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Effectiveness of Ultrasound and Colour Doppler In Prediction of Oesophageal Varices in Chronic Liver Disease Patients.

KEYWORDS: Oesophageal Varices (OV), USG and Colour Doppler, Chronic liver disease, Non invasive prediction of esophageal varices.

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ABSTRACT *Purpose-It is recommended that all the cirrhotic / chronic liver disease patients should be screened for presence of OV (Oesophageal Varices) by endoscopy but it has many disadvantages such as it is expensive, adds to patient discomfort and bears a risk of complications (like oesophageal perforation, aspiration of gastric contents and bacteremia). Our study aimed to determine whether ultrasound and Colour Doppler indices can be used to predict the presence or absence of OV.*

Materials and methods- Fifty six patients with chronic liver disease attending our hospital from August 2011 to August 2013 were included in this cross sectional study. They underwent thorough clinical, biochemical and hematological examination. USG (Ultrasonography) and Colour Doppler parameters relevant in prediction of oesophageal varices were studied. Upper GIT(Gastrointestinal Tract) endoscopy was performed to confirm presence or absence of oesophageal varices. Significance and P values of quantitative and qualitative parameters were found using unpaired 't' test and chi square test. Receiver Operating Characteristic curves (ROC curves) were drawn for significant variables. A scoring system was developed which could predict oesophageal varices.

Results -- Statistically significant parameters in the prediction of OV were platelet count, WBC count, splenic length, splenic index, platelet count/splenic length, mean PV(portal vein) velocity, splenoportal index, SPV(splenic vein) and SMV(superior mesenteric vein) caliber and presence of collaterals. Based on these parameters we developed a scoring system which could predict OV. On statistical analysis of scoring system we found that 55.35% of diagnostic endoscopies can be avoided.

Conclusion-- Some USG, Colour Doppler and biochemical parameters can be used as an alternative to more invasive and more expensive upper GIT endoscopy.

Introduction

It is estimated that upto 1% of world's population could have histological cirrhosis (chronic liver disease) [1]. Portal hypertension is associated with presence of chronic liver diseases and causes oesophageal varices [2].

It is recommended that all cirrhotic / chronic liver disease patients should be screened for presence of OV every 1-2 years [2,3]. In future this social and medical burden will increase due to greater number of patients with chronic liver disease. Upper GIT endoscopy also has disadvantages such as it is expensive, adds to patient discomfort and bears a risk of complications like oesophageal perforation, aspiration of gastric contents and bacteremia [2].

Presence of OV correlates with severity of liver diseases. OV are present in 30% - 40% of patients in compensated cirrhosis (Child Pugh class A) and in 60% - 85% patients in decompensated cirrhosis (Child Pugh class B and C). Screening endoscopy is not cost effective in patients with compensated cirrhosis [4].

Our study aimed to determine whether ultrasound, Colour Doppler and biochemical indices can be used to predict the presence of oesophageal varices and to develop a scoring system which will help rural centers and centers without endoscopy facilities to predict the presence of OV. It will also reduce the endoscopy burden in urban areas.

Methods-

Fifty six patients with a chronic liver disease (all patients in whom liver function tests are raised for more than 6 months [5]) during the period from August 2011 to August 2013 were included in the study. The patients with cardiac failure, portal vein thrombosis, budd chiari syndrome, pregnant patients and patients in whom the cause of oesophageal varices was other than portal hypertension were excluded. The study was approved by the ethical committee of the institute and written informed consent was obtained from all patients.

Detailed history and clinical examination was done. Hematological and biochemical tests included measurement of s. bilirubin (total), s.albumin, prothrombin time, platelet count, WBC count , SGOT , SGPT , s. creatinine. For each patient modified Child Pugh (CP) score was calculated.

Thorough USG and Colour Doppler examination was done using Mindray (Mindray diagnostic ultrasound system, model DC-7, made in China) and GE Logiq (GE Logiq -3 expert machine, made in Korea) machine. Following parameters were studied—

1. Splenic length – length of long axis of spleen.
2. Splenic index – product of three measurements of spleen – length, breadth, and thickness.
3. Platelet count / splenic length was calculated.
4. Mean portal vein velocity -- measured on spectral

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waveforms.

5. Splenoportal index was calculated as splenic index / mean portal vein velocity.
6. Hepatic venous waveform – was classified as triphasic / biphasic / monophasic .
7. Ascites was graded as nil / mild /moderate /severe as per following criteria – Mild—detectable only by ultrasound, Moderate—visible moderate symmetrical abdominal distension, Severe—marked abdominal distension.

8 Hepatic size – was classified as normal/ enlarged/ shrunken by measuring liver size in midclavicular plane.

9 Portal vain caliber -- Outer-to-outer main portal vein diameter (mm) was measured midway between the splenoportal confluence and its intrahepatic bifurcation.

10 Splenic vein caliber -- was measured at splenic hilum.

11 Superior mesenteric vein caliber –was measured 1cm proximal to SMV – PV junction.

12 Collaterals – Presence or absence was detected .

Upper GIT endoscopy was performed using Olympus actera 150 series videoscope (endoscope) to confirm presence or absence of oesophageal varices.

Data was tabulated and analysed with the help of computer assisted software, SPSS ver. 16.0. The statistical tests of significance used for quantitative data was Unpaired "t" for comparison of two independent groups in terms of their means. Probability "P" was determined at 0.05 level of critical significance.

For estimating the significance of difference between proportions (i.e. for qualitative data), the statistical test used was X^2 (Chi-square test). Pooled data was used wherever applicable. Similarly Yate's correction factor was applied wherever the expected value in any cell was less than 5.

All variables that were found to be of significance were included in further statistical analysis.

Receiver Operating Characteristic curves (ROC curves) were drawn for significant variable to find best sensitivity and specificity cut off values of continuous variables for the presence or absence of oesophageal varices (software used is R software).

Using above cut off values of significant variables a scoring system was developed which could predict oesophageal varices.

Results

Out of 56 patients with chronic liver diseases 45 (80.36%) patients were with oesophageal varices and 11(19.64%) patients were without varices.

The commonest age group was 30-49 years and age range was 20-76 years (See Figure- 1).

There was preponderance of males and alcoholism was the commonest aetiology (See figure -2 &3).

The biochemical/hematological factors statistically significant in prediction of oesophageal varices were platelet count (P=0.014) and WBC count (P=0.001) (see Table -1).

Table- 1: Biochemical parameters in patients with and without oesophageal varices

Parameters	With varices (n = 45)	Without varices (n = 11)	t value	P value
	Mean ± SD	Mean ± SD		
Serum albumin (gm/dl)	3.17 ± 0.62	2.96 ± 0.79	0.953	0.345
Serum bilirubin (mg/dl)	4.68 ± 6.83	7.79 ± 14.15	1.067	0.291
PT (sec)	18.05 ± 3.98	15.80 ± 1.94	1.814	0.075
Platelet count (per mm^3)	113355.56 (70642.88)	172818 (64275.68)	2.54	0.014*
SGOT (IU/L)	92.50 ± 96.32	115.52 ± 64.51	0.75	0.457
SGPT (IU/L)	47.34 ± 25.80	61.67 ± 62.67	1.196	0.237
WBC count (per mm^3)	6221.33 (2866.60)	9591.0 (3425.92)	3.364	0.001**
Serum creatinine (mg/dl)	1.14 ± 0.55	1.35 ± 0.82	1.025	0.310

* P < 0.05, statistically significant ** highly significant

SD = Standard Deviation (Test used- unpaired't' test)

The USG and Colour Doppler parameters statistically significant in prediction of oesophageal varices were splenic length, splenic index, platelet count/splenic length, mean portal vein velocity, splenoportal index, superior mesenteric and splenic vein caliber and presence of collaterals (See Table-2).

Table-2: USG and Colour Doppler parameters in patients with and without oesophageal varices

Parameters	With varices (n = 45)	Without varices (n = 11)	t value	P value
	Mean ± SD	Mean ± SD		
Splenic length (mm)	141.98 ± 26.01	113.0 ± 22.33	3.396	0.001**
Splenic index (cm^3)	467.76 ± 256.79	262.22 ± 151.51	2.538	0.014**
Platelet count / splenic length (mm^4)	856.32 ± 610.44	1545.44 ± 499.39	3.464	0.001**
Mean PV Velocity (cm/ sec)	11.66 ± 3.64	16.22 ± 5.29	3.392	0.001**
Spleno portal index (cm^2 sec)	44.89 ± 34.24	18.56 ± 13.21	2.491	0.016**
PV caliber (mm)	12.53 ± 1.81	11.63 ± 1.42	1.534	0.131 (N.S)
SPV caliber (mm)	9.12 ± 2.21	7.58 ± 1.40	2.197	0.032*
SMV caliber(mm)	11.36 ± 1.49	9.75 ± 1.77	3.097	0.003**

Where *--statistically significant ** -- highly statistically significant

(N.S.) – Not Significant , SD—Standard Deviation

PV-Portal Vein, SPV- Splenic Vein, SMV-Superior Mesenteric

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Vein.

Other parameters like age, sex, aetiology, CP(Child Pugh) class, biochemical parameters other than platelet count and WBC count, HV (hepatic venous) waveform, ascites, hepatic size and portal vein caliber though clinically important, were **not** statistically significant in prediction of oesophageal varices. Presence or absence of collaterals was a statistically significant parameter in prediction of esophageal varices (P=0.012). (Details of these parameters not provided considering length of article.)

We drew ROC(receiver operating characteristic) curves to find out best cut off values, sensitivity, specificity, positive and negative predictive values for above significant parameters (See Table -3).

(ROC curves not provided here considering length of article.)

Table-3: Cut off values, sensitivity, specificity, positive and negative predictive values of statistically significant parameters

Variable	Cut off	Sensitivity (%)	Specificity (%)	PPV (%)*	NPV (%)*
Platelet count	<120000	71.1111	90.9091	96.9697	43.4783
WBC count	< 8725	84.4444	72.7273	92.6829	53.3333
Splenic length	> 128.5	60	81.8182	93.1035	33.3333
Splenic index	> 303.3	68.8889	72.7273	91.1765	36.3636
Platelet count/ splenic length	< 923.35	73.3333	90.9091	97.0588	45.4545
Mean PV vel	< 14.425	80	63.6364	90	43.75
Spleno-portal index	> 27.15	66.6667	81.8182	93.75	37.5
SPV caliber	>7.0625	77.7778	54.5455	87.5	37.5
SMV caliber	> 9.9	84.4444	72.7273	92.6829	53.3333
collaterals		46.6667	100	100	31.4286

Where PPV- Positive Predictive Value and NPV- Negative Predictive Value

Scoring system

As the cut offs mentioned above (in Table 3) give maximum sensitivity, specificity, positive and negative predictive value, we used these cut offs (of statistically significant parameters) for developing a novel scoring system for prediction of oesophageal varices as follows:

We assigned scores 0 or 10 for values above or below the respective cut off values as follows:

1 Platelet count -- optimal cut off – 1,20,000 (per mm^3)
So, for platelet count > 1, 20, 000 --- score = 0
And for platelet count < 1, 20,000 --- score = 10
2 WBC count– optimal cut off – 8725 (per mm^3)
So, for WBC count > 8725 --- score = 0
And for WBC count < 8725 ---score = 10
3 Splenic length – optimal cut off – 128. 5 (mm)
So, for splenic length < 128.5 –score = 0
And for splenic length > 128.5 –score =10
4 Splenic index – optimal cut off – 303.3 (cm^3)
So, for splenic index < 303.3 –score = 0
And for splenic index > 303.3 – score = 10
5 Platelet count/ splenic length (PC/SL)—
Optimal cut off—923.35 (mm^4)
So, for PC/SL > 923.35 –score = 0
And for PC/ SL < 923.35 –score = 10
6 Mean PV velocity – optimal cut off – 14.425 (cm/sec)
So, for mean PV velocity > 14.425 –score = 0
And for mean PV velocity < 14.425 –score = 10
7 Splenoportal index – optimal cut off—27.15 (cm^2sec)
So for splenoportal index < 27.15 –score = 0
And for splenoportal index > 27.15 –score = 10
8 Splenic vein caliber (SPV caliber) –Optimal cut off – 7.0625 (mm)
So, for SPV caliber <7.0625 –score = 0
And for SPV caliber > 7.0625 –score = 10

9 Superior mesenteric vein caliber –(SMV caliber) –
Optimal cut off—9.9 (mm)
So, for SMV caliber < 9.9—score = 0
And for SMV caliber > 9.9 –score = 10
10 Collaterals – either present or absent
So, for collateral absent –score = 0
And for collateral present –score = 10

By assigning scores as mentioned above, we calculated scores for each patient included in the study. Maximum score was–100 and minimum score was– 0 (**When USG, Colour Doppler and biochemical parameters were taken together).** We observed that following was the distribution of scores in a total of 56 patients:

Table -4: Scoring distribution of total 56 patients based on USG, Colour Doppler and biochemical parameters (which were statistically significant)

Score	0-25	26-50	51-75	76-100
With varices**(no. of patients)**	0	11	11	23
Without varices**(no. of patients)**	8	2	1	0

Table -5: Statistical analysis for efficacy of scoring system developed above by taking different cut offs (USG, Colour Doppler and biochemical parameters together)

Cut off score	25	50	75
True Positive	45	34	23
False Negative	0	11	22
False Positive	3	1	0
True Negative	8	10	11
Sensitivity (%)	100	75.56	51.11
Specificity (%)	72.73	90.91	100
PPV (%)	93.75	97.14	100
NPV (%)	100	47.62	33.33

Where PPV=Positive Predictive Value and
NPV= Negative Predictive Value

Genereal trend of above table—
As cut off score increases from 25 to 50 to 75
1 Sensitivity decreases,
2 Specificity increases,
3 Positive predictive value increases,
4 Negative predictive value decreases.

Detailed explanation –
1 Cut off score 25-- The above table states that statisti-

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cal assumption that –"patients with score > 25 will have varices and score < 25 will not have varices" has 100% sensitivity and 100% negative predictive value, which means- this assumption correctly identifies all patients with varices as having varices and no patient with score < 25 has oesophageal varices. **Thus patients with score < 25 can be safely excluded from performing diagnostic endoscopy.**

2 Cut off score 50—The above table states that statistical assumption that – "patients with score >50 will have varices and score < 50 will not have varices" has very high i.e, 97.14% positive predictive value , which means most patients with score > 50 have chances of having varices, but there is still chance of false positive finding. Also sensitivity (75.56 – low), specificity (90.91—low) and negative predictive value (47.62—very low) of this assumption is low. **Thus these patients cannot be safely excluded from performing diagnostic endoscopy.**

3 Cut off score 75 – The above table states that statistical assumption that "for patients with score > 75 will have varices and score <75 will not have varices" has 100% specificity and 100% positive predictive value. This means this assumption correctly identifies all patients without varices as patients without varices and all patients with score > 75 will have varices. **Thus patients with score >75 can be safely excluded from performing diagnostic endoscopy.**

Thus in a nutshell, total diagnostic endoscopies that can be avoided = patients with score <25 (8 patients in our study) + patients with score >75 (23 patients in our study) = 31 patients (out of total 56 patients in our study). Thus 55.35 % of diagnostic endoscopies can be avoided.

Similarly, by assigning scores as mentioned earlier, we calculated scores of **USG and Colour Doppler parameters only** (i.e, excluding biochemical parameters- platelet count and WBC count) for each patient included in the study. Maximum score was –80 and minimum score was-- 0. We observed that following was the distribution of scores in a total of 56 patients:

Table 6: -- Scoring distribution of total 56 patients based on USG and Colour Doppler parameters only (which were statistically significant)

score	**0-20**	**21-40**	**41-60**	**61-80**
With varices(**no. of patients**)	4	6	14	21
Without varices(**no. of patients**)	9	1	1	0

Table –7: Statistical analysis for efficacy of scoring system developed above by taking different cut offs (USG and Colour Doppler parameters only)

Cut off score	**20**	**40**	**60**
True Positive	41	36	21
False Negative	4	9	24
False Positive	2	1	0
True Negative	9	10	11
Sensitivity (%)	91.11	80	46.67
Specificity (%)	81.82	90.91	100
PPV (%)	95.35	97.30	100
NPV (%)	69.23	52.63	31.43

Where PPV= Positive Predictive Value and
NPV=Negative Predictive Value

General trend of table –

As cut off score increases from 20 to 40 to 60
1 Sensitivity decreases,
2 Specificity increases,
3 Positive predictive value increases,
4 Negative predictive value decreases.

Also, maximum sensitivity observed in this table is 91.11% compared to 100 % maximum sensitivity observed in scoring done by USG, Colour Doppler and biochemical parameters together. Thus this scoring system is less sensitive.

Detailed explanation –

1 Cut off score 20 – The above table states that – the statistical assumption that -- "patients with score > 20 will have varices and score < 20 will not have varices" has high positive predictive value (95.35%). Thus most of patients with score > 20 will have varices but still there is chance of false positive finding. Also, sensitivity (91.11—comparatively low), specificity (81.82—low) and negative predictive value (69.23 –very low) are on lower side. **Thus these patients can't be excluded from performing diagnostic endoscopy**.

2 Cut off score 40 – The above table states that – the statistical assumption that --"patients with score > 40 will have varices and score < 40 will not have varices" has very high positive predictive value (97.30%). which means most patients of score >40 will have varices. But still there is chance of few false positive patients. Also this assumption has very low negative predictive value (52.63%) and low sensitivity (80%) and comparatively low specificity (90.91). **Thus these patients can't be excluded from performing diagnostic endoscopy.**

3 Cut off score 60 – The above table states that – the statistical assumption that -- "patients with score > 60 will have varices and score < 60 will not have varices" has 100% specificity and 100% positive predictive value. Thus this assumption correctly identifies all patients without varices as patients without varices and all patients with score > 60 will have varices**. Hence, patients with score > 60 can be safely excluded from performing diagnostic endoscopies.**

In a nutshell, total number of diagnostic endoscopies avoided = patients with score > 60 (21 patients in our study), out of total 56 patients. Hence 37.5% of diagnostic endoscopies can be avoided.

Scoring system summary –

1 Total number of diagnostic endoscopies avoided **using statistically significant USG, Colour Doppler and biochemical parameters** are **55.35%.**

2 Total number of diagnostic endoscopies avoided **using statistically significant USG and Colour Doppler parameters only** are **37.5%.**

Discussion

Chronic liver disease causes portal hypertension, which further leads to oesophageal varices(OV) [2]. It is recommended that all chronic liver disease patients should be screened for presence of OV [2,3]. As the presence of OV correlates with severity of liver diseases [4], investigators have attempted to identify characteristics (USG, Colour Doppler and biochemical) that noninvasively predict presence of OV [2,3,4]; so that number of diagnostic endoscopies can be reduced resulting in lesser expenditure and lesser patient discomfort.

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In our study we studied 56 patients who were diagnosed as having chronic liver disease. Various USG, Colour Doppler and biochemical parameters were studied for prediction of oesophageal varices.

Our study comprised of total 45 males (80.36%) and only 11 females (19.64%) and alcoholism was the commonest aetiology. Similar findings were noted by Sarangapani A et al [3].

Platelet count was significantly lower in patients with oesophageal varices, consistent with the findings of Mahassadi AK et al [6].

WBC count was significantly lower in patients with oesophageal varices. But Sarangpani A et al. did not find any association [3].

Splenic length was significantly higher in patients with oesophageal varices, consistent with findings of Sarangapani A et al [3]. (See figure -4).

Splenic index was significantly higher in patients with varices, consistent with findings of Liu CH et al [4].

Platelet count /splenic length ratio was significantly lower in patients with varices and it was more accurate than platelet count alone or splenic length alone in prediction of oesophageal varices. Similar findings were noted by Sarangapani et al [3].

Mean portal vein velocity was significantly lower in patients with oesophageal varices, similar to the findings of Liu Ch et al [4]. (See figure -5).

Splenoportal index was significantly higher in patients with varices and it was more accurate than splenic index alone or mean portal vein velocity alone in prediction of oesophageal varices. This was consistent with findings of Liu CH et al [4].

Splenic vein caliber was significantly higher in patients with varices, consistent with findings of ElNaggar et al [7]. (See figure -6).

Superior mesenteric vein caliber was significantly higher in patients with oesophageal varices, and this parameter is yet to be studied by other investigators in prediction of oesophageal varices.

Presence of collaterals was significant in prediction of oesophageal varices. But Mahassadi AK et al. did not find any statistically significant association [6]. (See figure -7).

By developing a scoring system which takes into account all significant parameters in prediction of oesophageal varices, we found that 55.35% diagnostic endoscopies can be avoided, similar to study of Cherian JV et al., who found that 59.4% endoscopies can be avoided when all statistically significant USG, Colour Doppler and biochemical parameters were considered together [8].

Conclusion

Some USG, Colour Doppler and biochemical parameters can effectively predict presence / absence of oesophageal varices in chronic liver disease patients. Thus they can be used as an alternative to more invasive and more expensive upper GIT endoscopy.

By using scoring system developed in our study, we found that we can significantly reduce / avoid (upto 55.35%) diagnostic endoscopies which are to be performed in chronic liver disease patients.

We state that these noninvasive predictors are of immense help to physicians practicing in rural areas without endoscopy facilities and in urban settings where endoscopy load is very high.

In effect reduction in number of diagnostic endoscopies has an immense bearing on reduction in cost and discomfort to patients having chronic liver disease.

APPENDIX

Table for Figure-1

Distribution of patients with and without esophageal varices according to age

Age (years)	Esophageal varices present		Esophageal varices absent		Total	
	No.	%	No.	%	No.	%
< 30	2	4.44	0	0.00	2	3.57
30-49	21	46.67	9	81.81	30	53.57
50-69	18	40.00	1	9.09	19	33.93
≥70	4	8.89	1	9.09	5	8.93
Total	45	100.0	11	100.0	56	100.0

Table for Figure -2

Distribution of patients with and without esophageal varices according to sex

Sex	Esophageal varices present		Esophageal varices absent		Total	
	No.	%	No.	%	No.	%
Males	36	80.00	9	81.82	45	80.36
Females	9	20.00	2	18.18	11	19.64
Total	45	100.00	11	100.00	56	100.00

Table for Figure -3

Distribution of patients with and without esophageal varices according to etiology

Etiology	Esophageal varices present		Esophageal varices absent		Total	
	No.	%	No.	%	No.	%
Alcohol	16	35.56	8	72.73	24	42.86
HBV	7	15.56	1	9.09	8	14.28
AIH	2	4.44	0	0.00	2	3.58
Others	20	44.44	2	18.18	22	39.28
Total	45	100.00	11	100.00	56	100.00

Where HBV – Hepatitis B Virus.
AIH – Auto immune hepatitis

Figures

Figure-1: Age distribution of patients with & without varices

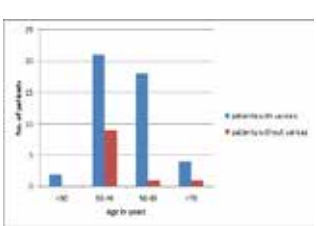

Figure-2: Distribution of patients with & without varices according to sex

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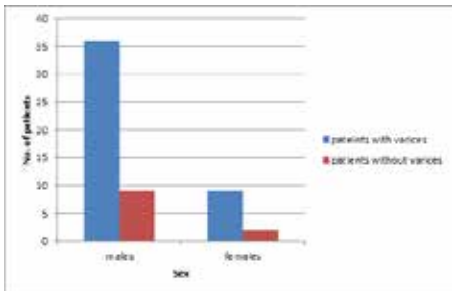


Figure -3: Distribution of patients with and without esophageal varices according to etiology

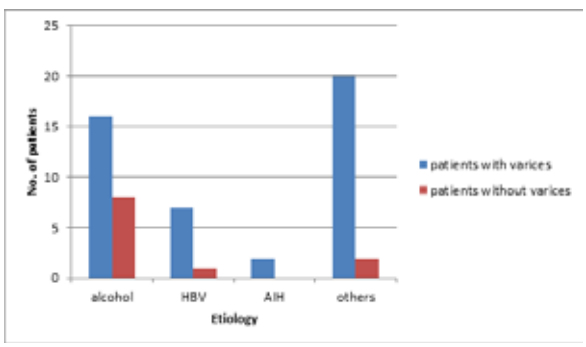


Figure-4: Longitudinal grayscale USG demonstrates splenomegaly.

(Spleen length measuring 18.09 cm)

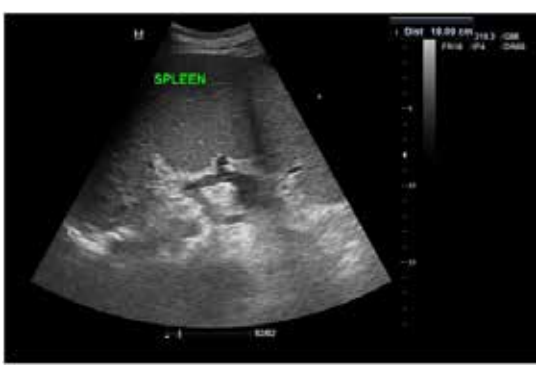
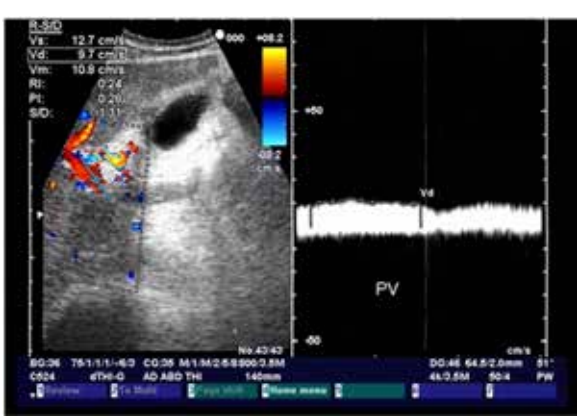


Figure-5: Colour Doppler study shows diminished Portal vein velocity of 9.7 cm /sec



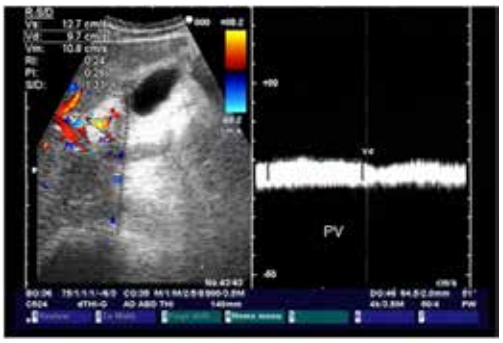


Figure-6: Dilated splenic vein

(splenoportal confluence measures 2.4 cm and splenic vein measures 1.62cm)

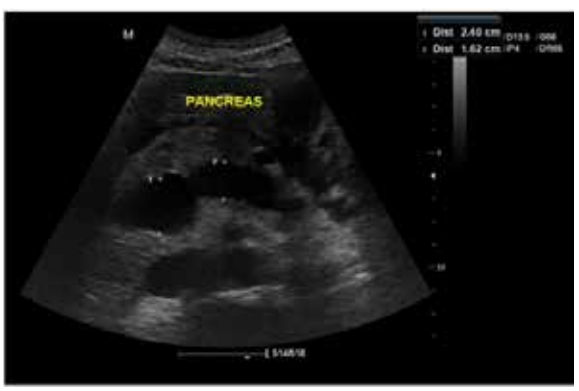
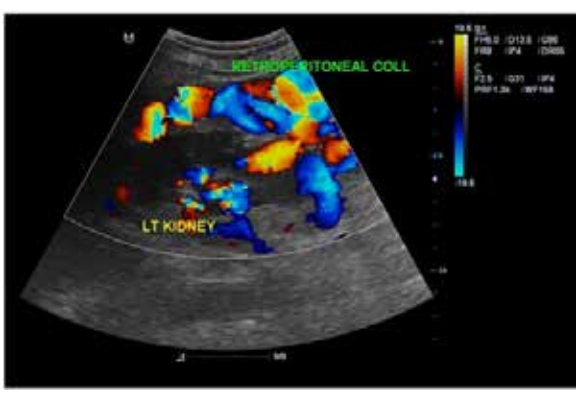


Figure-7: Colour Doppler study at left kidney shows dilated collateral veins in retroperitoneum



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