

Frequency and pattern of WHO warning signs among patients with dengue fever admitted to Mufti Mehmood Memorial Teaching Hospital, Dera Ismail Khan, Pakistan: a hospital-based cross-sectional study

Anwar Ullah^{1*}, Nisar Khan¹, Muhammad Imran Ullah², Muhammad Anan Khan³, Amir Inayat Khan¹ and Afaq Akbar⁴

¹ Department of Medicine, Gomal Medical College, DHQ Teaching Hospital, Dera Ismail Khan, ²Department of medicine, MTI DHQ/Mufti Mehmood Memorial Teaching Hospital, Dera Ismail Khan, ³ Intensive Care Unit, Mufti Mehmood Memorial Teaching Hospital, Dera Ismail Khan, ⁴Department of Internal Medicine, Bacha Khan Medical Complex, Swabi, Khyber Pakhtunkhwa

ABSTRACT

Background: Dengue is an emerging mosquito-borne viral infection. Clinical deterioration is often seen around defervescence, and the World Health Organization (WHO) warning-sign framework is designed to identify the patient who is deteriorating and needs closer monitoring and timely treatment. The study determined the frequency and pattern of recorded WHO warning signs among patients admitted with dengue fever to Mufti Mehmood Memorial Teaching Hospital, Dera Ismail Khan, and explored their distribution across recorded dengue severity categories.

Methods: This hospital-based cross-sectional record analysis included 384 admissions aged 15–60 years. Demographic variables, previous dengue exposure, six recorded warning signs, platelet count, hematocrit, WHO classification, and discharge outcome were analyzed. Frequencies were reported with Wilson 95% confidence intervals (CIs).

Results: Of 384 records, 270 (70.3%) were classified as dengue with warning signs, 79 (20.6%) as dengue without warning signs, and 35 (9.1%) as severe dengue. At least one recorded warning sign was present in 305 patients (79.4%; 95% CI 75.1–83.2). Persistent vomiting was the most frequent warning sign (197; 51.3%), followed by lethargy (97; 25.3%), hepatomegaly (85; 22.1%), abdominal pain (74; 19.3%), mucosal bleeding (18; 4.7%), and clinical fluid accumulation (16; 4.2%). Patients classified as severe dengue had a median of 3 warning signs (IQR 3–3), compared with 1 (IQR 1–2) among those with dengue with warning signs. Overall, 368 patients (95.8%) were discharged, 14 (3.6%) were referred, and 2 (0.5%) died.

Conclusion: Warning signs were recorded in approximately four-fifths of admissions, and persistent vomiting was the predominant manifestation. A structured warning-sign checklist may support triage and serial clinical reassessment, but individual warning signs should not be interpreted in isolation. Prospective validation using verified clinical records, serial hematocrit platelet measurements, and independently adjudicated severe-dengue outcomes is required.

Keywords: Dengue Fever, Hepatomegaly, Lethargy, Severe dengue, Vomiting

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Corresponding author:**Anwar Ullah**Department of Medicine, Gomal Medical College,
DHQ Teaching Hospital, Dera Ismail KhanEmail: anwarkan.ak20@gmail.com**Introduction**

Dengue is an acute infection caused by four antigenically distinct dengue virus serotypes and transmitted principally by *Aedes aegypti* mosquitoes. Its clinical spectrum ranges from asymptomatic infection and self-limited febrile illness to plasma leakage, shock, severe hemorrhage, and major organ involvement. About half of the world's population lives in areas at risk, and WHO recorded unprecedented global transmission in 2024, which has increased the demand for safe, scalable clinical care (1,2,3).

The main clinical challenge is that defervescence does not always mean recovery. Around the transition from the febrile to the critical phase, a minority of patients develop increased vascular permeability, hemoconcentration, thrombocytopenia, shock, bleeding, or organ dysfunction. Recognition of this transition is therefore essential, because appropriate monitoring and judicious fluid management can substantially reduce preventable mortality (3).

The WHO 2009 classification divides symptomatic infection into dengue without warning signs, dengue with warning signs, and severe dengue. Warning signs include abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleeding, lethargy or restlessness, liver enlargement greater than 2 cm, and an increase in hematocrit concurrent with a rapid decline in platelet count. The classification was developed to improve triage and to capture clinically important disease that was difficult to classify under the older dengue fever/dengue hemorrhagic fever/dengue shock syndrome framework (1,4).

Multi country and single-country evaluations have generally found the revised system easier to apply and more sensitive in identifying patients who need increased observation or intervention, although greater sensitivity can move more patients into a higher-acuity category. Definitions of some warning signs, particularly persistent vomiting, vary between settings, and the predictive value of an individual sign depends on timing, age, comorbidity, serotype, immune status, and the local prevalence of severe disease (5,6). Pakistan has experienced repeated dengue outbreaks; all four serotypes have been documented, and transmission varies substantially by region. Khyber Pakhtunkhwa carries a considerable burden, and hospital-based Pakistani studies have described thrombocytopenia, gastro intestinal symptoms, bleeding manifestations, and occasional severe or fatal outcomes. Local estimates of warning-sign frequency remain useful because they inform staffing, bed allocation, observation protocols, and patient counseling during seasonal surges (7,8,9,10). For Dera Ismail Khan, such local data may help support hospital triage, monitoring, and resource planning during seasonal dengue surges.

The present study quantified the frequency and pattern of six recorded WHO warning signs among dengue admissions at Mufti Mehmood Memorial Teaching Hospital, Dera Ismail Khan. Secondary objectives were to describe the demographic, laboratory, severity, and outcome profile; characterize the number and co-occurrence of warning signs; and compare dengue with warning signs and severe dengue in exploratory analyses.

Methods

A hospital-based retrospective cross-sectional study was conducted in the

medical units of Mufti Mehmood Memorial Teaching Hospital, Dera Ismail Khan, Khyber Pakhtunkhwa, Pakistan, during a defined dengue transmission period. The hospital is a tertiary-care teaching facility that receives patients from Dera Ismail Khan and the surrounding districts. All eligible records of patients aged 15–60 years who were admitted with laboratory-confirmed dengue and had a documented assessment of warning signs and hospital outcome were included. Records were excluded when dengue was not laboratory confirmed, when the same admission was duplicated, or when the principal warning-sign variables were unavailable. A total of 384 records met the eligibility criteria.

Laboratory confirmation followed a timing-based diagnostic algorithm. Patients presenting during the first five days of illness were assessed for dengue non-structural protein 1 (NS1) antigen using a validated rapid immune chromatographic assay. Patients presenting on or after the fifth day of illness were assessed for dengue-specific IgM antibodies by serological testing; IgG findings were used as supportive evidence of prior or secondary infection rather than as the sole criterion for acute dengue. Reverse-transcription polymerase chain reaction was used when available for early cases with inconclusive or discordant results. All laboratory tests were performed and interpreted in accordance with the manufacturer's instructions and routine hospital laboratory quality-control procedures (1).

No prior sample-size calculation was performed. A census sampling strategy was used: all records meeting the eligibility criteria during the study period were included, yielding a final sample of 384 patients. For descriptive purposes, a sample

of this size estimates proportions near 50% with a Wilson 95% confidence interval half-width of about 5 percentage points, which was considered adequate for the stated objectives.

The available variables were age, sex, previous dengue exposure (yes, no, or unknown), persistent vomiting, lethargy, hepatomegaly, abdominal pain, mucosal bleeding, clinical fluid accumulation, platelet count, hematocrit, recorded WHO classification, and outcome (discharged, referred, or expired). A warning sign was considered present when coded "Yes" in the database. The total warning-sign burden was the sum of the six binary warning-sign fields and therefore ranged from 0 to 6. The seventh WHO warning sign—an increase in hematocrit concurrent with a rapid decline in platelet count—could not be evaluated because only one hematocrit and one platelet value were available. Likewise, the database did not include shock, respiratory distress, severe bleeding, transaminases, creatinine, neurologic status, or other variables required to independently reconstruct severe dengue. Recorded WHO classifications were consequently analyzed as provided rather than re-adjudicated (1). Platelet values were recorded as cells/ μL and converted to $\times 10^9/\text{L}$ by dividing by 1,000. Hematocrit was reported as a percentage. The first available admission platelet count and hematocrit value were used for the descriptive and comparative analyses. Previous dengue exposure was identified from the corresponding medical-record/database field and coded as yes, no, or unknown.

Patient identifiers were checked for duplication, and all variables were reviewed for completeness, valid ranges, and internal consistency. The analytic

dataset contained 384 unique records and no missing values in the variables included in this study. Categorical codes were standardized before analysis.

Analyses were performed using Python with SciPy and statsmodels-compatible procedures. Continuous variables were assessed descriptively and reported as mean $\pm$ standard deviation (SD) and median with interquartile range (IQR). Categorical variables were summarized using counts and percentages. Wilson score 95% CIs were calculated for warning-sign proportions. Age, platelet count, and hematocrit were compared across the three recorded WHO categories using Kruskal-Wallis tests because category sizes were unequal and normality could not be assumed. Sex and previous dengue exposure were compared across categories with Pearson chi-square tests. Unadjusted odds ratios (ORs), 95% CIs, and two-sided P values were calculated for exploratory associations between individual warning signs and severe dengue among patients classified as dengue with warning signs and severe dengue; these six comparisons were corrected using the Benjamini-Hochberg false-discovery-rate procedure. Non-routine disposition (referral or death) was compared by Fisher exact test. No multivariable prognostic model was fitted because there were only 35 severe-dengue cases and 16 non-routine dispositions, no timing variables were available, and key confounders could be associated with the recorded classification, which would introduce incorporation bias. A two-sided $P < 0.05$ was considered statistically significant, and exploratory estimates are presented with CIs and should not be regarded as causal estimates.

The research proposal was reviewed and approved unanimously by the Ethical Review Committee, Gomal Medical College, Dera Ismail Khan (Approval No. 163/GJMS/JC; committee meeting held on 01 November 2024; approval dated 08 November 2024).

Results

There were 384 unique records in the database, and no missing data in the 14 variables analyzed. The mean age was 38.6 ± 13.2 years, with a median of 39 years (IQR 27–50) and a range of 15–60 years. There were 201 male patients (52.3%) and 183 female patients (47.7%). Prior dengue exposure was recorded as yes in 124 (32.3%), no in 122 (31.8%), and unknown in 138 (35.9%). The median platelet count, after conversion from cells/ μL to $\times 10^9/\text{L}$, was $108.7 \times 10^9/\text{L}$ (IQR 73.0–143.0); the mean hematocrit was $43.3 \pm 5.0\%$. According to the recorded WHO category, 79 patients (20.6%) had dengue without warning signs, 270 (70.3%) had dengue with warning signs, and 35 (9.1%) had severe dengue (Table 1).

Table 1. Demographic, laboratory, classification, and outcome profile of the study records (n = 384)

Characteristic	n or Summary	%
Age, years		
Mean $\pm$ SD	38.6 ± 13.2	
Median (IQR)	39 (27–50)	
Age group 15–29 years	116	30.2
Age group 30–44 years	119	31.0
Age group 45–60 years	149	38.8
Male sex	201	52.3
Female sex	183	47.7
Previous dengue exposure: yes	124	32.3
Previous dengue exposure: no	122	31.8
Previous dengue exposure: unknown	138	35.9
Platelet count, median (IQR), $\times 10^9/\text{L}$	108.7 (73.0–143.0)	
Hematocrit, mean $\pm$ SD, %	43.3 ± 5.0	

Dengue without warning signs	79	20.6
Dengue with warning signs	270	70.3
Severe dengue	35	9.1
Discharged	368	95.8
Referred	14	3.6
Expired	2	0.5

Note: SD, standard deviation; IQR, interquartile range. At least one of the six recorded warning signs was present in 305 patients (79.4%; 95% CI 75.1–83.2). Persistent vomiting was the most common warning sign, affecting 197 patients (51.3%; 95% CI 46.3–56.3). Lethargy occurred in 97 (25.3%), hepatomegaly in 85 (22.1%), abdominal pain in 74 (19.3%), mucosal bleeding in 18 (4.7%), and clinical fluid accumulation in 16 (4.2%) (Table 2 and Figure 1).

Table 2. Frequency and Wilson 95% confidence intervals of recorded warning signs

Warning sign	n	%	95% CI
Persistent vomiting	197	51.3	46.3–56.3
Lethargy	97	25.3	21.2–29.8
Hepatomegaly	85	22.1	18.3–26.6
Abdominal pain	74	19.3	15.6–23.5
Mucosal bleeding	18	4.7	3.0–7.3
Clinical fluid accumulation	16	4.2	2.6–6.7

Note: CI, confidence interval.

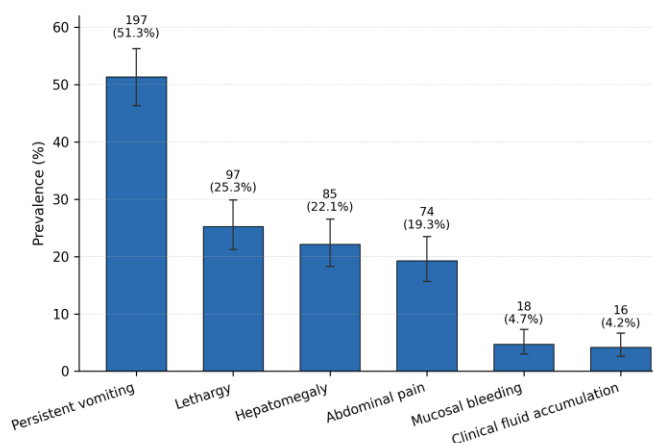


Figure 1. Frequency of the six recorded warning signs among all admissions (n = 384). Counts and percentages are shown above the bars; error bars show Wilson 95% confidence intervals.

Age, sex distribution, previous dengue exposure, platelet count, and hematocrit did not differ statistically across the three recorded WHO categories (all $P > 0.40$). The warning-sign count increased sharply by category: the median was 0 in dengue without warning signs, 1 (IQR 1–2) in dengue with warning signs, and 3 (IQR 3–3) in severe dengue. Because this pattern is closely linked to the recorded categorization and may reflect incorporation of the warning signs into classification, no inferential P value was assigned to warning-sign count (Table 3).

Table 3. Characteristics according to recorded WHO dengue category

Variable	Dengue without warning signs (n=79)	Dengue with warning signs (n=270)	Severe dengue (n=35)	P value
Age, median (IQR), years	39 (30–48)	39 (26–49)	38 (28–52)	0.983
Male sex, n (%)	42 (53.2)	142 (52.6)	17 (48.6)	0.892
Previous exposure: yes, n (%)	26 (32.9)	89 (33.0)	9 (25.7)	0.506
Platelet count, median (IQR), $\times 10^9/L$	110.8 (73.1–151.2)	108.2 (74.2–141.3)	107.3 (66.0–137.0)	0.756
Hematocrit, median (IQR), %	44.0 (39.5–48.3)	42.7 (38.6–47.4)	44.2 (38.8–48.6)	0.412
Warning-sign count, median (IQR)	0 (0–0)	1 (1–2)	3 (3–3)	—

Note: Kruskal–Wallis tests were used for continuous variables and chi-square tests for categorical variables. No P value is shown for warning-sign count because the count is structurally related to the recorded classification. IQR, interquartile range.

Among the 305 patients classified as dengue with warning signs or severe dengue, every

recorded warning sign was more frequent in severe dengue. After false-discovery-rate correction, the strongest unadjusted association was observed for hepatomegaly (OR 14.95; 95% CI 6.21–35.98), followed by mucosal bleeding (OR 10.04; 95% CI 3.66–27.51), clinical fluid accumulation (OR 5.38; 95% CI 1.82–15.88), lethargy (OR 5.08; 95% CI 2.40–10.72), persistent vomiting (OR 3.70; 95% CI 1.39–9.84), and abdominal pain (OR 3.53; 95% CI 1.71–7.28). These estimates are exploratory, unadjusted, and potentially affected by incorporation bias (Table 4).

Table 4. Exploratory unadjusted associations between individual warning signs and severe dengue

Warning sign	Severe dengue n (%)	Dengue with warning signs n (%)	OR	95% CI	FDR q
Persistent vomiting	30 (85.7)	167 (61.9)	3.70	1.39 – 9.84	0.005
Lethargy	23 (65.7)	74 (27.4)	5.08	2.40 – 10.72	<0.001
Hepatomegaly	28 (80.0)	57 (21.1)	14.95	6.21 – 35.98	<0.001
Abdominal pain	17 (48.6)	57 (21.1)	3.53	1.71 – 7.28	0.002
Mucosal bleeding	9 (25.7)	9 (3.3)	10.04	3.66 – 27.51	<0.001
Clinical fluid accumulation	6 (17.1)	10 (3.7)	5.38	1.82 – 15.88	0.005

Note: Analysis restricted to severe dengue and dengue with warning signs. Fisher exact tests; Benjamini-Hochberg false-discovery-rate (FDR) correction. OR, odds ratio. CI, confidence interval.

Overall, 368 patients (95.8%) were discharged, 14 (3.6%) were referred, and 2 (0.5%) died. Both deaths occurred in the severe-dengue category; discharges were recorded for 75 of 79 (94.9%) patients without warning signs, 261 of 270 (96.7%) with warning signs, and 32 of 35 (91.4%) with severe dengue. A non-routine disposition (referral or death) occurred in 3 of 35 severe-dengue records (8.6%) and 13 of 349 non-severe records (3.7%), corresponding to an unadjusted OR of 2.42 (95% CI 0.66–8.95; Fisher exact $P=0.171$). The CI was wide and included no association because only 16 non-routine dispositions occurred.

Discussion

The study provides a local description of warning-sign patterns in Dera Ismail Khan and shows the value of reporting both the frequency of individual signs and the total warning-sign burden. The results also caution against treating warning signs as a single binary label; they function better as a dynamic clinical checklist in which less common signs acquire greater significance when they accompany hemodynamic, hematologic, or organ-function changes.

Gastrointestinal manifestations are common in dengue and may reflect systemic inflammation, hepatic involvement, gastrointestinal edema, or evolving plasma leakage. A Vietnamese cohort evaluating the operational definition of persistent vomiting found that two or more episodes per day had high sensitivity but modest specificity for subsequent severe dengue, emphasizing that a clear frequency threshold and serial reassessment are needed (6). This predominance of gastrointestinal manifestations is broadly consistent with Pakistani hospital reports describing gastrointestinal symptoms among admitted dengue patients (7,8,9).

Vomiting was recorded as a binary clinical variable and did not include episode count,

duration, inability to tolerate oral fluids, day of illness, or associated dehydration. Consequently, the measured 51.3% frequency cannot distinguish transient vomiting from clinically persistent vomiting as defined in a protocol. Abdominal pain was less common than vomiting but was also enriched among severe-dengue records, consistent with studies identifying abdominal pain and gastrointestinal manifestations among patients who later required greater intervention (10,11,12,13,14).

Lethargy occurred in one-quarter of the cohort and in nearly two-thirds of severe-dengue records. Lethargy is clinically important but potentially subjective; it may indicate reduced perfusion, systemic inflammation, dehydration, hepatic dysfunction, metabolic disturbance, or neurologic involvement. Recent observational evidence and meta-analytic work support altered mental status, lethargy, and organ dysfunction as markers of increased risk, while also showing that their predictive performance varies with the study population and timing of assessment (13,14,15,16,17).

Hepatomegaly was recorded in 22.1% overall and was the warning sign most strongly associated with severe dengue in the exploratory analysis. Hepatic enlargement can accompany inflammatory hepatic injury and vascular congestion, but the WHO criterion specifies liver enlargement greater than 2 cm. The association may be observer dependent and dependent on documentation; liver span, tenderness, transaminases, and imaging confirmation were not included in the dataset. Future studies could use standardized examination and liver-function testing for a more reproducible evaluation (1,13,18).

Mucosal bleeding and clinical fluid accumulation were uncommon overall but significantly more frequent in severe-dengue

records. The pathophysiological relevance of these manifestations is evident: mucosal bleeding can reflect thrombocytopenia, coagulopathy, or mucosal lesions, and pleural effusion or ascites is clinically detectable plasma leakage. Extensive bleeding should be differentiated from minor mucosal bleeding, and ultrasonography can help identify occult fluid accumulation. The present analysis cannot determine the severity or mechanism of these findings because imaging, albumin, coagulation indices, and serial hematocrit measurements were unavailable (1,14,15,19,20).

Patients classified as severe dengue had a median of 3 recorded warning signs, while patients classified as dengue with warning signs had a median of 1. This gradient is clinically plausible, because multiple signs may reflect a more complex systemic disorder than a single symptom. However, warning signs are themselves components of the WHO clinical classification; therefore, associations between individual warning signs, total warning-sign burden, and the recorded category are subject to incorporation bias.

Platelet count and hematocrit did not differ significantly across recorded WHO categories. This finding should not be interpreted as evidence that these markers are unimportant. Dengue is dynamic, and single measurements can miss the rapid platelet decline and rising hematocrit that characterize the critical phase. Several cohorts and meta-analyses have linked thrombocytopenia, hemoconcentration, hypotension, and other laboratory abnormalities with severe disease, but the diagnostic value depends on illness day, serial trend, baseline values, fluid therapy, and comorbid conditions (1,13,16,18). The absence of serial laboratory measurements is an important limitation. Although the admission platelet count and hematocrit provide a useful baseline

description, a single measurement cannot characterize the rapid platelet decline and rising hematocrit that may occur near the critical phase.

The recorded discharge rate was high, and both deaths occurred in severe dengue. The non-routine disposition rate was numerically higher in severe disease, but the estimate was imprecise because only 16 events occurred. Other adult dengue cohorts have shown that mortality is associated particularly with shock, severe bleeding, organ dysfunction, delayed presentation, comorbid disease, and secondary infection. These variables were not available, so the analysis was not designed to develop or validate a mortality model (10,13,17,21).

Clinically, the findings support a standardized admission and monitoring sheet that records the exact warning-sign definition, illness day, vital signs, perfusion, fluid balance, oral tolerance, bleeding severity, liver size, and serial hematocrit and platelet values. Persistent vomiting alone should prompt reassessment of hydration and oral tolerance, but escalation decisions should integrate the full clinical trajectory. Patients with multiple signs, fluid accumulation, mucosal bleeding, lethargy, rising hematocrit, falling platelets, hypotension, or organ dysfunction require particularly close observation and timely referral according to local capacity and WHO guidance (1,3,6,17,22).

In Pakistani hospital settings, changing clinical patterns, significant thrombocytopenia, gastrointestinal and bleeding symptoms, and occasionally severe complications have been recorded. In addition, data from Khyber Pakhtunkhwa show that the burden is high in the economically active age group and highlight the importance of surveillance and prompt clinical evaluation (7,10,21,23).

An individualized warning-sign profile can help a hospital prepare before the transmission season. Clinical teams should assess hydration status promptly, use antiemetics according to local protocols, and apply clear oral-fluid-tolerance and admission criteria when vomiting is the predominant symptom. A single platelet reading does not rule out severe illness; repeat assessment near defervescence is important, as are streamlined referral pathways for shock, bleeding, fluid collection, and organ failure.

Strength of study: The strengths of the analysis are a clearly defined denominator, complete data for the analyzed variables, confidence intervals around prevalence estimates, a clear description of sign co-occurrence, correction for the multiple exploratory comparisons, and a clear distinction between descriptive findings and claims concerning prognosis.

The manuscript also highlights the elements of data needed to enhance future dengue surveillance at the hospital.

Limitation of study: Severe dengue could not be independently re-adjudicated because detailed information on shock, severe bleeding, organ impairment, imaging findings, and serial laboratory results was unavailable.

Warning signs were recorded as binary variables without detailed thresholds or timing.

The single-center hospitalized population may also be affected by referral and admission selection and cannot be used to estimate community prevalence.

Finally, the small numbers of severe cases and adverse outcomes limited adjusted modeling and the precision of outcome estimates.

Future Recommendations

A prospective multicenter study should record clinical data daily from admission through at least 24–48 hours after

defervescence. Standardized definitions should be used for persistent vomiting, liver enlargement, mucosal bleeding, and clinical fluid accumulation. Serial platelet and hematocrit trajectories, vital signs, lactate, liver and renal function, coagulation markers, imaging findings, serotype, immune status, comorbidities, fluid therapy, intensive-care use, length of stay, and mortality should be captured.

Conclusion

Persistent vomiting was the most frequently recorded manifestation, and the warning-sign burden increased across recorded severity categories. A structured warning-sign checklist may support triage and serial clinical reassessment, but individual warning signs should not be interpreted in isolation. Systematic, repeated warning-sign assessment may support early recognition of deterioration, provided individual findings are interpreted alongside the illness phase, hemodynamic status, and serial laboratory trends.

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