE in normal daily practice, particularly in cases of anemia and/or hemoccult-positive stool, in the absence of explanatory findings at EGD, and colonoscopy. Next step, enteropscopy should be used according to the findings of CE. Our recommendation is in agreement with those of **De Palma et al. 2005** and **Figueiredo P et al. 2008.**

Portal hypertensive enteropathy is considered the newest discovered entity of portal hypertensive vasculopathy. Moreover, PHE has not been studied fully until the discovery of the new endoscopic methods; DBE, and CE. Currently, there is no classification system with which to grade the severity of the mucosal lesions of PHE detected by CE. **De Palma et al. 2005** proposed that PHE lesions could be simply classified into two categories, mucosal inflammatory-like abnormalities (edema, erythema, granultity, and friability) and vascular lesions (cherry-red spots, telangiectasias, angiodysplasia-like lesions and varices).

Rana SS et al. 2006 defined the diagnosis of ileopathy as the presence of lesions similar in appearance to spider angioma, diffuse or patchy regions of hyperemia, cherry-red spots, and prominent veins.

Beside the classification system, there is no scoring system until now was reported to be used for mucosal lesions of PHE using CE. **Kodama M et al. 2008** was the first to provide a scoring system using DBE. Mucosal lesions were classified in his trial into two categories, villous abnormalities, and vascular lesions. Next, each category was sub-classified into three subcategories. Villous abnormalities category was sub-classified into; ① edema, ② villous atrophy, and ③ eryhema. Vascular lesions category was sub-classified into; ④ angiodysplasia-like lesions that further classified into, a- red spots, b- vascular spiders, and c- lymphoid follicles with dilated vessels, ⑤ dilated/proliferated vessels that further classified into, a- tree-like dilated vessels, b- coil-like fine vessels, and ⑥ small-bowel varices.

A finding of each of these lesions was scored as a point, to provide a final score with a maximum of six points. Cirrhotic patients with four or more positive findings of PHE were compared with those with fewer than four positive findings to determine if PHE was associated with liver disease severity or with specific endoscopic findings of EGD, or colonoscopy.

However, **Kodama M et al. 2008,** using his scoring system, didn't find any significant relation between PHE and parameters of liver disease, and PHT severity except with presence of ascites.

In our study, we made great modifications of both classification system of De **Palma et al. 2005,** and scoring of **Kodama M et al. 2008.** Although we didn't investigate the histology of the mucosal lesions in this study, we classified the CE findings into main four categories. Three comprised the vascular lesions, ① red spots, ② angioectasias, and ③ small-bowel varices. The forth is ④ inflammatory-like lesions (erythema, edema, and erosions). Although, it is unclear if these finding were specific for PHE, our observations indicated their prominence in cirrhotic patients with PHT.

Our scoring depended on giving each of these four category two points if it was multiple (more than two lesions), and just one point if it was not. We calculated the positive points for every patient to make a final score out of a maximum eight points. In contrast to that of **Kodama M et al. 2008,** our scoring gave great attention to the vascular components of PHE, as they might be potential source of GI bleeding.

Using our scoring, we reported that cirrhotic patients with higher serum level of bilirubin, lower level of albumin, higher Child score, larger EV, prior EIS/EVL, and higher TE score were all significantly associated with higher PHE score.

We emphasized that the severity, as well as presence of the PHE is quite related to the liver function indices as well as PHT parameters.

Our data using scoring system greatly support our previously mentioned recommendations, cirrhotic patients with worsening Child score, and higher EV, prior EIS/EVL, and higher TE score are candidates for CE procedures especially if they presented with anemia or OGIB, and negative EGD, and colonoscopy. However, further large scaled studied are required to validate our scoring system.

Our newest data is the relation between TE scores and the presence and severity of mucosal lesions of PHE detected by CE. Surprisingly, we found that cirrhotic patients with higher TE scores were significantly related to the presence as well as the severity of PHE (PHE scores). This is considered new data had been added to the literature regarding that field. In the clinical practice, we think that CE is an expensive than could not be used in the daily practice. As a result, we proposed using the TE as it is easy, rapid, cheap and available in many centers could be the first one in the daily use, then patients with higher TE scores are the only subjected to the CE if

they fulfilled the previously mentioned situations. We thought that, using TE in daily practice will be so beneficial for prediction of PHE; beside it is a non invasive method. However, large studies are strongly recommended to validate this data and to declare a definite cut-off values of TE at which PHE is suspected. Very important question is could TE be helpful in follow up patients with PHE or not? We proposed in the future we can get the answer.

The strength of this prospective study is that we are the first to make a reliable scoring system for small-bowel mucosal lesions of PHE using CE. Next, we are the first to study the relation between TE scores and presence and severity of PHE. Moreover, using TE as a diagnostic method for PHT was a new thing that was not present in all similar studies.

However, our study has some limitations. The most important limitation is the lack of hisopathological study of the mucosal findings, that we could not be sure whether these finding detected by CE are specific of PHE or not? Next, lack of significant data obtained using multivariate analysis. This is explained by small size sample of the patients' population. Moreover, the control arm is not the ideal one, since healthy volunteers are the best for the control group. At last, our study is single center study.

In conclusion, CE is a useful diagnostic procedure for detection of PHE mucosal lesions. Mucosal lesions compatible with PHE are more common in cirrhotic patients with PHE than non- cirrhotic patients who have no evidence of PHE. The presence of PHE is quite related to the severity of liver disease as well as PHE degree. The exact clinical significance of PHE is still unknown. Our scoring system is a simple easily applicable one that can give us a reliable data about the severity of PHE mucosal lesions detected by CE. Transient elastography could be new non-invasive method that could predict the presence as well as the severity of the PHE. However,

the use of our scoring system and TE in such clinical settings has to be validated by further studies in the future.

SUMMARY AND CONCLUSION

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Background and Aim:

There is limited data about the frequency, and characteristics small-bowel lesions in cirrhotic patients with portal hypertension (PHT) detected by capsule endoscopy (CE) as well as, there is no scoring system to evaluate their severity. To date, there is no published study showed the association between portal hypertensive enteropathy (PHE) and transient elastography (TE). The objective of this study was to better define the mucosal abnormalities of PHE, and to determine whether these findings are associated with the severity of liver disease, esophageal varices, portal gastropathy, or other clinical characteristics.. Moreover, we aimed to explore the clinical impact of TE in the field of PHE, and to create a reliable scoring system for mucosal findings of PHE detected by CE.

Materials and Methods*:*

We compared medical records of 31 cirrhotic patients complicated with portal hypertension (PTH) with 29 control patients who underwent CE. Our scoring system of PHE depends on classification of small bowel (SB) mucosal lesions into main four types; 1- red spots, 2- angioectasias, 3- SB varices, and 4- inflammatory like lesions. The first three types comprised the vascular lesions of PHE. Each of these four lesions worthy 2 points if it was multiple (more than 2 lesions), and only one point if it was not. We calculated the positive points for every patient to make a final PHE score of maximum 8 points.

Results:

Mucosal lesions compatible with PHE were significantly more common in cirrhotic patients than control patients (67.7% vs. 6.9%, $p < 0.001$). The mucosal findings in cirrhotic patients included red spots (17 patients, 54.8%), angioectasias

(16 patients, 51.6%), inflammatory like abnormalities (13 patients, 41.9%), and SB varices (5 patients, 16.1%). In control group, SB mucosal findings were present only in two patients and included red spots (one patient, 3.4%) and inflammatory-like abnormalities (one patient, 3.4%).

Cirrhotic patients with low serum albumin level, high bilirubin level, low platelets count, worsening Child Pugh class, large EV, portal gastropathy, and history of endoscopic variceal injection sclerotheraphy or ligation (EIS/EVL) were significantly associated with PHE. On the other side, there is no difference between patients without PHE and those without PHE regarding hemoglobin concentrations and hemocrite values.

Comparison between our proposed PHE score and clinical data of patients showed that patients with lower serum albumin level (p <0.02), higher serum bilirubin level (p = 0.005), higher TE score (p= 0.004), higher Child-Pugh score (p = 0.011), larger EV (p= 0.006), and prior EIS/EVL (p = 0.006) were significantly associated with higher PHE score.

Conclusion*s*:

Mucosal lesions compatible with PHE were significantly more common in cirrhotic patients than control patients (67.7% vs. 6.9%, p < 0.001). Cirrhotic patients with high TE score, worsenig Child-Pugh, large EV, and prior EIS/EVL are clinically associated with severe PHE. Transient elastography might be a new non-invasive tool that has a clinical impact for predicting presence and severity of PHE in cirrhotic patients especially if presented with occult gastrointestinal bleeding and the esophagogastroduodenoscopy and colonoscopy are negative.

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ARABIC SUMMARY

مرضى التليف الكبدى الذين يعانون من- أقل نسبة البيومبين بالدم وأعلى نسبة بليروبين وأقل عدد صفائح دموية و الأسوء من حيث مقياس Child-Pugh و أكبر دوالى مرئ حجما و مصابين بالأعتلال المعوى الناتج عن أرتفاع ضغط الدورة البابية و الذين لديهم تاريخ مرض بالتدخل العلاجى لدوالى المرئ أو المعدة عن طريق المنظار- وجد أنهم الأكثر اصابة من غيرهم بأعتلال الامعاء الدقيقة الناتج عن أرتفاع ضغط الدورة البابية PHE. على الناحية الأخرى لم تكن هناك علاقة بين المرضى المصابين بأعتلال الأمعاء الدقيقة PHE و المرضى الغير المصابين من حيث نسبة تركيز الهيموجلوبين و قيمة Hemocrite value .

وبتطبيق نظامنا المستحدث لقياس شدة أعراض أعتلال الأمعاء الدقيقة PHE و جدنا أن مرضى التليف ذوى نسبة الألبيومين الأقل ($p < 0.02$) ونسبة البليروبين الأعلى ($p = 0.005$) ومقياس TE score الأعلى (p =0,004) و قياس Child-Pugh score الأعلى (p =0.011) و دوالى المرئ الأكبر حجما (p =0.006) و التاريخ المرضى للتدخل العلاجى لدوالى المعدة والمرئ من خلال المنظار (p =0.006) هم أصحاب أعلى درجة فى مقياس الشدة لأعراض اعتلال الأمعاء الدقيقة الناتج عن أرتفاع ضغط الدورة البابية.

الأستنتاج

- أعراض الأمعاء الدقيقة المتمشية مع أعتلال الأمعاء الدقيقة الناتج عن أرتفاع ضغط الدورة البابية أكثر شيوعا بصفة واضحة بين مرضى التليف الكبدى عن غيرهم ممن لا يعانون من التليف.
- مرضى التليف الكبدى ذو المعايير السيئة لوظائف الكبد (مثل أرتفاع مقياس Child-Pugh score) و أرتفاع ضغط الدورة البابية (مثل دوالى المرئ ذات الحجم الكبير و أرتفاع مقياس TE score) مرتبطين أكثر بصفة واضحة بشدة أعتلال الأمعاء الدقيقة PHE عن غيرهم من ذوى المعايير الغير سيئة.
- أستخدام Transient Elastography ربما يكون وسيلة جديدة لها دلالة أكلينيكية هامة فى التنبؤ بوجود وشدة أعتلال الأمعاء الدقيقة الناتج عن أرتفاع ضغط الدورة البابية PHE خاصة فى حالات مرضى التليف الذين يعانون من النزيف مجهول السبب و نتائج المنظار العلوى والسفلى سلبية.

الوسائل التى شخص بها أرتفاع الدورة البابية هى وجود دوالى المعدة أو المرئ من خلال المنظار العلوى أوأن درجة قياس صلابة الكبد بواسطة Transient Elastography تكون ≤ 13.6 kPa.

يعتمد نظامنا القياسى لأعراض الأمعاء الدقيقة نتيجة أعتلالها بأرتفاع ضغط الدورة البابية على تقسيمها إلى أربعة أنواع أساسية هى:

① النقط الحمراء

② التمدد الغير طبيعى للأوعية الدموية (Angioectasia)

③ دوالى الأمعاء الدقيقة

④ أعراض شبيهة لأعراض الألتهابات مثل الحمرة وتورم النسيج المخاطى و التقرحات السطحية.

الأنواع الثلاث الأولى خاصة بتغيرات الأوعية الدموية.

يحسب لكل نوع من الأعراض الأربعة نقطتين أذا كان العرض متعددا (بمعنى أنه موجود بأكثر من مرتين) ونقطة واحدة فقط أذا لم يكن متعددا.

تجمع النقاط كلها لكل مريض على حده ويحتسب المجموع كوحدة قياسية (بحد أقصى ثمانية نقاط) لأعتلال الأمعاء الدقيقة الناتج عن أرتفاع ضغط الدورة البابية.

النتائج:

الأعراض المعوية المتمشية مع أعتلال الأمعاء الدقيقة الناتج عن أرتفاع ضغط الدورة البابية PHE كانت منتشرة بصفة واضحة جدا فى مرضى التليف الكبدى عن المرضى (المحايدين) الغير مصابين بالتليف (67.7% مقابل 6.9% . $p < 0.001$).

شملت هذه الأعراض فى مرضى التليف من التالى: نقط حمراء فى 54.8% من أجمالى مرضى التليف الكبدى (17 مريض) وتمدد غير طبيعى للأوعية الدموية فى 51.6% من مرضى التليف (16مريض) و أعراض شبيهة لأعراض الألتهابات فى 41.9% (13 مريض) و دوالى أمعاء دقيقة فى 16.1% (5 مرضى).

أما فى مجموعة المرضى المحايدة (الخالية من التليف وأرتفاع ضغط الدورة البابية) كانت الأعراض المتمشية مع أعتلال الأمعاء الدقيقة الناتج عن أرتفاع ضغط الدورة البابية قليلة جدا و موجودة فى مريضين فقط وهى نقط حمراء فى مريض واحد (3.4%) و أعراض شبيهة لأعراض الألتهابات فى مريض واحد (3.4%).

دراسة أعراض الأمعاء الدقيقة فى مرضى التليف الكبدى بأستخدام المنظار الكبسولة

المقدمة والهدف من البحث

الدراسات العلمية حول وصف وشيوع أعراض الأمعاء الدقيقة فى مرضى التليف الكبدى المكتشفة بواسطة أستخدام المنظار الكبسولة تكاد تكون قليلة جدا. أيضا لا يوجد نظام قياسى موحد لهذة الأعراض يعتمد عليه فى تقييم شدتها.

من ناحية أخرى لا توجد حتى الأن أية أبحاث توضح العلاقة بين قياس درجة صلابة الكبد (LSM) بواسطة أستخدام Transient Elastography و أعتلال الأمعاء الدقيقة الناتج عن أرتفاع ضغط الدورة البابية (PHE).

الهدف من هذه الدراسة هو توضيح تفصيلى للتغيرات الغير طبيعية فى الجدار المخاطى للأمعاء الدقيقة التى قد تصاحب أعتلال الأمعاء الدقيقة الناتج عن أرتفاع الدورة البابيةPHE وأيضا معرفة ما أذا كانت هذه التغيرات لها علاقة بدرجة (شدة) التلف الكبدى ودوالى المرئ و الأعتلال المعدى لأرتفاع الدورة البابية PHG وباقى المضاعفات الإكلينيكية المصاحبة للتليف الكبدى فى المرضى.

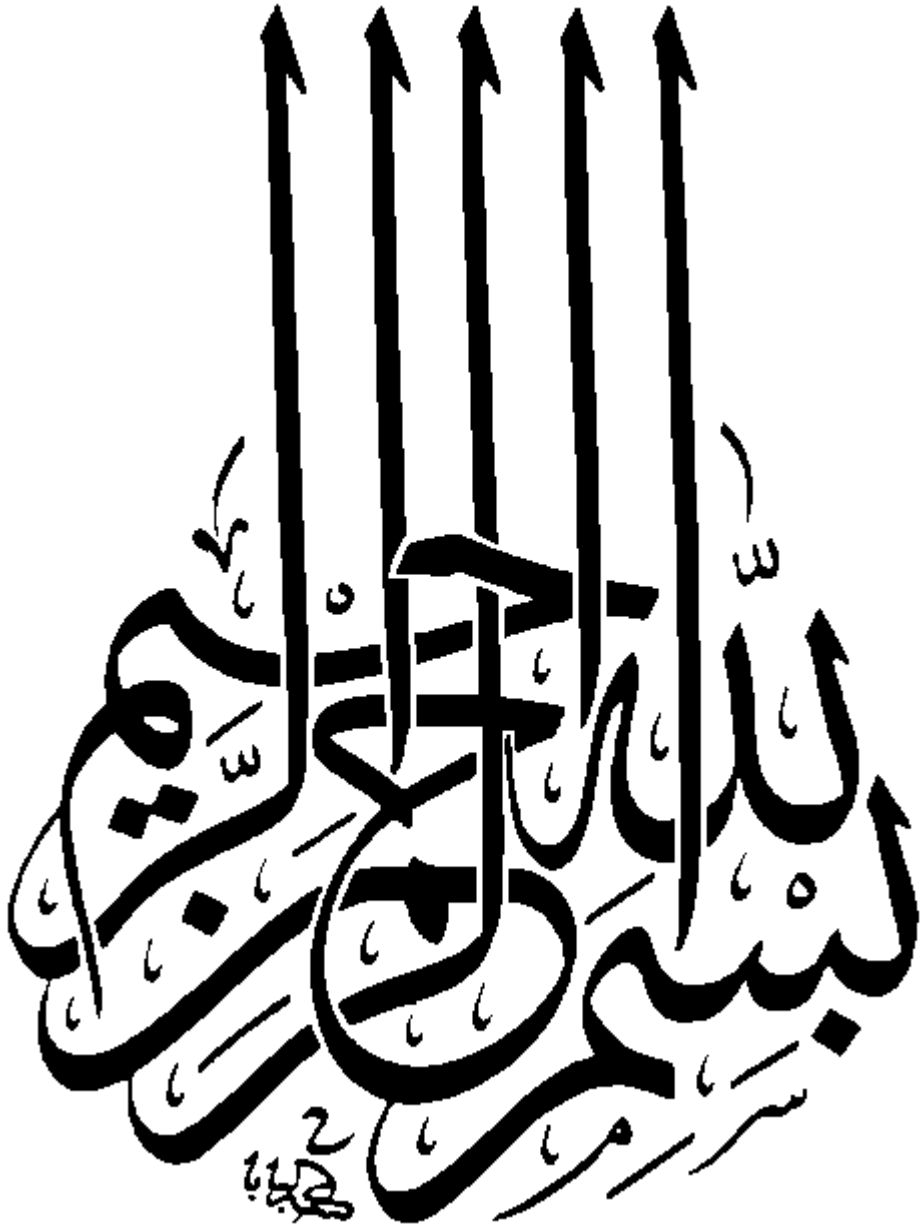
علاوة على هذا لقد هدفنا فى هذه الدراسة الى كشف أحتمالية وجود دلالة إكلينيكية ل Transient Elastography فى مجال أعتلال الأمعاء الدقيقة التاتج عن أرتفاع ضغط الدورة البابية PHE من عدمه و محاولة صنع نظام قياسى للتغيرات المصاحبة ل PHE و دراسته بكل الجوانب الإكلينيكية للمرضى.

الأدوات وطريقة البحث:

البحث يشمل مقارنة مجموعة مرضى(عددها 31 مريض) تعانى من تليف كبدى مصاحب بأرتفاع فى ضغط الدورة البابية و مجموعة أخرى –حيادية- من المرضى (عددها 29 مريض) تخلو تماما من أى مرض كبدى أو أرتفاع ضغط الدورة البابية.

الوسائل التى شخص بها التليف الكبدى هى التاريخ المرضى والفحوصات المعملية للدم و الأشعة التلفزيونية على البطن و الفحص المعملى لأنسجة الكبد.

الملخص العربى


بسم الله الرحمن الرحيم

جامعة سوهاج
كلية الطب

دراسة أعراض الأمعاء الدقيقة فى مرضى التليف الكبدى بأستخدام المنظار الكبسولة

دراسة مقدمة من الطبيب

أسامه محمد عبدالعال عبدالقادر

توطئة للحصول علي درجة الدكتوراه في الأمراض الباطنة

تحت إشراف

الأستاذ الدكتور/ على محمود قاسم
أستاذ ورئيس قسم الأمراض الباطنة
كلية طب سوهاج – جامعة سوهاج

الأ ستاذ الدكتور / هيجوتشى كازوهيد
أستاذ الأمراض الباطنة ورئيس قسم الجهاز الهضمى والكبد
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