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Original Research Article

To Correlate the Variability of Platelet Indices with Improvement or Deterioration of Viral Hemorrhagic Fever

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Abstract:

Background: Viral hemorrhagic fevers (VHFs), caused by Arenaviruses, Filoviruses, Bunyaviruses, and Flaviviruses, are globally distributed. In India, Dengue fever, Dengue hemorrhagic fever (DHF), and Kyasanur Forest Disease (KFD) are endemic, with Dengue being hyperendemic in many regions. VHFs are highly infectious and potentially fatal, presenting with symptoms such as fever, vomiting, bleeding, edema, and hypotension.

Diagnosis of Dengue fever primarily relies on NS1 antigen detection, while thrombocytopenia is a common finding due to bone marrow suppression, platelet destruction, and viral replication. Platelet indices, including mean platelet volume (MPV) and platelet distribution width (PDW), serve as important markers for assessing platelet activation and bleeding risk.

Methods: A prospective observational study at Ballari Medical College and Research Center (June 2022–December 2024) includes 200 febrile thrombocytopenia patients in the early defervescence stage. EDTA blood samples are analyzed for hematological parameters, including hemoglobin, leukocyte count, red cell indices, and platelet count. Platelet indices (MPV, PDW, PCT) are assessed within two hours of venipuncture. Serological tests (dengue NS1, IgM, IgG) and additional renal and liver function tests are also conducted.

Results: In this prospective study of 200 pediatric patients with viral hemorrhagic fever, the most affected age group was 6–10 years, with a male predominance (59.5%). Fever was universal, and common symptoms included abdominal pain (90%), right hypochondrial tenderness (81.5%), vomiting (68.5%), and nausea (64%). Most children were hemodynamically stable at presentation, though 68% had hepatomegaly. Platelet indices showed significant trends over 11 days: platelet count and plateletcrit progressively increased, while mean platelet volume (MPV) and platelet distribution width (PDW) decreased ($p<0.001$), indicating hematological recovery. Liver dysfunction was common (57%), but renal involvement was rare (1%). NS1 antigen was positive in 91%, confirming dengue as the major etiology. Confirmed diagnoses included classic dengue fever (74%), dengue hemorrhagic fever (9%), Dengue Shock syndrome(7%) and rare cases of dengue encephalitis (1%).

Conclusion: This study demonstrates that serial monitoring of platelet indices—rising platelet count, Plateletcrit and declining MPV & PDW and plateletcrit—effectively correlates with disease severity and recovery in pediatric viral hemorrhagic fever. The findings justify the study's objective, highlighting these indices as reliable, non-invasive prognostic tools that aid in clinical assessment, timely intervention, and improved outcomes in affected children.

Keywords: Viral hemorrhagic fevers (VHFs); Dengue hemorrhagic fever (DHF); Kyasanur Forest Disease (KFD); Mean platelet volume (MPV); Platelet distribution width (PDW); Hepatomegaly.

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Introduction

Viral hemorrhagic fevers (VHFs) are caused by viruses from four families: Arenaviruses, Filoviruses, Bunyaviruses, and Flaviviruses. Humans are not the natural reservoirs for these viruses and typically become infected through contact with infected hosts. However, human-to-human transmission has been documented for viruses such as Ebola, Marburg, and Crimean-Congo hemorrhagic fever, primarily through direct contact with infected blood and bodily fluids. VHF-causing agents are distributed worldwide. In India, Dengue fever, Dengue hemorrhagic fever (DHF), and Kyasanur Forest Disease (KFD) are endemic, with Dengue hyperendemic in many regions[1]. The incubation period for VHFs ranges from 2 to 21 days[2].

VHFs are highly infectious and potentially fatal, characterized by symptoms such as fever, malaise, vomiting, mucosal and gastrointestinal bleeding, edema, and hypotension. An essential pathological defect in VHF is increased vascular permeability. The viruses primarily target the vascular system, causing early symptoms like flushing, conjunctival injection, petechial hemorrhages, fever, and myalgia. Advanced stages often lead to mucous membrane hemorrhages, hypotension, shock, and circulatory collapse[2].

Dengue fever is caused by one of four serotypes of the dengue virus (DEN-1 to DEN4) belonging to the Flaviviridae family. Both Aedes aegypti and Aedes albopictus mosquitoes are competent vectors, with the close association of A. aegypti with humans driving transmission in tropical urban areas[1]. Dengue was first reported in Bangladesh in 1964 as "Dacca fever." Its incidence increases during the monsoon and post-monsoon seasons[3]. Globally, dengue affects 390 million individuals annually, with 96 million manifesting clinical symptoms[4]. India reported an average of 1.93 lakh cases in 2021[5].

Dengue presents a wide disease spectrum, from dengue fever characterized by biphasic fever, myalgia, arthralgia, leukopenia, and lymphadenopathy to severe syndromes like DHF and dengue shock syndrome (DSS), which can be fatal[1]. DHF is marked by high fever, hemorrhagic phenomena, hepatomegaly, circulatory disturbances, and shock. Initial symptoms include a sudden rise in temperature, facial flushing, anorexia, vomiting, severe frontal headache, retro-orbital pain, nausea, and skin eruptions. Severe muscle and bone pain ("break-bone fever") is typical. Biphasic fever patterns may occur, with temperatures reaching up to 40°C[1].

The detection of the non-structural protein 1 (NS1) antigen is a sensitive and specific method for diagnosing dengue[11]. Thrombocytopenia is a common laboratory finding in dengue, resulting from mechanisms such as direct bone marrow suppression by the virus, antibody-mediated platelet destruction, peripheral consumption of platelets, or isolated viral replication within platelets[3].

Novel platelet indices, including mean platelet volume (MPV) and platelet distribution width (PDW), are potential markers of platelet activation. MPV reflects platelet volume and is associated with marrow suppression and increased bleeding risk. Changes in platelet morphology due to activation are evaluated through MPV and PDW, while plateletcrit (PCT), a parameter combining MPV and platelet count, provides a reliable measurement of platelet biomass[3].

Methodology

Setting of the Study: This prospective observational study is being conducted at Ballari Medical College and Research Center, a tertiary care referral center, from June 2022 to December 31, 2024. The study includes 200 patients diagnosed with febrile thrombocytopenia who present to the hospital during the early defervescence stage. Informed consent is obtained from all participants, and the study protocol has received approval from the institutional ethics committee.

Study Design: An Observational Prospective Study.

Method of Collection of Data:

Inclusion Criteria: Patient with age group between 1 month – 14 yrs admitted with clinical diagnosis of viral hemorrhagic fever with varying severity and thrombocytopenia (Platelet count - < 1.5lakh/ cumm).

Exclusion Criteria: Patients with viral hemorrhagic fever with co-morbidities like congenital heart disease, cerebral palsy, co – infection.

Patient with viral hemorrhagic fever and received platelet transfusion.

Results

Table 1: Variation in the plateletcrit among the study subjects (N=200)

Plateletcrit (N=200)	Mean	SD	Minimum	Median	Maximum
Day 1 (%)	0.06	0.04	0.01	0.05	0.21
Day 2 (%)	0.07	0.04	0.01	0.06	0.23
Day 3 (%)	0.08	0.04	0.02	0.08	0.23
Day 4 (%)	0.10	0.05	0.02	0.09	0.24
Day 5 (%)	0.11	0.05	0.03	0.10	0.27
Day 6 (%)	0.13	0.05	0.03	0.12	0.27
Day 7 (%)	0.14	0.05	0.05	0.14	0.29
Day 8 (%)	0.16	0.04	0.07	0.15	0.30
Day 9 (%)	0.16	0.05	0.07	0.16	0.30
Day 10 (%)	0.17	0.05	0.08	0.17	0.31
Day 11 (%)	0.18	0.05	0.08	0.19	0.32

Normal Plateletcrit - 0.05% to 0.13%
Repeated measures ANOVA
p-value <0.001 (Statistically significant)

The plateletcrit levels, which reflect total platelet mass, demonstrated a steady and significant increase from day 1 (mean 0.06%) to day 11 (mean 0.18%), with $p<0.001$. This threefold rise over the 11-day period mirrored the upward trajectory in platelet count, confirming the increase in platelet mass. Median values followed a similar trend, reinforcing the consistency across the sample. The narrow standard deviation suggests that most subjects followed this pattern of recovery. Initially low plateletcrit levels correlated with severe thrombocytopenia, and as patients improved, values approached normal. The progressive rise in plateletcrit underscores its utility in tracking platelet recovery, especially when considered alongside mean platelet volume and platelet count. This suggests that a majority of the pediatric patients showed a proportional and consistent increase in plateletcrit, reflecting hematological recovery and serving as a robust marker of disease resolution

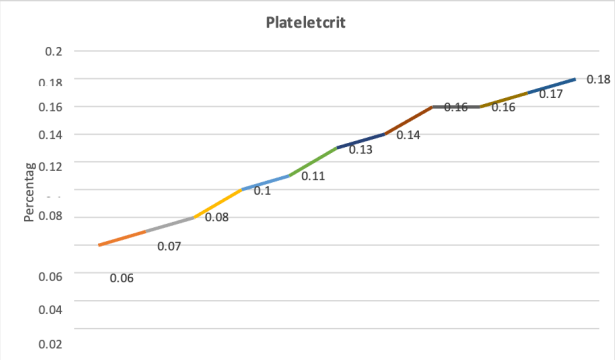

Figure 1: Variation in the plateletcrit among the study subjects (N=200)

Table 2: Other investigations among the study subjects (N=200)

Other investigations (N=200)		Frequency (N)	Percentage (%)
Renal Function Tests	**Normal**	198	99.0%
	Abnormal	2	1.0%
Liver Function Tests	**Normal**	86	43.0%
	Abnormal	114	57.0%
NS1 Antigen	**Absent**	18	9.0%
	Present	182	91.0%

The other investigations revealed that almost all children (99%) had normal renal function tests, while liver function abnormalities were present in the majority—114 out of 200 patients (57%). Additionally, NS1 antigen, a specific early marker for dengue, was detected in 91% of cases, confirming the diagnosis in the vast majority. The predominance of hepatic dysfunction, rather than renal, reflects the hepatotropic nature of viral hemorrhagic fevers like dengue. This high frequency of liver involvement aligns with the clinical signs of right hypochondrial tenderness observed earlier. The widespread NS1 positivity further strengthens the specificity of clinical and laboratory diagnosis in this cohort. Therefore, the inference is that while renal involvement was rare, hepatic dysfunction and NS1 positivity were prevalent in the majority, reinforcing the hepatic tropism and viral etiology in pediatric hemorrhagic fevers

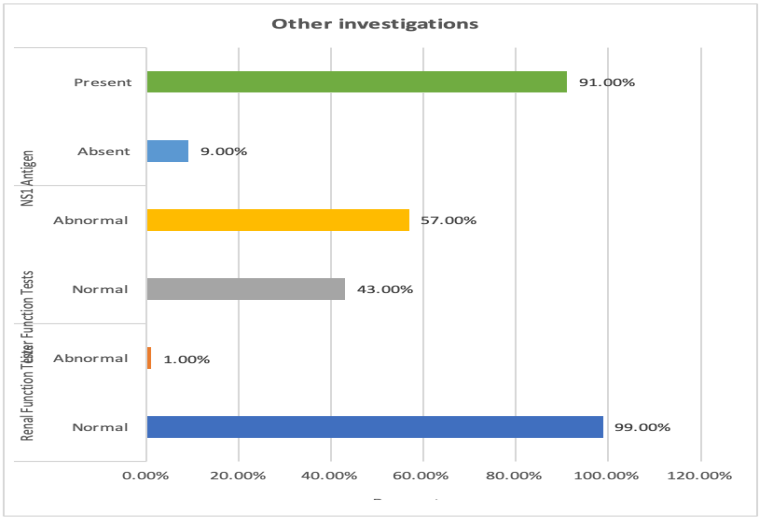

Figure 2: Other investigations among the study subjects (N=200)

Table 3: Distribution of the study subjects based on provisional diagnosis (N=200)

Provisional diagnosis (N=200)	Frequency (N)	Percentage (%)
Dengue like Illness	18	9.0%
Dengue Fever (including dengue hemorrhagic fever)	168	84.0%
Dengue Shock Syndrome	14	7.0%

Out of the 200 cases, a substantial majority—168 patients (84%)—were provisionally diagnosed with dengue fever, including both classic and hemorrhagic forms. A smaller fraction (9%) were categorized as dengue-like illness, and 7% were suspected of dengue shock syndrome. This skewed distribution highlights that classic dengue fever is the predominant clinical presentation in this setting. The small proportion of dengue shock syndrome cases reflects either early detection and intervention or relatively fewer instances of severe hemodynamic compromise at presentation. The provisional diagnoses appear to be strongly influenced by clinical features and epidemiological clues in endemic areas. Consequently, the inference is that the majority of pediatric patients presented with classic forms of dengue, confirming the diagnostic predictability of viral hemorrhagic fever based on clinical suspicion alone.

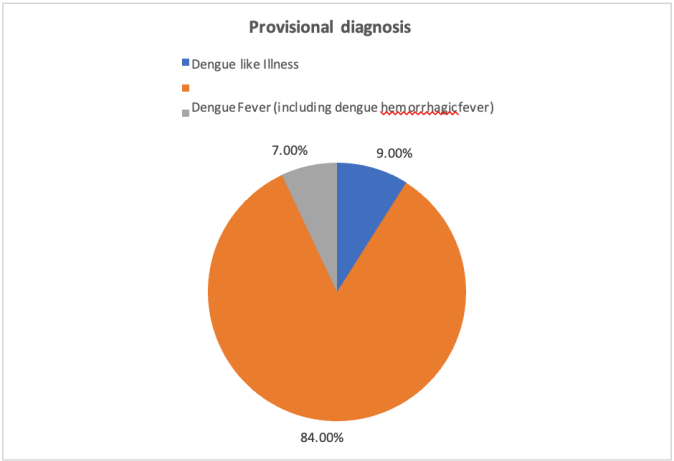

Figure 3: Distribution of the study subjects based on provisional diagnosis (N=200)

Table 4: Distribution of the study subjects based on confirmed diagnosis (N=200)

Confirmed diagnosis (N=200)	Frequency (N)	Percentage (%)
Dengue like Illness	18	9.0%
Dengue Fever	148	74.0%
Dengue Shock Syndrome	14	7.0%
Dengue Hemorrhagic Fever	18	9.0%
Dengue Encephalitis	2	1.0%

Upon confirmation, 74% of patients were diagnosed with dengue fever, and an additional 9% were clas-

sified under dengue hemorrhagic fever, while dengue shock syndrome remained at 7%. Notably, 9% retained the diagnosis of dengue-like illness and 1% were diagnosed with dengue encephalitis, indicating rare but significant CNS involvement. This data suggests that while most provisional diagnoses were confirmed, some cases were further differentiated into more specific categories such as hemorrhagic or encephalitic variants. The large majority diagnosed with classical dengue reflects the milder end of the disease spectrum, while the smaller percentages in severe forms emphasize the importance of vigilant monitoring to detect and manage complications. The impression is that most patients had classic dengue upon confirmation, but the spectrum of confirmed diagnoses also included severe and rare manifestations, underscoring the heterogeneity of clinical outcomes in pediatric viral hemorrhagic fever.

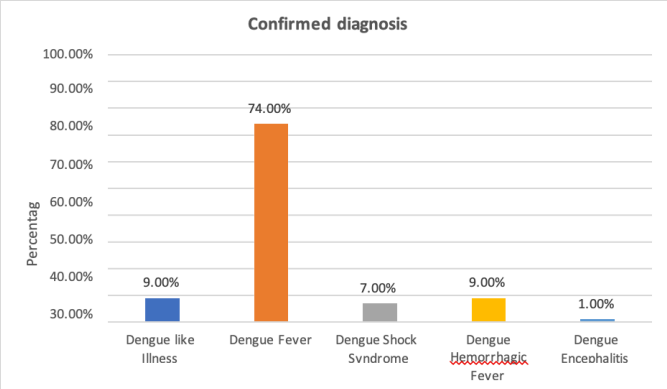

Figure 4: Distribution of the study subjects based on confirmed diagnosis (N=200)

Discussion

This prospective observational study was conducted over 18 months in a tertiary care hospital, enrolling pediatric patients aged 1 month to 14 years diagnosed with viral hemorrhagic fever (VHF) and thrombocytopenia (platelet count <1.5 lakh/cumm). Patients were included based on clinical suspicion and laboratory confirmation via serological tests like NS1 antigen. Exclusion criteria comprised neonates, children above 14 years, those with co-morbidities (e.g., congenital heart disease, cerebral palsy, co-infections), and those who had received platelet-rich plasma transfusions.

Table 5: Mean Platelet Volume Table 5: Comparison of MPV with other studies

Mean MPV	Present study	Makwana et al.[4]	Manoharan et al.[5]	Mukker et al.[6]	Sharma et al.[7]
Admission to Discharge	11.54 to 9.10	12.56 to 8.08	-	12.4 to 8.7	-

In the present study, mean platelet volume decreased significantly from 11.54 fL to 9.10 fL over the course of illness, indicating a transition from activated to normalized platelet production. This decline is strongly supported by findings from Mukker et al., who showed that MPV was significantly lower in patients with platelet counts below 20,000/µL and rose with recovery. Manoharan et al. also demonstrated that higher MPV was associated with poor transfusion response and bleeding risk, highlighting its prognostic role. Makwana et al. provided a more nuanced view, associating high MPV with ICU admission, shock, and liver dysfunction, while lower MPV was linked to bleeding complications. In contrast, Arora et al. and Elsewefy et al. observed that lower MPV values were associated with more severe disease, suggesting MPV as a diagnostic, rather than recovery marker. Sharma et al. found no significant association between MPV and severity, except for a marginal change in DF cases, thereby challenging its prognostic utility. These varying results may reflect differences in patient demographics, timing of measurements, or analyzer technology. Nevertheless, the present study's findings are in strong agreement with those of Mukker et al., Makwana et al., and Manoharan et al., supporting the clinical utility of MPV trends in monitoring dengue progression

Platelet Distribution Width

Table 6: Comparison of PDW with other studies

Mean PDW	Present study	Makwana et al.[4]	Bashir et al.[8]	Mukker et al.[6]
Admission to discharge	16.09 to 13.03	15.06 to 8.88	-	59.4 to 48.3

The present study found a statistically significant decrease in platelet distribution width (PDW) from 16.09 fL on day 1 to 13.08 fL on day 11 ($p<0.001$), indicating a reduction in platelet size variability with clinical recovery. Among previous studies, Makwana et al. provided strong supportive evidence by correlating high PDW values with worse clinical outcomes, including bleeding, prolonged hospitalization, and ICU admission, further noting a decline in PDW during recovery. Mukker et al. also reported the highest PDW levels in patients with platelet counts <20,000/μL and a significant difference across groups based on platelet severity, reinforcing its role as a severity marker. Bashir et al. documented high PDW in 26–28% of DF and DHF cases, although without linking it directly to clinical outcomes. Arora et al. found no significant correlation between PDW and severity despite its high prevalence. Elsewefy et al., Sharma et al., Manoharan et al., and Jayashree et al. did not evaluate PDW. Thus, while some variability exists, particularly in adult studies, the findings of Makwana et al. validate the present study's observation that PDW decreases with recovery and may serve as a dynamic indicator of disease stabilization Plateletcrit.

Table 7: Comparison of plateletcrit with other studies

Mean Plateletcrit	Present study	Makwana et al[4]	Mukker et al[6]
Admission to discharge	0.06 to 0.18%	0.03 to 0.25%	0.02 to 0.1%

In the present study, plateletcrit (PCT) was shown to increase significantly from 0.06% on day 1 to 0.18% by day 11 ($p<0.001$), reflecting restoration of total circulating platelet mass and correlating with clinical improvement. Among previous studies, Makwana et al. strongly supported this trend, finding that patients with lower PCT values had worse outcomes, including more frequent ICU admissions, need for fluid therapy, and longer hospitalization. Similarly, Mukker et al. reported that patients with platelet counts below 20,000/μL had the lowest PCT values and that PCT showed significant variation across severity groups. These studies emphasized PCT's utility not just as a passive reflection of platelet count, but as a clinically meaningful parameter indicating both severity and recovery potential. Other previous studies by Arora et al., Bashir et al., Jayashree et al., Sharma et al., and Manoharan et al. did not report on plateletcrit, limiting broader comparisons. However, the consistency among the few studies that assessed this index affirms the present study's conclusion that patients with platelet counts below 20,000/μL had the lowest PCT values and that PCT showed significant variation across severity groups. These studies emphasized PCT's utility not just as a passive reflection of platelet count, but as a clinically meaningful parameter indicating both severity and recovery potential Other investigations

Table 8: Comparison of other investigation findings with other studies

Other investigations	Present study	Makwana et al.[4]	Jayashree et al.[9]	Arora et al.[10]	Mukker et al.[6]	Sharma et al.[7]	Bashir et al.[8]
Deranged LFT	57%	66%	44.7%	-	100%	-	12.8%
Deranged RFT	2%	17%		-		-	-
NS1 antigen Positive	91%	100%	100%	63%	100%	-	100%

The present study showed that 91% of patients were NS1 antigen positive, 57% had elevated liver function tests (LFTs), and renal function was largely preserved. These results were closely matched by Makwana et al., who also observed high NS1 positivity and noted that deranged LFTs (66%), particularly elevated SGPT and creatinine, were more frequent in patients with high MPV and low PCT. Mukker et al. provided additional evidence by correlating elevated AST, ALT, and bilirubin levels(100 % of cases) with lower platelet counts, suggesting hepatic dysfunction as a potential marker of dengue severity. Jayashree et al. discussed abnormal LFTs(44.7%) in severe cases but did not quantify them. Arora et al. reported 63% of NS1 positivity cases and highlighted its utility for early diagnosis, while Bashir et al. relied on IgM/IgG serology for confirmation. Sharma et al. examined IgM and IgG but found no significant correlation between serological markers and MPV levels. and Manoharan et al. did not report on NS1 or LFT/RFT data. Collectively, the present study's findings on NS1 and liver involvement are well supported by previous studies, particularly those of Makwana et al. and Mukker et al., reinforcing the combined diagnostic and prognostic value of these investigations Diagnostic classification

Table 9: Comparison of diagnostic classification with other studies

Diagnosis	Present study	Jayashree et al.[9]	Makwana et al.[4]	Bashir et al.[8]	Sharma et al.[7]	Arora et al.[10]	Manoharan et al.[5]	Elsewefy et al.[11]	Mukker et al.[6]
DF	74%	-	72%	86.5%	68%	-	-	-	-
DHF	9%	32.5%	12%	13.5%	23%	-	-	-	-
DSS	7%	9.5%	16%	-	9%	-	-	-	-

The present study classified patients as 74% having classical dengue fever (DF), 9% with dengue hemorrhagic fever (DHF), and 7% with dengue shock syndrome (DSS), using WHO criteria. These proportions are consistent with the stratifications reported in several previous studies. Sharma et al. observed 68% DF, 23% DHF, and 9% DSS, while Makwana et al. reported 72% DF, 12% DHF, and 16% DSS. Jayashree et al. found a slightly higher proportion of DHF (35.2%) but a comparable DSS proportion (9.5%). Bashir et al. reported 86.5% DF and 13.5% DHF without DSS figures, maintaining the trend of DF predominance. Manoharan et al. focused on DSS-related complications but did not provide complete breakdowns. Arora et al. applied WHO 2009 classification but did not detail proportions, and Mukker et al. referred to disease severity levels but omitted diagnostic grouping. Elsewefy et al. studied thrombocytopenia unrelated to dengue and thus lacked classification data. The similarity in diagnostic distribution across multiple studies underscores the robustness of WHO classification in defining the clinical spectrum of dengue, and the present study's findings are well within the expected epidemiological range observed in recent dengue cohorts.

Conclusion

The present study highlights the prognostic significance of platelet indices (like platelet count, MPV, PDW and PCT) and hemodynamic indicators in assessing disease severity and recovery in pediatric viral hemorrhagic fever, particularly dengue. Mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT) demonstrated dynamic associations with clinical outcomes, reinforcing their role as reliable biomarkers. Lower MPV and PDW correlated with severe disease, while their normalization aligned with recovery. Additionally, lower PCT values were linked to worse outcomes, emphasizing its utility beyond platelet count alone. Elevated liver function test levels further indicate hepatic dysfunction, serving as a marker of dengue severity.

These findings underscore the importance of routine monitoring of platelet indices and hemodynamic parameters for early risk stratification. Their systematic assessment can aid in guiding clinical decision-making and optimizing the management of pediatric viral hemorrhagic fever, particularly dengue.

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