

“Evaluation Of The Role Of Portal Venous Doppler In Predicting Capillary Leak Syndrome In Dengue Fever Patients”

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Abstract:

Background: In tropical and subtropical areas across the world, dengue fever—a virus spread by mosquitoes and brought on by the dengue virus (DENV) - poses a serious threat to public health¹ Dengue fever's clinical spectrum includes both severe and potentially fatal types as well as mild, self-limiting febrile illnesses like fever, headache, retro-orbital pain, myalgia, and rash. However, a subset of patients progresses to severe manifestations, including dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).^{5,6} CLS is one of the serious side effects and a key pathogenic event in the development of DHF and DSS. The necessity for novel, sensitive, and dynamic instruments to identify plasma leakage early is highlighted by the unpredictability of CLS and the shortcomings of current diagnostic techniques. Portal venous Doppler ultrasonography has shown promise in evaluating hemodynamic alterations associated with plasma leakage. These changes often precede overt clinical manifestations, making Doppler an invaluable tool for early identification of patients at risk for severe complications like DSS. The purpose of this study is to assess how well portal venous Doppler ultrasonography predicts CLS in dengue fever patients.

Materials and Methods: In this prospective randomised controlled study, 144 patients diagnosed with Acute fever patients with thrombocytopenia, IGM positive and NS1 positive were enrolled for the study. A general liver examination was conducted to rule out chronic liver diseases. Greyscale and color Doppler modes, real-time ultrasound imaging of the chest wall and abdomen was carried out. The sonographic characteristics such as Gall-bladder wall edema, Gall-bladder wall thickness, Ascites, Pleural effusion and Splenomegaly were assessed. In Portal Doppler study, parameters such as Portal vein diameter and Cross-sectional area were noted during a greyscale evaluation of the portal vein. Spectral and color Doppler evaluations of the portal vein were carried in order to assess velocity and direction of the flow along with the congestive index. The clinical results and laboratory results of the patients were then compared with the ultra-sonographic characteristics & Doppler results.

Results: The study compared different portal venous Doppler features and lab findings in 144 patients. GB Wall Edema had good accuracy, with high specificity (89%) and a high positive predictive value (98.13%), though its sensitivity was lower. Ascites and Pleural Effusion had perfect specificity (100%) but lower sensitivity, making them less reliable for detecting the condition. PV Diameter and Cross-Sectional Area showed moderate sensitivity and specificity. PV Velocity had the highest sensitivity (94.58%) but lower specificity. Overall, GB Wall Edema and Pleural Effusion were better at identifying the condition, while PV Velocity was more sensitive.

Conclusion: This study highlights the emerging role of portal venous Doppler ultrasonography as a valuable, non-invasive tool for the early identification of CLS in patients with dengue fever.) Given its accessibility, repeatability, and cost-effectiveness, integrating portal venous Doppler assessment into standard dengue management protocols may significantly enhance risk stratification and guide therapeutic decision-making.

Key Word: Dengue hemorrhagic fever, dengue shock syndrome, Pleural effusion

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I. Introduction

In tropical and subtropical areas across the world, dengue fever—a virus spread by mosquitoes and brought on by the dengue virus (DENV) - poses a serious threat to public health.¹ Its worldwide burden has

increased drastically in recent decades, according to estimates from the World Health Organization (WHO) 96 million of the 390 million illnesses that occur each year show clinical symptoms² Regions, such as Southeast Asia, the Western Pacific, the Americas, and parts of Africa, bear the brunt of the disease, with periodic outbreaks³ while in endemic regions, dengue fever affects the lower socioeconomic populations, where inadequate vector control and healthcare access exacerbate its impact.⁴

Dengue fever's clinical spectrum includes both severe and potentially fatal types as well as mild, self-limiting febrile illnesses. However, a subset of patients progresses to severe manifestations, including dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).^{5,6} The salient features of DHF are plasma leakage, thrombocytopenia, and bleeding tendencies; while DSS, the most severe form, is marked by profound shock and multi-organ dysfunction due to critical hypovolemia.⁷ CLS is one of the serious side effects and a key pathogenic event in the development of DHF and DSS.^{8,9} CLS is characterized by increased vascular permeability¹⁰ that allows plasma to flow from the intravascular compartment into the interstitial regions. Mild forms of CLS may present as transient hemoconcentration or minor pleural effusions, whereas severe forms can lead to profound shock, multi-organ failure, and mortality if not managed effectively. Serious consequences like hypovolemic shock, multi-organ failure, and death might be avoided with early and prompt diagnosis of CLS. However, there are serious drawbacks to the CLS diagnostic techniques used today, which prevent prompt detection.

The necessity for novel, sensitive, and dynamic instruments to identify plasma leakage early is highlighted by the unpredictability of CLS and the shortcomings of current diagnostic techniques. Portal venous Doppler ultrasonography has shown promise in evaluating hemodynamic alterations associated with plasma leakage. These changes often precede overt clinical manifestations, making Doppler an invaluable tool for early identification of patients at risk for severe complications like DSS.⁸ The purpose of this study is to assess how well portal venous Doppler ultrasonography predicts CLS in dengue fever patients.

II. Material And Methods

This study was designed to assess the role of portal venous doppler in predicting CLS in patients with dengue fever. This prospective cohort study was carried out at Krishna Vishwa Vidyapeeth, Karad, in the Department of Radio-Diagnosis in a total of 144 patients after due approval of the institutional ethics committee (protocol no. 361/2022-2023).

Study design: Prospective cohort study

Study location: Dept. of Radiodiagnosis, Krishna Vishwa Vidyapeeth, Karad, Maharashtra

Study duration: June 2023- Dec 2024

Sample size: 144

Sample size calculation: Based on the study “Sonographic Evidence of Ascites, Pleura-Pericardial Effusion and Gallbladder Wall Edema for Dengue Fever” by M. Motla et al., the proportion of capillary leak syndrome detected on ultrasonography was considered to be 90%. Assuming a relative precision of 5% and a desired confidence interval of 95% (Alpha error of 5%), the sample size was calculated using the formula: $N = Z^2 \times P \times Q/L^2$ where:

✓ Z = Standard constant value at 95% CI = 2

✓ P = Capillary leak syndrome percentage predicted on USG = 90%

✓ Q = Contradictory findings = 100% – P = 10%

✓ L = Allowable error or precision rate = 5%

Substituting these values into the formula, the sample size for the study was calculated to be 144. Therefore, 144 subjects were selected for the study.

Inclusion criteria:

- Patients having acute fever with thrombocytopenia,
- IGM positive antibodies,
- NS1 positive antigens and
- Willing to participate in follow-up visits

Exclusion criteria:

- Patients with hepatic tumors / chronic liver disease,
- Hypoalbuminemia,
- Hypotension,
- Positive MP (malarial parasite) and MF (microfilaria)

- Portal vein or splanchnic vessel thrombosis

Procedure methodology: After obtaining informed/written consents, imaging was performed on all included cases. The patients were scanned in a supine / left decubitus position following 4-6 hours of fasting using Siemens Acuson Juniper Color Doppler, Wipro GE Voluson E6 BT 20, GE Logic P9 in grey scale and colour doppler modes. The ultrasonographic parameters assessed were; *Gall-bladder wall edema, Gall-bladder wall thickness, Ascites, Pleural effusion and Splenomegaly.*

For the Portal Doppler Study either a right intercostal approach pointing medially or a subcostal approach pointing poster cephalad were used to examine the portal vein. Parameters like *Portal vein diameter and Cross-sectional area* were noted during a greyscale evaluation of the portal vein. Spectral and color Doppler evaluations of the portal vein were carried out using the proper machine settings in order to assess the velocity of the flow and direction of the flow. The congestive index was calculated using the formula: $\text{Congestive Index} = \frac{\text{Cross-sectional area (sq.cm)}}{\text{Portal vein velocity (cm per sec)}}$

A general liver examination was conducted to rule out chronic liver diseases. The clinical results and laboratory results of the patients were then compared with the ultra-sonographic characteristics & Doppler results.

Statistical analysis:

The analysis was performed using SPSS software, version 20, with an alpha level set at 5%. Categorical variables were presented as numbers and percentages and compared using the Chi-Square test. Continuous variables were expressed as mean \pm standard deviation and analyzed using the independent samples t-test. The diagnostic utility of Portal Venous Doppler in predicting Capillary Leak Syndrome in dengue patients was assessed by calculating sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy, all with 95% confidence intervals. A p-value of less than 0.05 was considered statistically significant.

III. Result

A total of 144 (n= 144) patients were enrolled in this study. Among these registered, 84 cases were females whereas 60 cases were males. The mean age range of the patients was 26.32 ± 9.74 years.

Table no. 1 shows the distribution of patients based on the presence or absence of gall bladder (GB) wall edema. Among the 144 patients, 43.06% (62 cases) had GB wall edema, with 60% (57 cases) in the CLS-positive group and 10.20% (5 cases) in the CLS-negative group. Conversely, 56.94% (82 cases) did not have GB wall edema, with 40% (38 cases) in the CLS-positive group and 89.80% (44 cases) in the CLS-negative group. The p-value of <0.0001 indicated a highly significant association between the presence of GB wall edema and the occurrence of CLS in dengue fever patients.

Table no. 1: Distribution according to Gall Bladder wall Edema in the study group

| GB wall Edema | CLS Positive | | CLS Negative | | Total | |
|----------------|--------------|------------|--------------|------------|--------------|------------|
| | No. of cases | Percentage | No. of cases | Percentage | No. of cases | Percentage |
| Present | 57 | 60.00% | 5 | 10.20% | 62 | 43.06% |
| Absent | 38 | 40.00% | 44 | 89.80% | 82 | 56.94% |
| Total | 95 | 100.00% | 49 | 100.00% | 144 | 100.00% |
| P-value | <0.0001 | | | | | |

Table no. 2 shows the distribution of patients based on the presence or absence of ascites. Among the 144 patients, 33.33% (48 cases) had ascites, with 45.26% (43 cases) in the CLS-positive group and 10.20% (5 cases) in the CLS-negative group. The remaining 66.67% (96 cases) did not have ascites, with 54.74% (52 cases) in the CLS-positive group and 89.80% (44 cases) in the CLS-negative group. The p-value of <0.0001 indicated a highly significant association between the presence of ascites and the occurrence of CLS in dengue fever patients.

Table no. 2: Distribution according to Ascites in the study group

| Ascites | CLS Positive | | CLS Negative | | Total | |
|----------------|--------------|------------|--------------|------------|--------------|------------|
| | No. of cases | Percentage | No. of cases | Percentage | No. of cases | Percentage |
| Present | 43 | 45.26% | 5 | 10.20% | 48 | 33.33% |
| Absent | 52 | 54.74% | 44 | 89.80% | 96 | 66.67% |
| Total | 95 | 100.00% | 49 | 100.00% | 144 | 100.00% |
| P-value | <0.0001 | | | | | |

Table 3 shows the distribution of patients based on the presence or absence of pleural effusion. In this study, 32.64% (47 cases) of the total 144 patients had pleural effusion, with 49.47% (47 cases) in the CLS-positive group and none in the CLS-negative group. The remaining 67.36% (97 cases) did not have pleural effusion, with 50.53% (48 cases) in the CLS-positive group and all 49 cases in the CLS-negative group showing no pleural

effusion. The p-value of <0.0001 highlighted a highly significant correlation between the presence of pleural effusion and the likelihood of developing CLS in dengue fever patients.

Table no. 3: Distribution according to Pleural effusion in the study group

| Pleural effusion | CLS Positive | | CLS Negative | | Total | |
|------------------|--------------|------------|--------------|------------|--------------|------------|
| | No. of cases | Percentage | No. of cases | Percentage | No. of cases | Percentage |
| Present | 47 | 49.47% | 0 | 0.00% | 47 | 32.64% |
| Absent | 48 | 50.53% | 49 | 100.00% | 97 | 67.36% |
| Total | 95 | 100.00% | 49 | 100.00% | 144 | 100.00% |
| P-value | <0.0001 | | | | | |

Table 4 shows the clinical parameters in the study group. In the study, the CLS-positive group had significantly higher GB wall thickness (3.89 ± 2.54 mm) and PV diameter (13.46 ± 1.84 mm) compared to the CLS-negative group (2.09 ± 0.60 mm and 11.29 ± 1.96 mm, respectively). PV velocity was lower in the CLS-positive group (19.16 ± 5.35 cm/sec) compared to the CLS-negative group (24.28 ± 6.29 cm/sec). The CLS-positive group also had a lower platelet count ($51,200.39 \pm 29,314.17$) and higher congestion index (0.11 ± 0.10). Haematocrit values were lower in the CLS-positive group.

Table no. 4: Clinical parameters in the study group

| Clinical characteristics | CLS Positive | CLS Negative |
|--|-------------------------|-------------------------|
| GB wall thickness (mm) | 3.89 ± 2.54 | 2.09 ± 0.60 |
| PV diameter | 13.46 ± 1.84 | 11.29 ± 1.96 |
| PV velocity (cm/sec) | 19.16 ± 5.35 | 24.28 ± 6.29 |
| Cross sectional area(cm ²) | 1.51 ± 0.38 | 1.76 ± 0.45 |
| Congestion index | 0.11 ± 0.10 | 0.07 ± 0.03 |
| Platelet count | 51200.39 ± 29314.17 | 98179.58 ± 53675.29 |
| Haematocrit PCV | 38.48 ± 5.72 | 35.17 ± 2.73 |
| HB (%) | 13.33 ± 1.97 | 11.70 ± 0.59 |

Table 5 shows the analysis of ROC curve. In a study examining the role of portal venous Doppler in predicting capillary leak syndrome in dengue fever patients, several parameters were evaluated using ROC curve analysis. The results showed that the GB wall thickness (AUC = 0.787, $p < 0.0001$) and congestion index (AUC = 0.827, $p < 0.0001$) were the most significant predictors, with high Youden index values of 0.628 and 0.5556, respectively. Other parameters, such as PV diameter (AUC = 0.732, $p = 0.0212$), PV velocity (AUC = 0.778, $p = 0.0015$), and platelet count (AUC = 0.751, $p = 0.0090$), also showed statistically significant associations. Cross-sectional area (AUC = 0.721, $p = 0.0034$), hematocrit (AUC = 0.669, $p = 0.0099$), and hemoglobin (AUC = 0.671, $p = 0.0018$) had moderate predictive value, but ascites and pleural effusion did not demonstrate significant findings in the study.

Table no. 5: Analysis of ROC curve

| Parameters | AUC curve | SE | 95% Confidence Interval | Z-statistics | P-Value | Youden index J |
|--|-----------|--------|-------------------------|--------------|---------|----------------|
| GB wall thickness (mm) | 0.787 | 0.0048 | 0.651 to 0.830 | 4.451 | <0.0001 | 0.628 |
| Ascites | - | - | - | - | - | - |
| Pleural effusion | - | - | - | - | - | - |
| PV diameter | 0.732 | 0.0992 | 0.635 to 0.820 | 2.325 | 0.0212 | 0.5231 |
| PV velocity (cm/sec) | 0.778 | 0.0914 | 0.690 to 0.861 | 3.34 | 0.0015 | 0.4901 |
| Cross sectional area(cm ²) | 0.721 | 0.0753 | 0.623 to 0.797 | 2.936 | 0.0034 | 0.4092 |
| Congestion index | 0.827 | 0.0633 | 0.738 to 0.895 | 5.164 | <0.0001 | 0.5556 |
| Platelet count | 0.751 | 0.0941 | 0.653 to 0.831 | 2.619 | 0.0090 | 0.5193 |
| Haematocrit PCV | 0.669 | 0.0650 | 0.570 to 0.762 | 2.579 | 0.0099 | 0.3942 |
| HB (%) | 0.671 | 0.059 | 0.571 to 0.763 | 3.039 | 0.0018 | 0.4531 |

Table 6 shows the significance of Portal Venous Doppler features with respect to clinical outcome by binary logistics. In the analysis of the significance of portal venous Doppler features with respect to clinical outcomes using binary logistic regression, the results revealed that PV velocity ($p = 0.005$) was statistically significant, indicating its potential role in predicting clinical outcomes. In contrast, PV diameter ($p = 0.487$) and cross-sectional area ($p = 0.289$) were not found to be statistically significant.

Table no. 6: Significance of Portal Venous Doppler features with respect to clinical outcome by binary logistics

| Parameter | Significance (p-value) |
|---|------------------------|
| PV Diameter (cm) | 0.487 |
| PV Velocity (cm/sec) | 0.005 |
| Cross-sectional area (cm ²) | 0.289 |

Table 7 shows the comparative analysis of ROC curve of portal venous doppler features and laboratory findings. The study compared different portal venous Doppler features and lab findings in 144 patients. GB wall edema had good accuracy, with high specificity (89%) and a high positive predictive value (98.13%), though its sensitivity was lower. Ascites and Pleural Effusion had perfect specificity (100%) but lower sensitivity, making them less reliable for detecting the condition. PV Diameter and Cross-Sectional Area showed moderate sensitivity and specificity. PV Velocity had the highest sensitivity (94.58%) but lower specificity. Overall, GB Wall Edema and Pleural Effusion were better at identifying the condition, while PV Velocity was more sensitive.

Table no. 7: Comparative Analysis of ROC curve for Portal Venous Doppler features and laboratory findings in study group (N= 144)

| Ultrasonography Feature | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Diagnostic Accuracy (%) |
|-------------------------|-----------------|-----------------|---------|---------|-------------------------|
| GB Wall Edema | 62 | 89 | 98.13 | 23 | 66 |
| Ascites | 38.50 | 100 | 100 | 18 | 45 |
| Pleural Effusion | 50.19 | 100 | 100 | 19.48 | 58 |
| PV Diameter | 77.26 | 73 | - | - | - |
| PV Velocity | 94.58 | 63 | - | - | - |
| Cross-Sectional Area | 62.94 | 80 | - | - | - |
| Congestive Index | 57.34 | 100 | - | - | - |

IV. Discussion

This prospective study assessed how well portal venous Doppler predicts CLS in patients with dengue fever. The results were examined using a variety of criteria, such as laboratory results, portal venous Doppler indices, clinical aspects, and demographic traits. The current study found a substantial correlation between gallbladder wall edema and CLS, with 60% of patients with CLS exhibiting edema compared to just 10.20% of patients without CLS. A powerful predictor of CLS in dengue fever is GB wall edema, according to the very significant p-value (<0.0001). Gallbladder wall thickening was found by Pothapregada et al.¹⁴ to be a major ultrasonographic characteristic linked to severe dengue infection. Edematous thickening of the gallbladder wall was also identified by Nagaraj et al.⁹ as the most frequent ultrasonographic result. Gallbladder wall edema was seen in three of twelve patients by Meltzer et al.¹⁰, whereas the most common finding in Charan et al.'s investigation was gallbladder wall thickening with edema. Together, these results demonstrate that gallbladder wall edema is an important ultrasonographic indicator of plasma leakage in dengue fever, hence confirming its significance as a critical CLS predictor.

With a very significant p-value (<0.0001) ascites was seen in 45.26% of CLS positive patients in the current investigation, compared to just 10.20% of CLS negative individuals. In line with the pathophysiological mechanism of plasma leakage in severe dengue cases, this implies that ascites is a valid marker of CLS. Furthermore, 49.47% of patients with CLS had pleural effusion, but none of the CLS negative patients had any instances. Additionally, a significantly significant p-value (<0.001) was obtained, indicating a substantial correlation between CLS and pleural effusion. One well-established characteristic of severe dengue is the occurrence of pleural effusion, which frequently corresponds with the severity of the illness. Twenty-four (48%) of the CLS-positive individuals had ascites, and six (12%) had bilateral pleural effusion, according to Nagaraj et al.⁹ Meltzer et al.¹⁰ deemed the presence of ascites, pleural effusion, or a swollen, edematous gallbladder to constitute sonographic evidence of capillary leakage. In a similar vein, Charan et al.¹¹ found that 8 (15.3%) of the subjects had bilateral pleural effusion, while 26 (50%) had ascites. According to Satwik et al.¹², ascites was discovered in 44 instances, or 5% of the patients, and bilateral pleural effusion was reported in 17 cases, or 21.25% of the patients. When taken as a whole, these investigations demonstrate the close correlation between dengue's ascites, pleural effusion, and CLS, hence confirming their significance as indicators of severe illness and plasma leakage.

Portal venous Doppler results from the current investigation revealed notable distinctions between the CLS-positive and CLS-negative groups. Hemodynamic changes in CLS were suggested by the bigger portal vein diameter (13.46 ± 1.84 mm vs. 11.29 ± 1.96 mm), lower portal vein velocity (19.16 ± 5.35 cm/sec vs. 24.28 ± 6.29 cm/sec), and higher GB wall thickness (3.89 ± 2.54 mm vs. 2.09 ± 0.60 mm) in CLS-positive patients. These findings are consistent with Satwik et al.¹², who similarly found that patients with CLS had a higher congestion index (0.097 vs. 0.036), a lower PSV (15.7 cm/sec vs. 28.8 cm/sec), and a larger portal vein width (14.8 mm vs. 9.4 mm). These results emphasize the importance of Doppler ultrasound in dengue and the part that portal venous changes and hepatic congestion play in the pathophysiology of CLS.

According to hematological characteristics, patients with CLS had a considerably lower platelet count (51,200.39 ± 29,314.17) than those without the disease (98,179.58 ± 53,675.29). In line with hemoconcentration seen in plasma leaks, hematocrit values were greater in CLS-positive patients (38.48 ± 5.72) than in CLS negative individuals (35.17 ± 2.73). The significance of hemoconcentration in CLS etiology was further supported by the

fact that hemoglobin levels were greater in CLS-positive patients (13.33 ± 1.97 g/dL) than in CLS-negative patients (11.70 ± 0.59 g/dL).

The most significant predictors of CLS, according to ROC curve analysis, were the congestion index (AUC = 0.827, $p < 0.0001$) and GB wall thickness (AUC = 0.787, $p < 0.0001$). Significant predictors were portal vein diameter (AUC = 0.732, $p = 0.0212$), portal vein velocity (AUC = 0.778, $p = 0.0015$), and platelet count (AUC = 0.751, $p = 0.0090$). Hematocrit, hemoglobin, and cross-sectional area all demonstrated a reasonable predictive value; however, ROC analysis did not provide statistically significant findings for ascites or pleural effusion. The sole statistically significant predictor of clinical outcomes, according to binary logistic regression analysis, was portal vein velocity ($p = 0.005$). This result emphasizes how crucial portal venous hemodynamics are for estimating the severity of dengue-related CLS.

GB wall edema was found to have a high positive predictive value (98.13%) and a high specificity (89%) in a comparative investigation of diagnostic accuracy, making it a powerful diagnostic marker for CLS. Portal vein velocity was an excellent screening technique for early CLS identification since it had the highest sensitivity (94.58%).

This work sheds important light on how portal venous Doppler measurements might be used to predict capillary leak syndrome in patients with dengue fever. According to clinical findings, portal venous Doppler may be used as a non-invasive method for early CLS identification, enabling prompt action to avoid consequences. Clinical results and prognosis accuracy may be enhanced by routinely evaluating patients for dengue fever with Doppler ultrasonography, especially those who are at high risk of developing a severe case.

V. Conclusion

CLS is a defining characteristic of DHF and DSS, as well as a sign of severe dengue fever. Early detection is critical to improving prognosis, yet reliable clinical predictors remain limited. This study highlights the emerging role of portal venous Doppler ultrasonography as a valuable, non-invasive tool for the early identification of CLS in patients with dengue fever. Given its accessibility, repeatability, and cost-effectiveness, integrating portal venous Doppler assessment into standard dengue management protocols may significantly enhance risk stratification and guide therapeutic decision-making. The ultimate goal is to close the gap in current diagnostic procedures so that prompt clinical interventions can enhance the management of severe dengue, lower morbidity and mortality, and improve patient outcomes especially in areas with limited resources.

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