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Clinical and paraclinical predictors of severe dengue progression in adults: A retrospective cross-sectional analysis

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Abstract
Background: Dengue is the most important vector-borne viral infection worldwide. Due to its variable clinical presentation, identifying factors associated with progression to severe disease is crucial. The objective was to determine clinical and paraclinical factors associated with severe dengue in adults.
Methods: A retrospective cross-sectional study was conducted on 149 adult patients diagnosed with dengue at a General Hospital in Oaxaca, Mexico. Data on age, sex, BMI, comorbidities, and hematological parameters were analyzed. Patients were classified into severe and non-severe dengue groups.
Results: Of 149 patients, 9.4% presented with severe dengue. Significant risk factors for severity included advanced age ($p = 0.006$), chronic kidney disease ($p = 0.04$), elevated hemoglobin ($p = 0.01$), and leukocytosis ($p = 0.01$). Diabetes and hypertension were frequent but not statistically associated with severity in this cohort.
Conclusions: Advanced age, chronic kidney disease, and elevated hemoglobin and leukocyte levels are significant predictors of severe dengue in adults. Early identification of these markers can optimize therapeutic management.

Keywords: Dengue, severe dengue, risk factors, chronic kidney disease, leukocytosis

Introduction

Dengue is the most important vector-borne viral infection worldwide, caused by an RNA virus (*Flavivirus*) with four serotypes (DENV-1 to DENV-4) and transmitted by *Aedes* mosquitoes (primarily *Aedes aegypti*) (1). Its incidence has multiplied 30 times over the last 50 years, affecting 50 to 100 million people annually and being endemic in nearly 100 countries [2]. The disease's expansion is closely linked to climatic factors (temperature and precipitation) and socioeconomic factors (housing, population density, and waste management) [2, 3].

Primary infection grants permanent immunity against the causative serotype; however, secondary infections with different serotypes tend to be more severe due to a lack of cross-immunity [4, 5]. The WHO estimates that dengue causes approximately 390 million annual infections, with 500,000 severe cases and a fatality rate close to 2.5% [6]. Due to its impact, it is a mandatory notifiable disease [7]. The main risk is associated with residing in endemic areas, especially those with deficient potable water supply [7, 8].

Although most patients have a benign clinical course, progression to the severe form is difficult to predict [9]. Risk factors for severity include the viral strain, previous infections, immune status, age, genetic background, and the presence of comorbidities (e.g., asthma, diabetes, hypertension) [9, 10]. The clinical course is divided into three phases: the acute febrile phase (2-7 days), where symptoms are indistinguishable between severe and non-severe dengue; the critical phase (defervescence, 24-48 hours), marked by increased capillary permeability, hemoconcentration, and risk of shock; and the recovery phase [2, 11].

The WHO classification (2010) divides dengue into non-severe (with or without warning signs) and severe dengue (SD), defined by severe plasma leakage, hemorrhage, or organ compromise [2, 12, 13]. Unique reliable clinical indicators to predict mortality do not exist [14], although demographic characteristics such as extremes of age and the presence of

chronic disease, along with certain pre-hospital symptoms (e.g., gingival bleeding), have been associated with poorer outcomes [15, 16].

Optimal diagnosis occurs within the first 10 days of fever, utilizing direct methods (viral isolation, antigen) and indirect methods (IgM antibodies starting on the fifth day) [17]. There is no specific treatment, with the decisive management being intravenous fluid support, escalating care according to classification (Cases A, B, C, D) [2, 18]. The most accepted pathogenesis is the theory of antibody-dependent immune amplification, where a "cytokine storm" causes capillary leakage and shock [19, 20].

Findings in Mexico and Latin America:

In multicenter studies, SD and advanced age (≥ 46 years) have been associated with a higher risk of in-hospital mortality in Mexico, where comorbidities increased the case fatality rate between 3 and 17 times [21]. Dengue represents a significant economic and Disability-Adjusted Life Years (DALY) burden [22]. Incidence correlates with an increase in minimum temperature [23]. High seroprevalence has been reported, increasing with age, reaching 83% in older adults in Yucatán [24]. Historically, the 15-to-24 and 45-to-64 age groups have been the most affected in outbreaks in Mexico [25]. Furthermore, active migration of the Ae. aegypti vector to new risk areas exists [26], and vector control interventions have proven to be cost-effective in reducing incidence [27, 28].

Materials and Methods

Study Design and Setting

A retrospective, observational, analytical, and cross-sectional study was conducted at the Hospital General de Zona No. 1 of the Instituto Mexicano Del Seguro Social (IMSS) in Oaxaca, Mexico. The operational phase of data collection took place between January and June 2024, reviewing medical records from the previous two years.

Participants

We included 149 medical records of patients diagnosed with dengue who met the following inclusion criteria: age over 18 years, confirmed diagnosis of dengue (severe or non-severe), and medical care provided at HGZ 1. Patients with confirmed viral co-infections were excluded, and records with incomplete information were eliminated.

Variables and Data Collection

The study population was divided into two groups: patients with severe dengue (cases) and patients with non-severe dengue (controls), according to the 2009 WHO classification. Data were collected from clinical files (Urgency, Internal Medicine, and ICU logs). The independent variables included:

- **Sociodemographic:** Age (years), sex.
- **Clinical:** Body Mass Index (BMI), history of previous dengue infection, and comorbidities (diabetes mellitus, hypertension, chronic kidney disease, heart disease, etc.).
- **Paraclinical:** Hematological parameters upon admission (hemoglobin, leukocytes, and platelets).

Statistical Analysis

Data were analyzed using SPSS version 26. Descriptive statistics were performed using frequencies and percentages for qualitative variables and means with standard deviations (SD) for quantitative variables. For bivariate analysis, the Chi-square test was used for categorical variables and Student's t-test for continuous variables. A p-value of <0.05 was considered statistically significant, with a confidence interval of 95%.

Results

Introduction and Sample Features

A total of 149 patients diagnosed with dengue at the General Hospital of Zone No. 1 in Oaxaca were analyzed. The sample presented diverse demographic and clinical characteristics, allowing the identification of factors significantly associated with progression to severe dengue. The results are presented below organized by categories of variables.

Demographic Characteristics

The study population included adults with ages distributed around a mean of 45.1 years (range: variable according to records). The distribution by sex showed a predominance of women, with women representing 55.7% (n=83) of the population, while men constituted 44.3% (n=66). This pattern of gender distribution reflects a greater consultation of women during the study period.

Table 1: Demographic Characteristics

Variable	Category	Frequency (%)
Sex	Women	83 (55.7%)
	Men	66 (44.3%)
Average Age	Medium (SD)	45.1 (16.8) years

Severity of the Disease

The severity classification showed that the vast majority of patients had non-severe dengue. Only 14 patients (9.4%) were classified as having severe dengue, while 135 individuals (90.6%) had non-severe dengue. This distribution is consistent with epidemiological reports that indicate that most cases of dengue evolve without serious complications.

Comorbidities

The prevalence of comorbidities in the cohort was 45.0%, with 67 patients presenting at least one chronic disease. The most frequent conditions were:

- **Diabetes mellitus:** 21 patients (14.1%)
- **Arterial hypertension:** 19 patients (12.8%)
- **Heart disease:** 12 patients (8.1%)
- **Chronic kidney disease:** 6 patients (4.0%)
- **Other conditions:** Cancer (2.7%), Thyroid disease (2.0%), HIV (1.3%)

4. Nutritional Status (Body Mass Index)

The analysis of the body mass index of the population showed a mean of 24.7 kg/m² (SD: 4.3). The distribution was as follows:

- **Normal weight:** 82 patients (55.0%)
- **Overweight:** 43 patients (28.9%)
- **Obesity:** 20 patients (13.4%)
- **Underweight:** 4 patients (2.7%)

History of Previous Dengue

Prior dengue infection was rare in the cohort. Only 8 patients (5.4%) reported a history of previous dengue, while 141 individuals (94.6%) had no documentation of previous infection. This low prevalence limits the assessment of the

impact of secondary infection on progression to severe dengue.

Laboratory Parameters

The hematological results showed the following distribution of values (Table 2)

Table 2: Hematological results

Parameter	Minimal	Maximum	Medium (SD)
Platelets (cells/µL)	2,000	480,000	50,919 (53,868)
Hemoglobin (g/dL)	7.6	19.9	15.0 (2.3)
Leukocytes (cells/µL)	1,000	18,400	5,223 (2,900)
BMI (kg/m²)	Min. var.	Max. var.	24.7 (4.3)

7. Bivariate analysis: factors associated with severe dengue

Bivariate analysis was performed using chi-square test (χ^2) for qualitative variables and Student's t-test for quantitative variables. The statistical significance criteria were $p<0.05$. The results were as follows

Table 3: Significantly associated factors

Factor	Severe (n=14)	Non-Serious (n=135)	P-Value
Age (years)	56.8 ± 15.1	43.9 ± 16.6	0.006*
Hemoglobin (g/dL)	13.7 ± 3.8	15.2 ± 2.0	0.01*
Leukocytes (cells/µL)	7,000 ± 5,248	5,039 ± 2,500	0.01*
Chronic Kidney Disease	14.3% (n=2)	3.0% (n=4)	0.04*

*Statistical significance $p<0.05$

Table 4: Factors without significant association:

Factor	Statistic Used	P-Value
Sex	χ^2	0.31
BMI	t for Student	0.16
Platelets	t for Student	0.23
Diabetes mellitus	χ^2	0.98
High blood pressure	χ^2	0.85
Antecedent of Dengue	χ^2	0.75

Discussion

International scientific literature has identified multiple factors associated with progression to severe dengue through various meta-analyses and cohort studies. These findings vary significantly depending on the population studied, the geographic context, and local epidemiological characteristics, which highlights the importance of contextualizing risk factors according to each specific clinical environment.

Tsheten *et al.*'s meta-analysis based on 143 studies identified secondary infection (OR 3.23), renal disease (OR 4.54), and diabetes (OR 2.88) as main predictors of severe dengue, with special emphasis on the pediatric population as a vulnerable group [29]. The relevance of hematological findings such as increased hematocrit associated with thrombocytopenia (OR 5.13) and clinical signs of vascular leakage as robust predictors was highlighted.

In relation to the studied population (n=149), partial concordance was observed. Chronic kidney disease showed significant association (p 0.04), coinciding with the meta-analysis. However, diabetes was not associated with severity in the local cohort (p 0.98), possibly due to its lower relative frequency (14.1%) and limited number of severe cases. Secondary infection also showed no significance (p 0.75) due to its low prevalence (5.4%). Regarding hematological parameters, association was identified between elevated hemoglobin (p 0.01) and leukocytes (p 0.01) with severe dengue, reflecting hemoconcentration similar to the mechanism described by Tsheten *et al.* In contrast, thrombocytopenia was not significant (p 0.23). Advanced age was a significant factor in the local cohort (p 0.006), contrasting with the pediatric pattern of the meta-analysis, reflecting regional epidemiological variations [29].

Yuan *et al.* analyzed 64 variables from 87 studies with over 43,000 patients, identifying secondary infection, pediatric age, metabolic comorbidities, and hematological alterations as factors significantly associated with severe dengue [30].

Important concordances were observed in hematological biomarkers. Hemoglobin (p 0.01) and leukocytes (p 0.01) showed significance in the local cohort, coinciding with the meta-analysis regarding the fact that early hematological alterations reflect greater risk of severity. However, platelets showed no association (p 0.23), differing from the meta-analysis due to wide dispersion of values and low number of severe cases. Chronic kidney disease was significantly associated with severity (p 0.04), confirming the importance of renal dysfunction identified by Yuan *et al.* Nevertheless, variables such as diabetes and hypertension did not reach significance, possibly due to moderate prevalence and potential confounding effect. Similar to Tsheten *et al.*, previous dengue infection showed no association (p 0.75) due to its low frequency (5.4%). Advanced age was significant in the local cohort (p 0.006), in opposite direction to pediatric age reported by Yuan *et al.*, again reflecting regional epidemiological variations [30].

Sangkaew *et al.* integrated 122 studies evaluating 25 clinical and laboratory factors during the febrile phase. They identified as most consistent predictors comorbidities (diabetes, hypertension, renal disease, heart disease), clinical warning signs (persistent vomiting, abdominal pain, spontaneous bleeding, fluid accumulation) and laboratory alterations (low platelets, hypoalbuminemia, elevated AST/ALT). The meta-analysis showed that women presented slightly higher risk [31].

Sangkaew *et al.* report comorbidities as factors associated with increased risk. In the local cohort, only chronic kidney disease showed significance (p 0.04), directly coinciding with the meta-analysis (OR 4.67), while diabetes (p 0.98) and hypertension (p 0.85) did not reach significance, probably due to low frequency of severe dengue and temporal clinical variability. Regarding sex, although Sangkaew *et al.* report slight female predominance (OR 1.13), in the local cohort (55.7% female) sex showed no significant association (p 0.31). Hematological predictors were not completely replicated: while platelets were not significant (p 0.23), hemoglobin (p 0.01) and leukocytes (p 0.01) were, coinciding with the relevance of hematological parameters during the febrile phase. Previous dengue infection was infrequent (5.4%) and not significant (p 0.75), limiting comparison with the strong predictive power reported by Sangkaew *et al.* [31].

Cruz-Paraná *et al.* focused their analysis exclusively on Latin American population, integrating 45 studies that evaluated clinical, demographic, and symptomatic factors. They identified as main risk factors secondary infection, female sex, Caucasian ethnicity, and symptoms such as headache, myalgias, vomiting, abdominal pain, diarrhea, prostration, and lethargy. For mortality, they found significant association with age less than 18 years and respiratory symptoms [32].

Cruz-Paraná *et al.* identify female sex as a risk factor, while in the local cohort (55.7% female) no significant association was observed (p 0.31), a difference explainable by sample size and age distribution. Regarding comorbidities and previous infection, the local cohort identified significant association with chronic kidney disease (p 0.04), a finding consistent with pathophysiology described in other meta-analyses, although not specifically emphasized by Cruz-Paraná *et al.* as a predominant predictor in Latin America. Previous infection was infrequent (5.4%) and not significant (p 0.75), limiting comparison. Symptomatic variables analyzed by Cruz-Paraná *et al.* (abdominal pain, vomiting, lethargy) were not part of the local analysis, limiting direct comparison. However, significant association with hemoglobin (p 0.01) and leukocytes (p 0.01) conceptually coincides with the relevance of hematological biomarkers in Latin American literature. Platelets were not significant (p 0.23) despite being widely reported as a severity marker, probably due to temporal sample variability. Age showed significant association (p 0.006) in opposite direction to that reported by Cruz-Paraná *et al.*, again reflecting regional epidemiological differences [32].

Copaja-Corzo *et al.* evaluated 152 Peruvian patients (2019-2023) identifying variables strongly associated with mortality: bilirubin >1.2 mg/dL (aHR 11.38), AST ≥251 U/L (aRR 6.79), fibrinogen ≥400 mg/dL (aRR 2.23), in addition to one to three comorbidities (aRR 1.92) and previous dengue infection (aRR 1.84). 8.6% of patients died, 19.1% developed severe dengue, and 20.4% required ICU admission (33).

An important similarity is observed in the association between comorbidities and worse outcomes. Although global analysis of comorbidities did not reach significance in the local cohort, chronic kidney disease showed significant association (p 0.04), partially coinciding with the notion that comorbidity burden increases risk, although the specific type of comorbidity differs. Previous dengue infection was associated with worse prognosis in Peru (aRR 1.84), concurring with previous meta-analyses; in the local cohort it was infrequent (5.4%) and not significant (p 0.75), limiting predictive power. Regarding biomarkers, Copaja-Corzo *et al.* emphasized hepatic and hemostatic parameters; the local cohort identified significant associations with hemoglobin (p 0.01) and leukocytes (p 0.01), conceptually coinciding with the importance of hematological alterations. The absence of thrombocytopenia as a predictor in the local cohort contrasts with Latin American trends. Age showed bimodal behavior in Peru without being a main predictor; in the local cohort it was significantly associated (p 0.006), pointing to clear demographic differences. Both populations coincide in the prognostic value of comorbidity and hematological/biochemical alterations, but differ in specific markers, weight of reinfection, and age influence [33].

Senavong *et al.* analyzed 402 hospitalized patients, of whom more than half developed severe dengue, a proportion considerably higher than other contexts. They identified as main predictors the presence of nausea in children and persistent vomiting in adults, in addition to higher serum creatinine in severe cases. The pediatric population presented greater frequency of symptoms, greater severity, and slightly longer hospital stays [34].

Specific concordance is observed related to renal function. While Senavong *et al.* identified elevated serum creatinine, in the local cohort chronic kidney disease was significantly associated (p 0.04), suggesting shared vulnerability derived from compromised renal status. However, gastrointestinal symptoms (nausea, vomiting) identified as robust predictors in Laos showed no significant role in the local cohort, probably due to epidemiological differences, timing of clinical evaluation, or age distribution, given that Senavong *et al.* demonstrated greater relevance in the pediatric population. The magnitude of severe dengue differed substantially: more than half in Laos versus 9.4% in the local cohort, suggesting variations in epidemiology, access to early care, initial management, or circulating serotypes. Although both studies demonstrated association between hematological/biochemical variables and severity, specific markers diverged: the local cohort identified elevated hemoglobin (p 0.01) and leukocytosis (p 0.01), while in Laos the key marker was creatinine, reflecting dengue complexity with variable predictors depending on population characteristics, hydration, comorbidities, and regional inflammatory response. Both studies converge on the importance of timely detection of early signs, although specific predictors differ according to epidemiological context, highlighting the need for stratification algorithms adjusted to each setting [34].

Review of multiple meta-analyses and cohort studies reveals that although chronic kidney disease emerges as a factor consistently associated with severe dengue across diverse populations, other predictors vary significantly depending on geographic context and local epidemiological characteristics. Secondary infection, a potent factor in meta-analyses, showed low prevalence in the local cohort, limiting its predictive power. Hematological parameters such as hemoglobin and leukocytes proved to be important markers in the local cohort, although others such as platelets and bilirubin reported in other populations did not reach significance. Age presents opposite behaviors between populations: pediatric in international contexts versus advanced in the local cohort, reflecting clear epidemiological differences. These findings underscore that although universal predictors of severe dengue exist, contextualization according to specific clinical and geographic environment is fundamental for optimizing early stratification algorithms and clinical management.

Conclusion

The present study successfully characterized the main clinical and paraclinical factors significantly associated with progression to severe dengue in the adult population treated at a secondary-level hospital institution. Although the majority of patients (90.6%) presented with non-severe forms of the disease, specific findings were identified demonstrating the relevance of certain clinical and laboratory parameters for predicting unfavorable outcomes.

From the perspective of internal medicine, these results provide practically valuable information that facilitates early risk stratification at the time of hospital admission. Knowledge of these factors enables the establishment of objective criteria that can guide therapeutic and monitoring decisions, thereby improving clinical response capacity in patients with dengue.

A relevant finding was the association between advanced age and higher probability of developing severe dengue (p=0.006). This result underscores the need to implement a differentiated and specialized approach in caring for older adults, a population group that frequently presents

alterations in immunological response, greater burden of concomitant chronic diseases, and reduced compensatory capacity facing pathophysiological challenges. Early identification of older adults as a risk group facilitates their prioritization in monitoring and clinical management.

Significant association between elevated hemoglobin (p=0.01) and increased leukocytes (p=0.01) with severe dengue suggests an intense inflammatory pattern or hemoconcentration that can anticipate complications and adverse outcomes. These hematological parameters, readily determined in any hospital center, represent accessible markers that can contribute to early identification of patients at higher risk of progression to severe forms.

The presence of chronic kidney disease as a factor significantly associated with severe dengue (p=0.04) reinforces the importance of comprehensive evaluation of previous health status in dengue patients. This association suggests that patients with prior renal organ dysfunction might present reduced capacity for adaptation to pathophysiological changes induced by dengue virus, especially facing intravascular volume loss or alterations in vascular permeability. Recognition of this vulnerability justifies strict monitoring and individualized management based on specific renal characteristics.

These findings significantly improve understanding of clinical variability of dengue in adults, allowing explanation of why certain patients develop more severe forms while others maintain a benign course. This information facilitates adoption of more timely and personalized therapeutic decisions, adapted to the individual risk profile of each patient.

Systematic application of these risk factors in daily clinical practice could significantly optimize selection of patients requiring strict hospital observation or early clinical intervention. Better identification of high-risk patients allows for more efficient resource allocation, potentially reducing serious complications, decreasing dengue-associated mortality, and improving population health indicators.

From a public health perspective, research of this type generates local scientific evidence that strengthens the response capacity of internal medicine services, improving their preparedness to manage epidemic outbreaks. This information is especially valuable in hospitals functioning as reference centers in endemic zones, where dengue represents a significant cause of morbidity and mortality.

The study adequately achieved its proposed objectives. It successfully determined which clinical and paraclinical factors are significantly associated with severe dengue in adults, fulfilling the proposed general objective. Similarly, specific objectives were correctly accomplished, allowing identification of associations with age, chronic kidney disease, hemoglobin, leukocytes, and other variables of clinical interest. (Table 5)

Table 5: Key Factors Identified

Factor	p-value	Main Finding	Clinical Implication
Advanced Age	0.006*	56.8 vs 43.9 years	Differentiated monitoring
Hemoglobin	0.01*	13.7 vs 15.2 g/dL	Hemoconcentration
Leukocytes	0.01*	7,000 vs 5,039/µL	Marked inflammation
Chronic Kidney Dis.	0.04*	14.3% vs 3.0%	Specialized management
*p<0.05	Statistical significance		

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