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A Multi-Stage Machine Learning Model for Early Prediction of Neurological Complications in Dengue Patients

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ABSTRACT

Dengue fever is still a major public health problem, especially in tropical and subtropical areas. Neurological complications are now being reported more often in dengue patients, but detecting them early is still not very easy. In this study, we tried to develop a multi-stage machine learning model to predict these complications early using routine clinical and lab parameters which are easily available.

The approach is based on two stages. In stage 1, the model checks if there is any chance of neurological complication in the patient. Then in stage 2, it tries to predict specific conditions like neck rigidity, papilloedema and seizures. The XGBoost model performed best in stage 1, giving an AUC of 0.9286 and F1-score of 0.9167, which shows quite good performance, although not perfect.

Some additional steps like handling class imbalance, probability calibration and selecting a proper threshold were also used, so that the model can work better in real clinical settings. The results are fairly good, especially for predicting neck rigidity and seizures, but still there can be some variation depending on data.

One advantage is that the model is non-invasive, so it may help doctors in early decision making, mainly in places where resources are limited or advanced tests are not easily available. In future, the model should be tested on external datasets and maybe integrated into clinical decision systems for practical use.

1. Introduction

Dengue fever is one of the most rapidly spreading viral infections that spreads from infected to uninfected person through the mosquitoes, which has became a major problem in tropical regions (Bhatt et al., 2013). The dengue virus (DENV) is transmitted by *mosquitoes of Aedes aegypti* and *Aedes albopictus* belonging to the Flaviviridae family (Fong et al., 2024).This disease has become a major problem throughout the world, with millions of cases reported annually, and the main reason behind it is climate change, urbanization, and globalization (Bhatt et al., 2013).

Dengue infection can grow from a normal fever to life-threatening conditions like dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). In 2009, the World Health Organization (WHO) redefined its classification system to enhance early detection and clinical treatment, stratifying dengue into: dengue without warning signs, dengue with warning signs, and severe dengue (Naderian et al., 2025). Severe dengue is associated with plasma leakage, bleeding, and multi-organ involvement, including central nervous system (CNS) involvement (Carod-Artal et al., 2013).

Although dengue was traditionally regarded as non-neurotropic, accumulating evidence demonstrates that the virus may attack the nervous system. Neurological manifestations are now recognized as significant components of dengue infection and can involve both central and peripheral nervous systems (Guzman and Martinez, 2024). These manifestations include encephalitis, encephalopathy, meningitis, and neuromuscular disorders, with reported incidence rates ranging from approximately 0.5% to 20% (Carod-Artal et al., 2013).

The pathogenesis of dengue-related neurological complications is multifactorial, involving direct viral neuroinvasion, immune-mediated processes, and systemic or metabolic imbalances (Naderian et al., 2025). Experimental and clinical research has demonstrated that dengue virus is capable of breaching the blood-brain barrier and infecting neuronal tissues, leading to neuronal damage and inflammation (Calderón-Peláez et al., 2019).

The most common and serious neurological complications in dengue patients are found in Dengue encephalitis and encephalopathy. Some of these cases like seizures, impaired consciousness, and focal neurological deficit are hard to differentiate from complications due to their similar clinical manifestations (Noronha et al., 2025). Underdiagnosis and misclassifications are results of these diagnoses because of limited diagnostic resources and nonspecific symptoms (Sivakumar et al., 2025).

The growing recognition of neurological involvement in dengue has important implications for clinical management, as the chances of severe illness and death are higher in patients with neurological complications (Trivedi and Chakravarty, 2022). However, existing diagnostic methods mostly rely on tests such as cerebrospinal fluid (CSF) analysis and neuroimaging, which can be time-consuming and are not very effective for early-stage detection, especially in low-resource settings

Multiple studies in recent years have shown that machine learning can give good results in disease prediction and help in clinical decision making. Many of these studies focus on predicting disease severity and clinical outcomes, but only a few have worked on early prediction of neurological complications. Also, most of these approaches rely on parameters that are considered late-stage indicators, which limits their use in real-world situations.

To address these limitations, this paper proposes a multi-stage machine learning model for early prediction of neurological complications in dengue patients using routinely available clinical and laboratory parameters. The framework first identifies patients at risk of neurological complications, then predicts specific manifestations such as neck rigidity, papilloedema, and seizure episodes.

The key contributions of this work are:

1. Development of a two-stage predictive model for neurological dengue complications;
2. Use of non-invasive, early-stage clinical and laboratory characteristics;
3. Implementation of class imbalance handling and probability calibration techniques;
4. Creation of a clinically applicable model for early risk stratification.

2. Related Work

2.1. Epidemiology and Clinical Spectrum of Dengue

Dengue is among the most rapidly increasing mosquito-borne viral diseases worldwide, with significant growth in incidence, mortality, and disease burden over recent decades (Zhang et al., 2025). The disease exhibits a wide clinical spectrum ranging from mild febrile illness to severe forms such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), which are associated with plasma leakage, organ failure, and increased mortality risk (Khosla et al., 2024).

Early identification of patients at risk of severe disease is essential for timely clinical intervention and mortality reduction. Several studies have identified key clinical and laboratory predictors associated with severe dengue outcomes. For example, age, hematological abnormalities, and biochemical markers have demonstrated significant roles in disease progression and severity (Gupta et al., 2011). However, predicting disease progression at early stages remains a major clinical challenge.

2.2. Neurological Complications in Dengue

Dengue infection with neurological involvement has been identified as serious complication. The types of complications which may involve both types of nervous systems include encephalitis and encephalopathy, seizures, myelitis, and neuro-muscular disorders. (Kulkarni et al., 2021; Kakde and Khatib, 2024).

There have been clinical studies showing range of neurological complications with varying occurrence in different population. Retrospective studies and case series show outlines of a certain population subset where dengue showed neurological complications, which had, in turn, seizure and altered level of consciousness, and had some focal neurological deficits. (Wasay et al., 2008). There is enough data that holds studies in hospitals or any medical institutions showing that both encephalopathy and encephalitis occur most neurological disorders. (Kulkarni et al., 2021).

There are various nervous system involvement complications that require multiple cause components such as viral infection of neurons, immune response, and various some complications like biochemical and other metabolic systemic Verma et al. (2011). There is evidence of dengue virus in lymphatic fluid and nervous tissues Solomon et al. (2000). These complications are underdiagnosed even with increased awareness, because are misdiagnosed as other clinical disorders that are for which do not have sufficient laboratory or other diagnostic methods available.

2.3. Machine Learning and Predictive Modeling in Dengue

The development of predictive models for determining dengue severity and clinical outcomes has evolved positively alongside progress in machine learning. Several machine learning techniques have been implemented in early detection and risk stratification.

Huang et al. (2020) describes a predictive model utilizing demographic and laboratory data, and highlights strong performance and high discriminative power by artificial neural networks. Likewise, Park et al. (2018) used a structural equation model to predict phenotypes of dengue illness and found significant predictors of disease progression.

The prediction of dengue shock syndrome has been the focus of other research. Early detection, which can decrease mortality, is emphasized in Chaw et al. (2024) model proposals based on physiological and biochemical parameters.

The prediction of dengue in these studies has been proven effective with the use of machine learning; however, the models have a general focus on disease severity, shock, or hospitalization risk, and do not consider neurological complications.

2.4. Research Gap

Numerous developments have occurred in dengue studies, but gaps in our knowledge remain. A majority of these studies have concentrated on the overall severity outcomes, including the dengue shock syndrome, and have not taken into account the prediction of neurological complications in early stages.

Most predictive models have been formulated based on late-stage clinical variables or based on complex diagnostic measures, and this restricts their applicability to early decision-making and low-resource conditions. Most importantly, there are no multi-stage predictive models that are integrated into clinical pathways where patients are initially assessed for dengue and then screened for relevant complications.

To address these issues, there is a need for non-invasive and clinically oriented hierarchical machine learning models that will allow for the early prediction of dengue patients' complications.

3. Methodology

3.1. Study Design and Problem Formulation

This study suggests a multi-phase machine learning model to predict neurological comorbidities early in dengue patients using non-invasive clinical and laboratory measures, which are simply available on a routine basis. The ultimate aim is to create a clinically useful decision support system that can detect high-risk patients at an early disease stage.

The prediction problem is defined in two stages hierarchically. Stage 1: a binary classification model is trained on the presence of any neurological complication as captured by the variable, *has_neuro*, i.e. has neurological complication. Stage 2 involves the development of separate models to estimate particular neurological manifestations, such as neck rigidity, papilloedema, and seizure episodes. Such hierarchy is based on the clinical practice in the real world, whereby first-line screening is followed by an elucidative diagnostic process.

3.2. Dataset Description and Preprocessing

The data is a combination of clinical and lab characteristics of dengue patients. Preprocessing of the data included systematic cleaning of the data to eliminate non-informative records, such as records with entirely invalid values, and irrelevant identifiers.

This algorithm was imputed using the K-Nearest Neighbors (KNN) algorithm with $k = 5$ to maintain local data structure by averaging the values of nearby samples. Categorical variables like sex were numerically encoded to be compatible with machine learning models.

Only non-invasive and routinely available features were retained to ensure that they could be applicable in early-stage clinical settings. Variables that involve invasive measures or complex diagnostics, including cerebrospinal fluid (CSF) measurements, Glasgow Coma Scale, were not analyzed.

3.3. Feature Processing and Exploratory Analysis

All quantitative attributes were normalized with Z-score to make them have equal scales and enhance convergence in the models. The transformation is defined as:

$$z = \frac{x - \mu}{\sigma} \tag{1}$$

where x represents the original feature value, μ is the mean, and σ is the standard deviation.

A feature correlation heatmap was created to study inter-feature relationships and determine the possible presence of multicollinearity with the use of Pearson correlation coefficients. This figure presented an overview of linear relationships between the hematological variables, biochemical variables and symptomatic variables and allowed to identify highly correlated variables. This kind of analysis enabled the selection of features in an informed way and the reduction of redundancies, enhancing stability and generalization of the models. The corresponding heatmap is presented in Fig. 1.

After the exploratory analysis, the data was stratified (stratified sampling) into training (80%) and testing (20%) subsets based on the variable *has_neuro*. This allowed the storage of the classes and reduced sampling bias.

3.4. Handling Class Imbalance

Since the prevalence of some neurological outcomes was relatively low, a hybrid approach was used to deal with the problem of class imbalance. In case the imbalance rate was higher than a pre-determined value (more than 2), the Synthetic Minority Oversampling Technique (SMOTE) was used to sample synthetic examples of the minority group.

To deal with all the cases in which SMOTE was not appropriate, the learning algorithms were modified with class-weight balancing, which adversely penalize the minority cases that were incorrectly classified. This integration method enhances sensitivity of the model and minimizes biasness to the majority group.

3.5. Model Development and Probability Calibration

Different machine learning algorithms were tested including Logistic Regression, Random Forest, Extra Trees Classifier and Extreme Gradient Boosting (XGBoost). Among them, XGBoost had better performance in cross-validation AUC and strength, due to its capability of capturing non-linear relationships and addressing imbalance between classes.

$$P(y = 1 \mid x) = \frac{1}{1 + e^{(Ax+B)}} \tag{2}$$

where A and B are parameters learned from the calibration dataset.This transformation guarantees that the probabilities that are predicted are highly consistent with the observed values, hence enhancing clinical interpretability.

3.6. Two-Stage Prediction Framework

To enhance predictive performance and clinical practice congruency, a hierarchical two-stage classification framework was used.

During Stage 1, a binary classifier is used to determine patients at risk of developing any neurological complication. This is a sort of preliminary screening mechanism.

Stage 2, only high-risk patients are further tested in order to forecast the particular neurological outcomes, such as neck rigidity, papilloedema, and seizure attacks. Owing to the extreme imbalance in the classes in the neck rigidity subset, this target was fitted with the entire dataset so that there was sufficient representation and predictive stability.

The hierarchical structure minimizes unnecessary computations, and the model is more clinical-relevant as in high-risk individuals, the detailed predictions are concentrated.

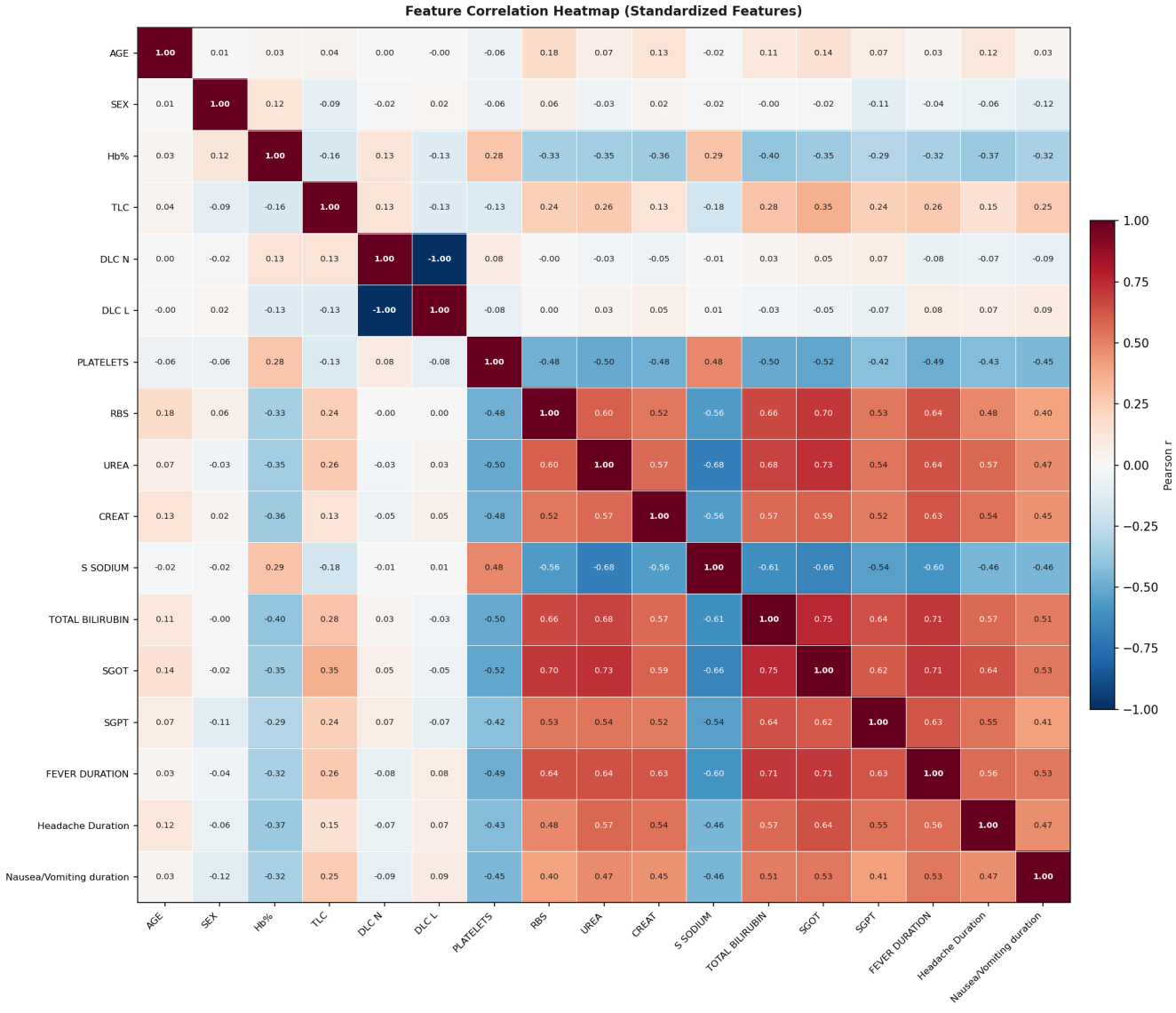

Figure 1: Feature correlation heatmap

3.7. Model Evaluation and Statistical Validation

Model performance was evaluated using multiple complementary metrics, including Receiver Operating Characteristic Area Under the Curve (ROC-AUC), Precision–Recall AUC, F1-score, sensitivity, specificity, accuracy, Matthews Correlation Coefficient (MCC), Brier score.

Instead of using a default classification threshold of 0.5, an optimal threshold was determined by maximizing the following composite objective function:

$$\text{Score} = F1 + 0.3 \times \text{Sensitivity} \tag{3}$$

subject to the constraints:

$$\text{Sensitivity} \geq 0.85, \quad \text{Specificity} \geq 0.50 \tag{4}$$

This formulation prioritizes early detection while maintaining acceptable specificity, which is critical in clinical applications.

To ensure robustness and generalizability, 5-fold stratified cross-validation was employed. Additionally, bootstrap resampling ($n = 300$) was used to estimate 95% confidence intervals for key performance metrics:

$$CI = \bar{x} \pm 1.96 \cdot \sigma \tag{5}$$

where $\bar{x}$ represents the mean estimate and σ denotes the standard deviation.

4. Results and Discussion

A comparative evaluation of multiple machine learning models (Table 1) showed that ensemble-based methods outperformed linear models. Among them, XGBoost achieved

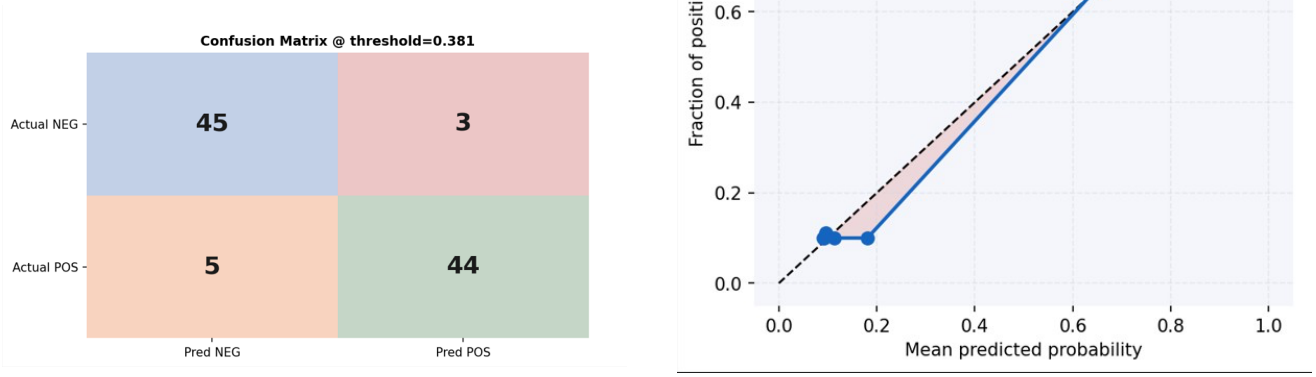

Figure 2: Stage 1 model evaluation: (a) Confusion matrix for stage 1, (b) Calibration curve for stage 1 model

Table 1
Comparative performance of machine learning models

Model	CV-AUC	F1-score	Sensitivity	Specificity
Logistic Regression	0.937 ± 0.017	0.890 ± 0.033	0.877	0.917
Random Forest	0.941 ± 0.013	0.905 ± 0.024	0.898	0.912
Extra Trees	0.939 ± 0.014	0.907 ± 0.026	0.882	0.958
XGBoost	**0.949 ± 0.011**	0.906 ± 0.026	0.892	0.922

Table 2
Performance of Stage 2 models for predicting neurological complications

Target	CV-AUC	Test AUC	F1-score	Accuracy	Sensitivity	Specificity	Brier
Neck Rigidity	0.923 ± 0.069	**0.9058**	**0.8889**	**0.8969**	0.8696	**0.9216**	**0.0954**
Papilloedema	0.832 ± 0.060	0.8052	0.6667	0.7872	0.7143	0.8182	0.1673
Seizures	0.841 ± 0.074	0.8353	0.8788	0.8298	**0.9667**	0.5882	0.1424

the best cross-validation AUC and demonstrated strong stability, supporting its selection for the proposed framework.

In Stage 1, XGBoost was selected as the final model for predicting neurological complications. On the independent test set, it achieved an AUC of 0.9286 and an F1-score of 0.9167, with sensitivity of 0.8980 and specificity of 0.9375. The confusion matrix (Fig. 2(a)) indicates low false positives and false negatives, reflecting robust classification performance.

The calibration curve (Fig. 2(b)) indicates that the predicted probabilities are well aligned with observed outcomes, suggesting that the model provides reliable probability estimates in addition to strong discrimination.

In the second stage, models were trained to predict specific neurological complications among patients identified as high-risk. The overall performance is summarized in Table 2. Neck rigidity prediction demonstrated strong and balanced performance with high sensitivity and specificity. Seizure prediction achieved high sensitivity, indicating effective detection of true positive cases, albeit with relatively lower specificity. Conversely, the prediction of papilloedema was relatively inferior, probably because it was less prevalent, and there was an imbalance in the classes.

Stage 2 performance is thoroughly assessed in Fig. 3, with ROC curves, score distributions, confusion matrices, and cross-validation stability. The best discriminative performance (AUC = 0.906) was obtained with neck rigidity, then seizures (AUC = 0.835) and papilloedema (AUC = 0.805). Scores in distributions show that there is a separation between classes in neck rigidity, whereas papilloedema has more overlap. Confusion matrices also indicate that neck rigidity retains balanced classification, seizure prediction has more emphasis on sensitivity with more false positives, and papilloedema displays moderate performance as it is in line with its class imbalance.

Clinically, SHAP analysis can give important insights into the effects of individual features on the estimated risk of neurological complications. Characteristics that have larger SHAP values have a greater contribution to the increment of the predicted probability of adverse outcomes.

An increase in urea levels, length of fever and headache duration is linked to increased risk scores, which indicates systemic involvement and progression of the disease. In line with this, the presence of the signs of abnormal liver functioning (SGOT, SGPT) and reduced platelet count are the indicators of underlying pathophysiological processes, i.e., inflammation, vascular leakage, organ dysfunction, which are often related to the severe manifestation of dengue.

Notably, SHAP allows risk interpretation on a patient-specific scale by evaluating the contribution of each feature to a prediction of a specific patient. This will enable clinicians to not only know whether a patient is a high- or low-risk, but *why* a specific probability is placed. As shown in Fig. 4, Fig. 5, and Fig. 6, the case of high-risk, intermediate-risk, and low-risk patients shows that the combination of

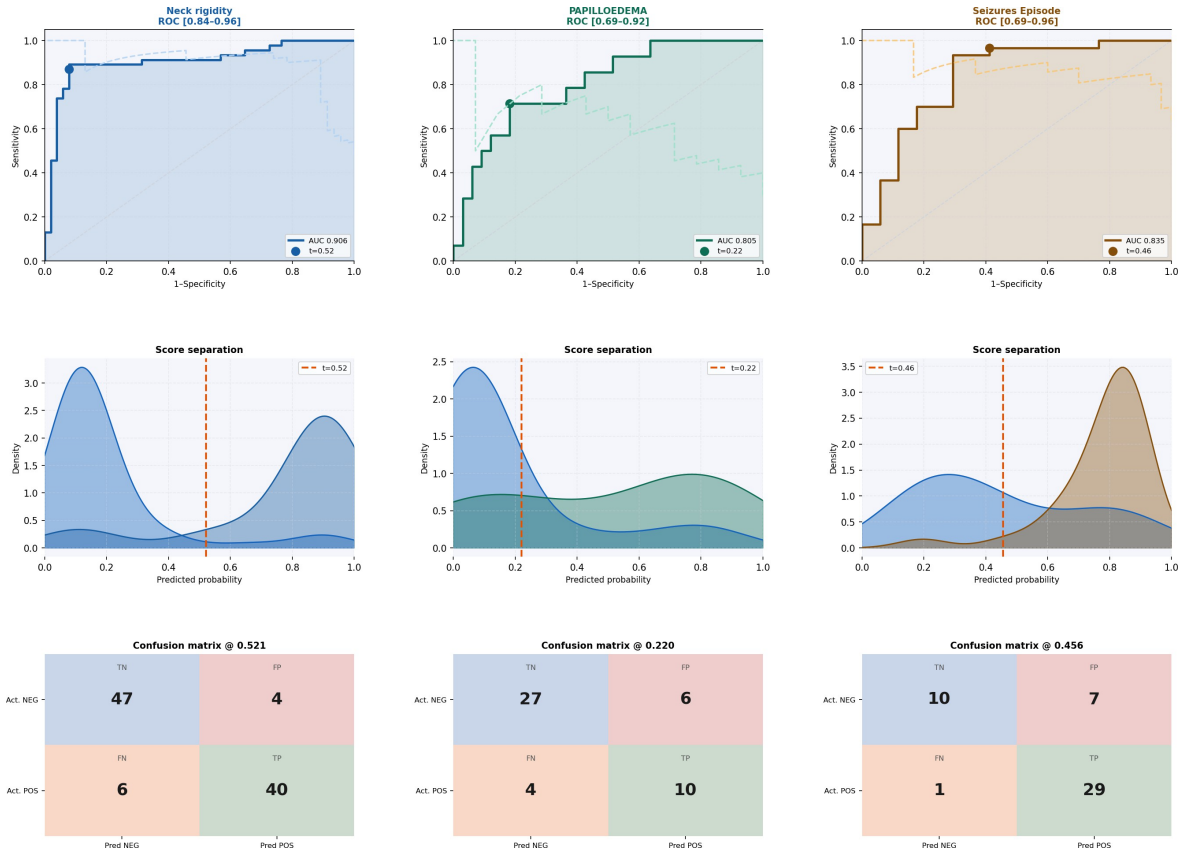

Figure 3: Comprehensive performance comparison for Stage 2 models across neurological outcomes

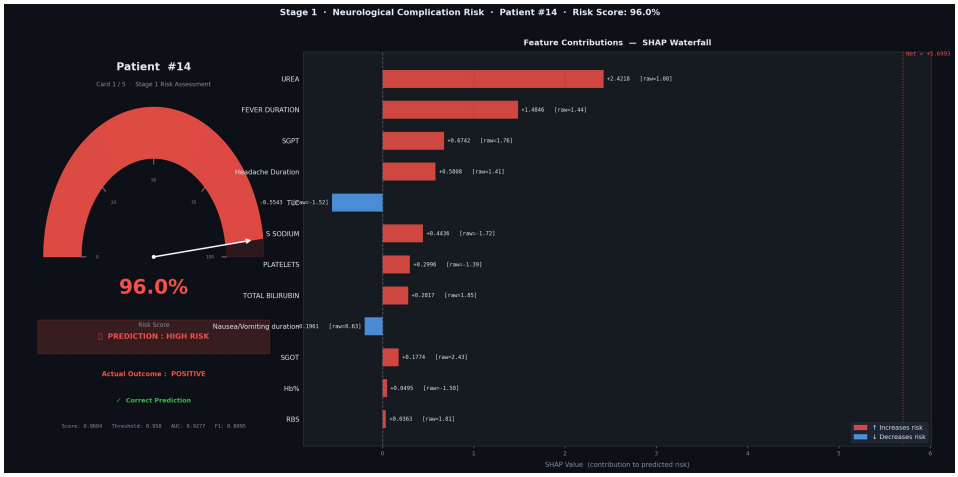

Figure 4: SHAP waterfall plot for a patient with high risk prediction

both risk-increasing and risk-decreasing features can have a significant effect on the final prediction.

The high-risk case, high levels of urea, long headache duration, high levels of liver enzymes (SGPT) and high levels of longer fever duration become the major factors that contribute to a high predicted probability of neurological complications. Conversely, the intermediate-risk scenario shows a balance between the risk-promoting variables like high serum sodium and total leukocyte count, and the protective variables such as low urea and platelet count, with an intermediate probability score. Protective factors, especially low urea levels and stable hematological parameters dominate the prediction, resulting in a much smaller risk estimate in the case of the low-risk patient.

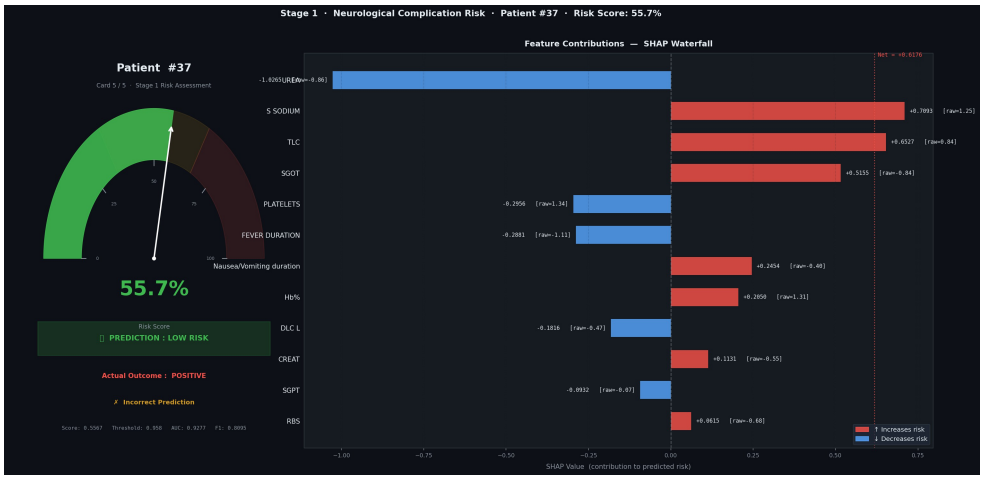

Figure 5: SHAP waterfall plot for a patient with intermediate risk prediction

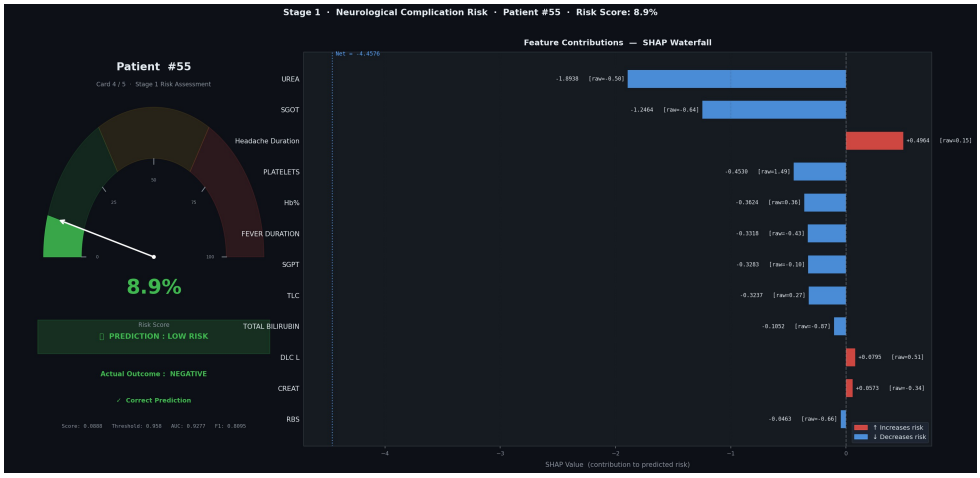

Figure 6: SHAP waterfall plot for a patient with low risk prediction

This interaction underscores how the model is able to describe complex clinical patterns as opposed to having a single dominant predictor.

This model increases trust in its predictions and aids in making clinical decisions in borderline or uncertain situations. Because the model links feature contributions to predicted probabilities, it enables clinically justifiable risk discrimination with the higher cumulative SHAP contributions corresponding to higher risk.

In the ranking, contributions to features are small and thus likely to mean little in earlier stage predictions. The features in question are creatinine, random blood sugar (RBS), and differential leukocyte counts (DLC). The model, with its integration of biochemical, hematological, and symptom-related variables, demonstrates the identification of clinically relevant patterns and supports its explainability and prospective clinical deployment, as illustrated by the SHAP analysis.

The integrated visualization further supports clinical utility and confirmability of the framework, demonstrating predictability of performance variability with respect to the neurological outcomes.

The study outlines the importance of differentiating risk from certainty in the diagnosis, which has notable clinical implications. It illustrates identification of patients at risk of rapid neurological decline, presenting symptoms such as neck rigidity, papilloedema, and seizures, using the non-invasive clinically and laboratory parameters, including CBC, biochemical markers, liver function tests, and symptom profiles.

However, the model does not aim to provide a definitive diagnosis or establish the exact cause or degree of neurological involvement. Such as diagnosis can only be acquired with more advanced techniques, such as imaging (CT or MRI), and analysis of cerebrospinal fluid (CSF) which are not available in the early or resource-limited settings.

Rather, the framework operates as a clinical decision support tool at the earliest point in time, determining the *probability of risk*. An XGBoost model captures the intricate, non-linear associations in the input features in relation to a patient's neurological outcome and provides calibrated

scores based on the probability of the outcome. The probabilities are assessed against a threshold that has been optimized to maximize sensitivity at the expense of specificity, and classify the patient into high- or low-risk categories.

This model of risk stratification based on probabilities facilitates the earlier identification of patients who require increased surveillance, earlier referral for more advanced diagnostic testing, or clinical intervention more expeditiously. The model effectively closes the distance between an initial clinical assessment and a definitive diagnosis, and enables more accurate, timely, and direct decision-making.

In summary, the results illustrate that the proposed two-stage framework successfully diverts general risk assessment from specific complication forecasting. The considerable achievement in Stage 1 offers the prospect of high confidence in determining the high-risk patient, while Stage 2 delivers a prediction of neurological outcomes that is relevant and of clinical utility. This tiered approach mirrors clinical practice, where initial identification is followed by more focused assessment.

Unlike previous works that mostly looks at general dengue severity or shock forecasting, the current study aims at neurological complications, as it is one of the least studied areas. Moreover, the reliance on non-invasive clinical and laboratory features increases the model's applicability in everyday and resource-limited healthcare settings.

There are a number of considerations and limitations that should be mentioned. The dataset is of a moderate size, and external validation is needed to evaluate generalizability. Moreover, the class imbalance, particularly for papilloedema, affects the quality of predictions. Research should be directed at more extensive datasets from multiple centers and more refined modeling approaches to further enhance predictive quality and reliability.

5. Conclusion

This study proposes an innovative multi-stage machine learning framework providing early predictions of neurological complications in dengue patients using available clinical and laboratory parameters. This method proposes an initial screening model for high-risk patient identification, followed by prediction of specific neurological complications, like neck rigidity, papilloedema, and seizure episodes.

The framework predictive performance is outstanding for initial risk detection with highly calibrated response and probability estimates. The second stage of the framework allows for clinically important differentiation of neurological outcomes, where strong prediction performance for neck rigidity and seizures was evident. Although prediction of papilloedema was class imbalanced and therefore more difficult, the model was still able to provide modest levels of prediction.

The main strength of the of the paper include the use of non-invasive and early signs, thus increasing the relevance of the framework to real-life and limited-resources clinical environment. In addition, the hierarchical nature of the framework is also highly relevant to clinical processes and allows making appropriate decisions at an early stage.

However, despite all the aforementioned positive results, there were some limitations of the paper as well. Namely, the paper includes only one dataset and does not contain any evidence of external validation. Therefore, the future works needs to be focused on external validation and possible improvements to the framework for better performance with rare classes of outcomes.

Overall, the proposed approach provides a clinically relevant, interpretable, and scalable solution for the early identification of neurological complications in dengue patients, with the potential to improve patient outcomes through timely and targeted intervention.

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