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Correlation Of Coagulation Profile With Severity Of Dengue Fever With Emphasis On D-Dimer Levels: An Analytical Cross-Sectional Study

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Abstract

Background*: Dengue is a major arboviral infection associated with significant morbidity and mortality, with severe disease characterised by plasma leakage, coagulopathy, and bleeding. Early identification of severe cases is crucial, particularly in resource-limited settings. This study aimed to evaluate the utility of D-dimer as a pragmatic biomarker to rule out severe dengue.*

Methods: *96 patients with serologically confirmed dengue were enrolled, of whole 87 had non-severe dengue and 9 had severe dengue. Clinical characteristics and laboratory parameters including platelet counts, packed cell volume (PCV), D-dimer, and other coagulation parameters. Group comparisons were performed using Mann-Whitney U-test, correlations and predictive ability.*

Results: *Severe dengue patients had significantly higher D-dimer levels [2800.0 (2300.4–3846.3) vs 1841.8 (917.5–2757.4) mg/L, p=0.038], higher INR [1.05 vs 0.97, p=0.035], and lower platelet counts [28,000 vs 60,000/μL, p=0.004]. D-dimer correlated negatively with platelet count (ρ –0.365, p<0.001) and positively with PCV (ρ-0.245, p0.016) and aPTT (ρ0.211, p0.039). ROC analysis identified an optimal cut-off at 2300 ng/mL (sensitivity 88.9%, specificity 62.1%, AUC 0.711). Both 2000 and 2300 ng/mL thresholds demonstrated high negative predictive values (~98%), supporting their utility as pragmatic rule-out markers.*

Conclusion: *D-dimer levels are significantly elevated in severe dengue and correlated with key haematological parameters. A threshold around 2000-2300mg/L offers excellent Negative predictive value, making D-dimer a feasible tool to exclude severe dengue and support triage in resource limited healthcare settings. Validation in larger multicentric cohorts is warranted.*

Keywords: *Dengue; D-dimer; Coagulation; Prognosis*

INTRODUCTION

Dengue remains a major global health threat with recurrent outbreaks and rising incidence with an estimate of 390 million infections annually and a rising trend in both incidence and geographic expansion[1]. Although most infections are self-limiting, a notable proportion develop severe dengue characterised by plasma leakage, bleeding and/or organ involvement drives morbidity and mortality particularly in endemic tropical and subtropical regions[2,3]. Early identification of patients at risk of severe dengue is therefore paramount to improve clinical outcomes and optimise resource allocation in healthcare settings[1].

Dengue pathobiology includes endothelial dysfunction driven in part by non-structural protein-1 (NS-1), which increases vascular permeability and promotes plasma leakage are the central features of severe

dengue[4,5]. Mechanistically, NS1 and MMP-9 act in concert to disrupt endothelial integrity in-vitro and in-vivo, supporting the biological plausibility of leakage-linked biomarkers[4–6].

Haemostatic disturbances in dengue encompass thrombocytopenia and coagulation pathway derangements (prolonged prothrombin time (PT)/ activated partial thromboplastin time (aPTT)), and evidence of disseminated intravascular coagulation (DIC). Thus, coagulopathy is a hallmark of severe dengue. A 2021 systematic review by Adane et al[7], found aPTT prolongation frequent in prognostication. Subsequent hospital-based studies link deranged a PTT and overall coagulopathy with bleeding and worse outcomes[8,9].

Among biomarkers, D-dimer, a fibrin degradation product indicating concurrent activation of coagulation and fibrinolysis has emerged as a candidate predictor of sever dengue[10]. Evidence from observational cohorts and early-phase meta-analyses suggests higher D-dimer in patients with shock, fluid accumulation or dengue haemorrhagic syndrome (DHF) or dengue shock syndrome (DSS), and potential early prognostic value in the febrile phase[11–13]. Recent single-centre series report that higher D-dimer cut-points discriminate severe disease with reasonable accuracy[13].

Although individual coagulation parameters such as platelet count (PC), PT/aPTT and D-dimer have been studied separately, their combined evaluation to enhance early severity prediction remains underexplored. Integrating D-dimer measurement with standard coagulation profiles could improve sensitivity and specificity for identifying patients at-risk of severe dengue, yet few studies have formally compared D-dimer alongside aPTT or PC within the same cohort[7,10]. There is a clear need for local validation of combined markers especially given regional variations in patient demographics, viral serotypes, and healthcare resources.

Despite promising individual findings for D-dimer and traditional coagulation markers, robust evidence from recent cohorts in India, particularly from tertiary care centres is lacking. On this background, our study, therefore, address this gap by concurrently evaluating D-dimer, PC, PT and aPTT in laboratory-confirmed dengue patients and assessing their correlation with clinical severity. We also aim to determine a pragmatic D-dimer threshold to aid rule-out of severe dengue, suitable resource-limited settings.

Objectives

The primary objective is to estimate he D-dimer level among the dengue patients. The secondary objective is to find the diagnostic utility of D-dimer levels in differentiating between non-severe and severe dengue infections and to correlate between D-Dimer levels and clinical outcome in dengue infection.

MATERIALS AND METHOD

Study design and setting:

This hospital-based analytical cross-sectional study was conducted in the Department of General Medicine at Mahatma Gandhi Medical College and Research Institute, Puducherry, India, a tertiary-care teaching hospital. The study was carried out over a 23-month period from September 2022 to August 2024 and included in-patients admitted with dengue infection. The Institutional Human Ethics Committee (IHEC) approved the protocol, and informed consent was obtained from all participants.

Study population:

Eligible patients were the adolescents and adults presenting with clinical features of dengue infection, confirmed by serological testing (NS1-antigen or IgM ELISA positive) and with thrombocytopenia (platelets <1.5lakh/mm^3) with and without bleeding manifestations. Among the included patients, categorised into two groups using the World Health Organisation (WHO) 2009 classification system[3]:

i) Non-sever dengue (with or without warning signs)

ii) Severe dengue (Defined by severe plasma leakage, severe bleeding, or severe organ involvement).

Patients were excluded if they were serology negative, pregnant, had co-morbid conditions such as chronic liver disease, chronic kidney disease, autoimmune disorders, chronic infections, neoplasia, or a history of thromboembolic events (deep vein thrombosis, pulmonary embolism, or cerebral sinus venous thrombosis).

Sample size calculation and sampling technique:

According to Ganeshkumar P et al[14], the prevalence of dengue is 38.3% in India. The sample size was calculated according to the formula $n = \frac{Z^2_{\frac{1-\alpha}{2}} \times p(1-p)}{d^2}$, (where p (prevalence) = 0.383; Z (95% confidence interval (CI)) = 1.96; d (precision) = 10%) yielded the sample size of 91, rounded to highest figure of 95. Patients were selected by consecutive sampling techniques.

Study procedure:

Upon admission, data was collected using a pre-designed, pre-tested, semi-structured proforma which consists of demographic details, and past medical history. History and clinical assessment regarding clinical features indicating the severity of dengue by evaluation for warning signs such as bleeding manifestation, ascites, pleural effusion, and dehydration. Blood samples were collected for haematological indices (PC, total leukocyte count (TLC), packed cell volume (PCV)) and coagulation parameters (PR, international normalised ratio (INR), aPTT and D-dimer levels). All samples were processed using standardised laboratory protocols. D-dimer was quantified in ng/mL (fibrinogen-equivalent units, FEU). Imaging studies such as chest radiography and ultrasonography were undertaken when clinically indicated to confirm the presence of pleural effusion or ascites. The clinical and laboratory data were systematically recorded and used for correlation with disease severity based on WHO classification.

Statistical analysis:

Data were analysed using SPSS version 25.0. Continuous variables were expressed as mean and standard deviation (SD) or medians with interquartile range (IQR) depending on the distribution, and categorical variables as proportions. Group comparisons were performed using Student's t-test or Mann-Whitney U test for continuous variables, and chi-square test or Fisher's exact test for categorical variables. Receiver operating characteristics (ROC) curve analysis was applied to determine the optimal cut-off value of D-dimer for predicting severe dengue. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 96 patients with serologically confirmed dengue infection with a mean age of 32.14±13.84 years ranging from 13 to 73 years, with a male predominance (75%). Based on the WHO criteria, 87 patients (90.6%) were classified as non-severe dengue, while nine patients (9.4%) fulfilled criteria for severe dengue. Clinical manifestations included dehydration in 94 patients (97.9%), ascites in eight (8.3%), pleural effusion in six patients (6.3%), and bleeding manifestation in three patients (3.1%). The biochemical and coagulation profile of the study participants was provided in **table 1.**

Table 1: Biochemical and coagulation profile of dengue among the study participants

Variables	Mean ± SD	Range	Median (IQR)
PC (cells/mm^3)	72761.46 ± 51856.05	4100 – 244000	59500 (30000 – 110000)
TLC (cells/mm^3)	3532.66 ± 1837.86	1600 – 10600	3200 (2400 – 4225)
PCV (%)	43.25 ± 7.20	25.00 – 63.50	43.4 (38.4 – 47.7)
Coagulation parameters			
D-dimer (FEUs) (mg/L)	2262.68 ± 1674.19	241.08 – 8599.98	1860.7 (957.7 – 2869.6)
PT (seconds)	12.20 ± 2.87	9.70 – 31.70	11.7 (11.0 – 12.6)
INR	1.03 ± 0.24	0.45 – 2.34	0.98 (0.92 – 1.06)
aPTT (seconds)	34.45 ± 6.49	0.98 – 49.40	33.6 (30.4 – 38.3)

PC – platelet count; TLC – Total leucocyte count; PCV – Packed cell volume; PT – prothrombin time; INR – international normalised ratio; aPTT – activated partial thromboplastin time; FEU - Fibrinogen Equivalent Units; SD – standard deviation.

Table 2 shows the association of various biochemical and coagulation profiles with the dengue severity. Patients with severe dengue had significantly higher D-dimer levels [2800.0 (2300.4–3846.3) vs 1841.8 (917.5–2757.4) mg/dL, p 0.038], higher INR [1.05 (0.98–1.84) vs 0.97 (0.91–1.04), p 0.035] and low PC [28000 (20000–33000) vs 60000 (34500–114000) ells/mm^3, p 0.004] compared to their non-severe group indicating the severity of the dengue and its effect on coagulation profile. Similarly, when association of D-dimer with the clinical profile shown that patients presented with ascites and pleural effusion had higher D-dimer when compared to their counterparts **(Table 3).**

Table 2: Association of biochemical and coagulation parameters based on the severity of the dengue patients

Variables	Dengue severity		P – value
	Non-severe dengue (n = 87)	Severe dengue (n = 9)	
D-dimer (mg/dL)	1841.8 (917.5–2757.4)	2800.0 (2300.4–3846.3)	**0.038**[a]
Age (years)	29.0 (22.0–38.0)	27.0 (22.0–37.0)	0.880[a]
PC (cells/mm^3)	60000 (34500–114000)	28000 (20000–33000)	**0.004**[a]
TLC (cells/mm^3)	3000 (2400–4050)	4700 (3300–5000)	0.077[a]
PCV (%)	43.03 ± 7.05	45.33 ± 8.73	0.382[b]
PT (seconds)	11.8 (11.0–12.6)	11.5 (11.2–11.9)	0.724[a]
aPTT (Seconds)	33.1 (30.4–38.1)	34.8 (33.5–41.1)	0.247[a]
INR	0.97 (0.91–1.04)	1.05 (0.98–1.84)	**0.035**[a]

[a]Mann-Whitney U-test; [b]Student t-test. P-value <0.05 was statistically significant and indicated in boldface. PC – platelet count; TLC – Total leucocyte count; PCV – Packed cell volume; PT – prothrombin time; INR – international normalised ratio; aPTT – activated partial thromboplastin time; FEU - Fibrinogen Equivalent Units; SD – standard deviation. Data were presented as mean ± SD or median (IQR) based on the distribution.

Table 3: Association of biochemical and coagulation parameters based on the D-dimer level

Variables		D-dimer	p-value[a]
Ascites	**Present**	3050.0 (2600.1–4062.9)	**0.010**
	Absent	1763.7 (911.3–2717.8)	
Pleural effusion	**Present**	3573.1 (2925.0–4496.1)	**0.007**
	Absent	1842.9 (914.4–2672.9)	
Bleeding manifestation	**Present**	2700.0 (2500.0–2750.0)	0.302
	Absent	1844.0 (923.7–2875.6)	
Dehydration	**Present**	1869.0 (979.2–2873.6)	0.092
	Absent	712.8 (712.8–712.8)	

[a]Mann-Whitney U-test; P-value <0.05 was statistically significant and indicated in boldface. Data were presented as median (IQR).

Correlation analyses demonstrated a significant negative correlation between D-dimer and PC (ρ -0.365; p <0.001), while it had positive correlation with PCV (ρ 0.245, p 0.016) and aPTT (ρ 0.211, p 0.039). PC indicates that in severe dengue, every one unit decreases in PC, around 36% increase in D-dimer implying the relationship between them. **(Table 4 and figure 1).** The scatter plot for the above was provided in **figure 1.**

Table 4: Correlation between the D-dimer with biochemical and coagulation parameters among the study participants

D-dimer	Spearman's rho (ρ)	p-value
Age (years)	0.044	0.667
PC (/mm^3)	–0.365	**0.0003**
TLC (/mm^3)	0.034	0.740
PCV (%)	0.245	**0.016**
PT (sec)	0.033	0.751
aPTT (sec)	0.211	**0.039**
INR	0.043	0.680

P-value <0.05 (two-tailed) was statistically significant and indicated in boldface. PC – platelet count; TLC – Total leucocyte count; PCV – Packed cell volume; PT – prothrombin time; INR – international normalised ratio; aPTT – activated partial thromboplastin time.

Figure 1: Panel of analyses evaluating the relationship of D-dimer with clinical and laboratory parameters in dengue patients ((A) Receiver operating characteristic (ROC) curve for D-dimer in predicting severe dengue (AUC = 0.711). Candidate thresholds (2000, 2300, and 2500 ng/mL) are highlighted, with corresponding sensitivity and specificity values. (B) Scatter plot showing a significant

negative correlation between D-dimer and platelet count (Spearman's ρ = –0.37, R^2 = 0.13). (C) Scatter plot showing a positive correlation between D-dimer and packed cell volume (PCV) (ρ = 0.25, R^2 = 0.06). (D) Heatmap of Spearman's correlation coefficients between D-dimer and selected continuous clinical variables, showing significant associations with platelet count, PCV, and activated partial thromboplastin time (aPTT)).

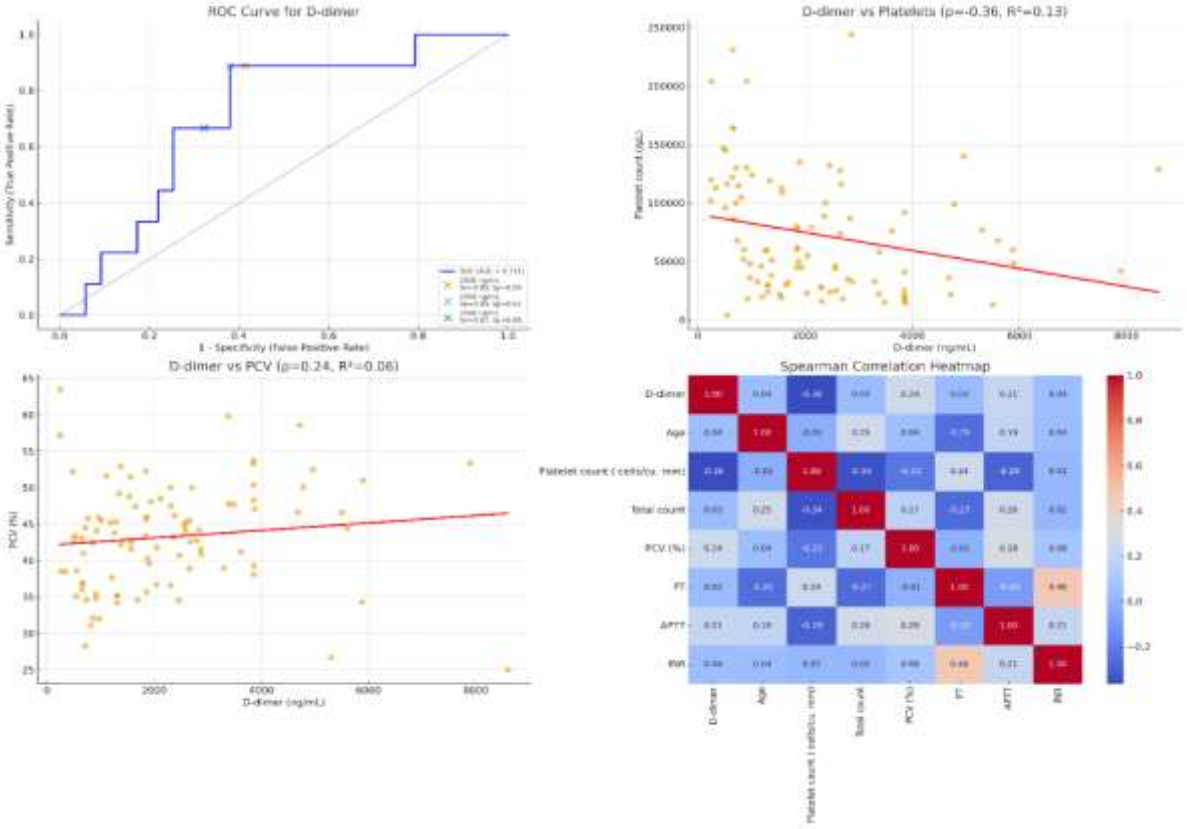

Table 5 and figure 1 shows the ROC curve analysis identified D-dimer as the moderate predictor of sever dengue, with an area under curve (AUC) of 0.711. The optimal threshold by Youden's Index was 2300mg/dL, providing sensitivity of 88.9% and specificity of 62.1%. Importantly, both 2000mg/dL and 2300mg/dL threshold demonstrated excellent negative predictive value (NPV ~98%), supporting their utility as pragmatic cut-offs to rule out severe dengue in resource-limited settings. At 2500mg/dL, sensitivity declined (66.7%) with a lower NPV (95.2%).

Table 5: ROC of D-dimer for the predicting dengue severity

Variables	Result		
Cut-off point	2000	2300	2500
Sensitivity (%)	88.9	88.9	66.7
Specificity (%)	58.6	62.1	67.81
PPV (%)	18.2	19.5	17.6
NPV (%)	98.1	98.2	95.2
AUC	0.711	0.711	0.711
Youden's index	0.48	0.51	0.34
PPV – positive predictive value; NPV – negative predictive value; AUC – area under curve			

DISCUSSION

In this study, we evaluated the potential of D-dimer as a marker for predicting severe dengue in a tertiary care setting. Among 96 confirmed cases, severe dengue occurred in 9.4% of patients. The patients with severe dengue had significantly higher D-dimer levels (median 2800.0 vs 1841.8mg/L, p 0.038), higher INR (1.05 vs 0.97, p 0.035), and lower PC (28,000 vs 60,000/mm^3, p 0.004). Moreover, strong rule-out potential was demonstrated with D-dimer thresholds especially around 2000 – 2300 mg/L yielding very NPV (~98%). Spearman correlation showed a notable inverse association between D-dimer and PC (ρ -0.365; p<0.001), and positive correlation with PCV (ρ 0.245,

p 0.016) and aPTT (ρ 0.211; p 0.039). Finally, ROC analysis identified an optimal Youden's index cut-off at 2300mg/L (sensitivity 88.9%, specificity 62.1%), reinforcing the utility of D-dimer in early risk stratification.

D-dimer reflects fibrin turnover during concomitant activation of coagulation and fibrinolysis. In dengue, NS1-driven endothelial injury and MMP-9-mediated junctional disruption promote plasma leakage, the same pathophysiology that clinically manifests as pleural effusion and ascites, in which our cohort showed higher D-dimer (ascites and pleural effusion, both $p<0.05$). This mechanistic link accords with Pan et al,[4] who demonstrated that DENV NS-1 cooperated with MMP-9 to impair endothelial adhesion and tight junctions, inducing vascular leakage in-vitro and in-vivo and the author proposed MMP-9 as a potential therapeutic target in DSS/DHF. The coagulation derangement with secondary fibrinolysis provide further biological plausibility for D-dimer elevation in severe disease[7]. Early-phase prognostic work also suggests that rising D-dimer in the febrile stage foreshadows progression, reinforcing its role as an early signal of clinically meaningful vascular involvement[15].

We found a moderate inverse correlation between D-dimer and platelets (ρ -0.365; $p<0.001$), consistent with reports that higher D-dimer tracts with deeper thrombocytopenia in severe dengue. In pediatric DHF, Sridhar et al[16] reported a significant negative association between PC and D-dimer, supporting the concept that consumptive coagulopathy and fibrinolysis intensify as platelets fall. More recently, an adult series concluded that elevated D-dimer accompanies lower PC and greater severity, underscoring the complementary prognostic signals of these markers[13]. Beyond bivariate associations, multiple contemporary cohorts reaffirm thrombocytopenia as a core severity feature in dengue, providing the clinical backdrop against which D-dimer adds incremental risk information[17,18]

In our data, INR was higher in severe dengue (median 1.05 vs 0.97; $p=0.035$), aPTT correlated positively (ρ 0.211; $p=0.039$) and PT did not differ significantly, illustrating the heterogenous sensitivity of conventional assays. The literature similarly shows frequent aPTT/PT prolongation in dengue, but with variable prognostic strength. A meta-analysis estimated pooled prevalence of prolonged aPTT and PT ~43% and 16%, respectively[7]. Clinical series link coagulopathy with bleeding risks, although single parameters may perform inconsistently across settings as for Patel et al[8] reported that coagulation abnormalities including aPTT/PT/INR derangements associated with bleeding manifestations in adults with dengue. Additional hospital-based work confirms variable PT/aPTT changes with concurrent D-dimer elevation, reflecting activation of both coagulation and fibrinolysis rather than isolated pathway failure[19]. Our pattern shows strong signal in INT that PT with a modest aPTT correlation that fits this broader heterogeneity.

In the present study, ROC analysis (AUC=0.711) identified 230mg/L as the Youden-optimal threshold, while 2000mg/L produced a very similar sensitivity with slightly lower specificity, yet both thresholds yielded NPV~98%, a property crucial for safe rule-out in constrained settings. This accords with broader evidence that D-dimer rises early and tracks severity, supporting its use as a front-line triage biomarker when laboratory panels are limited[15]. Observational studies also report higher D-dimer in severe categories/DSS and advocate its inclusion in pragmatic risk scores[13,20]. Taken together, the high-NPV in this present study provides an operational rule-out tool that complements warning signs and PC, with minimal added complexity, a clinically meaningful contribution for resources-limited care pathways.

The study is strengthened by its comprehensive evaluation of both coagulation markers and clinical outcomes in a well-defined dengue cohort, using standardized laboratory assays and robust statistical approaches. Importantly, the focus on D-dimer as a pragmatic rule-out marker for severe dengue offers direct clinical applicability in resource-limited settings. However, several limitations warrant considerations. The sample size was modest, with only nine cases of severe dengue, which may limit generalizability and contribute to wide confidence intervals around estimates. The cross-sectional design precludes dynamic assessment of D-dimer trends over the illness course, which might provide additional prognostic value. Furthermore, as this was a single-center study, external validation in diverse populations and healthcare environments is required. Despite these constraints, the study provides valuable preliminary evidence supporting D-dimer as a feasible and clinically relevant biomarker for early dengue triage.

CONCLUSION

This study demonstrates that D-dimer is a valuable marker for identifying severe dengue, with significantly higher levels observed in severe cases and strong correlations with PC, PCV, and aPTT. Among coagulation indices, INR also showed discriminatory potential, whereas PT and aPTT alone were less informative. D-dimer at the threshold of 2300mg/L cut-off yielded excellent NPV, making them pragmatic thresholds to safely rule out severe dengue. These findings suggest that D-dimer, when interpreted alongside PC and clinical warning signs, can be a simple, cost-effective tool to support triage decisions in resource-limited healthcare settings. Larger multicentric studies are warranted to validate these thresholds and establish D-dimer's role in standard dengue management algorithms.

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Ethical approval: The authors are responsible for all facets of the work, ensuring that inquiries regarding the accuracy or integrity of any component are thoroughly investigated and addressed. All procedures conducted in this study adhered to the ethical standards set forth by the relevant institutional and/or national research committees and complied with the Helsinki Declaration (revised in 2013). Informed consent was obtained from the patient for the publication of this case report and associated images. The Institutional Ethical Committee (MGMCRI/Res/01/2023/133/IHEC/153) approved this study.

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