

Predicting Clinical Outcome in Dengue Fever: A Retrospective Cohort Modeling Study



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[Visual Abstract](#)

ABSTRACT

Background: Dengue fever demonstrates a broad spectrum of clinical severity, ranging from self-limiting illness to life-threatening complications. Early identification of patients at risk of progression remains a clinical challenge, particularly in high-burden settings. Although platelet count and World Health Organization (WHO) dengue classification are routinely used in clinical practice, reliance on individual parameters may not adequately capture the multifactorial nature of disease severity. Development of multivariable predictive models integrating clinical and laboratory markers available at admission may improve early risk stratification and support evidence-based triage decisions.

Methods: This retrospective predictive analysis included 667 consecutively hospitalized patients with laboratory-confirmed dengue infection. This retrospective cohort study was conducted in a tertiary care teaching hospital in Western Maharashtra over a 1.5-year period. Data were extracted from hospital records of patients evaluated during their admission period. An ordinal logistic regression model was developed to predict clinical outcome. Internal validation was performed using bootstrap resampling.

Results: Of 667 patients, 585 (87.7%) had uncomplicated recovery, 69 (10.3%) had complicated recovery, and 13 (1.9%) had adverse outcomes. WHO classification, platelet count, neutrophil-to-lymphocyte ratio (NLR), and warning sign count at admission independently predicted clinical outcome, with an optimism-corrected C-index of 0.820.

Conclusion: Admission WHO classification, platelet count, NLR, and warning signs enable accurate early prediction of dengue severity and may assist in triage and monitoring decisions.

Keywords: Clinical outcome, Dengue fever, Neutrophil-to-lymphocyte ratio, Predictive modeling, Thrombocytopenia.

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INTRODUCTION

Dengue fever is one of the most rapidly expanding mosquito-borne viral infections worldwide, with an estimated 100–400 million infections annually, particularly in tropical and subtropical regions.^{1,2} India remains a major endemic region, with recurrent outbreaks contributing substantially to the healthcare burden.³ The disease spectrum ranges from self-limiting febrile illness to severe dengue characterized by plasma leakage, hemorrhage, shock, and organ dysfunction.⁴

Thrombocytopenia is a hallmark feature of dengue infection and arises from bone marrow suppression, immune-mediated platelet destruction, and peripheral consumption.^{5,6} Severe thrombocytopenia has been associated with increased bleeding risk and adverse outcomes.⁷ While platelet count is widely used in disease monitoring, it represents a global measurement and does not provide insight into bone marrow response or recovery potential.

Platelet indices such as immature platelet fraction (IPF) have been explored as

markers of thrombopoietic activity, though their role in predicting clinical severity remains uncertain.^{8,9} Prior studies have demonstrated the predictive value of IPF in various thrombocytopenic conditions.^{10–12}

Markers such as neutrophil-to-lymphocyte ratio (NLR) have also been associated with disease severity in dengue infection.^{13,14} However, most studies have evaluated predictors individually rather than integrating them into validated multivariable prediction models.

Regression modelling strategies enable integration of multiple predictors to generate individualized risk estimates and improve clinical decision-making.¹⁵ The objective of this study was to develop and internally validate a multivariable predictive model for clinical outcome in hospitalized dengue patients.

METHODS

Study Design and Population

This retrospective cohort study was conducted at a tertiary care teaching

hospital in Western Maharashtra over a 1.5-year period. A total of 667 consecutive patients admitted with laboratory-confirmed dengue infection during the study period were included in the analysis. Patients were evaluated during their hospital stay, and clinical and laboratory data—including demographics, World Health Organization (WHO) dengue classification, hematological parameters, biochemical parameters, and clinical outcomes—were extracted from hospital records using a structured data abstraction form. Patients were eligible for inclusion if they were aged ≥ 18 years, had laboratory-confirmed dengue infection according to the hospital diagnostic protocol, and had complete clinical and laboratory data required to predict clinical outcome. These included baseline WHO category, platelet count, NLR, and warning sign count recorded on the first day of admission. Patients were excluded if admission laboratory records were incomplete or if an alternative confirmed diagnosis was established during hospitalization.

Outcome Definitions

Clinical outcomes were categorized into three ordered levels based on in-hospital clinical course and disease severity at discharge.

Uncomplicated recovery ($n = 585$) was defined as hospitalization without development of severe dengue, organ dysfunction, or major complications.

Complicated recovery ($n = 69$) was defined as development of warning signs, organ dysfunction (including acute kidney

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injury), requirement of platelet transfusion, or other complications requiring intensified monitoring or therapeutic intervention during hospital stay, but with eventual recovery.

Adverse outcome ($n = 13$) was defined as progression to severe dengue with significant clinical deterioration, including shock, requirement of intensive care support, or in-hospital mortality.

Predictor Variables

Predictors were restricted to day 1 admission values to enable early prognostication. Laboratory parameters were measured using automated hematology analyzers as per hospital laboratory standard operating procedures. All measurements were obtained from admission samples. The predictors are shown in Table 1.

Statistical Analysis

Variable Selection Strategy

Variable selection followed a 5-step strategy prespecified before model fitting. It was based on domain-specific knowledge from published literature, parameter budgeting, unsupervised data reduction using variable clustering and redundancy analysis, prespecification of nonlinearity based on recommendations by Harrell,¹⁵ and internal validation using bootstrap resampling. Parameter budgeting was used as a prespecification strategy that limits model complexity to avoid overfitting. The maximum number of predictor terms (degrees of freedom) was set at $Lm/15J$, where m represents the number of events in the least frequent outcome category. This more conservative threshold, compared with the commonly cited 10 events-per-variable minimum, follows the recommendations of Harrell,¹⁵ to ensure stable coefficient estimates. Variable clustering (varclus) was performed as an unsupervised data reduction technique that groups correlated predictor variables into clusters using hierarchical clustering on Hoeffding's D or Spearman's ρ^2 similarity matrices. This identifies collinear predictors before examining any predictor-outcome associations, thereby preventing data-driven variable selection bias. Redundancy analysis (redun) was subsequently used as a complementary step to identify predictors that can be almost perfectly predicted by other predictors ($R^2 > 0.3$), flagging them for removal to avoid multicollinearity.

Model Specifications

Clinical Outcome

Eighty-two events (complicated and adverse outcomes combined) yielded a parameter budget of 5° of freedom using the more stringent 15 events-per-variable approach

recommended by Harrell.¹⁵ The final ordinal logistic regression model utilized the full 5°-of-freedom budget and included baseline WHO category (2° of freedom), platelet count day 1 (1° of freedom), NLR day 1 (1° of freedom), and warning sign count day 1 (1° of freedom). Under the more conventional 10 events-per-variable criterion, the available parameter budget would have been larger; however, the more conservative threshold was deliberately chosen to minimize overfitting risk and improve model stability. Continuous predictors were prespecified to be assessed for potential nonlinearity using restricted cubic splines with 3 knots placed at the 10th, 50th, and 90th percentiles, following the recommendations of Harrell.¹⁵ Restricted cubic splines were preferred over polynomial transformations because they remain linear in the tails, reduce instability at data extremes, and require fewer additional degrees of freedom. However, nonlinear terms were not incorporated into the final model because the available parameter budget was fully utilized by the clinically selected predictors in linear form. Internal validation using bootstrap resampling demonstrated stable model performance with minimal optimism, and the bootstrap shrinkage slope was 0.978, suggesting adequate control of overfitting.

Details of the model, including the number of events, model parameters, and number of events, are provided in Supplementary Table S1.

Missing Data

The model included WHO baseline classification, day 1 platelet count, NLR, and warning sign count; all predictors and outcome data were complete (0% missing) in the full cohort of 667 patients.

Supplementary Material

Detailed internal validation metrics, discrimination statistics, comparative model performance characteristics (Supplementary Tables S1–S2), and graphical outputs, including calibration plots and variable importance analyses (Supplementary Figures S1–S2), are presented in the online Supplementary Appendix.

RESULTS

Study Population

A total of 667 consecutive hospitalized patients met eligibility criteria during the study period and were included in the final analysis. Among 667 patients, 585 (87.7%) had uncomplicated recovery, 69 (10.3%) had complicated recovery, and 13 (1.9%) had adverse outcomes.

Baseline Characteristics

Baseline characteristics stratified by clinical outcome are presented in Table 2.

Clinical Outcome Prediction Model

In the multivariable ordinal logistic regression model, WHO dengue classification demonstrated the strongest association

Table 1: Predictor variables

Variable	Description
WHO baseline	WHO 2009 dengue classification at admission
PLT D1	Platelet count (lakh/ μ L) at admission
NLR D1	Neutrophil to lymphocyte ratio at admission
Warning signs	Number of WHO-defined warning signs present
IPF D1	IPF (%) at admission
MPV D1	Mean platelet volume (fL) at admission
HCT D1	Hematocrit (%) at admission
TLC D1	Total leucocyte count (/cumm) at admission
Albumin	Serum albumin (gm/dL)
Calcium	Serum calcium (mg/dL)
SGOT D1	Serum glutamic-oxaloacetic transaminase (AST) (IU/L) at admission
Age	Age (years)
BMI	Body mass index (kg/m^2)
DM	Diabetes mellitus (binary variable: present/absent)
HTN	Hypertension (binary variable: present/absent)
AKI	Acute kidney injury (binary variable: present/absent) Acute kidney injury was defined according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria, including an increase in serum creatinine by ≥ 0.3 mg/dL within 48 hours, or ≥ 1.5 times the baseline value within 7 days, or urine output < 0.5 mL/kg/hour for at least 6 hours during hospitalization. For this retrospective analysis, AKI status was ascertained based on documented clinical diagnosis in the hospital case records supported by corresponding laboratory and urine output data meeting KDIGO criteria
PLT transfusion	Platelet transfusion received during hospitalization (binary variable)
Antibiotics	Antibiotics administered during hospitalization (binary variable)

Table 2: Baseline characteristics

Variable	N	Uncomplicated (N = 585)	Complicated-recovered (N = 69)	Adverse (N = 13)
Age (years)*	667	25/31/38	20/29/33	21/21/34
Gender [#]	667			
Male (%) [#]		81% (475/585)	81% (56/69)	92% (12/13)
Body mass index (kg/m ²)*	667	21.50/23.50/25.59	20.93/24.10/27.00	22.40/22.40/24.24
WHO classification at admission [#]	667			
DWOWS		97% (567/585)	35% (24/69)	46% (6/13)
DWWS		2% (9/585)	42% (29/69)	15% (2/13)
Severe dengue		2% (9/585)	23% (16/69)	38% (5/13)
Platelet count day 1 (lakh/ μ L)*	667	0.66/1.18/1.57	0.68/0.90/1.38	0.60/1.30/2.03
NLR day 1*	667	1.28/1.90/3.52	1.93/2.84/4.75	2.30/3.63/3.63
Hematocrit day 1 (%)*	666	39.5/43.7/47.8	38.4/44.2/46.0	36.9/39.5/46.6
TLC day 1 (/cumm)*	667	2700/3480/5010	2500/3900/5590	2800/5070/5070
Diabetes mellitus (%) [#]	667	12% (72/585)	17% (12/69)	0% (0/13)
Hypertension (%) [#]	667	12% (71/585)	19% (13/69)	0% (0/13)
Acute kidney injury (%) [#]	667	3% (18/585)	23% (16/69)	0% (0/13)
Warning signs count [#]	667			
0 warning signs		72% (420/585)	46% (32/69)	38% (5/13)
1 warning sign		24% (143/585)	30% (21/69)	15% (2/13)
2 warning signs		4% (22/585)	9% (6/69)	46% (6/13)
3 warning signs		0% (0/585)	7% (5/69)	0% (0/13)
4 warning signs		0% (0/585)	7% (5/69)	0% (0/13)

*Values are expressed as median/interquartile range; [#]Values are expressed as number (%) of patients; DWOWS, dengue without warning signs; DWWS, dengue with warning signs; IPF, immature platelet fraction; MPV, mean platelet volume; NLR, neutrophil to lymphocyte ratio; TLC, total leukocyte count

Table 3: Adjusted odds ratios for worse clinical outcome

Variable	Upper value vs lower value	Adjusted odds ratio	95% confidence interval
Platelet count day 1 (lakh/ μ L)	1.57 vs 0.66	0.88	0.64–1.19
Neutrophil to lymphocyte ratio day 1 (ratio)	3.54 vs 1.32	1.07	1.01–1.13
Warning signs count	1 vs 0	1.48	1.07–2.05
WHO classification	DWWS vs DWOWS	27.79	12.96–59.62
WHO classification	Severe vs DWOWS	31.09	13.82–69.96

Continuous predictors (platelet count and NLR) are expressed as interquartile range (75th vs 25th percentile) contrasts. Reference category for WHO classification: dengue without warning signs (DWOWS). Odds ratios >1 indicate increased odds of worse clinical outcome

with worse clinical outcome. Compared with dengue without warning signs, patients presenting with dengue with warning signs had an adjusted odds ratio of 27.79 (95% CI 12.96–59.62), while those with severe dengue had an adjusted odds ratio of 31.09 (95% CI 13.82–69.96). Higher NLR was associated with increased odds of worse outcome (OR 1.07; 95% CI 1.01–1.13), and each additional warning sign increased the odds of progression (OR 1.48; 95% CI 1.07–2.05). Although lower platelet count showed a directional association with worse outcome (OR 0.88; 95% CI 0.64–1.19), the confidence interval included unity. Odds ratio estimates are depicted in Table 3. Partial effects of predictors on log odds of worse outcome are depicted in Figure 1. The nomogram for predicting clinical course is depicted in Figure 2. The optimism-corrected C-index was 0.820. Detailed discrimination indices,

calibration plot, and variable importance plot are given in Supplementary Table S2, Figure S1, and Figure S2.

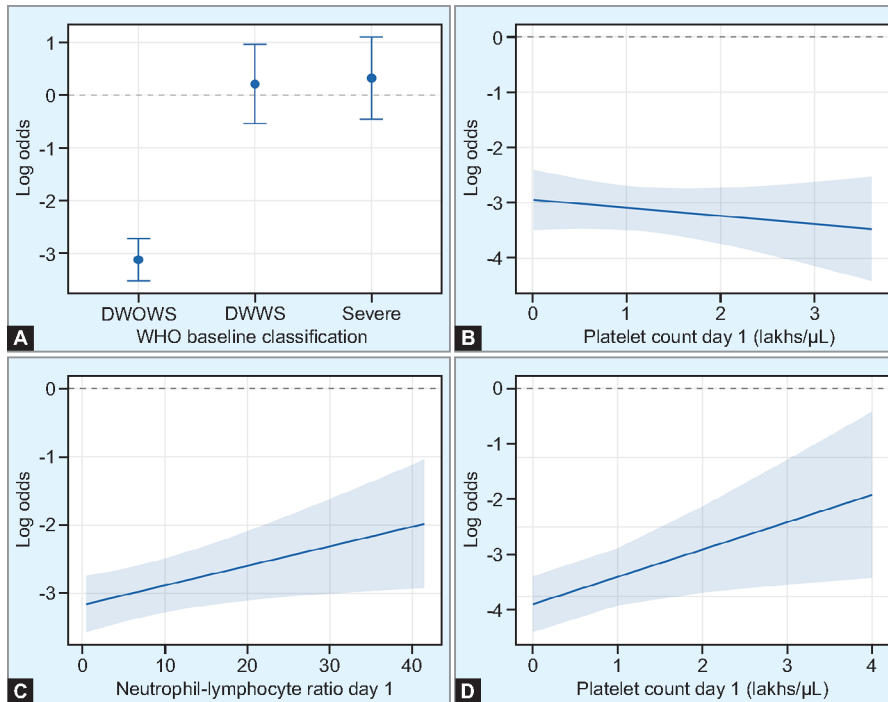
The nomogram provides an individualized estimate of the probability of developing a complicated or adverse clinical outcome based on admission variables. To use the nomogram, each predictor—WHO classification at admission, platelet count (day 1), NLR (day 1), and warning signs count—is located on its respective axis, and a vertical line is drawn upward to the “Points” scale to determine the corresponding score for that variable. The points assigned for each predictor are then summed to obtain the “Total Points.” This total is projected downward onto the “Linear Predictor” scale and subsequently onto the probability scale labeled “P (Complicated or Adverse)” to estimate the patient’s risk of worse clinical outcome. Higher total points correspond to a higher predicted

probability of developing complicated or adverse dengue. The nomogram therefore translates the multivariable ordinal logistic regression model into a clinically usable bedside tool for early risk stratification at the time of admission.

Detailed internal validation metrics and calibration statistics are provided in Supplementary Table S1, Supplementary Table S2, and Supplementary Figure S1.

DISCUSSION

This study developed and internally validated a multivariable prognostic model to predict clinical outcome in hospitalized adults with dengue using routinely available admission clinical and laboratory parameters. The magnitude of association was strongest for baseline WHO classification, followed by warning signs and inflammatory markers.



Figs 1A to 1D: Partial effects of predictors on log odds of worse outcome: (A) WHO baseline; (B) PLT D1; (C) NLR D1; (D) Warning signs count

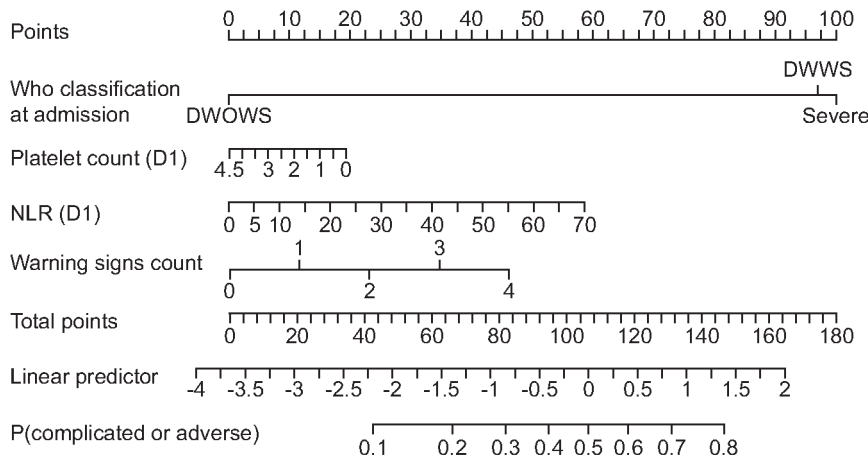


Fig. 2: Nomogram for predicting clinical outcome

These findings indicate that variables available at first presentation can be systematically integrated into an evidence-based framework to generate individualized risk estimates. Rather than relying on isolated laboratory thresholds, combining structured clinical classification with inflammatory and hematological markers offers a more comprehensive assessment of early disease trajectory.

Dengue infection is characterized by complex and dynamic hematological and inflammatory changes driven by viral replication, immune activation, cytokine release, and endothelial dysfunction.^{1–3} Thrombocytopenia remains a central laboratory feature and reflects contributions

from bone marrow suppression, immune-mediated platelet destruction, and peripheral consumption secondary to endothelial activation and systemic inflammation.^{4,5} Severe thrombocytopenia has consistently been associated with increased risk of bleeding, plasma leakage, organ dysfunction, and mortality.^{6–8} In the present multivariable analysis, the adjusted odds ratio for admission platelet count crossed unity, indicating that platelet count did not function as an independent prognostic factor after adjustment for WHO classification. This attenuation is biologically plausible because WHO classification partially captures information related to thrombocytopenia severity and evolving

clinical instability, thereby reducing the apparent independent contribution of platelet count in the multivariable model. Platelet count nevertheless retains clinical relevance as a continuous quantitative marker of disease severity and may provide incremental prognostic information when interpreted alongside structured clinical classification and inflammatory markers rather than as an isolated predictor. Its clinical utility may therefore lie more in quantifying thrombocytopenia severity within WHO categories than functioning as a stand-alone prognostic marker.

WHO dengue classification emerged as the dominant predictor of outcome, with a marked gradient in risk across severity categories. The WHO framework incorporates warning signs and evidence of plasma leakage, which reflect the underlying pathophysiology of increased vascular permeability and endothelial injury.^{4,16} Plasma leakage results from immune-mediated endothelial activation and disruption of endothelial junction integrity,¹⁷ processes central to progression from uncomplicated dengue to severe disease. The strong association between baseline WHO category and adverse outcomes in this model provides quantitative validation of its clinical utility and supports its continued application as a triage tool in hospital settings.

The very high adjusted odds ratio (aOR) for WHO classification (aOR >27) reflects near-complete separation between dengue without warning signs (DWOWS) and complicated outcomes, with 97% of uncomplicated cases classified as DWOWS at admission. This produces unstable maximum likelihood estimates with wide confidence intervals. Furthermore, a degree of definitional circularity exists: WHO classification incorporates warning signs and severity markers that overlap with the criteria defining the clinical course outcome. While the temporal separation—day 1 classification predicting subsequent course—partially mitigates this concern, the strength of the association is likely inflated by this incorporation bias and should be interpreted with caution.

The independent association between elevated NLR and worse clinical outcomes aligns with growing evidence that systemic inflammatory activation plays a critical role in dengue pathogenesis.^{13,14} NLR reflects the balance between innate immune activation and adaptive immune response, and elevated values may indicate heightened inflammatory stress and endothelial injury. Importantly, unlike specialized laboratory markers such as IPF, which require advanced hematology analyzers with optical fluorescence capability, NLR is

derived from the routine complete blood count, making it inexpensive, rapidly obtainable, and universally available even in resource-limited settings where dengue burden is highest. In the present model, inflammatory burden at admission contributed prognostic information beyond structured clinical classification, suggesting that NLR captures a dimension of dengue pathophysiology not fully reflected by platelet count or WHO classification alone. Its integration into prognostic assessment may therefore enhance early identification of patients at higher risk of deterioration while remaining practical for widespread bedside implementation and resource-constrained triage settings.

Notably, 38% of patients in our cohort presented with zero WHO warning signs at admission. That a subset of patients who subsequently developed complications lacked classical warning signs at presentation underscores a critical limitation of the current WHO triage framework: it may provide false reassurance in patients who appear uncomplicated at admission but are destined to deteriorate. This finding reinforces the value of laboratory-based predictors (platelet count, NLR) that may identify at-risk patients independently of clinical warning signs. The ordinal model's incorporation of both clinical (WHO classification, warning sign count) and laboratory (platelet count, NLR) predictors addresses this gap by enabling risk stratification even in the absence of overt warning signs. Clinically, this argues for maintaining vigilant monitoring of all dengue patients during the critical phase (days 3–5), regardless of warning sign status at presentation.

The model demonstrated good discrimination after bootstrap internal validation, suggesting stability and limited optimism in predictive performance. Importantly, the modeling strategy was prespecified, parameter budgeting was respected, and internal validation was undertaken using resampling techniques, which reduces the risk of overfitting. Multivariable modeling allows estimation of cumulative risk rather than reliance on binary thresholds, thereby enabling a more nuanced and clinically applicable assessment of severity at admission. In outbreak situations or high-burden settings, structured risk estimation may assist clinicians in prioritizing monitoring intensity, anticipating potential deterioration, and allocating high-dependency resources more efficiently.

Several limitations warrant consideration. The retrospective single-center design may limit generalizability, as practice patterns, admission thresholds, and case mix may differ across institutions and regions. Inclusion

of only hospitalized adult patients restricts extrapolation to outpatient, pediatric, or nonendemic populations. Although internal validation was performed using bootstrap resampling, external validation in independent cohorts is essential before routine clinical implementation. Additionally, residual confounding cannot be excluded, and unmeasured variables may have influenced risk estimates. Nevertheless, the large consecutive cohort and complete outcome ascertainment strengthen the internal validity of the findings.

Taken together, these results provide internally validated evidence that admission clinical classification and inflammatory markers, interpreted alongside platelet count, can be operationalized into a structured prognostic model for dengue severity, supporting more consistent and evidence-informed risk stratification in hospitalized patients.

CONCLUSION

A multivariable prognostic model incorporating WHO dengue classification, platelet count, NLR, and warning signs enables early prediction of disease severity in hospitalized adults with dengue. Integration of routinely available admission parameters into a validated risk framework may support structured triage decisions, guide monitoring intensity, and improve allocation of healthcare resources during dengue outbreaks. While internal validation demonstrates stable predictive performance, external validation across diverse healthcare settings and populations is required before widespread clinical adoption. Future prospective studies should evaluate the clinical impact of model-guided risk stratification on patient outcomes and healthcare resource utilization.

ETHICAL APPROVAL

The study was approved by the Institutional Ethics Committee of the participating tertiary care hospital. Given the retrospective design and use of anonymized hospital records, the requirement for informed consent was waived.

DATA AVAILABILITY

De-identified data underlying the findings are available from the corresponding author upon reasonable request, subject to institutional regulations.

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