RESEARCH PAPER

# WHO 2009 Warning Signs as Predictors of Time Taken for Progression to Severe Dengue in Children

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**Objective**: To identify WHO 2009 warning signs that can predict time taken for progression to severe dengue in a pediatric population.

**Design**: Prospective analytical study over 1 year and 2 months.

**Setting**: Tertiary care center.

**Participants**: 350 children aged 1 mo-12 y with serologically confirmed dengue without co-morbidities/co-infections; consecutive sampling.

**Procedure**: At admission, clinical and laboratory details were noted. Disease progression, time of onset of each warning sign, hematocrit, and platelet counts were recorded daily till discharge/death. If progressing to severe dengue, its time of onset was noted. Time to event analysis with Log Rank test, Kaplan Meier plots and Cox Proportional Hazards Model was done.

**Outcome Measures**: Primary outcome was time interval from onset of first warning sign to onset of severe dengue (defined as per WHO 2009 guidelines). Predictors were WHO 2009 warning signs: abdominal pain, lethargy, persistent vomiting, mucosal bleed, clinical fluid accumulation, hepatomegaly >2 cm, hematocrit ≥0.40 and platelet count <100x$10^9$/L.

**Results**: Among 350 children followed up completely till discharge/death, 90 developed severe dengue (event) while 260 did not (censored). Median age of study population was 7.75 y. Clinical fluid accumulation [(*P*=0.002, Hazard Ratio (HR) 2.19, 95% CI 1.33-3.60)] and hematocrit ≥0.40 [(*P*=0.009, HR (95%CI) 1.715, (1.13-2.60)] were significant in univariate analysis. Final multivariate model includes clinical fluid accumulation [(*P*=0.02, HR (95%CI) 1.89, (1.116-3.202)], hematocrit ≥0.40 (*P*=0.07), mucosal bleed (*P*=0.56) and persistent vomiting (*P*=0.32).

**Conclusion**: WHO warning signs that predict time taken for progression to severe dengue in children include clinical fluid accumulation, hematocrit ≥0.40, persistent vomiting and mucosal bleed. Study results have implications in policy making and practice guidelines to triage children attending a health care facility with or without warning signs.

**Keywords**: *Hematocrit, Management, Outcome, Prognosis.*

Dengue is a globally prevalent arboviral infection with high morbidity and mortality in India [1]. Kerala reported 19,912 dengue cases with 37 deaths in 2017 [2]. Dengue is dynamic with febrile phase, critical phase (appearance of warning signs at/around defervescence mark onset of capillary leak) and convalescent phase [3]. Seven warning signs *viz*. abdominal pain, lethargy, mucosal bleed, persistent vomiting, clinical fluid accumulation, hepatomegaly >2 cm and rising hematocrit with a concurrent fall in platelet count below $100\times10^9$/L are evidence-based signs selected by the World Health Organization (WHO) [3,4]. Potentially lethal severe dengue can manifest as shock, severe bleed or severe organ impairment in the critical phase or in the febrile phase without preceding warning signs [3]. Close monitoring and timely initiation of intravenous fluids in the presence of any warning signs remain the only effective treatment modality in dengue [3]. Severe dengue manifests as mostly shock in children and as severe bleeding and organ impairment in adults [5].

A prognostic prediction model using seven WHO warning signs to determine severe dengue in children has been published earlier [6]. Dynamicity of illness can be captured by taking into consideration the time to time variations in clinical and laboratory variables [7]. The present study aimed to identify warning signs which can predict time taken for progression to severe dengue in children admitted to a tertiary care center.

*Editorial Commentary: Pages 895-96.*

## METHODS

This prospective study was done in a tertiary care setting over one year and two months (2015-16). All serologically confirmed dengue patients (either NS1Ag positivity, if admitted within first 5 days of fever, or IgM positivity, if after 5 days of fever) between 1 mo-12 y without co-morbidities or co-infections were enrolled by consecutive sampling. At admission, baseline history, clinical examination and laboratory investigations (total

count, hematocrit, platelet counts, liver and renal function tests) were recorded. Close monitoring was done to note the time of onset of warning signs and severe dengue if any and need for administration of intravenous fluids till discharge or death. Daily examination for clinical fluid accumulation, hepatomegaly, hematocrit and platelet count were done in all patients. In case of rising hematocrit, intravenous fluids were started, titrated (as per WHO 2012 guidelines) and hematocrit repeated. In patients with clinical worsening, 4 hourly hematocrit, 12 hourly platelet count, and 2 hourly clinical examinations were done, as per hospital protocol. Ethical clearance was obtained from Institutional Review Board.

Primary outcome was time duration from onset of first warning signs to onset of severe dengue defined as attainment of either severe plasma leak leading to shock and/or fluid accumulation with respiratory distress, severe bleed or severe organ impairment [3]. Seven WHO, 2009 warning signs (dichotomized as yes/no) were: abdo-minal pain (severe enough to warrant medical attention), lethargy (without altered sensorium), persistent vomiting (≥2 episodes of vomiting that amounts to fatigue or requires intravenous fluids), mucosal bleed (any bleed from gastrointestinal/genitourinary mucosa, nose, conjunctiva), clinical fluid accumulation (either pleural effusion not severe enough to cause respiratory distress as evidenced by reduced intensity of breath sounds on auscultation of axillary areas or ascites as evidenced by shifting dullness), hepatomegaly >2 cm, hematocrit ≥0.40 (cut-off decided by constructing a receiver operating characteristic curve) and a fall in platelet count $<100\times10^9$/L [6].

Sample size for number of events in each group in survival analysis was calculated where in δ is natural logarithm of the expected ratio of hazards at a given time [8]. For a two-tailed test (α 0.05 and β 0.2), by keeping δ arbitrarily as 1.6, number of events (severe dengue) needed in each group was calculated as 71; by keeping δ arbitrarily as 2, events needed in each group was 33.

*Statistical analyses*: Descriptive statistics and time to event data analysis were performed with SPSS version 20. Univariate analysis was done for each warning signs with time taken for progression to severe dengue as outcome; Kaplan Meier graphs were drawn. Predictor significance for inclusion in the multivariate model was predetermined (α 20%). Cox proportional hazards model was checked by looking for parallel lines with and without each predictor in scatter plots with log time along *X*-axis and -log [-log (Survival function)] along *Y*-axis [9].

## RESULTS

Among 386 serologically confirmed dengue patients, 9 had co-morbidities, 8 had co-infections, 7 did not have any warning signs and 2 had onset of severe dengue before onset of the first warning signs. They were excluded and among remaining 350, 90 (25.7%) progressed to severe dengue (event); 4 patients with severe dengue died. Remained 260 children (74.3%) did not progress to severe dengue and were considered 'right censored' in time to event analysis.

Median (IQR) age of study population was 7.75 (4.75, 10.25) year. There were 21 infants and 188 (53.7%) were males. Proportion of children who progressed to severe dengue as evidenced by compensated shock, decompensated shock, respiratory distress, severe bleed and severe organ impairment as per WHO definitions were 23.1%, 16%, 4.6%, 1.4% and 4.6%, respectively. Median (IQR) day of admission to our center was on day 5 (4, 6). 154 subjects were NS1Ag positive, 163 were IgM positive and 33 were both positive; 22.1%, 29.4% and 24.2% progressed to SD respectively. Median (IQR) length of follow-up was 5 (4, 6) days **(*Table* I)**.

Log rank test was applied to the data and Kaplan Meier curves were drawn to compare between groups with and without each warning sign **(*Table* II**, ***Fig*. 2*a*, 2*b*)**. Final model includes all warning signs with $P<0.2$ in univariate analysis (clinical fluid accumulation, mucosal bleed, persistent vomiting and hematocrit ≥0.40) (***Table* III**).

Receipt of intravenous fluids could confound time taken for progression to severe dengue, but statistical significance was not obtained in univariate analysis with time to event as outcome.

## DISCUSSION

The study shows that clinical fluid accumulation, hematocrit ≥0.40, mucosal bleed and persistent vomiting predict time taken for progression to severe dengue. Earlier, authors developed a prognostic prediction model to determine severe dengue in children that included clinical fluid accumulation hematocrit ≥0.40 with platelet count $<100\times10^9$/L and persistent vomiting [6].

In the present study, clinical fluid accumulation appeared late with a median time of onset of 144 h from onset of fever. Moreover, median time of onset of severe dengue is only 2h from onset of clinical fluid accumulation. In most situations, authors were the first to identify clinical fluid accumulation; being a tertiary setting, exact time of onset of clinical fluid accumulation could not be delineated. In our study, hematocrit appeared late probably because the investigation was not sent before admission to our center. Even then, median time of onset of severe dengue was 5h after onset of

**Table I Time of Onset of Warning Sign and Time of Onset of Severe Dengue (*N*=350)**

| *Characteristic* | *Abdominal pain* | *Persistent vomiting* | *Lethargy* | *Hepatomegaly >2cm* | *Clinical fluid accumulation* | *Mucosal bleed* | *Platelet count <100×10⁹/L* | *Hematocrit ≥0.40* |
|---|---|---|---|---|---|---|---|---|
| Total with WS* | 217 (62) | 99 (28.2) | 327 (93.4) | 162 (46.2) | 64 (18.2) | 72 (20.5) | 284 (81.1) | 123 (35.1) |
| Time of onset of WS (h) | 72 (6,120) | 24 (6,120) | 6 (6,72) | 144 (120,168) | 144 (144,168) | 132 (96,162) | 120 (120,144) | 144 (120,168) |
| Total with WS before event* | 211 (60.2) | 98 (28) | 326 (93.1) | 143 (40.8) | 46 (13.1) | 56 (16) | 270 (77.1) | 113 (32.2 ) |
| Total events* | 58 (16.5) | 35 (10) | 86 (24.5) | 36 (10.2) | 26 (7.4) | 21 (6) | 69 (19.7) | 42 (12) |
| Time to onset of event after WS (h) | 48 (6,120) | 120 (24,144) | 120 (48,144) | 2 (2,3) | 2 (1,4) | 24 (4,48) | 18 (2,24) | 5 (2,24) |

*Values in median (IQR) except *n(%); WS-warning sign.*

**Table II Children With Each Warning Sign Who Progressed to Severe Dengue (Event) and Event Free Time**

| *Warning sign* | *Total* | *Events n= 90* | *Survival Time (95% CI), min* | *P value* | *Crude OR (95% CI)* |
|---|---|---|---|---|---|
| Yes | 211 | 58 (153) | 359.7 (328.98-390.43) | 0.87 | 1.04 |
| No | 139 | 32 (107) | 324.1 (291.19-357.02) | | (0.67-1.59) |
| Lethargy | | | | | |
| Yes | 326 | 86 (240) | 362.5 (337.46-387.60) | 0.69 | 1.26 |
| No | 24 | 4 (20) | 167.2 (141.90-192.59) | | (0.39-3.99) |
| Persistent vomiting | | | | | |
| Yes | 98 | 35 (63) | 276.4 (242.73-310.04) | 0.13 | 1.38 |
| No | 252 | 55 (197) | 384.1 (356.53-411.64) | | (0.90-2.10) |
| Clinical fluid accumulation | | | | | |
| Yes | 46 | 26 (20) | 178.3 (146.04-210.48) | 0.002 | 2.19 |
| No | 304 | 64 (240) | 379.1 (353.64-404.59) | | (1.33-3.59) |
| Hepatomegaly | | | | | |
| Yes | 143 | 36 (107) | 363.8 (339.18-388.35) | 0.81 | 1.01 |
| No | 207 | 54 (153) | 370.7 (338.81-402.67) | | (0.69-1.59) |
| Mucosal bleed | | | | | |
| Yes | 56 | 21 (35) | 204.8 (177.67-231.89) | 0.14 | 1.45 |
| No | 294 | 69 (225) | 370.3 (342.62-398.01) | | (0.89-2.36) |
| Hematocrit ≥0.40 | | | | | |
| Yes | 113 | 42 (71) | 265.5 (232.60-298.35) | 0.009 | 1.71 |
| No | 237 | 48 (189) | 392.3 (364.75-419.91) | | (1.13-2.59) |
| Platlet count <100x10$^9$/L | | | | | |
| Yes | 270 | 69 (201) | 314.6 (291.83-337.30) | 0.97 | 1.01 |
| No | 80 | 21 (59) | 382.0 (333.96-430.14) | | (0.61-1.66) |

hematocrit ≥0.40. This time gap is clinically valuable for initiating close monitoring, intensive care and early referral if needed. This makes hematocrit ≥0.40 a clinically relevant warning signs. Kaplan Meier curves drawn for clinical fluid accumulation and hematocrit ≥0.40 as predictors intersect at some points. Hence confounders do exist for which stratum specific analysis might have been helpful. Administration of intravenous fluids was thought of as a potential confounder but statistical significance was not obtained in univariate analysis. Possibility of unknown confounders should be thought of in this context.

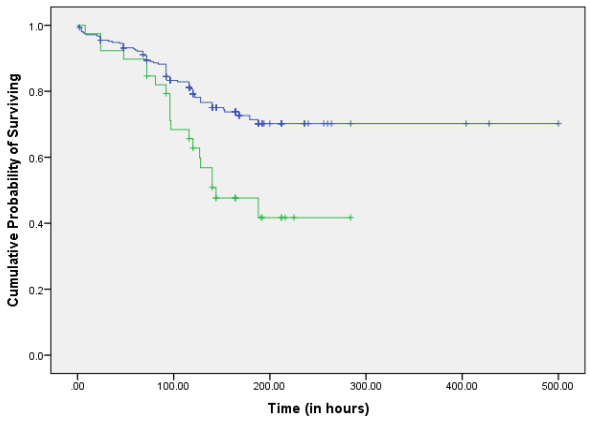


**Fig. 1** *Kaplan Meier Curve showing survival function over time in the absence (upper line) and presence (lower line) of CFA as predictor.*

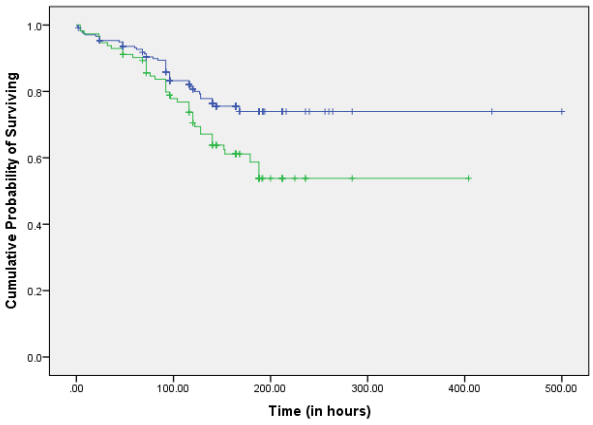


**Fig. 2** *Kaplan Meier curve showing survival function over time in the absence (upper line) and presence (lower line) of HCT >0.40 as predictor.*

Mucosal bleed and persistent vomiting are two objective symptoms, time of onset of which the caretaker may easily notice. An added advantage of persistent vomiting is its early appearance in the disease course. A sufficient time gap between time of onset of persistent vomiting and time of onset of severe dengue was also demonstrated in our study. Due to these clinical reasons, mucosal bleed and persistent vomiting were included in the final model.

In our tertiary care setting, some patients had onset of warning signs even before admission to our hospital. To minimize this recall bias, details from referral letters were collected and telephonic conversations with referring doctor were done wherever needed. Though technically, 260 patients were right censored, all were completely followed up till recovery as evidenced by fever free period of 48 hours, disappearance of clinical warning signs, rising trend of platelet counts and a normal hematocrit. Secondary infection is a strong risk factor of progression to severe dengue and hence may influence time to event. Detailed investigations to delineate infection as primary or secondary were not done in our study. Our study period included two dengue seasons, but only 90 patients progressed to severe dengue which was below the estimated sample size.

**Table III Cox Proportional Hazards Model With Selected Warning Signs**

| *Warning signs* | *Model including CFA, HCT ≥0.40, PV and MB* | | *Model including CFA, HCT≥0.40 and MB* | |
|---|---|---|---|---|
| | *HR (95% CI)* | *P value* | *HR (95% CI)* | *P value* |
| CFA | 1.89 (1.11-3.20) | 0.02 | 1.85 (1.09-3.12) | 0.02 |
| Hct ≥0.40 | 1.49 (0.96-2.29) | 0.07 | 1.54 (1.00-2.35) | 0.05 |
| MB | 1.17 (0.69-1.97) | 0.56 | 1.25 (0.76-2.07) | 0.38 |
| PV | 1.25 (0.80-1.95) | 0.32 | - | - |

*CFA: Clinical fluid accumulation; Hct: Hematocrit; PV: Persistent vomiting; MB: Mucosal bleed; HR: Hazard ratio.*

A previous survival analysis assessed survival of adult dengue patients in relation to the severity of liver dysfunction [10]. Survival analysis of a pediatric population has identified that acute renal failure adversely affects survival rates [11]. In these studies, event was mortality whereas in our study, event severe dengue. Lam, *et al*. [7] have found that prediction models with serial daily platelet counts demonstrated better ability to discriminate patients who developed shock than models based on enrolment information only [7]. They concluded that development of dynamic prediction models that incorporate signs, symptoms and daily laboratory measure- ments could improve dengue shock prediction. In our study, all seven WHO warning signs have been included for the purpose of prediction.

Our results may be generalized to children attending a health care facility with dengue. As India is hyperendemic for dengue, the study results have implications in policy making and practice guidelines, especially to triage children attending a health care facility with or without warning signs. To conclude, WHO warning signs that can predict time taken for progression to severe dengue in children include clinical fluid accumulation, hematocrit ≥0.40, persistent vomiting and mucosal bleed.

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**WHAT IS ALREADY KNOWN?**

- Among seven warning signs suggested by WHO in 2009, clinical fluid accumulation, rising hematocrit concurrent with rapid fall in platelet count <100x$10^9$/L and persistent vomiting predict severe dengue in children.

**WHAT THIS STUDY ADDS?**

- WHO warning signs that predict time taken for progression to severe dengue in children include clinical fluid accumulation, hematocrit ≥0.40, persistent vomiting and mucosal bleed.

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*Contribution*: PS: conceived the idea, designed the methodology, collected and analysed data and prepared the manuscript; GS: guided conduct of the study, critically reviewed the manuscript; SKA: elaborated the concept, interpreted the results, critically reviewed the manuscript and approved final version to be published. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.
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