Original Article

D-dimer a Clue for Severe Dengue / Dengue Shock Syndrome, An Observational Study

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How to cite this article: Aniket Khaladkar, Suvarna Patil, Amey Paranjape et. al. D-dimer a Clue for Severe Dengue / Dengue Shock Syndrome, An Observational Study. Indian Journal of Public Health Research and Development / Vol. 16 No. 1, January-March 2025.

Abstract

Background: Dengue fever, a mosquito-borne viral infection, poses a significant public health threat, particularly in tropical and subtropical regions. Caused by five serotypes of the dengue virus (DENV-1 to DENV-5), it affects an estimated 400 million people annually, leading to severe illness in around 96 million [1]. Dengue's clinical spectrum ranges from asymptomatic infection to mild febrile illness with flu-like symptoms, to severe dengue (SD) and dengue shock syndrome (DSS), characterized by plasma leakage, thrombocytopenia, and organ dysfunction [2].

Objective: To evaluate the correlation and diagnostic accuracy of D-dimer in differentiating severe dengue and dengue shock syndrome (SD/DSS) from mild dengue.

Method: This is an observational study carried in BKL Walawalkar medical college for a period of 6 months. 125 patients were enrolled in the study which were diagnosed as Dengue positive(NS1, IG-G, IG-M) after taking their informed consent. Dimer, platelet creatinine, SGOT SGPT levels were monitored.

Conclusion: The present study provides strong evidence for a link between D-dimer levels and the severity of dengue infection and it also address the correlation of low platelet count and high Ddimer levels. This suggests that D-dimer could be a valuable marker for assessing dengue severity.

Keywords: D-dimer, dengue haemorrhagic fever, platelet.

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Submission date: March 19, 2024 **Revision date:** April 20, 2024 **Published date: December 28, 2024:**

Introduction

Dengue fever, a mosquito-borne viral infection, poses a significant public health threat, particularly in tropical and subtropical regions. It affects an estimated 400 million people annually, leading to severe illness in around 96 million[1]. Dengue's clinical spectrum ranges from asymptomatic infection to mild febrile illness with flu-like symptoms, to severe dengue (SD) and dengue shock syndrome (DSS) [2].The primary vector for Dengue transmission is the Aedes mosquito, specifically Aedesaegypti and Aedesalbopictus[3]. These mosquitoes breed in stagnant water, making urban environments particularly susceptible to outbreaks, further exacerbated by factors like poverty, inadequate sanitation, and climate change [2].

Symptoms of dengue typically appear 4-10 days after infection, with the most common being high fever, severe headache, muscle and joint pain, nausea, and vomiting [2]. A characteristic skin rash may also develop. While most cases resolve within 1-2 weeks, SD and DSS can be life-threatening, requiring prompt medical attention and supportive care [4].

However, clinical diagnosis can be challenging, especially in the early stages, due to overlapping symptoms with other febrile illnesses. Hence, exploring reliable biomarkers for severe dengue and DSS diagnosis is paramount.[3]

D-dimer, a fibrin degradation product generated during clot breakdown, has emerged as a potential candidate. Studies suggest elevated D-dimer levels in patients with severe dengue compared to uncomplicated cases, potentially reflecting increased vascular leakage and coagulation abnormalities [5]. Furthermore, research indicates an association between D-dimer and the severity of organ dysfunction in DSS, highlighting its possible role in predicting clinical outcomes [6].

Researching D-dimer's potential as a diagnostic tool for severe dengue (SD) and dengue shock syndrome (DSS) holds significant importance due to the challenges in early and accurate diagnosis. While dengue fever is widespread, differentiating SD/DSS from mild dengue can be difficult, potentially delaying critical interventions. D-dimer, a marker of vascular dysfunction and coagulation abnormalities in SD/DSS, offers a promising avenue for more specific and timely diagnosis. Exploring its efficacy could lead to improved clinical outcomes, reduced healthcare costs, and better patient management, particularly in resource-limited settings. This research could contribute significantly to advancing dengue diagnostics and potentially saving lives

Methodology

Study Design:

It was anobservational study conducted at B.K.L. Walawalkar Rural Medical College from 1/8/2023 to 1/2/2024

Inclusion Criteria:

Patients presenting with clinical symptoms or Confirmed dengue positive by RT-PCR or NS1/IgG/IgM antigen test.

Exclusion Criteria:

a) Lack of confirmed dengue infection by RT-PCR or NS1/IgG/IgM / antigen test.

b) Incomplete clinical data or laboratory results.

Data Collection and Analysis:

Confirmation of dengue infection by RT-PCR or NS1/IgG/Ig Mantigen test. A standardized and validated assay to measure D-dimer levels(ACL ELITE turbidimetric immunoassay) was used. Complete blood count (CBC) to assess platelets, haematocrit, and other blood cell parameters were monitored till the discharge and was performed on HORIBA H 500 photometry. Serum chemistry to evaluate liver and kidney function was performed on fully automated analyser. Clinical monitoring of daily progress based on disease severity, recording for Vital signs like Temperature, pulse, respiratory rate, blood pressure. Look for signs of plasma leakage, bleeding, organ dysfunction.

Patients were classified as a) **Dengue Fever (DF)** which includes flu-like symptoms including fever, nausea, myalgia, headache, normal platelet count. b) **DF with warning signs (DFWS)** which include hepatomegaly, abdominal pain, vomiting, mucosal bleeding, and increasing haematocrit concurrent with rapidly declining platelets. c) Severe dengue/Dengue Shock syndrome(DSS). This phase is characterised by

shock, bleeding and organ involvement also called as dengue haemorrhagic fever [1].

Data was analysed using SPSS V25.0. Data was shown as Mean±SD for continuous variable and n (%) for categorical variables. ANOVA was used to compare continuous variables and Chi-square test was used for categorical variables.

Results

Total 125 patients admitted from 1/12/2022 to 1/2/2024were recruited for study. There were 86 (68.8%) males with mean age was 40±9 years and 39 (31.2%) females with mean age 40±12 years. We classified the patients in DF (n=40), DF with warning signs (n=73) and Severe dengue (n=12). We have compared the age and haematological parameters within the groups of severity of dengue(Table 1). Severity of dengue increases with age ($p<0.05$). We found that male patients were more affected than females but the association was not significant. Hb, RBC and PCV were significantly lower in DF group than the group of DF with warning signs ($p<0.05$). Mean D-DIMER levels were 174.4 ng/dl, 621.5 ng/dl and 7566 ng/dl in DF, DF with warning signs and Severe dengue respectively ($p<0.001$). We also found that SGOT levels were high than SGPT levels.

Table 1: Age, gender, hematological parameters and dengue classification.

Dengue Severity	Dengue classification				p
	All	DF (n=40)	DFWS (n=73)	Severe Dengue (n=12)	
Age (years)	40.26±10.41	38.90±10.22	39.75±10.06	47.83±10.85	0.026*
Male	86 (68.8%)	22 (55.0%)	56 (76.7%)	8 (66.7%)	0.058
Female	39 (31.2%)	18 (45.0%)	17 (23.3%)	4 (33.3%)	
Hb (g/dL)	13.39±2.73	12.15±2.63	14.11±2.52	13.04±3.04	0.001*
RBC Count	**4.69±0.93**	4.36±1.01	4.89±0.80	4.48±1.12	0.010*
PCV (%)	**40.16±8.95**	36.43±8.05	42.46±8.63	38.63±9.88	0.002*
M.C.V **(µm^3)**	**84.89±10.60**	84.15±9.52	85.02±11.13	86.50±11.24	0.790
M.C.H (pg)	**28.56±4.53**	27.83±4.89	28.82±4.44	29.34±3.81	0.454
M.C.H.C (g/dL)	**33.65±2.33**	33.57±2.33	33.65±2.44	33.95±1.77	0.887
Total WBC count	**4784.79±2787.02**	5347.95±3037.84	4417.53±2489.92	5188.71±3492.43	0.212
Neutrophils	**58.13±14.79**	62.02±15.79	55.33±13.99	62.56±13.27	0.040*
Lymphocyte	**32.05±14.31**	28.18±14.68	34.84±13.47	27.60±15.16	0.032*
Monocytes	**5.58±3.84**	5.17±2.32	6.05±4.56	4.01±2.36	0.170
Eosinophils	**1.24±2.56**	1.37±3.15	1.25±2.39	0.77±1.09	0.776
Basophils	**0.20±0.51**	0.21±0.41	0.21±0.59	0.13±0.27	0.869
Platelet Count	**82192.40±72084.47**	171876.25±58244.66	38835.62±21257.03	47000.00±22703.62	0.000*
Platelet Count **<1 Lakh**	85 (68.0%)	0 (0.0%)	100 (100.0%)	100 (100.0%)	0.000*
DDIMER (ng/ml)	1145.11±3725.43	174.40±27.84	621.52±488.43	7566.00±10230.66	0.000*
DDIMER **>250ng/dl**	76 (60.8%)	0 (0.0%)	64 (87.7%)	12 (100.0%)	0.000*
SGOT (mg/dl)	196.11±279.78	83.37±132.64	230.96±315.35	282.05±280.78	0.035*
SGPT (mg/dl)	127.83±184.85	96.99±233.56	138.88±171.33	149.12±149.73	0.567

*Mean±Standard deviation; *statistically significant.*

Table 2: Clinical profile of 12 patients with severe dengue.

No	1	2	3	4	5	6	7	8	9	10	11	12
Age (years)	53	60	48	40	29	63	59	16	53	24	48	34
Sex	Male	Female	Male	Male	Male	Female	Male	Female	Male	male	male	female
Fever (days)	3	8	5	3	6	5	7	1	6	8	4	3
Dengue status IgG/IgM/ NS1	NS1, IgM+	IgG +	NS1+	NS1+	NS1 and IgM+	IgM+	NS1, IgG, IgM+	Ns1,IgG	NS1	Ns1	Ns1	Ns1 IgM
DM	+	-	-	-	-	-	-	-	-	-	+	+
HTN/IHD	+	-	+	-	-	+	+	-	-	-	+	-
D dimer ng/ dl	3629	13255	2140	3793	1118	2800	2689	2000	22000	4886	2342	5250
Platelets	75000	70000	44000	37000	32000	59000	10000	65000	70000	25000	20000	74000
Complication	Hepatitis Pancreatitis	Hepatitis	Hepatitis	Hepatitis	Leucopenia	ARDS	Severe Thrombocytopenia	ARDS	Hem peritoneum	DIC	Hepatitis	DIC
Status at discharge dead/ recover/ referred	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	DAMA	DAMA	Death	Recovered	death
Total hospital stay in days	10	11	8	7	6	10	8	5	7	4	11	3

Table 2 shows the Biochemical and clinical characteristics of severe dengue. Out of 12 patients 2 patients who were critically ill took discharge against medical advice but, 8 patient showed improvement despite suffering from complications like ARDS, hepatitis, bleeding and required intensive critical care monitoring. Two patients died due to DIC(disseminated intravascular coagulation). The average hospital stay of all patients was 7 days.

Discussion

Ours is the first observational study on d dimer as a marker for severe dengue in patients from Konkan region, BKL Walawalkar rural medical college and hospital is a multispecialty tertiary care hospital in Konkan region of western Maharashtra catering to rural population. It is equipped with Intensive care units with blood component backup so most of the patients from Konkan region with dengue fever are referred to the hospital with majority patient being of dengue fever with warning signs. Patients with dengue fever having normal platelet levels showed fast recovery with short term hospital stay while it was observed that DF with warning signs showed low platelet count and long term hospital stay. Warning signs prominently seen in these patients were abdominal pain, nausea, declining platelet count, elevated HCT. Along with fluid therapy platelet transfusion were also required in these patients. Symptoms like hepatitis, acute respiratory distress syndrome (ARDS), leukopenia, Disseminated intravascular coagulation (DIC) were observed in few patients with severe dengue in such cases ICU admission was needed along with ventilator support. In these patients we observed very high levels of D-dimer (>7000 ng/dl) with low platelet count (<1 lakh) at the time of admission. So, d-dimer could be an early predictor for diagnosing the severity of dengue and it could help to decide further course of treatment for clinicians. The presence of the D-dimer (DD) indicated activation of the coagulation system resulting from the destruction of cross-linked fibrin and reflects clot formation and lysis[7,8] thus D-dimer assay, a specific marker for cross-linked fibrin, is

often used as a marker for disseminated intravascular coagulation[9].Studies support a connection between D-dimer and dengue severity. For instance, research by Yusof et al. [10] found significantly increased D-dimer levels in Dengue Haemorrhagic Fever (DHF) patients compared to Dengue Fever (DF).

In our study it was observed that severity of dengue increases with age which resonates with findings from the study by Annan on Direct and indirect effects of age on dengue severity. The association between increasing age and dengue severity among individuals with dengue infection has been established.[11] In dengue, accurate and reproducible PCV measurement would be important for making decisions about fluid management, in our study we observed that PCV values were significantly higher in patients with DFWS as compared to DF($p<0.05$) similar results was observed in a study done by Sahassananda D [12].

Lower platelet count increases the risk of bleeding tendency. Patients with DFWS showed significantly low platelet counts as compared to patients with DF($p<0.001$).

The previously discussed studies [13, 14] focused on D-dimer as a risk stratification tool for severe dengue however ours is the first study from Konkan region. Overall, the table provides evidence that D-dimer levels can be a potential marker for dengue severity. Patients with higher D-dimer levels are more prone to have dengue haemorrhagic fever and even to land up in dengue shock syndrome which is a life threatening complication.

In patients with Dengue fever with warning signs at initial stage may cause thrombocytopenia due to increased vascular permeability and plasma leakage and later because of disseminated intravascular coagulation (DIC). To identify the severity of dengue D-dimer can be used as a specific and sensitive marker of DIC[15].

The SGOT levels were elevated than SGPT levels in DFWS and severe dengue, almost all DFWS and SD had abnormal SGOT profile. (Table-1) SGOT raised more than SGPT in dengue may be due to involvement of myocytes. Very high levels of SGOT and SGPT indicate severity of the disease along with morbidity and mortality and similar results were shown in study done by Mamtakumari et.al. in children of age group of 1-12years[16].In the study done by Kittiya Setrkraising, Chansuda Bongsebandhu-phubhakdi et al. showed significantly higher D-dimer levels in DHF patient compared with DF patient with the sensitivity of D-dimer in predicting DHF of 90% [7]. Study done in Thailand shows similar correlation where D-dimer levels were monitored in children[15], but in our study adult population was involved. By implementing these recommendations, healthcare professionals can gain a deeper understanding of D-dimer's role in dengue severity assessment and potentially develop more effective strategies for managing this challenging illness.

Conclusion

The present study provides strong evidence for a link between D-dimer levels and the severity of dengue infection. Patients with high D-dimer levels (>250 ng/dL) were significantly more likely to have severe dengue compared to those with lower levels. This suggests that D-dimer could be a valuable marker for assessing dengue severity. While the present study does not only directly address D-dimer but it also highlights the importance of platelet levels, PCV, SGOT and SGPT levels in dengue severity. It may help clinicians in predicting dengue severity before the patient progress into toxic stage so that close monitoring and proper management can be arranged. To investigate how both D-dimer and platelet levels change over the course of the illness in these patients. A longitudinal analysis would provide a more dynamic picture.

Limitations

The study presents a single time point, and ideally D-dimer levels should be tracked throughout the illness. Additionally, D-dimer is not specific to dengue and can be elevated in other conditions. Therefore, D-dimer levels should be interpreted by a doctor in conjunction with other clinical findings and tests for a comprehensive diagnosis.

Conflict of Interest: None of the authors have any conflict of interest to declare.

Source of Funding: BKL Walawalkar Hospital Diagnostics and Research Centre, Sawarde, Chiplun, District Ratnagiri.

Ethics: The Study was approved by the Institute Ethics committee of BKL Walawalkar Rural Medical College and Hospital (Reference no.264). Our institute ethics committee is registered with the Government of India. Registration code is EC/755/INST/MH/2015/RR-18.

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