



Clinical, laboratory, and demographic determinants of hospitalization due to dengue in 7613 patients: A retrospective study based on hierarchical models



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ABSTRACT

In Brazil, the incidence of hospitalization due to dengue, as an indicator of severity, has drastically increased since 1998. The objective of our study was to identify risk factors associated with subsequent hospitalization related to dengue. We analyzed 7613 dengue confirmed via serology (ELISA), non-structural protein 1, or polymerase chain reaction amplification. We used a hierarchical framework to generate a multivariate logistic regression based on a variety of risk variables. This was followed by multiple statistical analyses to assess hierarchical model accuracy, variance, goodness of fit, and whether or not this model reliably represented the population. The final model, which included age, sex, ethnicity, previous dengue infection, hemorrhagic manifestations, plasma leakage, and organ failure, showed that all measured parameters, with the exception of previous dengue, were statistically significant. The presence of organ failure was associated with the highest risk of subsequent dengue hospitalization (OR = 5.75; CI = 3.53–9.37). Therefore, plasma leakage and organ failure were the main indicators of hospitalization due to dengue, although other variables of minor importance should also be considered to refer dengue patients to hospital treatment, which may lead to a reduction in avoidable deaths as well as costs related to dengue.

1. Introduction

Dengue virus, a well-known arbovirus, is a leading cause of morbidity and mortality in tropical and subtropical areas across the globe (Tristao-Sa et al., 2012). It is estimated that 3.97 billion people, more than 50% of the world population, are currently living at risk of dengue in 127 countries (Brady et al., 2012). Recent estimates suggest there may be approximately 50–100 million dengue cases worldwide, with 10.5 million cases requiring hospitalization, and approximately 13500–18500 deaths annually (Bhatt et al., 2013; Shepard et al., 2016; Stanaway et al., 2016). Dengue imposes an annual economic burden of approximately 9 billion US dollars among low- and middle-income

countries in the tropics (Lye et al., 2008; Shepard et al., 2016).

Dengue is caused by four antigenically distinct serotypes of dengue virus called DENV-1 to DENV-4, which are transmitted primarily through the bite of the female *Aedes aegypti*. All serotypes are capable of causing severe, even fatal, infection. However, it is unclear why some cases of dengue progress to severe forms of the disease while others remain asymptomatic. Although the literature is controversial on this topic, one plausible explanation is a phenomenon called antibody-dependent enhancement, which can result when an individual experiences sequential infections caused by different viral serotypes (Burnett, 2013; Halstead, 1981; Loroño-Pino et al., 1999). However, even during a dengue epidemic among populations with high concentrations of

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DENV antibodies, the proportion of severe dengue cases may be low, suggesting that other risk factors are involved in disease severity (Figueiredo et al., 2010). Age has been identified as an important risk factor for disease severity (Burnett, 2013), with the age group younger than 15 years or older than 60 years being associated with an increased risk of severe dengue (Burnett, 2013; Cavalcanti et al., 2011; Guzmán et al., 2002). In Brazil, the incidence of hospitalization due to dengue, as an indicator of disease severity, has drastically increased in all age groups in the past two decades (Siqueira et al., 2005; Cavalcanti et al., 2011; Teixeira et al., 2013). For example, in the years between 1998–2002, the incidence of dengue-related hospitalization jumped from 1.1/100,000 inhabitants to 10.3/100,000 inhabitants in the age group ranging from 0 to 4 years, from 2.1/100,000 inhabitants to 19.6/100,000 inhabitants in the age group of 5–14 years, from 4.5/100,000 inhabitants to 36.6/100,000 inhabitants in the age group of 15–29 years, from 4.7/100,000 inhabitants to 36.1/100,000 inhabitants in the age group of 30–49 years, and from 6.5/100,000 inhabitants to 43.7/100,000 inhabitants in the same period for people older than 50 years of age (Siqueira et al., 2005).

Some authors have advocated for a surveillance system that includes the hospitalization rate of dengue cases, which would potentially minimize hospitalizations or ensure more discretion when deciding treatment setting, owing to a better definition of hospitalization criteria, and may also facilitate the comparison of treatments across different endemic regions to track health progress (Beatty et al., 2010; Shepard et al., 2014). Laboratory and clinical markers could be used in a simple decision tree algorithm, both to avoid hospitalization and to reduce hospital length of stay (Lee et al., 2009), or, for example, to predict the risk of occurrence of a new shock episode (Huy et al., 2013). This is particularly relevant in the context of increasingly large dengue outbreaks, where the resulting health system congestion may lead to a degradation of the quality of treatment or sub-optimal treatment decisions, such as non-hospitalization of severe dengue cases or too early discharge. Some authors have also suggested the possibility of using molecular biomarkers to corroborate the 2009 World Health Organization (WHO) classification, when warning signs are present or not in early dengue infection (Pang et al., 2016). Others have suggested the use of serum lactate dosage and the presence of clinical signs of fluid accumulation as predictors of severe dengue in adult subjects (Thanachartwet et al., 2016).

The use of statistical models with multivariable analysis to examine risk factors for hospitalization due to dengue is therefore important (Carrasco et al., 2014; Diaz-Quijano et al., 2011; Leo et al., 2013; Tamibmaniam et al., 2016). These models may potentially lead to a more efficient use of resources, such as hospitalization of patients with severe dengue and decreasing the rates of unnecessary hospitalization (Carrasco et al., 2014; Lye et al., 2008; Tamibmaniam et al., 2016) thereby reducing hospital costs (Tamibmaniam et al., 2016).

The study of clinical and laboratory factors related to the occurrence of increasing dengue severity using multivariate logistic regression has already been proposed in the literature (Mallhi et al., 2005). These studies have shown that age > 40 years (OR = 4.1, $p < 0.001$), secondary infection (OR = 2.7, $p = 0.042$), diabetes mellitus (OR = 2.8, $p = 0.041$), lethargy (OR = 3.1, $p = 0.005$), and delayed hospitalization (OR = 2.3, $p = 0.037$) are independent predictors of severe dengue. However, previous studies have used relatively small sample sizes, a single dengue season, one or two DENV serotypes, and/or are based on the 1997 WHO dengue classification guidelines.

In this study, we provide more accurate estimates of the predictors of severe dengue, by drawing on a large sample of patients ($n = 7613$) encompassing several years of data using hierarchical models to define covariates at each stage of the analysis, and based on the 2009 WHO classification guidelines. The objective of our study was to identify risk factors determining hospitalization to provide evidence for clinicians to inform their decision-making and potentially save lives and resources.

2. Patients and methods

We analyzed 7613 dengue notifications, confirmed by serology (ELISA), non-structural protein 1, or polymerase chain reaction amplification. Of these notified symptomatic DENV infections, 834 patients were hospitalized and 28 resulted in death. All cases of dengue fever have to be notified, even if only suspected, to the Health Ministry of Brazil. Data were collected between January 2002 and June 2012, in the city of São José do Rio Preto, São Paulo, Brazil, which had 408,258 inhabitants in 2010.

The variables analyzed in this study were selected from the mandatory reporting forms of the disease. We categorized the subjects into three age groups (0–14 years, > 60 years, and 15–60 years, which was used as the reference); ethnicity (dichotomous; 1 = white, 0 = non-white); education (dichotomous; 1 = more than four years of study, 0 = four or fewer years of schooling), sex (dichotomous; 1 = female; 0 = male), previous DENV infection (confirmed via IgG test or reported by subject; dichotomous variable, 1 = seropositive, 0 = otherwise), presence or absence of at least one general symptoms (fever, headache, retro-ocular pain, abdominal pain, arthralgia, myalgia, prostration, nausea or vomiting and diarrhea; dichotomous variable, 1 = one or more general symptoms; 0 = otherwise), presence or absence of at least one hemorrhagic manifestation (epistaxis, petechiae, rashes, gingival bleeding, menorrhagia, hematuria, gastrointestinal bleeding, and positive tourniquet; dichotomous variable, 1 = one or more hemorrhagic manifestation; 0 = otherwise), presence or absence of plasma leakage (ascites, pleural effusion, pericardial effusion, and hemoconcentration; dichotomous variable; 1 = one or more symptoms of plasma leakage; 0 = otherwise), and organ failure (myocarditis, hypotension, neurological manifestation and hepatic failure; dichotomous variable, 1 = evidence of organ failure; 0 = otherwise).

We defined a parsimonious model based on the statistical significance of the covariates and our personal clinical experience with the disease. Specifically, we used a hierarchical framework to generate a multivariate logistic regression, as described by Victora et al. (1997), and estimated the variables that were predictive of the risk of hospitalization for dengue (Fig. 1). The covariates were included in our model if they showed a 10% significance threshold based on Rao's efficient score progressing to a subsequent hierarchical level, or if the variable was of well-established clinical or epidemiological importance, with a biologically plausible association or causal relation between the variables in the model, at the discretion of the examiners. We used a 5% significance level to accept or reject the null hypothesis of no relationship between the independent variables and the outcome in our final model.

To check whether our model was correctly specified, at each level, we used the Rao's efficient score to evaluate whether the variable improved the prediction of the probability of hospitalization. We used Nagelkerke's pseudo-R square to determine the percentage of the variance, explained at each hierarchical level, in the occurrence of hospital admissions due to dengue. We confirmed the goodness of fit of our model using the Hosmer and Lemeshow test. We used the Wald test to assess whether our sample estimate reliably represented the population parameter. Last, we calculated the odds ratio for each category of the variables, with the corresponding 95% confidence intervals.

We used the chi-square test for the bivariate analysis of the association between the independent variables versus death from dengue in the study period. We used Fisher's exact test whenever the criteria for the chi-square were not met. We used a 5% level of significance for both tests. All data were tabulated and analyzed using IBM SPSS software, version 19.

3. Results

During the study period, the average age of patients diagnosed with dengue was 38.6 years (standard deviation of 18.7 years), with a similar

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