Role of Portal Venous Ultrasonography and Doppler Evaluation in Predicting Capillary Leak Syndrome in Dengue Fever: A Prospective Cohort Study

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Abstract

Background & Objectives: Capillary leak syndrome (CLS) is a critical complication of dengue fever. Early recognition is essential for timely intervention.. Purpose of the study is to analyze the roles played by portal venous ultrasonography and color Doppler indices in detecting and predicting capillary leak syndrome in patients with dengue fever and correlating these imaging findings with clinical outcome. **Materials and Methods:** It is a prospective observational study conducted on 60 dengue fever cases that were serologically confirmed. The study was conducted from September 2022 to December 2023.On admission Grey –scale abdominal ultrasonography and portal venous Doppler was performed. Portal vein (PV) diameter, cross-sectional area (CSA), peak venous velocity, and congestion index (CI) were assessed and plasma leakage features were recorded sonographically. **Results:** Capillary leak syndrome developed in 54 (90%) patients. Gallbladder wall oedema detected in 56.7% cases and was the most frequent ultrasonographic sign. It followed by pleural effusion (48.3%) and ascites (35%). CLS patients exhibited significantly lower portal vein velocity (mean 17.41 ± 4.02 cm/s) compared to those without CLS (26.66 ± 3.33 cm/s) ($p < 0.001$). Congestion index was significantly elevated in CLS (0.103 ± 0.034). ROC analysis showed highest predictive accuracy for CI (AUC 0.898), followed by velocity (AUC 0.866). Conventional ultrasonographic features demonstrated high specificity but lower sensitivity. **Conclusion:** Portal venous Doppler parameters, especially velocity and congestion index, provide strong early indicators of CLS and outperform traditional ultrasonographic features in diagnostic accuracy. **Clinical Impact:** Portal venous Doppler integration in case evaluation can be added to early risk stratification in dengue fever and can potentially reduce morbidity and progression to shock.

Keywords: Dengue fever, capillary leak syndrome, portal vein, Doppler ultrasonography, congestion index

Introduction

Dengue major cause of acute febrile illness in tropical and subtropical regions became major public health issue. Dengue is caused by a positive-stranded enveloped RNA virus (DENV).It is principally transmitted by Aedes mosquitoes. It has 4 antigenic ally distinct serotypes, DENV-1 to DENV-4, with different genotypes and 3 structural proteins and seven non-structural proteins.[1]

The clinical spectrum of dengue fever ranges from asymptomatic infection to severe dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS). Although primary infection causes activation of immune responses against DENV serotypes, the disease severity is enhanced via heterotypic infection by various serotypes and antibody-dependent enhancement (ADE) and it is mediated through soluble mediators, compliment activation and cytokines [2]

No worry about self –limiting cases but it is about cases landing into dengue haemorrhagic fever or shock syndrome.. Capillary leak syndrome (CLS), resulting from increased vascular permeability, is the hallmark of severe dengue and often precedes circulatory collapse. Early detection is therefore critical.

Clinical presentation [3]

Incubation period of Dengue is 5–7 days, the course follows 3 phases

Febrile Phase: Lasts for 2–7 days.

Critical Phase: Begins at defervescence, typically lasts 24–48 hours.

Convalescent Phase: plasma leakage decreases, begins to reabsorb extravasated intravenous fluids and pleural and abdominal effusions.

Laboratory Diagnosis of Dengue [4]:

Acute phase: initial 0-7 days after symptom onset. During this period, laboratory diagnosis should be made using either 1 of these test combinations

Nucleic acid amplification test (NAAT), an IgM antibody test

(Or) - NS1 antigen test and an IgM detection test

The presence of the dengue virus non-structural protein 1 (NS1) in blood during the first 7 days of illness is indicative of recent dengue virus infection.

Convalescent Phase: >7 days post symptom onset When the acute sample is negative in the recommended test combinations or is not available, a convalescent serum sample can be collected and tested.

IgM ELISA is recommended as the primary test after day 7 of symptom onset.

Interpreting test results [5]

Patients with a positive NAAT (E.g., RT-PCR) or NS1 test have a confirmed acute infection. Patients who have IgM antibodies against dengue virus in a single sample are classified as having a presumptive, recent dengue virus infection.

In a diagnosed case of DF, the following laboratory values are serially monitored to detect the capillary leak syndrome early, thus avoid morbidity and mortality:

Platelet count, Haemoglobin, Haematocrit, WBC count LFT and RFT.
Laboratory findings commonly include leukopenia, thrombocytopenia, hyponatremia, elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

Pathophysiology of capillary leak syndrome

In dengue viral infection, there is hepatic sinusoidal capillary lumen obstruction, which results in reduced portal venous flow and velocity. In severe cases, there may be shunting of portal blood away from the liver along with a dilated portal vein and an increased congestive index.[6]

These observations are typically seen in patients with high hepatic sinusoidal capillary network resistance. Interestingly, clinical features of patients with dengue viral infection share similarities with those in sinusoidal obstruction syndrome such as ascites, right pleural effusion, GB wall edema, hepatomegaly and altered portal blood flow direction.

In a study by Wahid SF, Sanusi S, et al titled "A comparison of the pattern of liver involvement in DHF with classic DF" in 2000, indicated that degree of liver impairment was related to the severity of DHF and concluded that hepatomegaly and liver dysfunction were commoner in DHF than in DF.[7]

Fernando et al described the varying degrees of involvement of liver in acute dengue infection and postulated the causes to be hepatocyte apoptosis directly by virus, hypoxic injury due to impaired liver perfusion, oxidative stress or immune mediated injury.[8]

Sonographic Technique [9]

Pre- imaging instructions: Before the scan, patients are advised to avoid gas-producing foods and drinks (such as carbonated beverages, beer, and dairy products) for 24 hours.

During the B-mode examination, the liver, gall bladder, spleen, peritoneal cavity, and chest wall are evaluated for size and architecture.

ASSESSMENT OF LIVER: liver is examined using real-time sonography, done ideally after a 6-hour fasting both in supine and right anterior oblique views. Additionally, consider sagittal, transverse, coronal, and subcostal oblique views. For optimal imaging, use both standard abdominal transducer and higher frequency transducer[10]

FIGURE:1

Assessment of gall bladder[11] Routine sagittal and transverse sonograms are performed for the examination of the gallbladder. If the gallbladder is not visualized, it's crucial to assess the gallbladder fossa to avoid missing gallbladder pathology. This assessment involves subcostal oblique sonograms, where the transducer is positioned with the left edge higher than the right edge. The face of the transducer is directed

toward the right shoulder. Fasting for at least 4 hours before the examination is recommended to avoid obscuring abnormalities.

Figure: 2

Assessment of portal vein: [12] The portal vein is examined all along its length by using an anterior abdominal, subcostal approach. Depending on vessel orientation and body habitus, the PV and hepatic artery are best examined either by pointing the transducer postero cephalad (subcostal approach) or pointing it medially (right intercostal approach), with these approaches PV and hepatic artery are satisfactorily visualized.

Grey scale: The following were determined:
Presence or absence of the vessel image on real-time imaging
▪ Presence or absence of intraluminal echogenic material
▪ portal vein diameter
▪ cross-sectional area of portal vein.

Figure: 3

Figure: 4

Figure: 5

Portal venous doppler study

Colour and spectral doppler evaluation of pv is done with appropriate machine settings to evaluate the following: Colour uptake flow direction – hepatopetal / hepatofugal flow velocity flow volume congestive index: Csa (cm^2) / pv velocity cm/sec).

Figure: 6

This study investigates the utility of portal venous doppler parameters in predicting cls and compares them with conventional ultrasonographic findings.

Materials and methods

Study Design and Population

This prospective cohort study included 60 consecutive patients diagnosed with dengue fever using NS1 antigen and IgM ELISA testing. Patients were recruited from the Department of Radiodiagnosis between September 2022 and December 2023.

Inclusion Criteria

- Age ≥ 18 years
- Laboratory-confirmed dengue infection
- Hemodynamically stable at the time of ultrasound

Exclusion Criteria

- Pre-existing chronic liver disease
- Portal hypertension or thrombosis
- Cardiac failure or renal failure
- Pregnancy

Ultrasonography Protocol

All ultrasound examinations were performed by experienced radiologists using a high-resolution machine. Each patient underwent USG of the abdomen and chest, performed in real time, in grey scale and colour doppler modes, using 3.5- 5 MHz convex curvilinear probe in GE VOLUSON P8, GE –VOLUSON S8 machine at the time of admission.

1. Gray-scale ultrasound for:

- Gallbladder wall thickness
- Presence of ascites
- Pleural effusion
- Hepatomegaly or splenomegaly

Gallbladder wall thickness >3 mm was considered abnormal.

Portal Venous Doppler Evaluation

The portal vein was evaluated in the supine position during quiet respiration.

Parameters recorded:

- Portal vein diameter (mm)
- Cross-sectional area (CSA) calculated using transverse diameter
- Peak velocity (cm/s) obtained via spectral Doppler
- Congestion Index (CI)

Measurements were taken thrice and averaged.

Outcome measures-

CLS was defined using WHO clinical and ultrasonographic criteria:

- Hypotension or tachycardia
- Fluid accumulation (ascites/pleural effusion)
- Gallbladder wall edema
- Hemoconcentration

Statistical Analysis

Data were analyzed using SPSS version 26. Mean differences were assessed using t-tests. Diagnostic indices were evaluated using ROC curves with AUC, sensitivity, and specificity calculated for Doppler and ultrasonographic findings. A p-value <0.05 was considered statistically significant.

Results

Demographics and Clinical Features

Out of 60 patients, 32 were male and 28 female (mean age 33.4 ± 10.7 years). CLS occurred in 54 patients (90%).

Table 1: Ultrasound Findings for CLS along with following parameters

Findings	CLS present	CLS absent	Frequency [%]
Gallbladder wall edema	33	1	56.7
Pleural effusion	29	0	48.3
Ascites	21	0	35

Gallbladder wall edema showed high specificity (93%) but moderate sensitivity (70%)

Table 2: Portal Venous Doppler Parameters

Parameter	CLS present[n=54]	CLS absent[n=6]	p-value
PV Diameter[mm]	12.94 ± 1.82	10.73 ± 1.30	<0.01
CSA[cm^2]	1.44 ± 0.30	1.05 ± 0.19	<0.01
Velocity[cm/s]	17.41 ± 4.02	26.66 ± 3.33	<0.001
Congestion Index	0.103± 0.034	0.039 ± 0.008	<0.001

Velocity and CI demonstrated the most significant differences

Table: 3 ROC Curve analysis

Parameter	AUC	Sensitivity[%]	Specificity[%]
PV Diameter	0.812	76	73%
CSA	0.792	71	66
PV Velocity	0.866	82	91
Congestion Index	0.898	87	88

Congestion index had the highest predictive performance

Discussion

Dengue fever, DHF and DSS has a surge in incidence over recent decade. This rise in incidence is due to unchecked urban growth without proper water management strategies and the decline in measures to control the mosquitos. As there is Structural similarity of dengue virus with platelets it lead to dengue antibodies mistakenly targeting and destroying platelets. This reaction also impacts other blood cells, including white and red blood cells. The breakdown of platelets causes cytokines and other chemical mediators' release that affects vessel's endothelium and increases vascular permeability which ultimately results in Capillary leak syndrome. [13]

Therefore, it is inferred that the complications arising from dengue are primarily due to the destruction of platelets.

Severe dengue is marked by plasma leakage, abnormalities in blood homeostasis and disruptions in the blood clotting process. Low platelet counts and the resulting malfunction of platelets or disseminated intravascular coagulation causes bleeding.
In the current study, among the 60-dengue fever tested positive patients, follow-up clinical outcomes showed that 54 patients developed capillary leak syndrome, while 6 did not. Additionally, 4 out of the 54 capillary leak syndrome patients experienced coagulopathy and bleeding manifestations. Among the study population, the majority were within the 21-30 years age group. Notably, the highest number of patients who developed capillary leak syndrome (CLS) was also in this age range.

Ultrasonographic features
Capillary leak syndrome (CLS) is characterized by the accumulation of free fluid in various visceral spaces. The manifestations include ascites, pleural effusion, pararenal and perirenal fluid collections, hepatic and splenic subcapsular fluid collections, and pericardial effusion.

In this study, the ultrasonograhy focused on gallbladder wall edema and thickness, presence of ascites and pleural effusion. In the study 34 patients had GB wall edema while 26 patients had normal GB appearance. Among the 34 patients with GB wall edema, 33 (97.1%) developed CLS and only 1 (2.9%) did not and so the specificity was 90%, positive predictive value was 98.1%. But 21 of the 26 patients with normal GB appearance developed CLS, resulting in a negative predictive value 19%. The mean gallbladder wall thickness (GBWT) in patients who developed CLS was 4.379 mm, whereas in patients without CLS, it was 2.0667 mm.

Utilizing the ROC curve, an optimal criterion of >3.0 mm was formulated. The sensitivity at this threshold was 61.0 %, while specificity reached 100%. This finding aligns with a study by Setiawan MW et al., where a sonographic GBWT >3 mm to 5 mm had 93.8% sensitivity, indicating the need for admission and monitoring. Additionally, a GBWT of >5 mm had 91.7% specificity, identifying DHF patients at high risk of hypovolemic shock.[14]

Among the study patients, 21 individuals showed ascites, and all of them developed CLS. Conversely, none of the patients without CLS showed ascites. However, 61 % of the cases were false negatives, highlighting that although the positive predictive value was 100%, the negative predictive value was less. Consequently, specificity was 100%, while sensitivity was 39 %.

Regarding pleural effusion, it was observed in 53.7 % of the study patients, and all of these patients developed CLS. Conversely, pleural effusion was absent in patients who did not develop CLS. Interestingly, over 47% of CLS patients' pleural effusion was absent, resulting in a sensitivity of 53.7 % and a negative predictive value of 19 %.

In current study, gallbladder edema, ascites, and pleural effusion were present in 61%, 39%, and 53.7 % of patients, respectively. These ultrasonographic features were comparable to findings from other studies. In the study by Quiroz-Moreno et al. (2006), gallbladder wall thickening was present in 86% of patients, pleural effusion in 66%, ascites in 60%.[15]

Shruti Chandak and Ashutosh Kumar, in their study to assess the role of radiology in early diagnosis of Dengue Fever, found that the most common USG finding was hepatomegaly (62%), followed by splenomegaly (45%), gallbladder (GB) wall edema (45%), right-sided pleural effusion (37%), bilateral pleural effusion (22%), and ascites (36%).[16]

Similar results were found in study by Wu, et al where, sonographic included thickened GB wall in 38 patients (59%), ascites in 24 patients (37%), splenomegaly in 22(34%), pleural effusion in 21 patients (32%).[17]

In a study by Pandichelvan et al titled "Prognostic Value of Ultrasonography in Dengue Fever, Compared with Clinical , Laboratory Parameters." found that significant association present between thrombocytopenia and thickened gall bladder wall, present in 70 % of the study population, pericholecystic fluid collection seen in 61 %, Pleural effusion present in 50%. Ascites present in 43 %, also Hepatomegaly present in 24 % and splenomegaly in 19 percent[18]

Portal vein doppler features: Dengue fever causes immune-mediated injury of sinusoidal endothelial cells or Kupffer cells resulting in obstruction to the hepatic sinusoidal capillary network. This elevated sinusoidal resistance has a direct impact on the portal vein, which supplies 80% of the blood to liver and thus can be easily demonstrated by portal venous Doppler studies. Increased pressure within the portal vein results in lumen dilation and reduced velocity, ultimately causing flow reversal. Patients with CLS had a mean portal vein diameter of 12.944 mm, while non-CLS patients had a mean diameter of 11.700 mm.

When the portal vein diameter increases, its cross-sectional area also grows. The mean cross-sectional area was 1.4411cm² for CLS patients and 1.1483 cm² for non-CLS patients with a threshold of >1.0285 cm², sensitivity reached 61.1%, specificity was 78%, and the area under ROC curve was 0.677 with standard error of 0.05783, 95% confidence interval of 0.450–0.905. This was in correlation with the study conducted in a large series of normal patients to assess the portal vein measurements where the overall mean diameter in 107 patients aged 21 -40 years was 11 ± 2 mm and no difference between the portal venous measurements of male and female patients.[19]
In our study, patients who developed CLS had a mean portal vein velocity of 17.416 cm/sec, whereas those without CLS had a mean velocity of 26.666 cm/sec. using a criterion of < 15.3 cm/s and area under ROC curve was 0.88. [20]

Congestive index was calculated from the ratio of the cross-sectional area of the portal vein (cm^2) and the average flow velocity (cm/sec.). The congestive index reflects changes in both the cross-sectional area and velocity of the portal vein.

In our study, the increased cross-sectional area and reduced portal velocity yielded in increase in congestive index and so, the mean congestive index in patients who developed CLS was 0.10336 and in non CLS it was 0.04355. Using a criterion of >0.0687, a sensitivity of 59.3% and a specificity of 100% was achieved.

Khongphatthanayothin A, et al, in another study revealed that the PV was significantly more dilated, blood flow velocity of portal vein was lower and congestion index was higher in patients with shock (DSS) than DHF without shock, than DF.[21]

Laboratory findings: A mean platelet value of 51000 was found in patients who developed CLS while those without CLS had a mean value of 105733. However, it is proved that Dengue fever severity correlated primarily with platelet destruction. More the platelet destruction, there is greater the risk of developing capillary leak syndrome. Pandichelvan et al, in their study found that significant association present between thrombocytopenia and thickened gall bladder wall[18]. the patients who developed CLS had a mean haematocrit value of 37.839 while in non CLS patients it was 34.100. With a criterion of >37.9 the sensitivity was 44.4 % while specificity was 100%. A mean haemoglobin value of 12.556 g was found in the patients who developed CLS while the non CLS patients had a mean value of 11.283. Area under the ROC curve was 0.739 with a standard error of 0.0700 and 95% confidence interval of 0.601 to 0.877, With a criterion of >12.7 g the sensitivity was 50.0 % while specificity was 100%

This study demonstrates that portal venous Doppler parameters particularly reduced portal venous velocity and elevated congestion index are more sensitive indicators of early CLS. These findings support the growing evidence that Doppler assessment of splanchnic circulation can detect hemodynamic compromise before gross anatomical changes manifest.

Our results align with previous studies showing decreased portal venous flow in dengue due to increased vascular permeability and third spacing. The congestion index, which combines CSA and velocity, showed the highest diagnostic accuracy, reinforcing its reliability.

The strengths of this study include its prospective design and standardized imaging protocol. Limitations include a relatively small non-CLS group and lack of serial Doppler follow-up.

Conclusion

Portal venous Doppler evaluation is a valuable, non-invasive tool for early detection of capillary leak syndrome in dengue fever. Congestion index and portal vein velocity

outperform conventional ultrasound signs and should be incorporated into routine clinical assessment.

Clinical implications

- Early Doppler changes precede visible ultrasound findings.
- Helps triage dengue patients at risk of shock.
- Useful in resource-limited settings due to availability of ultrasound.

Figure Legends (Placeholders)

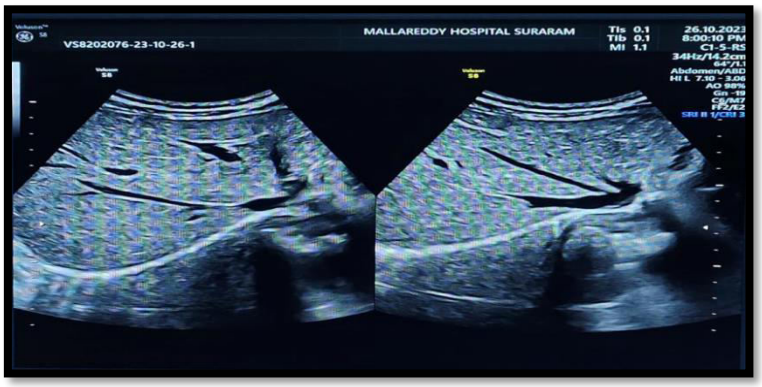

Figure 1: USG Subcostal scan plane showing right lobe of liver and hepatic veins

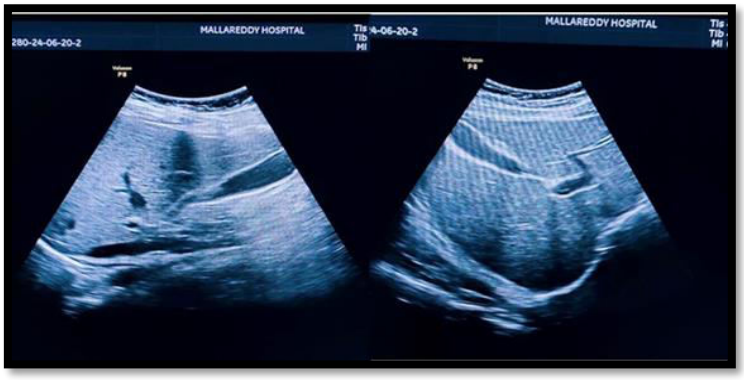

Figure 2: USG Intercostal and Subcostal scan planes showing Gall bladder

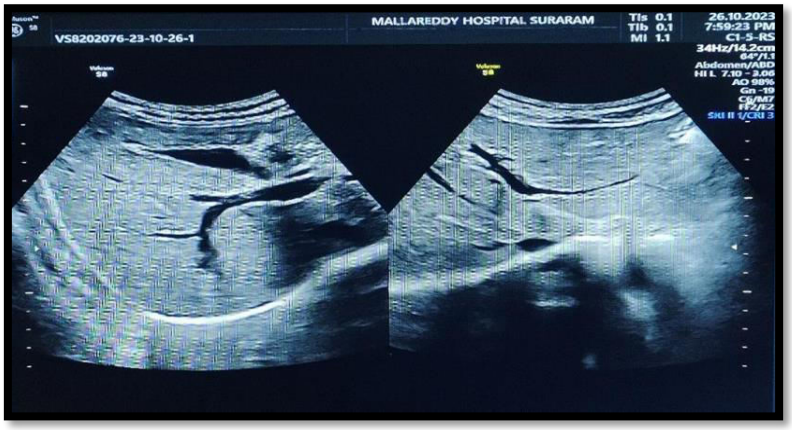

Figure 3: Portal vein best examined with a subcostal oblique view, PV is divided into the right and left branches at the porta hepatis

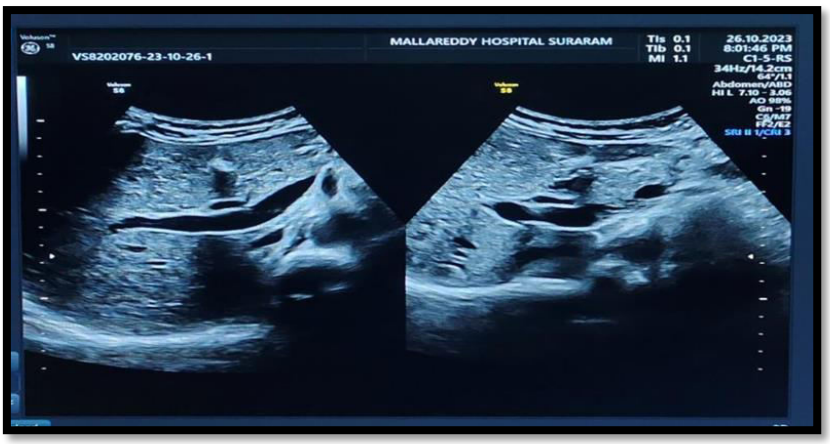

Figure 4: USG scan at the level of porta hepatis showing the portal vein and the CBD anterior to it.

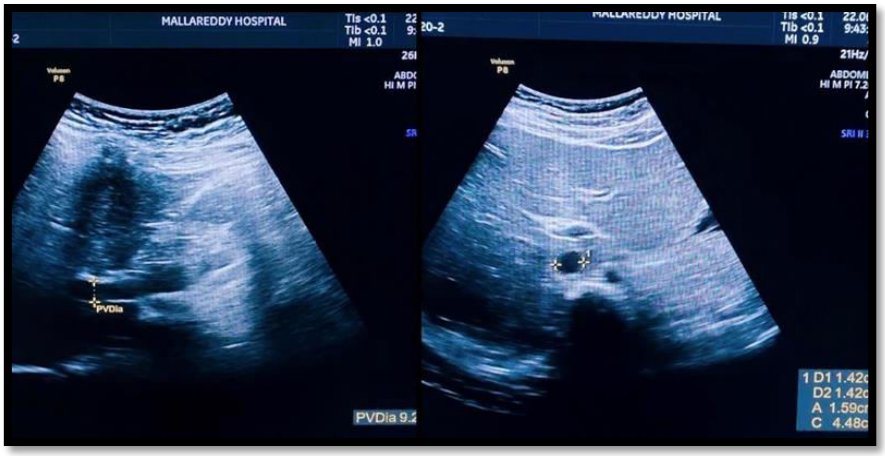

Figure:5 Grey scale USG subcostal right paramedian approach showing, PV diameter measured at the level of hilum 9.5 mm and USG showing measurement of CSA 1.50 cm2

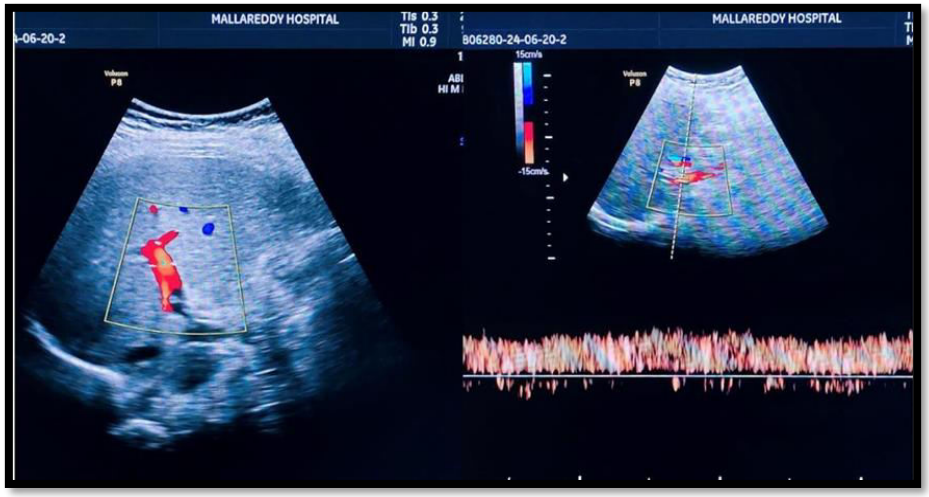

Figure6: Oblique colour Doppler image at porta hepatis showing colour uptake within the PV and Spectral Doppler tracing of normal portal vein flow. The flow velocity of 22 cm/s is uniform and in a hepatopetal direction

Ethical statement

This study was approved by the Institutional Ethics Committee (Approval No: PG2021/17) Written informed consent was obtained from all participants.

Conflict of interest

The authors declare no competing interests.

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Author contributions

Dr. Illuru Anusha: Supervision, methodology,Manuscript preparation, correspondence
Dr. P. Prathyusha: Data collection, image acquisition
Dr. B.Immanuel Navin Kumar: Study design, analysis

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