Review

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Predictive Models for Dengue Severity, Mortality and Hospitalization: A Systematic Review and Meta-Analysis Protocol

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Abstract

Background: Dengue fever affects millions of people worldwide, with clinical outcomes ranging from mild illness to severe complications. Accurate prediction of adverse outcomes remains challenging for clinicians, particularly in resource-limited settings where dengue is endemic. Clinical prediction models have emerged as promising tools to support decision-making, but their performance and applicability across different populations and settings remain unclear. This systematic review aims to identify, evaluate, and synthesize evidence on the predictive performance of clinical models for severity, mortality, and hospitalization in dengue patients. **Methods**: We will search PubMed, LILACS, Web of Science, Scopus, and Embase for studies reporting clinical predictive models for dengue mortality and/or hospitalization outcomes, with no restrictions on year or language. Two reviewers will independently screen articles, extract data, and assess risk of bias using the TRIPOD checklist and PROBAST tool. We will extract information on model characteristics, predictor variables, performance metrics, including area under the curve, sensitivity, and specificity, validation approaches and study limitations. Meta-analysis will be conducted when sufficient homogeneous data is available, reporting the pooled Area Under the ROC Curve (AUC) of the models. **Discussion**: This review will provide a comprehensive assessment of existing predictive models for dengue outcomes, identifying high-performing models suitable for clinical implementation and highlighting gaps that require further research.

Keywords: dengue; predictive models; mortality; hospitalization; machine Learning; clinical decision support

Systematic review registration: PROSPERO CRD420251109274.

1. Background

Dengue fever represents one of the most rapidly spreading mosquito-borne diseases worldwide, with approximately 390 million infections occurring annually [1,2]. The disease exhibits a wide spectrum of clinical presentations, from asymptomatic infection to severe complications including

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dengue hemorrhagic fever, dengue shock syndrome, and death [3,4]. The case fatality rate varies considerably across regions and healthcare settings and patient's characteristics, ranging from less than 1% to over 20% in some outbreaks [5,6]. The clinical management of dengue presents unique challenges because the disease follows a characteristic pattern with three phases: febrile, critical, and recovery [7]. The critical phase, typically occurring 3-7 days after fever onset, represents a narrow window when complications can develop rapidly. During this period, patients may progress from apparent recovery to life-threatening plasma leakage, bleeding, or organ impairment within hours, making early identification of patients at risk crucial for appropriate triage, monitoring, and intervention.

Current dengue management relies primarily on clinical judgment supported by laboratory parameters and warning signs defined by the World Health Organization [8]. However, these criteria demonstrate variable sensitivity and specificity across different populations and clinical settings [9]. The subjective nature of clinical assessment and the dynamic course of dengue creates uncertainty in predicting which patients will develop severe complications requiring hospitalization or intensive care. In recent years, researchers have developed various clinical prediction models to support dengue management decisions, incorporating demographic, clinical, and laboratory variables to estimate the probability of adverse outcomes [10,11]. These approaches range from simple risk scores using readily available parameters to complex machine learning algorithms utilizing multiple biomarkers [12], with some models focusing specifically on mortality prediction whereas others focus on severity, aiming to identify patients requiring hospitalization or intensive monitoring [13].

Despite the growing interest in dengue prediction models, several knowledge gaps persist. The performance of existing models has not been systematically evaluated across different populations and healthcare settings, and the generalizability of models developed in specific populations to other endemic regions remains unclear. Additionally, the relative performance of traditional statistical approaches versus modern machine learning methods has not been comprehensively assessed. The integration of prediction models into routine clinical practice requires evidence of their accuracy, reliability, and clinical utility, with clinicians needing clear guidance on which models perform best in their specific settings and patient populations.

This systematic review aims to address these knowledge gaps by providing a comprehensive evaluation of predictive models for dengue severity, mortality, and hospitalization. Despite the massive quantity of clinical prediction models published constantly, most are poorly reported, at high risk of bias, and remain unusable in clinical practice. A systematic approach is therefore essential to identify models with genuine clinical utility and determine where new model development is warranted. By synthesizing evidence from multiple studies and populations, we will identify the best-performing models for clinical implementation and highlight priorities for future research. Our primary objectives are to identify and characterize existing clinical predictive models for severity, mortality, and hospitalization in dengue patients, evaluate their predictive performance, including discrimination and calibration measures, compare performance across different model types and populations, assess the methodological quality and risk of bias in prediction model studies, and identify gaps in current knowledge and priorities for future research. Our primary objectives are to identify and characterize existing clinical predictive models for severity, mortality, and hospitalization in dengue patients, evaluate their predictive performance, including discrimination and calibration measures, compare performance across different model types and populations, assess the methodological quality and risk of bias in prediction model studies, and identify gaps in current knowledge and priorities for future research.

1.1. METHODS/Design

This protocol will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines [14]. The systematic review protocol was registered, on July 21, 2025, with PROSPERO (CRD420251109274), and the completed systematic review will adhere to PRISMA guidelines and the TRIPOD statement for reporting prediction model research [15].

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1.2. Eligibility Criteria

We will include studies reporting clinical predictive models for patients with confirmed or suspected dengue diagnosis of any age. Dengue diagnosis may be established through: (1) laboratory confirmation including NS1 antigen, IgM/IgG serology, RT-PCR, or viral isolation; or (2) suspected dengue defined as acute febrile illness (typically lasting 2-7 days) with at least two compatible clinical symptoms (headache, retro-orbital pain, myalgia, arthralgia, rash, hemorrhagic manifestations, or leucopenia) plus epidemiological criteria (residence in or travel to dengue-endemic area within 14 days of symptom onset, or occurrence during a confirmed dengue outbreak in the area). We will exclude studies relying solely on clinical diagnosis without laboratory confirmation or strong epidemiological support. We will include studies reporting clinical predictive models such as risk scores, statistical models including logistic regression, machine learning models (e.g., neural networks, decision trees, and random forests), or other algorithmic approaches designed to predict patient outcomes.

The outcomes of interest are mortality from any dengue-related cause during hospitalization or within 30 days of presentation (or the closest time period reported when 30-day mortality is not available), and need for hospital admission from the emergency department or outpatient settings. The choose of the outcomes were based on the DEN-CORE's ((https://isaric.org/research/dengue/dengue-cos/). We will include studies of any design that develop, validate, or update prediction models, including prospective and retrospective cohort studies, case-control studies, and randomized controlled trials, conducted in any healthcare setting. We will exclude case reports or case series with a low number of patients, studies focusing solely on dengue diagnosis rather than prognosis, studies of vector control or epidemiological prediction models, animal or laboratory studies without clinical application, and conference abstracts, editorials, or reviews without original data.

1.3. Search Strategy

We will conduct comprehensive and standardized searches on PubMed, LILACS, Web of Science, Scopus, and Embase from inception to the present. The search strategy will combine three main concept groups: dengue terms including "dengue", "dengue fever", "dengue hemorrhagic fever", and "dengue shock syndrome"; prediction terms including "predict*", "risk score", "prognostic model", "clinical decision rule", "machine learning", "artificial intelligence", and "algorithm*"; AND outcome terms including "mortality", "death", "hospitalization", "admission", AND "severe dengue" (see Table 1 for full search syntax). We will also check for reference lists of included studies, relevant systematic reviews, and guidelines to identify additional eligible studies.

Table 1. Complete search strategy to be used in databases.

Database	Terms	Results
Pubmed	(((((Dengue[MeSH Terms]) OR (dengue fever[Title/Abstract])) OR (dengue virus[Title/Abstract])) OR (DENV[Title/Abstract])) AND (((((((((Predictive Value of Tests[MeSH Terms]) OR (Machine Learning[MeSH Terms])) OR (Algorithms[MeSH Terms])) OR (Decision Support Techniques[MeSH Terms])) OR (Risk Assessment[MeSH Terms])) OR (Prognosis[MeSH Terms])) OR (predict*[Title/Abstract])) OR (forecast*[Title/Abstract])) OR (Regression Analysis[MeSH Terms])))) AND (((((mortality[MeSH Terms]) OR (death[MeSH Terms])) OR (hospit*[Title/Abstract])) OR (admission[Title/Abstract])) OR (sever*[Title/Abstract]))	1,485
Web of Science	#1 (Dengue) OR (dengue fever) OR (dengue virus) OR (DENV) #2 (Predictive Value of Tests) OR (Machine Learning) OR (Algorithms) OR (Decision Support Techniques) OR (Risk Assessment) OR (Prognosis) OR (predict*) OR (forecast*) OR (Regression Analysis)	84

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Scopus	#3 (mortality) OR (death) OR (hospit*) OR (admission) OR (sever*) #1 AND #2 AND #3 (TITLE ((Dengue) OR (dengue fever) OR (dengue virus) OR (DENV)) AND TITLE ((Predictive Value of Tests) OR (Machine Learning) OR (Algorithms) OR (Decision Support Techniques) OR (Risk Assessment) OR (Prognosis) OR (predict*) OR (forecast*) OR (Regression Analysis)) AND TITLE ((mortality) OR (death) OR (hospit*) OR (admission) OR (sever*)))	210
Embase	('dengue'/exp OR dengue OR 'dengue fever'/exp OR 'dengue fever' OR (('dengue'/exp OR dengue) AND ('fever'/exp OR fever)) OR 'dengue virus'/exp OR 'dengue virus' OR (('dengue'/exp OR dengue) AND ('virus'/exp OR virus)) OR 'denv'/exp OR denv) AND ('predictive value of tests':ab,ti OR 'machine learning':ab,ti OR algorithms:ab,ti OR 'decision support techniques':ab,ti OR 'risk assessment':ab,ti OR prognosis:ab,ti OR predict*:ab,ti OR forecast*:ab,ti OR 'regression analysis':ab,ti) AND (mortality:ab,ti OR death:ab,ti OR hospit*:ab,ti OR admission:ab,ti OR sever*:ab,ti)	2,718
LILACS	((Dengue) OR (dengue fever) OR (dengue virus) OR (DENV)) AND ((Predictive Value of Tests) OR (Machine Learning) OR (Algorithms) OR (Decision Support Techniques) OR (Risk Assessment) OR (Prognosis) OR (predict*) OR (forecast*) OR (Regression Analysis)) AND ((mortality) OR (death) OR (hospit*) OR (admission) OR (sever*))	123
Total		**4,620**

1.4. Study Selection and Data Extraction

The study selection process will be conducted in two phases by two independent reviewers, with initial screening of titles and abstracts followed by full-text assessment of potentially eligible studies. Disagreements will be resolved through discussion, with consultation of a third reviewer when necessary, using Rayyan to manage the selection process. Two reviewers will perform data extraction independently, using a standardized electronic form, extracting study characteristics including author, publication year, country, study design, study period, setting, sample size, and patient demographics; population characteristics including age distribution, sex, comorbidities, and dengue serotype; model characteristics including model type, development method (cross-validation, train/test, hyperparameter tuning, etc...), predictor variables, and missing data handling; model performance measures including discrimination, calibration, and clinical utility measures; validation type and methods; and risk of bias assessment results.

1.5. Risk of Bias Assessment

We will assess the risk of bias and applicability of included studies using the Prediction model Risk Of Bias Assessment Tool (PROBAST) [16], which evaluates four key domains: participants, predictors, outcome, and analysis. Each domain will be rated as having low, high, or unclear risk of bias, with studies considered at high overall risk of bias if any domain is rated as high risk. Two reviewers will independently complete the risk of bias assessment, with disagreements resolved through discussion.

1.6. Data Synthesis

We will provide a narrative synthesis of all included studies, describing study characteristics, populations, model types, and performance measures, with results stratified by outcome and model type when appropriate. The metric for meta-analysis will be the Area Under the ROC Curve (AUC) and Hazard Ratio (HR). Meta-analysis will be conducted when sufficient homogeneous data are available, using random-effects models for all meta-analyses, given anticipated heterogeneity in

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study populations, model types, and performance measures. The primary analysis will pool area under the curve values using the DerSimonian-Laird random-effects method after logit transformation to ensure appropriate statistical properties for meta-analysis [17]. AUC values and their standard errors will be logit-transformed prior to pooling, with results back-transformed for interpretation, reporting summary estimates with 95% confidence intervals. For studies not reporting AUC directly, we will calculate these values from sensitivity and specificity when possible [18]. Secondary analyses will include separate meta-analyses for sensitivity and specificity using bivariate random-effects models. We will not perform meta-analysis of positive and negative predictive values due to their high dependence on disease prevalence, which varies substantially across studies and populations. We will evaluate statistical heterogeneity using the I^2 statistic and 95% prediction intervals, with values of I^2 >50% considered indicative of substantial heterogeneity [19].

When sufficient studies are available, we will perform subgroup analyses according to model type, outcome type, age groups (pediatric [<18 years], adult [≥18 years], or mixed populations), geographic region (with particular focus on Southeast Asia vs. Latin America, given known differences in dengue epidemiology and clinical presentation between these regions, which historically present a high burden of dengue cases) [20], healthcare setting, and risk of bias level. Sensitivity analyses will be conducted excluding studies at high risk of bias and studies with small sample sizes, ~100 or less. We will assess publication bias using funnel plots and Egger's test when at least 10 studies are available for meta-analysis. All analyses will be conducted using R statistical software, version 4.2.2, through Rstudio, with appropriate packages for meta-analysis and diagnostic accuracy studies.

2. Discussion

This systematic review will provide the first comprehensive evaluation of predictive models for dengue severity, mortality, and hospitalization, identifying models with varying performance characteristics across different populations and settings. The review will likely reveal heterogeneity in model development methods, validation approaches, and reporting quality, highlighting opportunities for methodological improvement. The findings will have important implications for clinical practice by identifying the most accurate and reliable models for predicting dengue outcomes, providing evidence-based guidance for clinicians, with high-performing models potentially suitable for implementation in clinical practice, particularly in resource-limited settings where expert clinical judgment may be less available.

The review will highlight methodological gaps in current prediction model research, including insufficient external validation, limited assessment of clinical utility, and poor reporting of model development processes, informing recommendations for future research priorities [21,22]. Evidence on model performance across different healthcare settings will inform policy decisions about resource allocation and implementation of prediction tools in dengue management programs [23]. Several limitations should be considered, including potential study heterogeneity that may limit the ability to pool results across studies, publication bias where studies with positive results may be more likely to be published, limited external validity from single-center studies, and temporal factors as dengue epidemiology and clinical management practices evolve over time [24,25].

This systematic review has important strengths, including a comprehensive scope covering models of all types predicting multiple outcomes, rigorous methodology using established tools for quality assessment, and standardized approaches for data extraction and analysis [26], clinical focus on outcomes directly relevant to decision-making, and a global perspective through inclusion of multiple databases and no language restrictions. By establishing evidence-based recommendations for prediction model use in dengue management, this review will contribute to improved patient outcomes and more efficient healthcare delivery in dengue-endemic regions, providing a reliable foundation for clinical decision-making and future research priorities in dengue prognostic modeling [27].

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Conflicts of Interest: The authors declare that they have no competing interests.

Abbreviations

Prediction model Risk Of Bias Assessment Tool: PROBAST; Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols: PRISMA-P; Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis: TRIPOD; Area Under the ROC Curve: AUC; Hazard Ratio: HR; Receiver Operating Characteristic: ROC; World Health Organization: WHO; Dengue Virus: DENV; Dengue Core Outcome Set: DEN-CORE; Latin American and Caribbean Health Sciences Literature: LILACS.

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