# Clinical predictors for complicated forms of dengue fever in patients of the Colombian Amazon Region

## Predictores clínicos de formas complicadas de dengue en pacientes de la Amazonía colombiana

Héctor Serrano Coll[1-2], Lorena García-Agudelo[3], William Andrés Olivero[3], Luz Nelba Sotaban[3], Katherine Villamizar[1]

investigacion.horo@gmail.com

Fecha de recepción: febrero 20 de 2023
Fecha de aceptación: junio 12 de 2023

## Abstract

**Introduction:** Dengue is a viral infection caused by one of the four serotypes of the dengue virus and it is transmitted among humans by the bite of the female Aedes aegypti mosquito. Clinically this infection can be asymptomatic or to course with a range of severity, dengue without or with signs of alarm to severe forms, serious dengue. **Objective:** To determine in 2944 patients with confirmed diagnosis of dengue which clinical manifestations would be more useful to predict the appearance of dengue with alarm signs and severe dengue in the population of the of the Colombian Amazon Region. **Results:** The clinical manifestations of warning in dengue that were predictive for dengue with alarm signs were abdominal pain (P< 0.0001, OR=44, IC-95% 32-59), vomiting (P< 0.0001, OR=38, IC-95% 24-61), diarrhea (P< 0.0001, OR=18, IC-95% 12-29), altered state of consciousness (P< 0.0001, OR=12, IC-95% 5-31) , mucosal bleeding (P< 0.0001, OR=23, IC-95% 10-52), thrombocytopenia (P< 0.0001, OR=41, IC-95% 29-56). With respect to predictors of severe dengue, it was shown that bleeding and hemodynamic instability (P< 0.0001, OR=1.2, CI-95% 1.1-1.3) would be a predictor in the detection of this clinical form of dengue. **Conclusions:** Manifestations such as gastrointestinal alterations, alterations in the state of consciousness, bleeding and thrombocytopenia would be clinical predictors of dengue fever with alarm signs. In severe dengue, the presence of hemorrhages and hemodynamic instability would be predictive in the detection of this clinical form of dengue.

**Key words:** Dengue, bleeding, abdominal pain, thrombocytopenia, hemodynamic instability.

## Resumen

**Introducción.** El dengue es una infección viral causada por uno de los cuatro serotipos del virus del dengue y se transmite entre humanos por la picadura del mosquito

[1] Research Group in Education and Health Sciences (ICES), UNISANGIL.
[2] Colombian Institute of Tropical Medicine (ICMT), Medellín, Colombia.
[3] Research Program, Regional Hospital of Orinoco ESE.

hembra Aedes aegypti. Clínicamente esta infección puede ser asintomática o de curso con un rango de gravedad, dengue sin o con signos de alarma a formas graves, dengue grave. **Objetivo.** Determinar en 2944 pacientes con diagnóstico confirmado de dengue qué manifestaciones clínicas serían más útiles para predecir la aparición de dengue con signos de alarma y dengue severo en la población de la Amazonía colombiana**. Resultados.** Las manifestaciones clínicas de alarma en dengue que fueron predictivas para dengue con signos de alarma fueron dolor abdominal (P< 0.0001, OR=38, IC-95% 24-61), diarrea (P< 0.0001, OR=18, IC-95% 12-29), estados alterados de conciencia (P< 0.0001, OR=12, IC-95% 5-31), hemorragia de la mucosa (P< 0.0001, OR=23, IC-95% 10-52), trombocitopenia (P< 0.0001, OR=41, IC-95% 29-56). Con respecto a los predictores de dengue grave, se demostró que el sangrado y la inestabilidad hemodinámica (P< 0.0001, OR=1.2, CI-95% 1.1-1.3) sería un predictor en la detección de esta forma clínica de dengue. Conclusiones: Manifestaciones como alteraciones gastrointestinales, alteraciones en el estado de conciencia, hemorragias y trombocitopenia serían predictores clínicos de dengue con signos de alarma. En el dengue grave, la presencia de hemorragias e inestabilidad hemodinámica sería predictiva en la detección de esta forma clínica de dengue.

**Palabras clave:** Dengue, hemorragia, dolor abdominal, trombocitopenia, inestabilidad hemodinámica.

## Introduction

The dengue is a viral infection caused by one of the four serotypes of the virus of dengue (DENV-1, DENV-2, DENV-3, DENV-4), which make part of the genus flavivirus within the family Flaviviridae and are transmitted between humans by the bite of the female of the Aedes aegypti mosquito (1). In addition, this infection clinically can take place of asymptomatic way or to produce a febrile picture with a rank of gravity that can go from an infection without signs of alarm to dengue with signs of alarm, which can progress towards a more severe form as it is the serious dengue (2).

From an epidemiological point of view, approximately 390 million cases of dengue fever are reported worldwide each year and it is estimated that this infection is responsible for nearly 500,000 hospital admissions for severe dengue fever and approximately 10,000 deaths annually (3,4). In addition, this infection continues to be endemic mainly in tropical and subtropical countries despite the efforts made by the World Health Organization (WHO) for its control and in Colombia, dengue is considered a hyperendemic infection, since more than 100,000 cases of this disease are reported every year (5). Therefore, dengue, being a public health problem at the global and national level, requires the generation of strategies focused on the control of this infection and the reduction of its morbidity and mortality.

One strategy that may be useful in reducing the morbidity and complications caused by this infection is to deepen the understanding of clinical predictors related to dengue fever with warning signs and severe dengue fever. By predicting earlier the onset of these severe clinical forms, health care providers would be able to manage early complications and

reduce mortality from dengue fever. It is for this reason, that the objective of this investigation is to determine the clinical manifestations that would have a greater utility to predict the appearance of dengue with signs of alarm and serious in the population of the of the Colombian Amazon Region

## Materials and methods

### Type of study

A descriptive observational study was carried out with transversal analytical intention.

### Selection of the study population and source of information

This study selected 2944 individuals with confirmed diagnosis of dengue through convenience sampling, who were treated at the Orinoco Regional Hospital (HORO) ESE, between the years 2015-2020. In addition, the clinical data of these patients were obtained from secondary sources, after receiving authorization from the HORO ESE health research ethics committee, according to act No 003 of 2020.

### Definitions

The definitions of dengue used in this study were taken from the guide for the care of dengue patients in the Region of the Americas 2015 implemented by WHO (6).

***Dengue fever without warning signs:*** confirmed case of dengue fever with fever for 2 to 7 days, in which there is no evidence of hemorrhage, dehydration, warning signs or shock and which does not belong to any risk group.

***Dengue fever with alarm signs:*** confirmed case of dengue fever associated with severe and continuous abdominal pain or pain on palpation, persistent vomiting, diarrhea, fluid accumulation (ascites, pleural effusion, pericardial effusion), mucosal bleeding, lethargy or irritability, painful hepatomegaly >2 cm and progressive increase in hematocrit, thrombocytopenia, hypotension and hypothermia.

***Severe Dengue Fever:*** Confirmed case of dengue fever with the presence of severe extravasation which is manifested by shock or fluid accumulation with respiratory distress, hemodynamic instability, or target organ involvement (liver: TPG or GOT ≥ 1,000, central nervous system involvement or heart involvement).

### Data analysis

Data were recorded from two of the systematic databases created in Windows Excel® 2016. The data reflected in these databases were analyzed using the Statistical Package for the Social Sciences version 21 (SPSS). The univariate analysis for the qualitative variables was performed by calculating absolute and relative frequencies. For quantitative variables, measures of central tendency were calculated. In addition, the normality of these variables was determined with the Kolmogorov-Smirnov test.

The bivariate analysis for variables of a qualitative nature was carried out through Pearson's chi-square test and, in addition, the risk was estimated through the calculation of Odds Ratio (OR) with their respective 95% confidence intervals. The multivariate analysis was carried out through a binomial logistic analysis to generate an explanatory and predictive model with the manifestations and clinical signs described

in dengue with alarm signs and severe dengue. The significance of the P value was established < 0.05 for all the analyses made.

## Results

### Sociodemographic and clinical characteristics of the patients evaluated with dengue

Of the 2944 patients evaluated with dengue, 50.3% were female, with a median age of 14 years and an age range of 1 to 92 years. In addition, of this evaluated cohort only 1.7% had a positive epidemiological link with a recent case of dengue and 45.6% of the patients were classified with dengue with alarm or severe signs. With respect to the medical handling, 46.6% received ambulatory handling and 99.9% had a satisfactory evolution of their viral picture.

**Table 1. Sociodemographic and clinical characteristics of the patients with dengue**

| **Characteristics of patients evaluated** n=2944 (%) |
|---|
| **Sex** |
| Female 1481 (50.3) |
| **Median age in years 14 (1-92)** |
| **Epidemiological link** 50 (1.7) |
| Yes |
| **Classification of dengue** |
| Dengue fever without alarm signs 1603 (54.4) |
| Dengue fever with alarm signs 1285 (43. 6) |
| Severe dengue 55 (2) |
| **Medical Management** |
| Ambulatory 1368 (46.5) |
| Hospitalization 1207 (41) |
| Observation 337 (11.4) |
| ICU 26 (0.9) |
| **Final Condition** |
| Live 2941 (99.9) |

### Clinical manifestations of dengue warning and its relation to the development of dengue with signs of alarm or serious

When relating the warning or alarm clinical manifestations in dengue we found that the abdominal pain (P< 0.0001, OR=44, IC-95% 32-59), vomiting (P< 0.0001, OR=38 IC-95% 24-61), diarrhea (P< 0.0001, OR=18, IC-95% 12-29), altered state of consciousness (P< 0.0001, OR=12, IC-95% 5-31), the presence of hepatomegaly (P< 0.0001, OR=12, IC-95% 5-31), mucosal bleeding (P< 0, 0001, OR=23, IC-95% 10-52), evidence of hemoconcentration (P< 0.0001, OR=18, IC-95% 4.4-78), thrombocytopenia (P< 0.0001, OR=41, IC-95% 29-56) and fluid accumulation (P< 0.0001, OR=19, IC-95% 4.6-81), are variables that behave as relevant risk factors in the development of complicated forms of this disease such as dengue with alarm signs and severe dengue.

**Table 2. Relationship of warning signs to the risk of developing dengue fever with alarm or severe signs**

| Evidenced clinical manifestations | Dengue fever without alarm signs (%) | Dengue fever with alarm signs and/or severe (%) | P-Value | OR | CI 95% |
|---|---|---|---|---|---|
| Abdominal pain | 15 (0.9) | 774 (57.8) | < 0.0001 | 44 | (32-59) |
| Vomiting | 3 (0.2) | 411 (30.6) | < 0.0001 | 38 | (24 - 61) |
| Diarrhea | 6 (0.24) | 251 (18.7) | < 0.0001 | 18 | (12-29) |
| Sleepiness / irritability | 0 | 52 (1.8) | < 0.0001 | 12 | (5-31) |
| Hypotension | 0 | 17 (0.6) | 0.206 | 1.8 | (0.7-4.8) |
| Hepatomegaly | 0 | 51 (3.8) | < 0.0001 | 12 | (5-31) |

| | | | | | |
|---|---|---|---|---|---|
| Mucosal bleeding | 0 | 107 (8) | < 0.0001 | 23 | (5-31) |
| Hypothermia | 0 | 3 (0.22) | 0.052 | 1 | (0.99 -1) |
| Hemoconcentration | 0 | 31 (2.3) | < 0.0001 | 18 | (4.4-78) |
| Thrombocytopenia | 4 (0.25) | 705 (52.6) | < 0.0001 | 41 | (29-56) |
| Liquid accumulation | 0 | 32 (2.4) | < 0.0001 | 19 | (4.6 -81) |

Later, to establish which of the previous variables could explain or predict in a better way the appearance of dengue with signs of alarm or serious, we decided to make a multivariate analysis observing that the gastrointestinal alterations and the state of conscience in the patient, together with factors that predispose the bleeding of the mucous membranes as it is the thrombocytopenia, are that set of variables that could be considered as predictors so that a patient with dengue develops a complicated form of this disease (P< 0.0001).

**Table 3. Multivariate analysis of possible predictors of dengue fever with alarm signs**

| | Variables | Dengue fever with alarm signs p-value |
|---|---|---|
| Conglomerate | Abdominal pain, vomiting, diarrhea, altered state of consciousness, hepatomegaly, mucosal bleeding, hemoconcentration, thrombocytopenia, fluid accumulation | <0.0001 |
| Individuals | Abdominal pain | <0.0001 |
| | Vomiting | <0.0001 |
| | Diarrhea | <0.0001 |
| | Altered state of consciousness | <0.0001 |
| | Hepatomegaly | 0.54 |
| | Mucosal bleeding | <0.0001 |
| | Hemoconcentration | 0.86 |
| | Thrombocytopenia | <0.0001 |
| | Liquid accumulation | 0.855 |

### Clinical manifestations related to the appearance of severe dengue

By associating the signs of severe dengue, we show that plasma extravasation (P 0.001, OR=1.2, IC-95% 1.1-1.4), bleeding and hemodynamic instability (P< 0.0001, OR=1.2, IC-95% 1.1-1.3), the shock by dengue (P< 0.0001, OR=1.2, IC-95% 1.2-1.3) and the serious organic damage (P< 0.0001, OR=1.6, IC-95% 1.3-1.9), are variables that behave like risk factors in the appearance of the serious dengue.

**Table 4. Relationship of severe clinical manifestations with the risk of developing severe dengue**

| Evidenced clinical manifestations | Dengue with a sign of alarm (%) | Severe dengue (%) | p-value | OR | CI 95% |
|---|---|---|---|---|---|
| Plasma Extravasation | 0 | 12 (22) | < 0.0001 | 1.2 | (1.1-1.4) |
| Hemorrhages and hemodynamic instability | 1 (0.08) | 9 (16.3) | 0.001 | 1.2 | 1.1-1.3 |
| Dengue shock | 0 | 17 (31) | < 0.0001 | 1.2 | 1.1-1.3 |
| Severe organic damage | 0 | 21 (38.2) | < 0.0001 | 1.2 | 1.3-1.9 |

Then to determine which of these variables would explain or predict in a better way the appearance of the severe dengue we made a multivariate analysis, observing that the hemorrhages and the hemodynamic instability (P< 0.0001), is that variable that better explains or predicts that a patient with dengue develops a serious form of this disease.

**Table 5. Multivariate analysis of possible predictors of severity**

| Variables | | Dengue fever with alarm signs p-value |
|---|---|---|
| Conglomerate | Plasma extravasation, bleeding and hemodynamic instability, dengue shock, severe organ damage. | <0,0001 |
| Individuals | Plasma extravasation. | 0,998 |
| | Hemorrhages and hemodynamic instability | <0,0001 |
| | Dengue shock | 0,997 |
| | Severe organ damage. | 0,997 |

## Discussion

Clinical warning signs of dengue and its relationship to the development of dengue with warning signs or severe dengue.

The data show that gastrointestinal and consciousness alterations, in addition to thrombocytopenia and mucosal bleeding are clinical manifestations that could be considered early predictors of dengue with warning signs or severe dengue. These findings are in agreement with the studies published by Tun-Linn et al and by Thomas et al (7,8), in which they observed that abdominal pain, changes in the state of conscience of the patient and the evidence of bled in mucous membranes were three clinical manifestations of warning that were intimately related to the appearance of dengue with signs of alarm and used to precede the establishment of serious dengue. Nevertheless, it is important to emphasize that the individual utility of these warning signs as predictors of dengue with alarm signs has been demonstrated to be really low (9). Therefore, we recommend to the health personnel to make a joint evaluation of these clinical predictors in order to treat early the complications unleashed by this pathology.

Thrombocytopenia was discussed separately, since this clinical predictor is considered by the WHO as a potential indicator of clinical severity (10). However, we consider that thrombocytopenia together with bleeding should be considered as early predictors for severe dengue. Given that, platelet dysfunction induces changes in the permeability in the vascular endothelium, bleeding, coagulopathies and secondary metabolic alterations such as acidosis and hypoxia, which are the main triggers of the manifestations of severe dengue that are plasma extravasation, hemodynamic instability and severe organic damage (11).

Other clinical findings that should also be taken into account by health personnel, although they are not explanatory within this multivariate model for the development of dengue with alarm or severe signs, are hepatomegaly, hemoconcentration and accumulation of liquids (ascites, pleural effusion). Since, some publications have demonstrated that hepatomegaly and accumulation of liquids would be useful as predictors of dengue with alarm signs, nevertheless, around these variables there is no absolute consensus as far as their sensitivity and specificity as clinical predictors of the complicated forms of this disease (12,13). With respect to the hemoconcentration we consider that it should also be taken into account as an early predictor of severe dengue, since, an increase in the hematocrit ≥40% is usually a consequence of an increase in vascular permeability that is generally due to a severe endothelial dysfunction caused by this virus and usually these alterations precede the dengue shock (14).

**Clinical manifestations related to the appearance of severe dengue**

This work evidenced that hemorrhages and hemodynamic instability could be those clinical variables that would better predict the appearance of severe dengue. Since, the hemorrhages or important bleedings would be a trigger of the hemodynamic alterations of these patients (tachycardia, weak or filiform pulse, cold skin to the touch, slow capillary filling, decrease of diuresis) and in addition, they would have a direct relation with the generation of the shock and the serious organic commitment in dengue (15). However, it is exhorted that the extravasation or plasma leakage variable be taken into account as a predictor of severe dengue, since, this clinical manifestation is a hallmark of this form of dengue, which is a consequence of the damage of the secondary vascular endothelium to the proinflammatory environment triggered in this infection, leading to the leakage of liquid into the body cavities and the establishment of dengue shock (16,17).

## Conclusions

This research determined that manifestations such as gastrointestinal alterations, changes in the state of consciousness and bleeding together with thrombocytopenia would be relevant clinical predictors in the diagnosis of dengue with alarm signs. In addition, in severe forms of dengue, the presence of hemorrhages and signs of hemodynamic instability would be important predictors in the detection of this clinical form of dengue. However, we recommend that manifestations of vascular leakage or extravasation be also considered as an important prodrome of severe dengue.

Finally, we call for further progress in the study of this disease that threatens the lives of millions of people around the world, mainly those concentrated in tropical countries. Therefore, it is key to continue joining efforts in the clinical understanding and risk predictors of this disease and thus reduce complications and mortality generated by dengue.

**Declaration of data availability**

The databases generated and/or analyzed during this study will be publicly available, if a reasonable request is made to the authors.

**Ethical considerations**

This research was conducted in accordance with the international ethical standards given by the World Health Organization and the Pan American Health Organization, supported by the Helsinki Declaration, and the national legislation, resolution number 008430 of 1993 of the Colombian Ministry of Health that regulates health studies. In addition, this work was endorsed by the health research ethics committee of HORO ESE, according to act No 003 of 2020.

**Authors' contributions**

LGA, WAO and KV designed the study. LGA, WAO, LNS, and KV digitized the databases. HSC performed the data analysis. HSC wrote the manuscript and LGA, WAO, and LNS conducted the critical review. All authors read and approved the manuscript.

**Financial support**

This work was supported by the Orinoco Regional Hospital (HORO) ESE.

**Conflict of Interest**

The authors declare no conflict of interest.

**Acknowledgements**

The authors thank the dengue patients who participated in this study and the group of internal physicians at HORO, ESE. In addition, for the logistical support provided by UNISANGIL, University Cooperativa of Colombia.

**Bibliographic references**

1. Otu A, Ebenso B, Etokidem A, Chukwuekezie O. Dengue fever - an update review and implications for Nigeria, and similar countries. Afr Health Sci. 2019;19(2):2000–7.

2. Restrepo BN, Beatty ME, Goez Y, Ramirez RE, Letson GW, Diaz FJ, et al. Frequency and clinical manifestations of dengue in urban medellin, Colombia. J Trop Med. 2014; 2014:872608.

3. Xu C, Pang J, Hsu JP, Leo YS, Lye DCB. Differences in clinical features and dengue severity between local and migrant Chinese with dengue infection in Singapore. PloS One. 2018;13(8):e0201441.

4. Phakhounthong K, Chaovalit P, Jittamala P, Blacksell SD, Carter MJ, Turner P, et al. Predicting the severity of dengue fever in children on admission based on clinical features and laboratory indicators: application of classification tree analysis. BMC Pediatr. 2018;18(1):109.

5. Lim JK, Carabali M, Camacho E, Velez DC, Trujillo A, Egurrola J, et al. Epidemiology and genetic diversity of circulating dengue viruses in Medellin, Colombia: a fever surveillance study. BMC Infect Dis. 2020;20(1):466.

6. World Health Organization. Dengue: guidelines for patient care in the Region of the Americas. [Internet]. 2015. Available from: https://iris.paho.org/handle/10665.2/31207

7. Thein T-L, Gan VC, Lye DC, Yung C-F, Leo Y-S. Utilities and limitations of the World Health Organization 2009 warning signs for adult dengue severity. PLoS Negl Trop Dis. 2013;7(1):e2023.

8. Thomas L, Brouste Y, Najioullah F, Hochedez P, Hatchuel Y, Moravie V, et al. Predictors of severe manifestations in a cohort of adult dengue patients. J Clin Virol Off Publ Pan Am Soc Clin Virol. 2010;48(2):96–9.

9. Lee I-K, Liu J-W, Chen Y-H, Chen Y-C, Tsai C-Y, Huang S-Y, et al. Development of a Simple Clinical Risk Score for Early Prediction of Severe Dengue in Adult Patients. PloS One. 2016;11(5):e0154772.

10. World Health Organization. WHO. Dengue: Guidelines for Diagnosis, Treatment, Prevention and Control [Internet]. 2009. Available from: http://whqlibdoc.who.int/publications/2009/9789241547871_eng.pdf. [Google Scholar]

11. de Azeredo EL, Monteiro RQ, de-Oliveira Pinto LM. Thrombocytopenia in Dengue: Interrelationship between Virus and the Imbalance between Coagulation and Fibrinolysis and Inflammatory Mediators. Mediators Inflamm. 2015; 2015:313842.

12. Ahmad MH, Ibrahim MI, Mohamed Z, Ismail N, Abdullah MA, Shueb RH, et al. The Sensitivity, Specificity and Accuracy of Warning Signs in Predicting Severe Dengue, the Severe Dengue Prevalence and Its Associated Factors. Int J Environ Res Public Health. 2018;15(9).

13. Aroor AR, Saya RP, Sharma A, Venkatesh A, Alva R. Clinical Manifestations and Predictors of Thrombocytopenia in Hospitalized Adults with Dengue Fever. North Am J Med Sci. 2015;7(12):547–52.

14. Agrawal VK, Prusty BSK, Reddy CS, Mohan Reddy GK, Agrawal RK, Sekher Srinivasarao Bandaru VC. Clinical profile and predictors of Severe Dengue disease: A study from South India. Casp J Intern Med. 2018;9(4):334–40.

15. Halstead SB, Lum LC. Assessing the prognosis of dengue-infected patients. F1000 Med Rep. 2009;1.

16. Malavige GN, Ogg GS. Pathogenesis of vascular leak in dengue virus infection. Immunology. 2017;151(3):261–9.

17. Yacoub S, Mongkolsapaya J, Screaton G. Recent advances in understanding dengue. F1000Research. 2016;5.