Could Iron Deficiency Anemia affect Cardiac Functions among Portal Hypertensive Patients?

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Abstract

Anemia is one of the earliest and common complications of portal hypertension in children. It is responsible for a significant amount of morbidity resulting in poorer quality of life and is an important risk factor for the development and progression of cardiovascular complications. The severity of anemia increases with more advanced portal hypertension. It is one of the major causes of fatigability, reduced exercise tolerance and left ventricular hypertrophy. Based on the physiological significance of oxygen transported to myocardial tissue, anemia may be a cause of more severe cardiovascular diseases or a sign of other severe diseases that occur in the body. The physiologic response to anemia is a compensatory increase in cardiac output in order to maintain adequate oxygen delivery. It has reported that myocardial contractility would decrease when hemoglobin was below 7 g/dL and chronic anemia would result in increased LV end-diastolic pressure as well as decreased functional reserve. Patients with iron deficiency anemia (IDA) can present with symptoms that result from hypoxic functioning as dyspnea progressing to breathlessness at rest, vertigo, syncope, headache, tachycardia and cardiac systolic flow murmur.

Keywords: Iron deficiency anemia, Portal Hypertension, Cardiac Functions

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Introduction

Gastroesophageal varices are found in about 50% of patients with cirrhosis. Their presence correlates with the severity of liver disease *(1)*.

Prediction and Diagnosis of Esophageal Varices in Cirrhosis:

Non-Invasive Prediction:

Non-invasive predication of varices in cirrhotic patients is useful as generalized screening of all cirrhotic patients by endoscopy would increase the work load of endoscopy units **(1)**.

1) *Plain Radiographic Findings:*

Calcification may be seen in the portal vein after prolonged portal hypertension. The calcification is linear, and lies transversely across the upper abdomen, or it slopes upward and obliquely toward the liver hilum. In 5-8% of patients, esophageal varices (O.V.) may be seen as lobulated posterior mediastinal masses **(2).**

2) *Abdominal Ultrasonography:*

Abdominal ultrasonography is a rapid non-invasive method for prediction of portal hypertension, by measuring portal vein diameter. Increase in the portal vein diameter is considered a sign of portal hypertension. Several studies showed that portal vein diameter of greater than 13 or 15 mm has sensitivity for diagnosing portal hypertension of only 12.5 and 40 % respectively. The size of the portal vein may not be a reliable indicator of portal hypertension, its relative change in size with respiration is a more sensitive finding. An increase of portal vein diameter less than 20% with splenic vein diameter more than 1cm indicates portal hypertension **(3).**

With the development of porto-systemic collaterals, diagnosis of portal hypertension can be confirmed but the portal vein diameter may decrease. Moreover, the size of the spleen is not well correlated with the level of portal hypertension; however, if splenomegaly is absent, portal hypertension is unlikely. Ultrasonography has higher specificity but lesser sensitivity as it is operator dependent **(4).**

3) *Doppler Ultrasonography:*

Doppler ultrasound is also a non-invasive method. It estimates blood flow volume in portal circulation and it was widely used to explore the relationship between O.V. hemodynamics associated with portal hypertension and liver cirrhosis **(5).**

4) *CT Esophagography (Single or Multidetector):*

Is not entirely non-invasive, Thickening of the esophageal wall, scalloped contour and enhanced intraluminal protrusions after contrast injection are seen. The performance characteristic of this technique has been good in at least two available studies and in addition able to detect other pathology outside esophagus **(1).**

Invasive Prediction*:*

***Upper GIT Endoscopy*:**

Esophago-gastro-duodenoscopy (EGD) is the gold standard for evaluation of varices. The esophageal varices are recognized as tortuous bluish mounds which are graded into 4 grades. Endoscopy may also detect portal hypertensive gastropathy, a condition responsible for non-esophageal variceal bleeding episodes in portal hypertensive patients **(6).**

Endoscopy also detect the risky signs of bleeding O.V. that are red color signs on the varices (resulting from development of micro-telangectatic vessels on the variceal surface) and are classified into: red wale markings (dilated venules longitudinally seen on the variceal surface with appearance of a wale or whip mark); cherry red spots (small red spotty dilated venules about 2 mm in diameter on the variceal surface); hemocystic spots (large round red projections >4 mm in diameter looking

like blood blister); and diffuse redness (diffuse red area seen on the variceal surface due to the development of telangectatic network) (7).

Finally, predictive accuracy of noninvasive markers is still unsatisfactory, and until large prospective studies of noninvasive markers are performed, endoscopic screening stills the main mean for assessing for presence of esophageal varices (8).

Grading of Esophageal Varices:

- ✓ **Grade I:** Small straight cords of varices continued to lower 1/3 of the esophagus.
- ✓ **Grade II:** Moderate sized clubbed varices with well-defined areas of normal mucosa between them forming several distinct vertical cords and confined to lower third of esophagus.
- ✓ **Grade III:** Gross varices extending into the proximal half of the esophagus, which is so large and tortuous, that normal mucosa may not be visible in between unless the esophagus is fully distended with air.
- ✓ **Grade IV:** Varices are like those of grade III but with dilated capillaries on top or in between varices.

Esophageal varices can also, be graded according to their size into: (7).

(1) Small straight varices

(2) Enlarged, tortuous occupy less than one third of the lumen

(3) Large, coil-shaped, occupy more than one third of the lumen (F3)

Others classify according to their size into (small and large) with a diameter of cut-off value (5mm), with large varices (>5mm) (6).

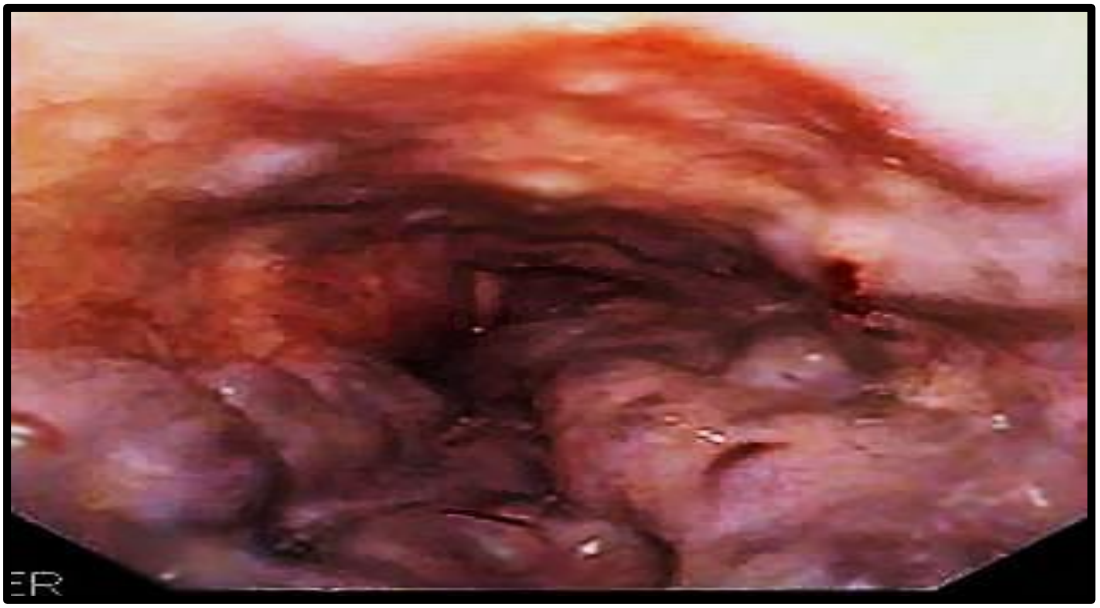

Figure (1): Gastroscopy image of esophageal varices with prominent cherry-red spots (9).

Risk Factors of Bleeding Related to Varices:

Despite many people with advanced liver disease develop O.V., most won't experience bleeding. Varices are more likely to bleed with high portal vein pressure; large varices, the larger

the varices, the more likely they are to bleed; red marks on the varices; severe cirrhosis or liver failure and continued alcohol use especially if the disease is alcohol related **(10)**

Also, bacterial infection, physical exercise and a bolus of rough food may increase risk of bleeding varices. Patients with advanced age are more likely to bleed due to impaired nutrition, poor healing, poor hepatic reserve and high incidence of morbidity. On the other side, it was found that, there is no relation between sex and risk of bleeding. However, the risk of bleeding may increase with pregnancy due to hyper dynamic circulation and increased portal pressure **(11).**

Although large volume paracentesis decreases variceal pressure, size and variceal wall tension**;** unexpectedly, paracentesis may be followed by an attack of hematemesis, may be due to dynamic changes in collateral flow, occurring with decompression up to acute hemoperitonium **(12).**

Table (1): Risk factors for esophageal varices and hemorrhage **(10)**

Development of Varices
High portal vein pressure: HVPG >10 mmHg in patients who have no varices at initial endoscopic screening
Progression from Small to Large Varices
Decompensated cirrhosis (Child-Pugh B/C) Presence of red wale marks at baseline endoscopy (longitudinal dilated venules resembling whip marks on the variceal surface)
Initial Variceal Bleeding Episode
Large varices (>5 mm) with red color signs Continuing alcohol consumption High HVPG >16 mm Hg Coagulopathy

Variceal Bleeding Outcome:

Variceal bleeding is one of the most frequent causes of death in cirrhotic patients. Mortality rate with each bleeding episode ranges from 20% -30%. About 20% of cirrhotic patients die within 6 weeks of 1st variceal bleeding, either because of variceal hemorrhage itself, or because of its complications such as sepsis and/or renal failure **(13).**

After stoppage of an active bleeding episode, there is risk of re-bleeding (occurs in 30% to 40% of patients) during the first 6 weeks. The risk peaks in the first 5 days, with 40% of all re-bleeding episodes occurring in this very early period. This risk remains high during the first 2 weeks, and then declines slowly in the next 4 weeks **(8).**

The 6 week re-bleeding rate decrease to 20% with the available therapy. Early therapeutic treatment is advised to control bleeding and prevent re-bleeding. Aggressive volume replacement may exacerbate the portal hypertension and precipitate early re-bleeding. Prognostic indicators for

early re-bleeding were assessed in most studies together with initial failure to control bleeding and 5-day risk for death, forming a composite end point referred to as ''5-day failure'' **(14).**

There are significant predictors of the risk ''5-day failure'' such as; bacterial infection, active bleeding at emergency endoscopy, Child-Pugh class, presence of portal vein thrombosis and a HVPG >20 mm Hg have been reported as significant predictors of risk for 5-day failure **(14).**

Treatment of Portal Hypertension and Esophageal Varices:

Management of esophageal varices include three lines, line of primary prophylaxis (preventing the first variceal bleeding), line of treatment of the acute variceal bleeding, and line of secondary prophylaxis (preventing the recurrent variceal bleeding) **(15).**

Primary Prophylaxis (Preventing the First Variceal Bleeding):

1) ***Cirrhotic Patients without Varices:***

A large multicenter trial concluded that no benefit of nonselective β-blockers usage in preventing the development of varices in patients with cirrhosis (with HVPG >5 mmHg) and had not developed varices. This patient should have a follow up endoscopy every 2 years (with ongoing liver injury or associated conditions, such as obesity and alcohol use) or every 3 years (if liver injury is quiescent, e.g., after viral elimination, alcohol abstinence). If decompensation occurs, endoscopy should be performed by the time of decompensation **(15).**

2) ***Cirrhotic Patients with Varices:***

I. ***Small Non-Bleeding Varices:***

The ***AASLD Guidelines*** suggest the usage of non-selective β-blockers for prevention of the 1st variceal bleeding in cirrhotic patients with small non-bleeding varices, regardless the presence or absence of criteria with the increased risk of bleeding (child B/C or presence of red wale marks on varices). While, if patients are not using β-blockers, endoscopy should be repeated every year (with ongoing liver injury) or every 2 years (if liver injury is quiescent). If decompensation occurs, endoscopy should be performed by the time of decompensation **(15).**

II. ***Medium/ Large Non-Bleeding Varices:***

Garcia-Tsao and his colleagues recommended, by consensus, that either non-selective β blockers (NSBBs) or endoscopic variceal ligation (EVL) can be used to prevent first variceal hemorrhage in patients with medium/large varices and that choice of treatment should be based on local resources and expertise, patient preference and characteristics, contraindications and adverse events **(15).**

NSBBs is inexpensive, easily administrated and do not need specific expertise. Its disadvantages is that about 15% of patients may have contraindications to NSBB use, and another 15% require dose reduction or discontinuation due to side effects (e.g., fatigue, weakness, and shortness of breath) that resolve when discontinued **(16).**

Advantages of esophageal variceal ligation (EVL) are that it can theoretically be done in the same session as screening endoscopy and has few contraindications. Disadvantages are the risks associated with sedation, plus the risk of causing dysphagia, esophageal ulcerations, strictures, and

bleeding. EVL should be repeated every 2-8 weeks until the eradication of varices then performed 3-6 months after eradication and every 6-12 months thereafter**(15).**

Treatment of Acute Variceal Bleeding:

1) ***General Measures:***

The management of the patient with acute variceal bleeding includes treating the hypovolemic shock (with volume replacement and blood transfusion) and preventing bleeding-associated complications (e.g. hepatic decompensation, renal failure and bacterial infections). Initial resuscitation (stabilization of airway, breathing and circulation) aims at maintaining a sufficient O_2 delivery to the tissues **(17).**

We should restore the blood volume rapidly but with caution for keeping hemodynamic stability and a hemoglobin level of nearly 8 g/dl. This recommendation depends on experimental studies which identified that restoration of all lost blood elevates portal pressure to levels above the normal level with more re-bleeding and mortality **(18).**

Furthermore, vigorous resuscitation with saline have to be avoided because this may precipitate re-bleeding and also worsen or precipitate the accumulation of ascites or fluid at other sites. The transfusion of fresh frozen plasma or factor VIIa to correct INR is not recommended in case of variceal hemorrhage; also platelets transfusion cannot be recommended **(15).**

Bacterial infection is an important indicator in the prognosis of variceal bleeding, with spontaneous bacterial peritonitis (50%) is the most frequent infection, followed by urinary tract infection (25%) and pneumonia (25%). Using prophylactic antibiotics in patients with variceal bleeding may decrease re-bleeding and mortality **(19)**

2) ***Specific Measures:***

I. ***Pharmacological Therapy:***

Variceal pressure is reduced by vasoactive drugs through reducing variceal blood flow. A recent study comparing the three most utilized worldwide (somatostatin; octreotide and terlipressin) found no significant differences among them, although terlipressin was used at doses lower than recommended **(20).**

Terlipressin acts through lowering the portal pressure by constriction of the splanchnic arterioles, so causing increase in resistance to blood inflow into the gut. The dose is 2mg/4h intravenous for 48 hours. It may be continued in a dose 1mg/4h for further 72 hours. As regard side effects, abdominal pain is the commonest side effect, while less than 3% of the patients may have serious side effects including peripheral or myocardial ischemia **(15).**

Octreotide is a synthetic analogue of somatostatin with longer half-life. It acts by reducing the portal pressure via increasing splanchnic arterial resistance. It also inhibits glucagon, a vasodilator peptide. Treatment is kept up to 5 days to prevent early re-bleeding **(21).**

II. ***Endoscopic Treatment:***

Inspite that both injection sclerotherapy and variceal band ligation are effective in controlling the acute variceal bleeding, band ligation is better for the initial control of bleeding and is

accompanied with less side effects and improved mortality. Thus, band ligation is the treatment of choice while injection sclerotherapy replaced it if not available or if technically difficult **(18).**

In 10 to 20% of patients, variceal bleeding is unresponsive to initial endoscopic and/or pharmacologic treatment. If bleeding is mild and the patient is stable, a second endoscopic therapy (if technically possible) might be attempted. In about 60-90% of massive variceal bleeding, hemostasis is achieved through balloon tamponade (Sengstaken-Blakemore tube). It should only be used for less than 24 hours as a bridge until definitive treatment is established **(15).**

III. Trans-Jugular Intrahepatic Portosystemic Shunt (TIPS):

In high risk patients defined as those with child class C cirrhosis with a score of 10-13 and those with child class B with active bleeding on endoscopy despite intravenous vasoactive drug therapy **(15).** an early (preemptive) TIPS within 72 hours should be performed if there is no contraindications.

For patients in whom an early TIPS is not performed, intravenous vasoactive drugs should be continued for 2-5 days and NSBBs initiated once vasoactive drugs are discontinued. Rescue TIPS is indicated if hemorrhage cannot be controlled or if bleeding recurs despite vasoactive drugs and EVL. Patients in whom TIPS is performed successfully, intravenous vasoactive drugs can be discontinued **(15).**

Preventive Measures for Re-bleeding:

Within one year of the 1st attack of variceal bleeding, more than 60% of surviving patients have a high risk of re-bleeding. So, those patients should receive active treatments for the prevention of re-bleeding **(1).**

Patients who had a TIPS performed during the acute episode do not require specific therapy for portal hypertension or varices, but should be referred for transplant evaluation. TIPS patency should be assessed by Doppler ultrasound every 6 months **(15).**

AASLD guidelines recommend combined therapy of NSBBs (propranolol or nadolol) plus EVL as a first line therapy for all other patients who did not have early TIPS **(15).**

A meta-analysis comparing combination therapy to monotherapy with EVL or drug therapy has revealed that combination therapy is significantly more effective than EVL alone in preventing variceal bleeding. Though, combination therapy is only marginally more effective than drug therapy (NSBB plus nitrates) alone, with a tendency for an increased survival with drugs alone **(22).**

It was found that combination of β-blockers (propranolol or nadolol) with isosorbide mononitrate (ISMN) has a greater reduction effect on portal hypertension than NSBB alone but with more side effects and no difference in overall re-bleeding or mortality. Moreover, combination of band ligation with nadolol plus ISMN was found to be better than nadolol plus ISMN alone in preventing re-bleeding **(23).**

Trans-Jugular Intrahepatic Portosystemic Shunt (TIPS)

TIPS were found to be superior to the combination of endoscopic therapy with pharmacotherapy in preventing the re-bleeding. This is accompanied by an increase in the risk of encephalopathy without early or late survival benefit **(24)**.

TIPS should be considered in patients who experience recurrent variceal hemorrhage despite combination pharmacological and endoscopic therapy. In centers where the expertise is available **(15)**.

Endoscopic Variceal Ligation (EVL)

Endoscopic variceal ligation (EVL) was developed to find an effective method of treating esophageal varices endoscopically with fewer complications than endoscopic sclerotherapy (ES). The concept was established upon many years of experience treating hemorrhoids with rubber band ligation in patients with or without portal hypertension. EVL works by ligating all or part of a varix resulting in occlusion from thrombus formation. The tissue then necrosis and sloughs off within few days to weeks, leaving a superficial mucosal ulceration, which rapidly heals **(**25**)**.

Another reason that EVL is an effective method for preventing further variceal bleeding is that collateral vessels near the cardia decrease after EVL **(**25**)**. Another interesting finding is the hepatic venous pressure gradient (which correlates with the risk of variceal bleeding) does not increase after EVL for acute variceal bleeding in contrast to ES **(**26**)**.

The first patient was treated with EVL in 1986. Since then, advances were developed in the technique that led to its routine use in the care of patients with esophageal varices. One of the biggest advances was the development of the multiple band-ligator (Saeed Six-Shooter and Speedbander), which has simplified and improved the safety of EVL **(27)**.

The majority of data suggest that there is no advantage to combine EVL and ES for management of variceal bleeding at each and every session, a conclusion also reached in a meta-analysis. However, adding ES toward the end of a series of EVL sessions to complete eradication of small varices may be useful **(27)**.

On the other hand combination of EVL plus argon plasma coagulation (APC) may be superior to EVL alone for managing endoscopic variceal recurrence without severe adverse events, yet the recurrent re-bleeding rate and mortalities showed no significant difference. Also APC after EVL can improve the therapeutic outcome in the prevention of esophageal varices recurrence by inducing mucosal fibrosis **(23)**.

Complications:

A meta-analysis comparing EVL with ES showed that there is no significant difference about mortality rate between the EVL and ES. Local complications such as esophageal strictures were less common in the EVL than in the ES. There were no significant differences about systemic complications such as pulmonary infections and bacterial peritonitis in the two groups **(28)**.

A number of uncommon complications of EVL have been reported. Examples include local esophageal wall necrosis and perforation, excessive bleeding from esophageal or gastric varices,

esophageal stenosis, altered esophageal motility (may be due to decreased cardiac output from a decreased preload) **(29).**

Sedation-Related Complications in Gastrointestinal Endoscopy:

1) ***Cardiovascular-Related Complications:***

I. ***Hypotension:***

Hypotension occurred during sedation is usually attributed to either vasovagal attacks or the use of sedative and anesthetic agents that depress sympathetic outflow to the cardiovascular system. Benzodiazepines, like midazolam and diazepam, have a mild vasodilator effect and usually produce a slight decrease in arterial blood pressure, even in normal sedative doses. Combination use of a benzodiazepine and an opioid can profoundly drop blood pressure. Propofol has been shown to be safe and effective for sedation during endoscopic procedures that require more time and patient co-operation such as retrograde cholangiopancreatography, endoscopic ultrasonography and small bowel enteroscopy before these procedures **(30).**

II. ***Myocardial Ischemia/Infarction:***

Increased myocardial oxygen demand is mainly due to an increase in heart rate. This can cause angina in patients with ischemic heart disease or occult symptomless myocardial ischemia. On the other hand, hypotension reduces myocardial perfusion. Stress-induced myocardial ischemia can occur even in patients with or without clinically significant coronary disease **(31).**

2) ***Respiratory-Related Complications:***

I. ***Respiratory Depression:***

Intravenous benzodiazepines such as midazolam and diazepam can cause respiratory depression. Intravenous opioids, such as meperidine and fentanyl, occupy opioid receptor sites within the brain and brainstem and can similarly cause respiratory depression. Drug induced hypoventilation may cause both hypoxemia and carbon dioxide retention **(31).**

II. ***Airway Obstruction:***

Upper airway obstruction may be due to anatomical structures or a foreign body. Independent predictors of airway modifications include male sex and increased body mass index. Laryngospasm is more likely to occur during deep sedation. Laryngospasm occurs more frequently in adults who are smokers. Bronchospasm may be a result of an anaphylactic reaction or a consequence of a hyper-reactive airway in asthmatic patients **(30).**

III. ***Hypoxia:***

Hypoxia may be a consequence of respiratory depression or airway obstruction. The incidence of hypoxia is 1.5% to 70%, which makes it the most common cardiorespiratory complication during endoscopy **(32).**

Effect of Iron Deficiency Anemia on Cardiac Functions in Patients with Portal Hypertension

Anemia is one of the earliest and common complications of portal hypertension in children. It is responsible for a significant amount of morbidity resulting in poorer quality of life and is an important risk factor for the development and progression of cardiovascular complications. The

severity of anemia increases with more advanced portal hypertension. It is one of the major causes of fatigability, reduced exercise tolerance and left ventricular hypertrophy **(33).**

Based on the physiological significance of oxygen transported to myocardial tissue, anemia may be a cause of more severe cardiovascular diseases or a sign of other severe diseases that occur in the body. The physiologic response to anemia is a compensatory increase in cardiac output in order to maintain adequate oxygen delivery **(33).**

Patients are asymptomatic with mild anemia but dyspnea and fatigue may occur when anemia is further aggravated. In severe cases, iron-deficiency anemia can lead to left ventricle (LV) dysfunction and heart failure **(33).**

It has reported that myocardial contractility would decrease when hemoglobin was below 7 g/dL and chronic anemia would result in increased LV end-diastolic pressure as well as decreased functional reserve **(34).**

Frequent research has been conducted on left atrium (LA) structural and functional remodeling, which is a cause of LV diastolic dysfunction, therefore the significance of LA has drawn much attention nowadays. Increased left atrial size has been shown as an important predictor of target organ damage and multiple adverse cardiovascular events **(35).**

Patients with iron deficiency anemia (IDA) can present with symptoms that result from hypoxic functioning as dyspnea progressing to breathlessness at rest, vertigo, syncope, headache, tachycardia and cardiac systolic flow murmur **(36).**

Moreover, anemia is considered to be an independent risk factor for cardiovascular disease (CVD) outcomes in the general population. Anemia is correlated with increased morbidity and mortality in patients with heart failure. As a result of anemia, adaptive cardiovascular mechanism happens which result in left ventricular hypertrophy and dilatation, and myocardial ischemia, which are risk factors for cardiovascular morbidity **(37).**

Two-dimensional speckle tracing echocardiography (2D-STE) is a new technology to accurately evaluate LA function in normal subjects. It has the advantage in accurate quantification of myocardial deformation and being angle independent. Evaluation of the left ventricle by echocardiographic examination could be done routinely to assess the diastolic and systolic function in portal hypertensive patients, which is both sensitive and repeatable **(38)**

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References:

[1] Gautam V., Khanna R., Sood V., Biharia B., Alam S. (2022): Prevalence and endoscopic features of rectal varices and colopathy in children with cirrhotic and non-cirrhotic portal hypertension. Journal of Clinical and Experimental Hepatology; (12)2:S81.

[2] Ali N and Sumaira M (2002): Portal Hypertension, J Gastrointestinal Radiology; (23): 234-9.

[3] Bolondi L, Gandolfi L, Arienti V, Caletti C, Corcioni E, Gasbarrini G and Labò G (1982): Ultrasonography in the diagnosis of portal hypertension: Diminished response of portal vessels to respiration. Radiology; 142(1):167-72.

[4] Augustine A., John R., Simon B., Chandramohan A., Keshava S. and Eapen A. (2023): Imaging Approach to Portal Hypertension. Journal of Gastrointestinal and Abdominal Radiology; 06(02):123-37

[5] Piscaglia F, Donati G, Serra C, Muratori R, Solmi L, Gaiani S, Gramantieri L and Bolondi L (2001): Value of splanchnic Doppler ultrasound in the diagnosis of portal hypertension. Ultrasound Med Biol;27 (7):893-9.

[6] Alatas F., Monica E., Ongko L. and Kadim M. (2023): Endoscopic Primary Prophylaxis to Prevent Bleeding in Children with Esophageal Varices: A Systematic Review and Meta-Analysis. Pediatr Gastroenterol Hepatol Nutr.; 26(5): 231–8..

[7] Sanyal A, Grace N and Carey W (2007): Practice Guidelines Committee of the American Association for the Study of Liver Diseases; Practice Parameters Committee of the American College of Gastroenterology: Prevention and Management of Gastroesophageal Varices and Variceal Hemorrhage in Cirrhosis. Am J Gastroenterol;(102):2086–102.

[8] D'Amico G and Morabito A (2004): Noninvasive markers of esophageal varices. Open Journal of Gastroenterology;(5):534-9.

[9] Biecker E, Schepke M and Sauerbruch T (2005): The role of endoscopy in portal hypertension. Dig Dis; 23(1): 11-7.

[10] WGO (2014): Esophageal Varices; World Gastroenterology Organization Global Guidelines, 2014.

[11] Vorobioff J and Groszman R (2014): Prevention of portal hypertension: From variceal development to clinical decomposition. Hepatology; 61(1):375-81.

[12] Saif- Al-Islam M., Abdelaal U., Mohammed S., Malakorcid M. and Mohammad A. (2022): Predictors of Recurrence of Spontaneous Bacterial Peritonitis in Cirrhotic Ascitic Patients. The Egyptian Journal of Hospital Medicine; (45)87: 1263-9.

[13] Del Olmo J, Pena A, Serra M, Wassel A, Benages A and Rodrigo J (2000): Predictors of morbidity after the first episode of upper GIT bleeding in liver cirhosis: European Association For the Study of the Liver. Journal of Hepatology; 32:19-24.

[14] Monescillo A, Sierra A, Buceta E, Pena E, Sanchez J, Cruz A, et al (2004): Influence of portal hypertension and its early decompression by TIPS placement on the outcome of variceal bleeding. Hepatology; 40(4):793-801.

[15] Garcia-Tso J and Bosch J (2010): Management of varices and variceal hemorrhage in cirrhosis. N Engl J Med; 362(9):823-32.

[16] Longacre A, Imaeda A, Fraenlei L and Garcia-Taso G (2008): A pilot project examined the predicted preferences of patients and physicians in the primary prophylaxis of variceal hemorrhage. Hepatology; (47):134-56.

[17] Augustin S, Gonzalez A and Genesca J (2010): Acute esophageal variceal bleeding: Current strategies and new presprectives. World J Hepatol; 2(7):261-74.

[18] Villanueva C, Colomo A, Bosch A, Concepcion M, et al (2013): Transfusion strategies for acute upper GIT bleeding: Original practice. N Engl J Med; (368):11-21.

[19] Chavez-Tapia N, Tellez-Avila F, Soares-Weiser K, Gluud C, et al (2011): Meta-analysis: Antibiotic prophy;axis for cirhotic patients with upper GIT bleeding: An update cochrane review. Aliment Pharmacol and Ther; (34):509-18.

[20] Seo Y (2018): Prevention and management of gastroesophageal varices. Clin Mol Hepatol; 24(1):20-42.

[21] Abraldes J, Albillos A, Bañares R, Turnes J, González R, García-Pagán J and Bosch J (2009): Simvastatin lowers. A randomized controlled trial. Gastroenterology; (136): 1651–8.

[22] Puente A, Graupera I, Aracil C, Villanueva C, Gich I, Poca M, Colomo A, et al (2014): Drugs plus ligation to prevent re-bleeding in cirrhosis: An updated systematic review. Liver Int; 34(6):823-33.

[23] Lin L, Du S, Fu Y, Wang L, Jian Z, Zhang C, Luo J, Shen X and Gu H (2017): Combination therapy versus pharmacotherapy and endoscopic variceal ligation or the trans-jugular intrahepatic portosystemic shunt alone in secondary prevention of esophageal variceal bleeding: A meta-analysis of randomized controlled trials. Oncotarget; 8(34):57399-408.

[24] Holster I, Tjwa E, Wils A, Hoek B, Buuren H, Pattynama P, Nicolai J, Scholten P, Kuipers E, et al (2016): Covered transjugular intrahepatic portosystemic shunt versus endoscopic therapy for prevention of variceal bleeding: A randomized controle trial. Hepatology; 63(2):581-9.

[25] Seno H, Konishi Y, Wada M, Fukui H, Chiba T and Okazaki K (2006): Endoscopic ultrasonography evaluation of vascular structures in the gastric cardia predicts esophageal variceal recurrence following endoscopic treatment. J Gstroenterol Hepatol; (21):227-31.

[26] Avgerinos A, Armonis A, Triantos C, Raptis S, Panani A, et al (2004): Sustained rise of portal pressure after sclerotherapy but not band ligation in acute variceal bleeding in cirrhosis. Hepatoogy; 36(6):1623-30.

[27] Stiegmann G, Goff J, Sun J, Davis D and Silas D (1989): Technique and early clinical results of endoscopic variceal ligation (EVL). Surg Endosc; (3):73-8.

[28] Dai C, Liu W, Jiang M and Sun M (2015): Endoscopic variceal ligation compared with endoscopic injection sclerotherapy for treatment of esophageal variceal hemorrhage: A meta-analysis. World J Gastroenterol; 21(8):2534-41.

[29] Debette S, Gauvrit J, Desseaux G, Nibbio A, Leys D and Pruvo J (2003):Paraplegia after ligation of esophageal varices. Neurology; 60(5):30-5.

[30] Amornyotin S (2016): Intravenous sedation teqniques for GIT endoscopy. Journal of Gastroenterology and Hepatology; 5(3):2050-7.

[31] Lacy C, Contrada R, Robbind M, Chelton S, Kostis J and Tannenbaum A (1995): Coronary vasoconstriction induced by mental stress. The American Journal of Cardiology; 75(7):503-5.

[32] Qadeer M, Lopez A, Vargo J and Dumot J (2011): Hypoxemia during moderate sedation for GIT endoscopy: Causes and associations. Gastroenterology; (103):23-56.

[33] Hegde N, Rich M and Gayomali C (2006): The cardiomyopathy of iron deficiency. Tex Heart Inst J;33(3):340–4.

[34] Rakusan K, Cicutti N and Kolar F (2001): Effect of anemia on cardiac function, microvascular structure and capillary hematocrit in rat hearts. Am J Physiol Heart Circ Physiol; 280(3):1407–14.

[35] Amin M, Tighiouart H, Weiner D, Stark P, Griffith J, MacLeod B, Salem D and Sarnak M (2004): Hematocrit and left ventricular mass: The Framingham Heart study. J Am Coll Cardiol;43(7):1276–82.

[36] Lopez A, Cacoub P, Macdougall C and Peyrin-Biroulet L (2016): Iron deficiency anaemia. The Lancet;(387):907-16.

[37] Lee K, Park E, Choi H, Kang H, Han K, et al. (2019): Anemia and iron deficiency in children with chronic kidney disease (CKD): Data from the know-ped CKD study. J Clin Med;(8)2:152.

[38] Cameli M, Lisi M, Mondillo S, Padeletti M, Ballo P, Tsioulpas C, Bernazzali S and Maccherini M (2010): Left atrial longitudinal strain by speckle tracking echocardiography correlates well with left ventricular filling pressures in patients with heart failure. Cardiovasc Ultrasound;21(8):14.