Are Hepatic Vein Waveform and Damping Index Valuable in Prediction of Esophageal Varices in Cirrhotic Patients?

Ebtsam Elsayed Abdelmonem Abdallah[1], Salama Shaaban Alghonaimy[2],Amira Mohammad Soliman [3], Mohamed Ibrahim Amin[4], Ahmed Abouelkhair Badawy[\]

[1] *Zagazig Fever Hospital,Egypt.*
[2] *Department of Tropical Medicine, Faculty of Medicine, Zagazig University, Zagazig, Egypt.*
[4] *Department of Radiodiagnosis, Faculty of Medicine, Zagazig University, Zagazig, Egypt.*

Corresponding Author
Ahmed Abouelkhair Badawy, MD

Mobile:
+201062609847

E mail:
AAAboelkher@medicine.zu.edu.eg

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Background and Study aim: Liver cirrhosis is the main leading cause of esophageal varices. Loss of architecture with subsequent portal hypertension leads to disturbance of blood flow in hepatic circulation. Hepatic venous waveform and its degree of damping are valuable non-invasive tools to foresee the existence of esophageal varices.The aim of this study is to evaluate the value of hepatic vein waveforms (HVW) and damping index (DI) in prediction of the presence of esophageal varices in cirrhotic patients as a non-invasive tool to discriminate the patients who need upper endoscopy from those who don't need.

Patients and Methods: This cross-sectional study included 48 cirrhotic patients (as evidenced with history, clinical examination, biochemical data and pelviabdominal ultrasound) which were divided into 2 groups according to presence of esophageal varices. Group (I): 26 patients with esophageal varices. Group (2): 22 patients without esophageal varices.

Results: Twenty five out of 26 patients (96.2%) with esophageal varices and 90% of patients in Child Pugh class C had monophasic waveform. There is no significant relation between severity of ascites and HVW. Among all patients, 30 patients (62.5%) had DI >0.6, without significant predominance to presence of esophageal varices, certain Child Pugh class, degree of ascites or certain HVW. There is significant correlation between damping index and Child Pugh score.

Conclusion: Monophasic hepatic vein waveform is a good non-invasive indicator for the presence of esophageal varices and advanced cirrhosis. DI is of no value in predicting esophageal varices, but significantly correlated with Child Pugh score.

INTRODUCTION

Liver cirrhosis is the leading cause of mortality and morbidity across the world. It's the 11th leading cause of death and 15th leading cause of morbidity **[1]**.

Portal hypertension is one of the most serious complications of liver cirrhosis. It can be manifested with portal hypertensive gastropathy, gastric varices and esophageal varices, **[2].**

If portal pressure upsurges greater than 12 mm Hg, esophageal varices will be formed. The frequency of esophageal varices in patients with upper gastrointestinal bleeding is form 2 to 9%. They are classified into small, medium, and large **[3].**

Despite improvement in diagnosis and therapy, mortality from acute variceal bleeding may still reach up to 20%. Moreover, it is the second most common cause of death in cirrhotic patients **[4,5].**

However upper gastrointestinal endoscopy is a an accurate diagnostic method for esophageal varices, it

cannot be used as a screening tool because it is invasive and not possible in several settings due to accessibility and cost **[6].**

Multiple noninvasive approaches have been evolved to diagnose esophageal varices. Non-invasive methods also currently have a distinct role in clinically significant portal hypertension (CSPH) in patients with compensated advanced chronic liver disease cACLD **[2].**

Hepatic veins Colour Doppler ultrasound has been developed as a qualitative non-invasive diagnostic method of portal hypertension and a predictive method of oesophageal varices. There are three types of Hepatic vein waveform (HVW) : - Monophasic: uniform waveform, Biphasic: no reversed stream with or without diminished phasic fluctuation and Triphasic: normal form. Monophasic and Biphasic HVW are accompanied with severe portal hypertension **[7]**. Damping Index (DI) is a quantitative method for measuring the little changes of HV waveform **[8]**.

We aimed at this work to find noninvasive predictors of esophageal varices in cirrhotic patients.

SUBJECTS AND METHODS

Our work is a retrospective study conducted in A **Study design:** Prospective cross sectional study.

Study setting: The study was performed at Tropical Medicine and Radiodiagnosis Departments, Zagazig University Hospitals during the period from 2-2021 to 2-2022.

Sample size: Forty eight patients as a comprehensive sample. These items are in the design of the journal

Inclusion criteria: Liver cirrhosis either with or without esophageal varices. Diagnosis of cirrhosis is based on clinical, laboratory and ultrasonographic assessment.

Exclusion Criteria:

- Esophageal varices due to causes other than liver cirrhosis.
- Patients with history of organ failure other than liver failure.
- Any chest or heart diseases that affect the blood flow in the right side of the heart.
- Patients presented with acute variceal bleeding or any case of hypo or hypervolemia.
- Currents treatment with beta blockers or any other medications that could affect portal pressure.
- Portal vein thrombosis
- Hepatic encephalopathy grades 3 or 4 or any condition interfering with endoscopy.
- Patients with hepatocellular carcinoma (HCC).
- Patients who don't sign in consent.

Methods:

From each patient the following data had been collected upon admission.

1. **Full history taking and thorough clinical examination:** with stress on presence of general signs of chronic liver disease and presence of ascites and splenomegaly.
2. **Laboratory assessment of:**
   - ♦ Complete blood count
   - ♦ Liver function tests (serum bilirubin, serum total protein, serum albumin, liver enzymes)
   - ♦ Kidney function tests
   - ♦ Coagulation profile
3. **Calculation of Child-Pugh Score:** A Child classification system based method was used to detect the severity of liver disease depending on clinical pictures like ascites and encephalopathy, in addition to laboratory features like serum levels of albumin, bilirubin and INR **[9].**
4. **Imaging evaluation:**
   - ♦ **Abdominal Ultrasonography**

     (Mindary, diagnostic ultrasound system, Model: DC-N2) to show cirrhosis, patency of portal vein, ascites, size of spleen and exclusion of HCC.
   - ♦ **Colored Doppler Studies:**

     Colored Doppler ultrasound for assessment of hepatic vein waveform and calculation of damping index. Doppler ultrasonography were assessed with an ultrasound sonography device (Canon applio I 500 tm Japan and with 3.5 Mhz curvilinear probe) via the right

intercostal or subcostal method. Only one operator evaluated all patients to minimize the inter-operators variations.

The Doppler recorded the wave pattern and velocity of the right hepatic vein. HV waveforms were recorded from three repeated measurements. After the HV was represented with colour Doppler flow plotting intercostally along its longitudinal axis, Doppler shift signals were attained in the right HV about 3–6 cm from the connection of the HV and the inferior vena cava. Recording Doppler HV waveforms was done for at least 5 s with end-expiration breath holding.

Categorization of Ultrasonic hepatic venous waveform:

1. Triphasic, which has normal hepatic waveform form. In this pattern the reserved stream is at least in one phase.
2. Biphasic, which has no inverted wave that may or may not be associated with a reduction in the phase oscillators amplitude.
3. Monophasic which has a smooth waveform with or without fluttering.

Damping index was calculated by dividing lowest /highest hepatic venous velocity, the values greater than 0.6 was well-thought-out significant for severe portal hypertension according to Kim and his colleagues who correlate the hepatic venous pressure gradient in their cirrhotic patients with DI **[8]**. The highest velocity and lowest velocity of downward HV stream at the right HV were considered in longitudinal scanning planes and DI was calculated by the lowest velocity/highest velocity of downward HV stream.

5. Upper endoscopy with grading of esophageal varices:

Upper GI Endoscopy was done by Pentax endoscope 3000 to look for and grading of esophageal varices if present. Witten consent was taken from all patients before the procedure.

Esophageal varices were graded according to Cale`s et al. [10] into:

- **Grade 1:** Varices flattened by insufflations.
- **Grade 2:** Varices not flattened by insufflations and separated by areas of normal mucosa.
- **Grade 3:** Confluent esophageal varices not flattened by insufflations. projecting by one-third of the liminal diameter that can't be compressed with air insufflation.

The patients were allocated after endoscopy into 2 groups:

Group (1): Involved 26 Patients with esophageal varices.

Group (2): Involved 22 Patients without esophageal varices.

Statistical Analysis:

Data was collected, then presented and statistically analysed on a computer using SPSS version 20. The chi-square and Fisher exact tests were used to analyse the categorial data. Pearson's correlation coefficient was used to assess relationships among various study variables. Receiver operating characteristic (ROC) curve was used to detect the best cutoff value of DI to predict presence of esophageal varices. P value <0.05 % was used to determine the significance of the result .

RESULTS

A total of 48 cases of cirrhosis were examined. The mean age of patients with and without esophageal varices was 56.3 and 49.5 respectively with significant difference (range from 37 to 72). There were 32 males and 16 females without significant gender difference between patients with and without esophageal varices.

Relation between presence of esophageal varices and ultrasonographic parameters and Child Pugh class:

There was significant relationships between presence of esophageal varices and grades of ascites, HVW and Child Pugh classes, as all patients with mild ascites didn't have esophageal varices. The percentage of tense ascites is significantly higher in patients with esophageal varices. Most patients in Child Pugh class B were without esophageal varices and 96.2% of patients with esophageal varices were in class C, while about 41% of patient without esophageal

varices represented with triphasic wave. There is no significant relation between esophageal varices and damping index of the studied patients **(Table 1).**

Relation between Child Pugh classes and HVW and damping index:

There was significant relationships between Child Pugh classes and HVW where 81.1% of patients in Child Pugh class C had monophasic HVW, while 68.6% of patients in Child Pugh class B had triphasic HVW (ie. the HVW tend to be monophasic with advanced cirrhosis) **(Table 2)**.

Correlation between damping index with age, laboratory parameters and Child Pugh score:

There was significant direct correlation between damping index with age, total bilirubin, INR, Child Pugh score and significant inverse correlation with HB, while other parameters were not significantly correlated with DI **(Table 3).**

Performance of damping index to discriminate the presence of esophageal varices among studied patients:

The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of DI at cutoff value of >0.6 were 53.85%, 27.27%, 46.67%, 33.33% and 41.67% respectively. So DI fail to discriminate the presence of esophageal varices among studied patients (**Table 4).**

Performance of HVW to discriminate the presence of esophageal varices among studied patients:

The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of monophasic HVW were 96.2%, 63.6%, 75.8%, 93.3% and 81.3% respectively. So monophasic HVW can discriminate the presence of esophageal varices among studied patients **(Table 5).**

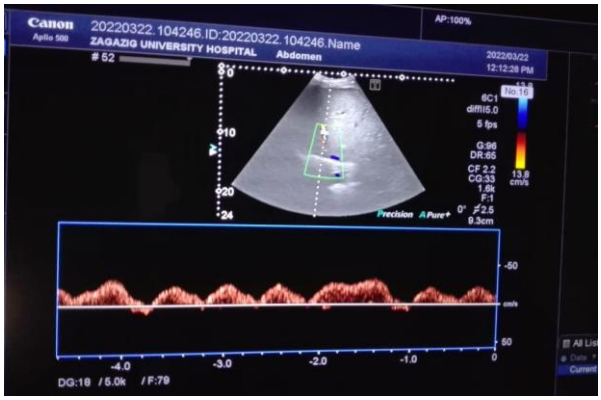

Figure 1: A 45-year-old female in Child Pugh class B without esophageal varices had triphasic HVW.

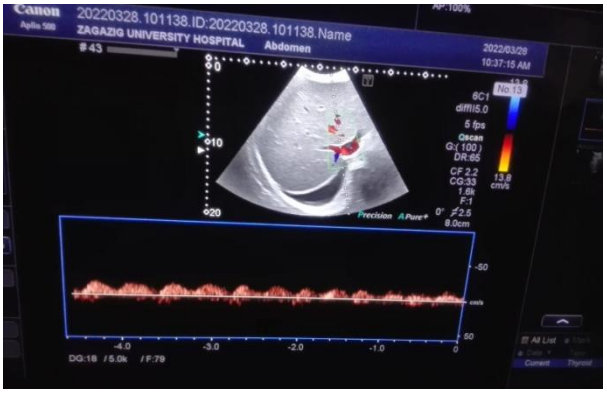

Figure 2: A 47-year-old male in Child Pugh class B with esophageal varices had biphasic HVW.

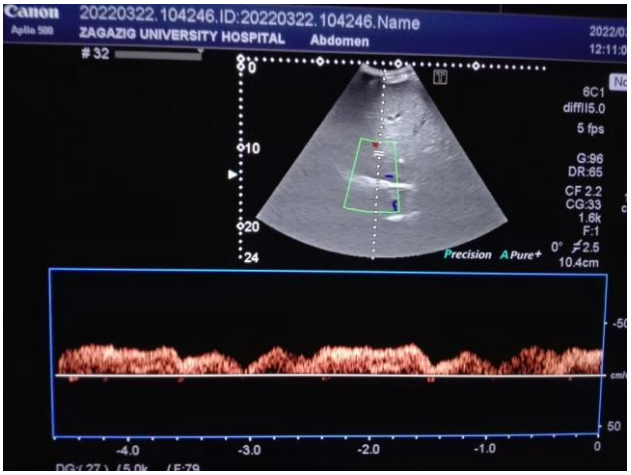

Figure 3: A 65-year-old male in Child Pugh class C with esophageal varices had monophasic HVW in most occasions.

(r) correlation coefficient

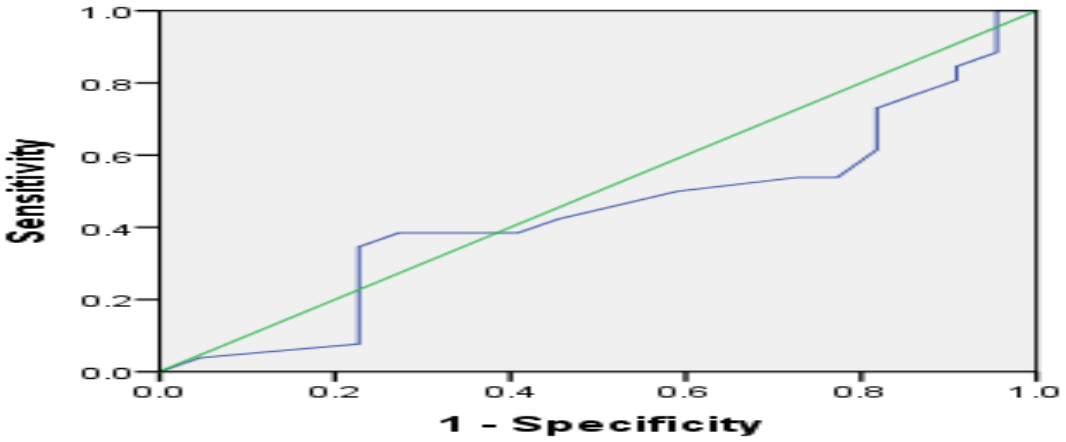

Figure 4: ROC Curve to detect the best cut-off value of damping index to detect esophageal varices among cirrhosis liver patients. Area under curve (AUC) 0.438, CI (0.27-0.604) p=0.46. So damping index fail to discriminate the presence of esophageal varices among studied patients.

Table (1): Relation between presence of esophageal varices and ultrasonographic parameters and Child Pugh class.

	Esophageal varices		χ^2	p-value
	Present n= 26 n (%)	**Absent** n= 22 n (%)		
Ascites grade			13.1	0.001
Mild ascites (n= 7)	0 (0.0)	7 (31.8)		
Moderate ascites (n= 28)	15 (57.7)	13 (59.1)		
Tense ascites (n= 13)	11 (42.3)	2 (9.1)		
Child Pugh class			11.6	0.001
Class B (n= 11)	1 (3.4)	10 (45.5)		
Class C (n= 37)	25 (96.6)	12 (54.5)		
Hepatic vein waveform			22.2	P (0.0001)€ P1(0.0004)* P2 (0.12)# P3 (0.0005)§
Monophasic (n= 33)	25 (96.2)	8 (36.4)		
Biphasic (n= 6)	1 (3.8)	5 (22.7)		
Triphasic (n= 9)	0.0 (0.0)	9 (40.9)		
Damping index			1.8	0.18
>0.6 (n= 30)	14 (53.8)	16 (72.7)		
≤ 0.6 (n= 18)	12 (46.2)	6 (27.3)		

€ significance between patients with and without esophageal varices and all types of HVW
*** significance between patients with and without esophageal varices regarding monophasic type of HVW**
 # significance between patients with and without esophageal varices regarding biphasic type of HVW
§ significance between patients with and without esophageal varices regarding triphasic type of HVW

Table (2): Relation between Child Pugh classes and HVW and damping index

	Child Pugh class		χ^2	p-value
	Class B (n=11) n (%)	Class C (n=37) n (%)		
Hepatic vein waveform Monophasic (n= 33) Biphasic (n= 6) Triphasic (n= 9)	 3 (27.3) 1 (9.1) 7 (63.6)	 30 (81.1) 5 (13.5) 2 (5.4)	19	0.0001
Damping index >0.6 (n= 30) ≤ 0.6 (n= 18)	9 (81.8) 2 (18.2)	21 (56.8) 16 (43.2)	f test	0.17

Table (3): Correlation between damping index with age, laboratory parameters and Child Pugh score.

	Damping Index	
	r	**P**
Age per years	**0.375**	**0.009**
Hemoglobin (g/dl)	**0.354**	**0.014**
WBCS (x 10^3/cm)	0.183	0.212
PLT (x10^3/cm)	0.135	0.361
Total serum protein(g/dl)	0.222	0.129
Serum Albumin (g/dl)	0.27	0.064
Total bilirubin (mg/dl)	**0.312**	**0.031**
ALT(µ/L)	0.152	0.303
AST(µ/L)	0.199	0.175
Urea	0.073	0.62
Creatinin	0.029	0.845
Pt (second)	0.153	0.299
INR	**0.302**	**0.037**
Child Pugh score	**0.499**	**0.0001**

(r) correlation coefficient

Table (4): Performance of damping index to discriminate the presence of esophageal varices among studied patients.

	Esophageal varices	
	Present (n=26)	**Absent (n=22)**
Cutoff value of DI >0.6 ≤ 0.6	 14 12	 16 6
Sensitivity	53.85%	
Specificity	27.27%	
Positive Predictive Value	46.67%	
Negative Predictive Value	33.33%	
Accuracy	41.67%	

Table (5): Performance of HVW to discriminate the presence of esophageal varices among studied patients.

	Esophageal varices	
Hepatic vein waveforms	Present (n= 26)	Absent (n= 22)
Monophasic (n= 33)	25	8
Non-monophasic (n= 15)	1	14
Sensitivity	96.2%	
Specificity	63.6%	
Positive predictive value	75.8%	
Negative predictive value	93.3%	
Accuracy	81.3%	

DISCUSSION

The angiotensin-converting enzyme 2 (ACE2) Liver cirrhosis changes the normal hepatic architecture and causes rise in resistance to the blood flow. Changes in hepatic venous drainage occur as a result of changes in hepatic arterial inflow **[11].**

Hepatic venous Doppler can be used to judge association between severity of cirrhosis and waveform changes. This may be helpful in early diagnosis and avoiding the possible complications **[12].**

Varices are a serious consequence of portal hypertension, and variceal bleeding is a severe complication occurring in up to 30% of patients with cirrhosis leading to death in 5% to 8% of patients during the first 48 hours **[13].**

In this study, about 23% of patients presented in Child-Pugh class B and 77% in class C. This is because the patients were recruited from the inpatient wards which receive the advanced cases while the early cases were managed at the outpatient clinic. This result agrees with that of **[14].**

The percentage of Child Pugh class C is significantly higher in patients with esophageal varices. Many researchers reported the advanced Child Pugh score as a risk factor for development of esophageal varices because it is an indicator of

advanced cirrhosis with subsequent increased portal pressure **[5].**

This study finds significant relation between existence of esophageal varices and hepatic vein waveform in cirrhotic patients. Almost all patients with esophageal varices had monophasic hepatic wave (96.2%), while patients without esophageal varices had the three forms of waves with the highest percentage for triphasic waveform (40.9%). The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of monophasic HVW to discriminate the presence of esophageal varices were 96.2%, 63.6%, 75.8%, 93.3% and 81.3% respectively. Study by **Joseph et al., [15]** stated that, loss of triphasic pattern in the hepatic venous tracing had a high sensitivity in predicting the presence of large varices; and the presence of a normal triphasic pattern in a patient with cirrhosis had a high negative predictive value for the presence of large esophageal varices.

In this study, there is significant relation between Child Pugh class and hepatic vein waveform. Almost monophasic or biphasic hepatic wave were found in Child Pugh class C patients versus triphasic wave represented mainly in Child Pugh class B. Normal triphasic waveform covert to biphasic and to lastly monophasic waveform with the increase of Child Pugh's score **[16, 14].**

These results agree with those of **Bolondi et al. [17]** and **Yasmin et al. [12]** who concluded that monophasic and biphasic waveforms had significant relation with advancing grade of cirrhosis. This could be because of the increasing architectural distortion of liver parenchyma with increasing portal pressure, resulting in loss of normal transmission of normal triphasic heart cycle to hepatic veins.

Sudhamshu et al., [18] and **Joseph et al., [15] reported that** no correlation is present between hepatic venous waveform and severity of liver disease. **They** explained their results by the statement of **Abu-Yousef [19]**; although the phases of hepatic vein waves is cardiac in origin, predominantly the change in right atrial pressure and respiratory motion can alter the HV waveforms and its components, and flat waveform are present in about 9% of normal subjects without liver or cardiac disease **[20]**.

There is no significant difference between severity of ascites and Hepatic vein waveform of the studied patients. This result is also reported by **Bhutto et al. [21]**.

In 2007, Kim and his coworkers measured both DI of Doppler HV waveform and HVPG before and after propranolol administration. They found that a reduction in DI from 0.61 to 0.33, simultaneous with a reduction in HVPG from 18 to 11 mmHg and they determined that 0.6 is the cut-off value of DI allowing the diagnosis of severe portal hypertension (>15 mmHg) with 75.9% sensitivity and 81.8% specificity **[8]**.

In this study, 62.5% of the studied patients had a damping index >0.6. Although this study failed to find relations between DI and presence of esophageal varices, Child Pugh class, degree of ascites and HVW, a significant direct correlation with Child Pugh scores was found. This is also reported by **Antil et al. [13]** and **Subodh et al. [16]** with matching of Child Pugh classes in the three studies.

Antil et al. [13] also didn't find relationship between DI and presence of esophageal varices and concluded that DI of no value in predicting presence of oesophageal varices. This is compatible with the current study, where the sensitivity and specificity obtained for damping index at cutoff value >0.6 to discriminate the presence of esophageal varices were 53.85% and 27.27% respectively with accuracy of 41.67%.

This study was limited by the fact that the sample size was small. This was expected because a sizable portion of cirrhotic patients were excluded, who presented with acute variceal hemorrhage or who were on non-selective beta blockers as this is known to change the portal pressures. Cirrhotic patients with ascites were included in the study with the contention that ascites is not known to change the hepatic venous waveform, although it may impair the diagnostic accuracy of the test.

CONCLUSION

Monophasic hepatic vein waveform is a good non-invasive indicator for the presence of esophageal varices and advancement of cirrhosis. Damping index is of no value in predicting esophageal varices, but significantly correlated with Child Pugh scores.

Ethical consideration:

Permission and official approval to carry out the study was obtained. All patients signed a written informed consent before inclusion into

this study and the institutional ethical committee at Faculty of Medicine, Zagazig University, approved the study. The study protocol conforms with the ethical guidelines of the 1975 Declaration of Helsinki.

Conflict of Interest: No

Acknowledgments: No.

Funding: No.

HIGHLIGHTS

- Presence of non-invasive method for prediction of esophageal varices will make the patients more adherent to follow up as invasive methods will be preserved only for treatment.
- Monophasic hepatic vein waveform is a good non-invasive indicator for the presence of esophageal varices and advancement of cirrhosis.
- Damping index is of no value in predicting esophageal varices in this study, but further larger, controlled studies are needed to evaluate its role in prediction and grading of esophageal varices.

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