Early diagnostic indicators of dengue versus other febrile illnesses in Asia and Latin America (IDAMS study): a multicentre, prospective, observational study

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Summary

Background Improvements in the early diagnosis of dengue are urgently needed, especially in resource-limited settings where the distinction between dengue and other febrile illnesses is crucial for patient management.

Methods In this prospective, observational study (IDAMS), we included patients aged 5 years and older with undifferentiated fever at presentation from 26 outpatient facilities in eight countries (Bangladesh, Brazil, Cambodia, El Salvador, Indonesia, Malaysia, Venezuela, and Viet Nam). We used multivariable logistic regression to investigate the association between clinical symptoms and laboratory tests with dengue versus other febrile illnesses between day 2 and day 5 after onset of fever (ie, illness days). We built a set of candidate regression models including clinical and laboratory variables to reflect the need of a comprehensive versus parsimonious approach. We assessed performance of these models via standard measures of diagnostic values.

Findings Between Oct 18, 2011, and Aug 4, 2016, we recruited 7428 patients, of whom 2694 (36%) were diagnosed with laboratory-confirmed dengue and 2495 (34%) with (non-dengue) other febrile illnesses and met inclusion criteria, and were included in the analysis. 2703 (52%) of 5189 included patients were younger than 15 years, 2486 (48%) were aged 15 years or older, 2179 (42%) were female and 3010 (58%) were male. Platelet count, white blood cell count, and the change in these variables from the previous day of illness had a strong association with dengue. Cough and rhinitis had strong associations with other febrile illnesses, whereas bleeding, anorexia, and skin flush were generally associated with dengue. Model performance increased between day 2 and 5 of illness. The comprehensive model (18 clinical and laboratory predictors) had sensitivities of 0·80 to 0·87 and specificities of 0·80 to 0·91, whereas the parsimonious model (eight clinical and laboratory predictors) had sensitivities of 0·80 to 0·88 and specificities of 0·81 to 0·89. A model that includes laboratory markers that are easy to measure (eg, platelet count or white blood cell count) outperformed the models based on clinical variables only.

Interpretation Our results confirm the important role of platelet and white blood cell counts in diagnosing dengue, and the importance of serial measurements over subsequent days. We successfully quantified the performance of clinical and laboratory markers covering the early period of dengue. Resulting algorithms performed better than published schemes for distinction of dengue from other febrile illnesses, and take into account the dynamic changes over time. Our results provide crucial information needed for the update of guidelines, including the Integrated Management of Childhood Illness handbook.

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Introduction

Dengue viruses are the most common arboviral pathogens that affect humans.[1] Half of the world's population lives in an area at risk of dengue,[2] resulting in 390 million infections per year, of which only approximately 25% are clinically apparent.[3] Over the past few years, the clinical overlap of dengue and COVID-19 and the effect of the COVID-19 pandemic efforts have presented additional challenges for diagnosis and control of dengue.[4–8]

Clinical manifestations of dengue vary from uncomplicated febrile illness to severe and potentially life-threatening disease. Clinical management relies on close monitoring and careful intravenous fluid treatment.[9,10] During the early phase of illness, laboratory diagnosis is based on detection of viral antigens using

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For the Spanish translation of the abstract see **Online** for appendix 5

For the Vietnamese translation of the abstract see **Online** for appendix 6

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Research in context

Evidence before this study

We searched PubMed for studies published between database inception and Dec 31, 2021, using the terms "dengue AND (diagnosis OR diagnostic) AND (algorithm OR model OR marker OR indicator OR feature OR classifier OR predictor OR predictive OR distinguish) AND (sensitivity OR sensitivities OR specificity OR specificities OR area under the curve OR area under the ROC) AND (early OR acute OR febrile)". The search was limited to Title and Abstract and no language restrictions were applied. The search resulted in 140 publications, of which 38 were considered in full text as they focused on the differentiation between dengue and other febrile illness. Of the 38 studies, the majority were based on fairly small samples and restricted to one geographical area. Available algorithms that differentiate between dengue and other febrile illness are usually based on single measurements of either clinical symptoms alone or in combination with simple laboratory tests. Eight of the 38 considered studies also examined novel biomarkers in addition to the traditional laboratory tests.

Added value of this study

This study was run across eight countries covering two major geographical regions: southeast Asia and Latin America. We included a sufficiently large number of patients to allow for the analysis of a broad range of candidate variables to be associated with dengue versus other febrile illnesses. Because of the daily follow-up, our analysis provides increased granularity compared with previous efforts, and we were able to assess the change in white blood cell and platelet counts between subsequent days.

Implications of all the available evidence

The resulting diagnostic models perform better than currently published schemes for distinction of dengue versus other febrile illness. The distinction became more accurate over time, between day 2 and 5 after symptom onset. Classic so-called warning signs for severe dengue, such as persistent vomiting or abdominal pain or tenderness, were either too infrequent or not useful for distinguishing dengue from other febrile illness. We anticipate that the results of our study will be of practical use in endemic settings when translated into locally validated algorithms, resulting in both improved case management and use of limited resources.

PCR or NS1 antigen tests.[11,12] Anti-dengue virus antibodies can usually be detected 3–5 days (IgM) or 7 days (IgG) after fever onset, but cross-reactivity between members of the genus *Flavivirus* must be considered.[12,13]

Unfortunately, confirmatory laboratory diagnostic tools are often not available in dengue-endemic settings. Rapid diagnostic tests, if available, have shown mixed performance, including low sensitivity.[14,15] Without a formal diagnosis, patient management can be adversely affected and the public health response to dengue outbreaks can be compromised.

Reliance on clinical diagnosis alone is widespread throughout dengue endemic countries, despite similarities in clinical symptoms between dengue and many other febrile illnesses. Available algorithms that differentiate between dengue and other febrile illnesses are mostly based on single measurements of either clinical symptoms alone or in combination with simple laboratory tests.[16] The most frequently cited clinical features used in these algorithms include vomiting[16,17] and myalgia,[18] and the laboratory tests almost invariably include platelet and white blood cell counts,[19] sometimes also including hepatic enzymes such as aspartate aminotransferase and alanine aminotransferase concentrations[20] or biomarkers such as albumin, fibrinogen, or thrombin time.[21] Sensitivity and specificity of these algorithms range from 75%[16] to 85%.[22] Additionally, most previous diagnostic studies have been based on quite small samples and restricted to one geographical area.

We aimed to conduct a multicentre, prospective, observational study as part of the EU's Seventh Framework Programme funded International Research Consortium on Dengue Risk Assessment, Management, and Surveillance (IDAMS) consortium, designed to provide improved algorithms to differentiate between dengue and other febrile illnesses during the early febrile phase using readily available clinical and laboratory parameters. Prognostic indicators, including warning signs and symptoms as risk factors for severe dengue, will be addressed in a separate analysis.

Methods

Study design and participants

We performed a multicentre, prospective, observational study and used the data to design several models that could be used to delineate between dengue and other febrile illness, the design of which has been provided elsewhere.[23] Briefly, we recruited patients aged 5 years or older who presented at 26 outpatient facilities in eight countries across Asia and Latin America (Bangladesh, Cambodia, Indonesia, Malaysia, Viet Nam, Brazil, El Salvador, and Venezuela) with an undifferentiated febrile illness consistent with dengue within the first 72 h of fever onset (for the analysis, this criterion was relaxed to 84 h [3·5 days] as, in practice, enrolment of patients was adjusted to the working day). Presence of fever was defined by at least one of the following criteria: body temperature at enrolment of greater than 37·5°C, self-reported fever at enrolment and antipyretic intake within

24 h before enrolment, or measured body temperature of greater than 37·5°C or self-reported persisting fever on the day after enrolment. The day of illness at enrolment was defined on the basis of hours since onset of fever, with day 1 of illness defined as being enrolled within 24 h of fever onset, day 2 of illness defined as being enrolled within 25–48 h of fever onset, and day 3 of illness defined as being enrolled within 49–84 h of fever onset.

Written informed consent was obtained from all study participants. Ethical approval was obtained from the Oxford Tropical Research Ethics Committee (reference 40-11) and the Institutional Review Boards of the Medical Faculty of Heidelberg University Hospital (S445/2011) and of all participating clinical sites.[23]

Procedures

After enrolment, study participants were followed up daily for up to 6 days (acute illness visits) using the same standardised protocol and structured case report forms at each site. The day of illness for each follow-up visit was determined on the basis of the day of illness at enrolment plus the difference in days between the date of the follow-up visit and the date of enrolment. A convalescent visit was scheduled at least 7 days after the last acute illness visit (usually day 10–14 of illness). Dengue was diagnosed using a prespecified diagnostic algorithm (appendix 7 p 5) that included the categories "laboratory-confirmed dengue", "acute flavivirus infection", "recent flavivirus infection", and confirmed "not dengue". Blood samples for diagnostics (EDTA plasma) were collected at enrolment, last acute visit, and convalescent visit. Testing was carried out locally for serology (Platelia NS1, Biorad; IgM and IgG Capture ELISA Kits, Panbio, Australia) and partially centralised for molecular testing (PCR).[23] Blood samples that were antibody negative and that did not fulfil the strict criteria for not dengue were classified as inconclusive. For the current analysis, we only included data from participants who could be classified as either laboratory-confirmed dengue or not dengue.

Statistical analysis

The primary outcome was the occurrence of confirmed dengue virus infection versus other febrile illness. For the analysis of the primary outcome, we considered 30 candidate variables for the full model (appendix 7 pp 3–4, 6–14). This initial list of variables reflects standard clinical investigations and laboratory tests commonly available in small hospital settings, established warning signs and symptoms for severe dengue (eg, mucosal bleeding and abdominal pain or tenderness),[24,25] and continent, because of the variability in the diagnosis of dengue versus other febrile illnesses by geographical location (appendix 7 pp 15–16).

We split the patient data into five datasets on the basis of the day of illness at each study visit. The illness day 1 dataset was not considered for this analysis because of the relatively low number of study participants who had a study visit on illness day 1. We performed multivariable logistic regression analyses on each of the four datasets (ie, from illness day 2 to 5). For each day of illness dataset, a complete case regression analysis was performed excluding visits from patients with missing values in any of the candidate variables. Regression coefficients are presented as odds ratios (ORs) with 95% CIs. Additionally, the 99% CIs are shown in the OR plots. To assess whether the association between each candidate predictor and the probability of dengue virus infection varied in different subgroups, we did heterogeneity assessments across countries, age groups, and sex (appendix 7 pp 17–20). To allow for variation in the probability of dengue versus other febrile illnesses by continent, age, and sex, we added two-way interactions with all other variables to the full model. Additionally, on the basis of a linearity assessment (appendix 7 p 21), we included non-linear terms for age, body temperature, systolic blood pressure, haematocrit, platelet count, white blood cell count ($\log_{10}$ scale), and percentage lymphocytes in the full model.

Starting with the full model, we selected potential predictors via bootstrap stepwise backward variable selection (using function fastbw of the rms package),[26] which we did separately for each of the illness day datasets 2–5 (appendix 7 p 27). For each of the illness day datasets we drew 500 samples with replacement with the same size as the original complete case dataset. We selected the variables, non-linear terms, and interaction terms that had a frequency of selection across the 500 samples above a specific threshold (the stability threshold) on at least one of the illness days. The range of stability thresholds considered was from 40% to 95%, such that with increasing threshold value the number of included variables and terms decreased. Here, we present the models based on variables selected using the stability thresholds of 40% and 95%. For the model based on the stability threshold of 40%, we defined this as the clinical and laboratory comprehensive model including interaction terms (model 1). The comprehensive model was also assessed without interaction terms (model 2; appendix 7 p 27). The model based on the stability threshold of 95%, defined as the clinical and laboratory parsimonious model (model 3), had fewer variables included and so was less complex and easier to communicate and compare with models reported in the literature than is the comprehensive model. None of the parsimonious models included interaction terms.

We also assessed models based on clinical variables only, referred to as the clinical comprehensive model including interaction terms (model 4), the clinical comprehensive model without interaction terms (model 5), and the clinical parsimonious model (model 6). Furthermore, we considered models that included a change value for the laboratory variables of platelet count, white blood cell count, percentage lymphocytes, and haematocrit. We calculated the change value as the difference between the current value and the value on the previous illness day

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See **Online** for appendix 7

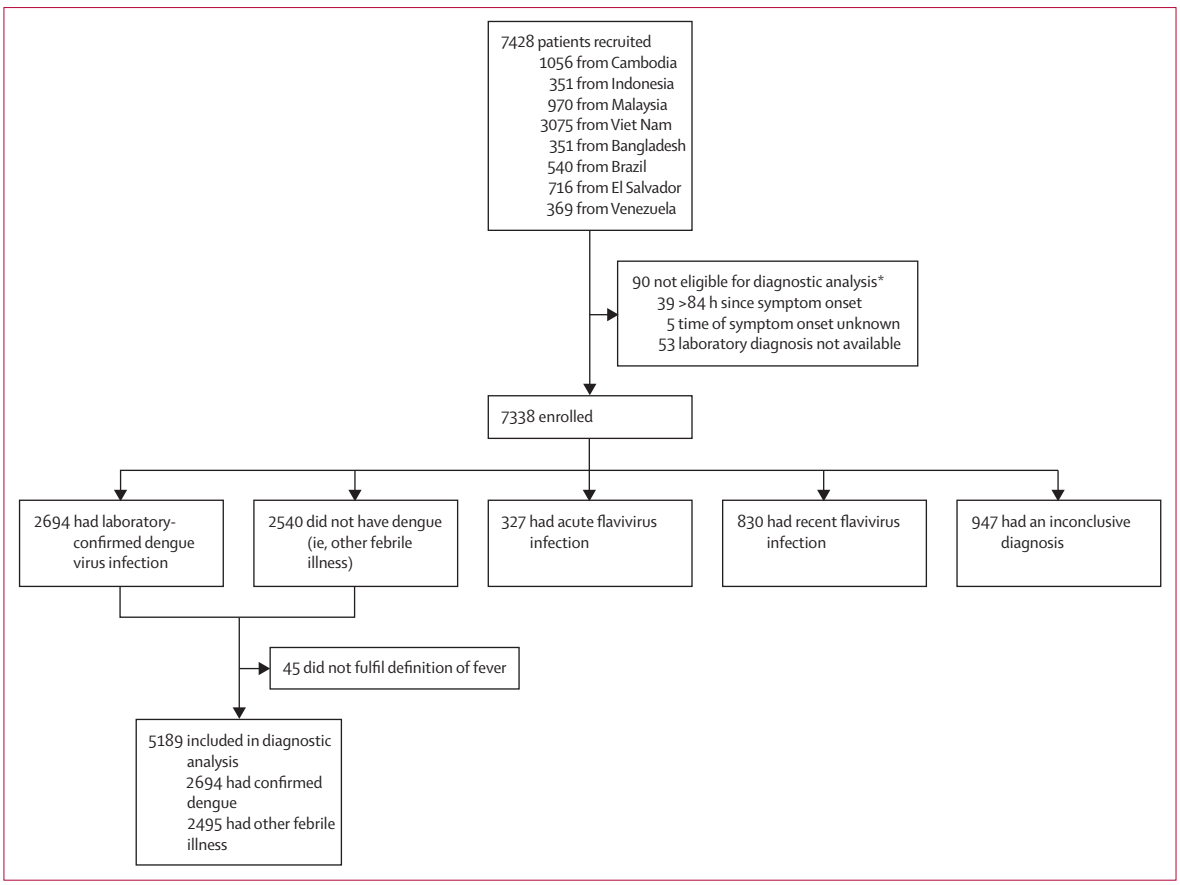

Figure 1: **Study profile**
2104 patients with acute (n=327) or recent (n=830) flavivirus infection or inconclusive laboratory results (n=947) were not included in the analysis because they were neither diagnosed with dengue nor could they be confirmed as not being infected with dengue virus. Of the 5189 patients, 15 confirmed with dengue had only a single study visit on day 1 of illness and were therefore not considered in the regression analyses based on the day 2–5 illness datasets. *Seven patients met more than one criterion, such that the numbers for each reason equate to more than 90.

(appendix 7 p 27). Because the distribution of the change values was skewed for platelet count and white blood cell count, we calculated them on the $\log_{10}$ scale. We modelled all change values as linear terms. We refer to the resulting models as the clinical and laboratory comprehensive change model without interaction terms (model 7) and the clinical and laboratory parsimonious change model (model 8). A summary of our model selection procedures is shown in the appendix 7 (p 28).

We compared the clinical and laboratory parsimonious change model (model 8) with two other compact models described in the scientific literature: the case definition of dengue according to the WHO 2009 guideline[24] (probable dengue plus warning signs model, comprising ten predictors plus one interaction term; appendix 7 p 30) and the algorithm published by Tuan and colleagues[16] (the Tuan model, comprising three predictors; appendix 7 p 30).

We assessed the performance of each model on the illness day 2, 3, 4, and 5 datasets via the area under the receiver operating characteristic curve (AUC), the scaled Brier score,[27] calibration-in-the-large (ie, comparing mean observed with mean predicted outcome), and calibration slope.[28] In addition, sensitivity and specificity of the comprehensive models without interaction terms (models 2 and 5) and the parsimonious models (models 3 and 6) are presented for two scenarios. In scenario 1, the cutoff value was selected such that the resulting point on the receiver operating characteristic curve was closest to the upper left corder, where both sensitivity and specificity are equal to 1. In scenario 2, either sensitivity or specificity was prespecified at 95% and the corresponding specificity or sensitivity was calculated. We used a bootstrap approach to correct the performance indices for over-optimism, as described by Harrell[29] (appendix 7 p 29).

Because children from Asia (ie, aged <15 years) constituted a large proportion of our study population, we repeated the model selection procedure in this subgroup and compared results with the whole study population. Due to the smaller sample size, we restricted our variable selection to illness day 2, 3, and 4 datasets. We could not do a separate analysis in children from Latin America because they comprised a much smaller proportion of our study population.

We did all analyses using Stata (release 13.1 and 15.1, Stata Corporation, College Station, TX, USA) and R (version 3.6.3 and 4.1.2, R Core Team, R Foundation for Statistical Computing, Vienna, Austria).

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to publish.

Results

Between Oct 18, 2011, and Aug 4, 2016, 7428 patients were recruited at 26 sites in eight countries across Asia (5803 [78%]) and Latin America (1625 [22%]), of whom 7338 (99%) were enrolled within 84 h of fever onset and had a laboratory diagnosis available (figure 1). Dengue virus infection was confirmed in 2694 patients, and 2540 were classified as having other febrile illness. The countries with the highest proportions of laboratory-confirmed dengue virus infection among all enrolled patients were Viet Nam and El Salvador, both above 40% of cases. Across all Asian sites, the proportion of confirmed cases of dengue amounted to approximately 40% of cases versus 30% in Latin America (appendix 7 p 16). 45 (2%) of 2450 patients with other febrile illnesses did not fulfil the definition of fever and so were excluded from the analysis, such that 5189 patients were included in the current analysis. 2703 (52%) were younger than 15 years, 2486 (48%) were aged 15 years or older, 2179 (42%) were female, and 3010 (58%) were male (table 1). Data on race and ethnicity were not collected. The distribution of the covariables in the two groups (other febrile illnesses *vs* dengue) and the univariable and full multivariable regression results by day of illness are presented in the appendix 7 (pp 36–43).

The typical signs and symptoms over day 1 to 5 of illness among patients with confirmed dengue and with other febrile illnesses are shown in figure 2. The clinical and laboratory comprehensive model including interaction terms (model 1) comprised 17 predictors and five interaction terms, and the clinical and laboratory parsimonious model (model 3) included eight predictors without any interaction terms (appendix 7 pp 32, 44–51). Both these models showed very good diagnostic performance, with optimism-corrected AUCs ranging from 0·874 to 0·948 and from 0·877 to 0·948, respectively. Scaled Brier scores ranged from 41·8% to 64·2% and from 43·3% to 63·6%, respectively (appendix 7 pp 32, 44–51). The models generated using different thresholds showed only slight variation in diagnostic performance, whereas the performance of the models improved over time from day 2 to 5 of illness (appendix 7 pp 32, 34).

The clinical comprehensive model including interaction terms (model 4) consisted of 23 predictors and 15 interactions. With a stability threshold of 95%, the complexity of the model was reduced to ten predictors and no interaction terms in the clinical parsimonious model (model 6; appendix 7 pp 33, 52–59).

Optimism-corrected model performance was minimally improved by omitting interaction terms from the comprehensive model (appendix 7 pp 44–51). The AUC of the clinical and laboratory comprehensive model including interaction terms (model 1) changed from 0·914 to 0·919 on day 3 of illness by omitting the interaction terms (model 2), with an average increase of 0·0045 across illness days 2 to 5.

For the change models, we considered daily changes of full blood count parameters (eg, platelet and white blood cell counts) over days 2 to 5 of illness. We observed several patterns in the clinical and laboratory comprehensive change model (model 7) and the parsimonious change model (model 8; figure 3). In the clinical and laboratory comprehensive change model (model 7), presence of cough and rhinitis showed a strong positive association

	Overall (N=5189*)	Confirmed dengue (n=2694)	Other febrile illness (n=2495)
Age, years	14 (8–25)	14 (9–24)	13 (8–26)
<15	2703 (52%)	1353 (50%)	1350 (54%)
≥15	2486 (48%)	1341 (50%)	1145 (46%)
Sex			
Female	2179 (42%)	1128 (42%)	1051 (42%)
Male	3010 (58%)	1566 (58%)	1444 (58%)
Country			
Viet Nam	2587 (50%)	1505 (56%)	1082 (43%)
Cambodia	758 (15%)	302 (11%)	456 (18%)
Indonesia	155 (3%)	92 (3%)	63 (3%)
Malaysia	596 (11%)	259 (10%)	337 (14%)
Bangladesh	229 (4%)	80 (3%)	149 (6%)
Brazil	215 (4%)	111 (4%)	104 (4%)
El Salvador	526 (10%)	306 (11%)	220 (9%)
Venezuela	123 (2%)	39 (1%)	84 (3%)
Year of enrolment			
2011	223 (4%)	122 (5%)	101 (4%)
2012	872 (17%)	535 (20%)	337 (14%)
2013	1065 (21%)	627 (23%)	438 (18%)
2014	1596 (31%)	644 (24%)	952 (38%)
2015	1401 (27%)	765 (28%)	636 (25%)
2016	32 (1%)	1 (<1%)	31 (1%)
Day of illness at enrolment			
Day 1	1168 (23%)	508 (19%)	660 (26%)
Day 2	2209 (43%)	1095 (41%)	1114 (45%)
Day 3	1812 (35%)	1091 (40%)	721 (29%)

Data are median (IQR) or n (%). Summary statistics of laboratory parameters stratified by day of illness are given in the appendix (pp 36–43). *Of the 5189 patients, 15 confirmed dengue cases had only a single study visit on day of illness 1 and were therefore not considered in the regression analyses based on the illness day 2–5 datasets.

Table 1: **Demographic and enrolment characteristics of participants, stratified by diagnosis**

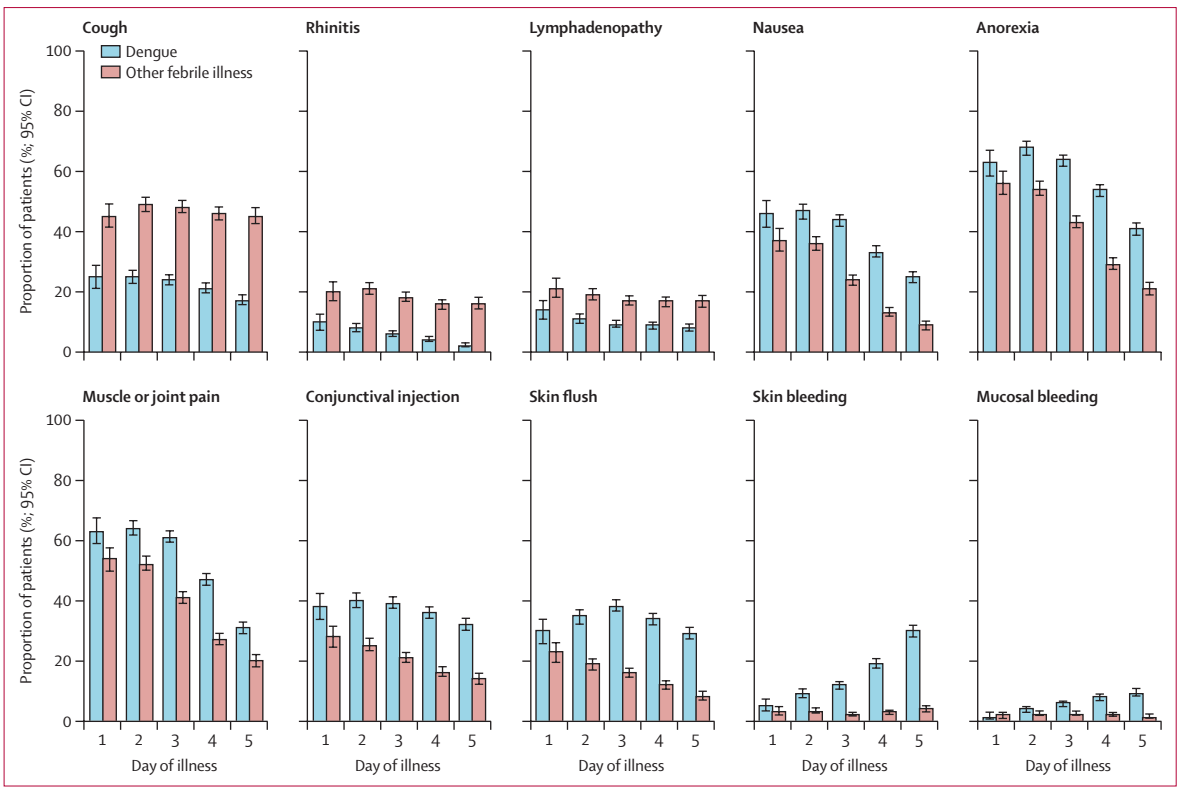

Figure 2: **Presence of clinical signs and symptoms in patients diagnosed with dengue and other febrile illness, stratified by day of illness (variables based on the clinical and laboratory comprehensive model)**
Data are proportion of patients within each day of illness dataset with error bars showing 95% CIs.

with other febrile illnesses, whereas anorexia, skin flush, mucosal bleeding (which includes gum, nose, gastrointestinal, melaena, haematuria, and in women unusual vaginal bleeding), skin bleeding, and body temperature were mostly positively associated with dengue. Between illness day 2 and day 5, cough was present in 17–25% of patients with confirmed dengue, compared with 45–49% in the other febrile illnesses group (figure 2). Rhinitis was present in 2–8% of patients with dengue, decreasing over time, compared with around 16–21% of patients with other febrile illnesses (figure 2; appendix 7 pp 36–43). The strength of the association of cough with other febrile illness and skin flush with dengue became stronger with number of days of illness, whereas the strength of association between increased body temperature and dengue weakened after day 3 (figure 3A). Reduced platelet count was associated with dengue and the strength of this association increased over time between illness days 2 and 5. Similarly, reduced white blood cell count was strongly associated with dengue and did not change much across the illness days. The association of percentage lymphocytes changed over time: with higher percentage being associated with other febrile illnesses on day of illness 2 and 3, and then being associated with dengue on day of illness 4 and 5. A greater decrease in $\log_{10}$ platelet count from the previous illness day was associated with dengue, but the strength of the association became weaker over time. By contrast, a greater decrease in $\log_{10}$ white blood cell count from the previous day was associated with other febrile illnesses, and the association became stronger over time (figure 3). These complex time-dependent associations might be explained by the fact that patients with dengue started with a lower white blood cell count at day 2 of illness with smaller subsequent decreases than did those with other febrile illnesses (appendix 7 pp 24, 36–43).

Details of the time-dependent non-linear association between body temperature, platelet count, and white blood cell count versus the probability of dengue are shown in the appendix 7 (pp 22–26).

For the clinical and laboratory comprehensive model without interaction terms (model 2), sensitivity ranged from 0·802 to 0·869 and specificity ranged from 0·803 to 0·907, increasing from illness day 2 to illness day 5 when optimising both sensitivity and specificity (scenario 1; table 2). Sensitivity ranged from 0·487 to 0·766 and specificity ranged from 0·518 to 0·756, when either sensitivity or specificity was fixed at 95% (scenario 2; table 2).

Models that included both laboratory predictors and clinical predictors performed better than models with clinical predictors only (table 2). The comprehensive

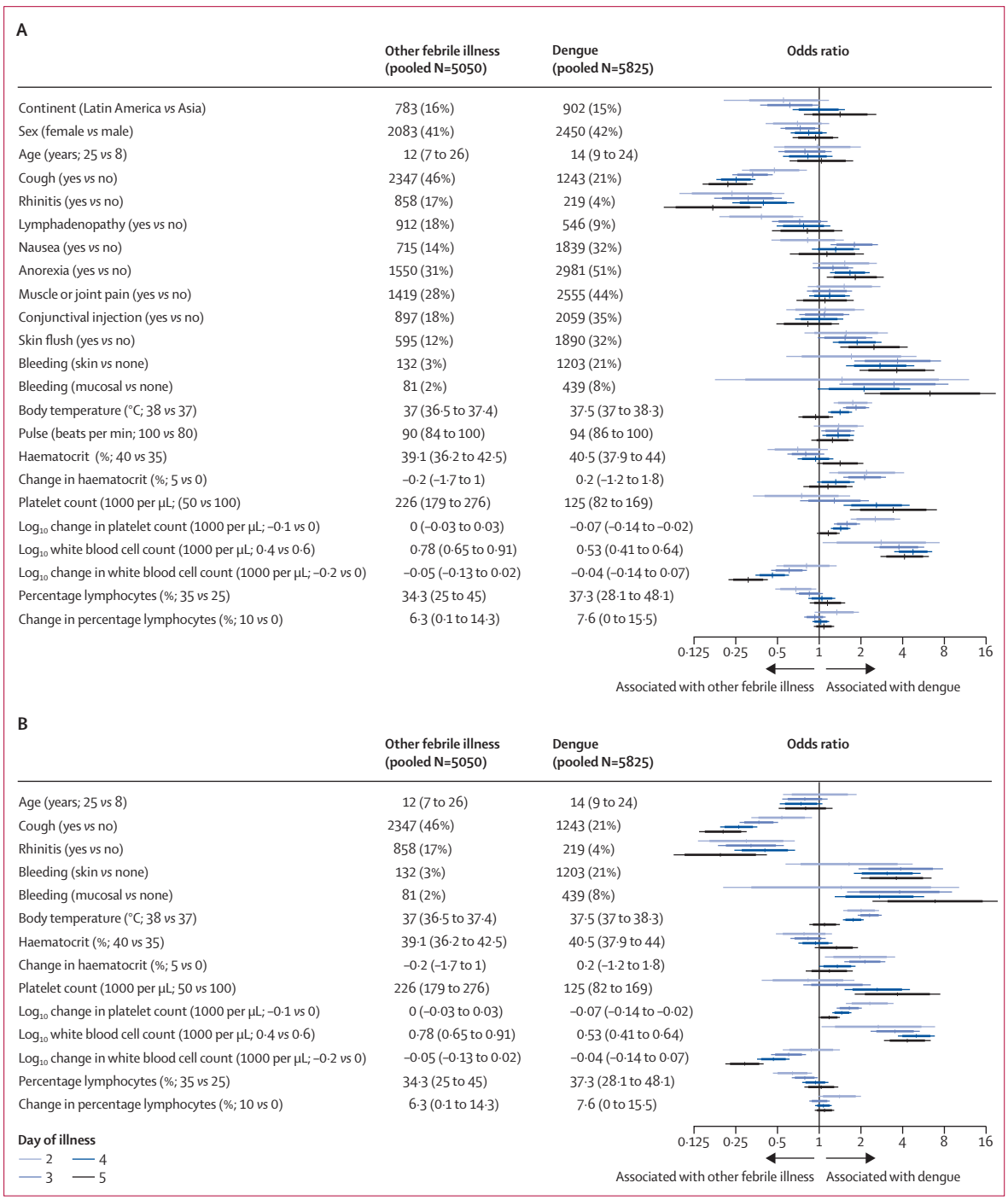

Figure 3: **Odds ratio for predictors, comparing patients with dengue to those with other febrile illness, determined using the clinical and laboratory comprehensive change model without interaction terms [model 7] (A) and the clinical and laboratory parsimonious change model [model 8] (B), for days 2–5 of illness**

Datapoints are odds ratios, with the thick horizontal line indicating the 95% CI, and the thin line representing the 99% CI. The odds ratio corresponds to the unit change displayed along with the variable name. For example, the odds ratio for platelet count correspond to a platelet count of 50 000 per µL compared with 100 000 per µL or, in other words, to a decrease in platelet count from 100 000 to 50 000 per µL. Data to the left of the plot shows n (%) for categorical variables and median (IQR) for continuous variables, based on the pooled dataset of illness day 2 to 5. Change in a variable indicates change in that variable from the previous illness day. Estimates are based on observations without missing values in any of the candidate predictors and change variables on the respective day of illness.

	Day 2 of illness (n=3128)	Day 3 of illness (n=4687)	Day 4 of illness (n=4129)	Day 5 of illness (n=3167)
Scenario 1				
Clinical and laboratory comprehensive model without interaction terms (model 2)				
Sensitivity	0·802	0·848	0·855	0·869
Specificity	0·803	0·844	0·881	0·907
AUC	0·881	0·919	0·937	0·951
Scaled Brier score	0·440	0·549	0·608	0·652
Clinical and laboratory parsimonious model (model 3)				
Sensitivity	0·795	0·844	0·857	0·875
Specificity	0·808	0·838	0·880	0·888
AUC	0·877	0·915	0·934	0·948
Scaled Brier score	0·433	0·538	0·598	0·636
Clinical comprehensive model without interaction terms (model 5)				
Sensitivity	0·719	0·731	0·758	0·772
Specificity	0·684	0·732	0·778	0·797
AUC	0·763	0·806	0·842	0·865
Scaled Brier score	0·206	0·280	0·350	0·391
Clinical parsimonious model (model 6)				
Sensitivity	0·716	0·694	0·755	0·776
Specificity	0·664	0·754	0·761	0·777
AUC	0·748	0·795	0·832	0·857
Scaled Brier score	0·183	0·260	0·329	0·372
Scenario 2				
Clinical and laboratory comprehensive model without interaction terms (model 2)				
Sensitivity	0·487	0·622	0·745	0·766
Specificity	0·518	0·626	0·662	0·756
AUC	0·881	0·919	0·937	0·951
Scaled Brier score	0·440	0·549	0·608	0·652
Clinical and laboratory parsimonious model (model 3)				
Sensitivity	0·476	0·640	0·733	0·766
Specificity	0·520	0·623	0·633	0·741
AUC	0·877	0·915	0·934	0·948
Scaled Brier score	0·433	0·538	0·598	0·636
Clinical comprehensive model without interaction terms (model 5)				
Sensitivity	0·238	0·338	0·423	0·492
Specificity	0·268	0·342	0·373	0·456
AUC	0·763	0·806	0·842	0·865
Scaled Brier score	0·206	0·280	0·350	0·391
Clinical parsimonious model (model 6)				
Sensitivity	0·221	0·293	0·423	0·465
Specificity	0·256	0·326	0·369	0·432
AUC	0·748	0·795	0·832	0·857
Scaled Brier score	0·183	0·260	0·329	0·372

Scenario 1 refers to when the cutoff value was selected such that the resulting point on the receiver operating characteristic curve was closest to the upper-left corner, where both sensitivity and specificity are equal to one. Scenario 2 refers to when sensitivity is estimated at a cutoff value that yields a specificity of 95% and when specificity is estimated at a cutoff value that yields a sensitivity of 95%. n refers to the number of observations in each illness day dataset which had no missing values in any of the candidate predictors. AUC=area under the receiver operating characteristic curve.

***Table 2*: Optimism-corrected sensitivity, specificity, AUC, and scaled Brier score values of comprehensive (stability threshold of 40%) and parsimonious (stability threshold of 95%) models, fitted to illness days 2–5 datasets**

model based on clinical predictors only (model 5) had optimism-corrected AUC values between 0·763 and 0·865, whereas the inclusion of laboratory variables increased AUC values to between 0·881 and 0·951. The same pattern could be seen in the parsimonious models (models 3 and 6). An improvement from illness day 2 to 5 was observed for AUC values and scaled Brier scores in all models (table 2). The calibration slope curves show that on day 2 of illness (with smaller sample size), model calibration was slightly worse and yielded predictions that were usually more extreme (appendix 7 p 35).

Comparing our clinical and laboratory parsimonious change model (model 8) with two published compact models,[16,24] we found that optimism-corrected model performance, as determined in our study population, was lowest with the probable dengue plus warning signs model (AUC range: 0·778–0·844, scaled Brier score range: 0·216–0·355), higher in the Tuan model (AUC: 0·836–0·918, scaled Brier score: 0·333–0·527), and highest in our clinical and laboratory parsimonious change model (AUC: 0·884–0·954, scaled Brier score: 0·456–0·665; figure 4).

When we restricted our analysis to the subgroup of children from Asia, the selected models for clinical and laboratory predictors and for clinical predictors only consisted of fewer variables due to the smaller sample size (appendix 7 pp 60–61). However, the association pattern of the covariates selected remained similar to that in the main analysis (appendix 7 pp 62–63). Model performance with optimism-corrected AUC values varied between 0·883 and 0·959 on illness days 2 to 5 for the clinical and laboratory comprehensive change model for children (model 7-CH) and between 0·763 and 0·881 for the clinical comprehensive model for children (model 5-CH), which is in the same range as the model performance in the whole dataset (appendix 7 p 64). The clinical and laboratory parsimonious model for children in Asia (model 3-CH) consisted of only three predictors: cough, platelet count, and white blood cell count (appendix 7 p 63). The performance of this model was still very good with optimism-corrected AUC values between 0·844 and 0·951 (appendix 7 p 60).

Discussion

We described the diagnostic performance of several models integrating a substantial number of clinical

signs and symptoms and laboratory variables of dengue virus infection and other febrile illness over the first 2–5 days of illness. Overall, the performance of each model measured with AUC, scaled Brier score, sensitivity, and specificity increased over time between day of illness 2 and 5, showing that the clinical and laboratory features of dengue become more distinct from other febrile illnesses as the disease progresses. The identified trends highlight the importance of the day of illness in clinical algorithms of dengue. Because of the daily follow-up, our analysis provides more granularity than previous efforts[16] and can help inform clinicians about the frequency of each clinical sign and symptom or the distribution of simple laboratory markers by day of illness, comparing dengue versus other febrile illness.

We built flexible statistical models, stratified by day of illness in the early phase of the disease, and included interaction terms to address heterogeneity. However, when we compared the fit of models with and without interaction terms, we found that omitting the interaction terms showed similar or even slightly improved performance. Therefore, in our Results, we focused on estimates obtained by the models without interaction terms, which facilitates interpretation and communication of the results. All selected models had good diagnostic performance with AUCs between 0·748 and 0·956.

Although the primary focus of our study was diagnosis, to help aid in the challenges encountered by clinicians in resource-limited health-care settings (eg, with restricted availability of simple laboratory parameters or repeated daily measurements), we also report the size of the associations we identified and their trends over time. For example, we found that the negative association of cough and the positive association of lower platelet count with dengue became stronger over time. We found the strength of association between body temperature and dengue to decrease from day 3 to 5, highlighting that this variable can potentially be useful to distinguish dengue from other febrile illness in the early phase of the illness, but might not be as useful from day 3 onwards. A lower absolute white blood cell and platelet

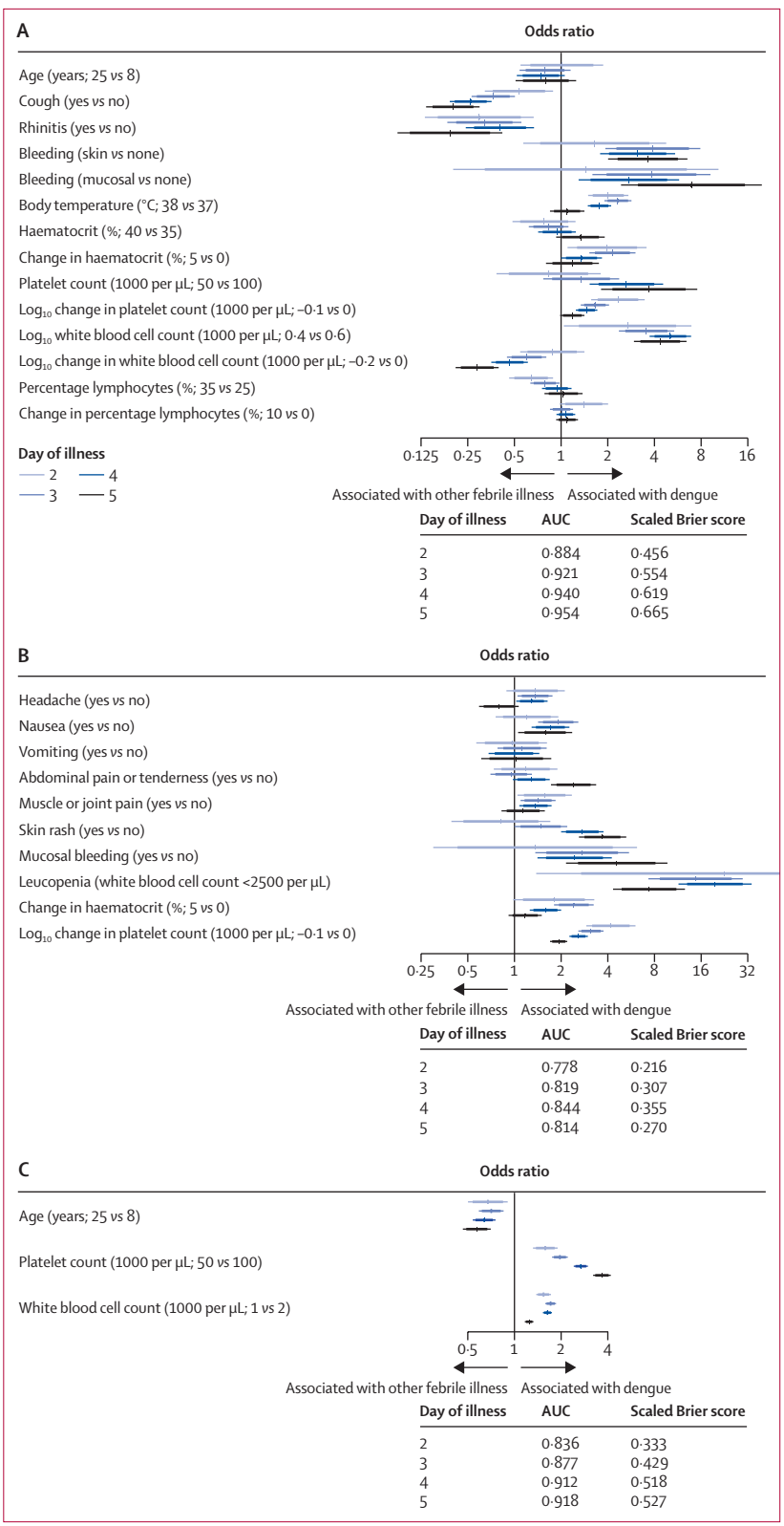

Figure 4: **Comparison of odds ratio estimates by day of illness and model performance (optimism-corrected area under the curve and scaled Brier score) between the clinical and laboratory parsimonious change model [model 8] (A), the probable dengue plus warning signs model (B), and the Tuan model (C)**

Datapoints are odds ratios, with the thick horizontal line indicating the 95% CI, and the thin line representing the 99% CI. The odds ratio corresponds to the unit change displayed along with the variable name. For example, the odds ratio for platelet count correspond to a platelet count of 50 000 per µL compared with 100 000 per µL or, in other words, to a decrease in platelet count from 100 000 to 50 000 per µL. Change in a variable indicates change in that variable from the previous illness day. Estimates of the three models are based on observations without missing values in any of the candidate predictors and change variables on the respective day of illness.

count on any day between day 2 and 5 of illness was associated with dengue. However, unlike platelet count, a greater decrease in white blood cell count between two subsequent days of illness was associated with other febrile illnesses, and the association was strongest on days 4 and 5.

We also assessed typical so-called warning signs and symptoms of severe dengue, such as mucosal bleeding or abdominal pain or tenderness, although these signs and symptoms are typically used to distinguish severe disease in confirmed cases of dengue rather than distinguishing dengue from other febrile illnesses. A considerable number of typical signs and symptoms, such as persistent vomiting, clinical fluid accumulation, lethargy or restlessness, and liver enlargement, occurred in fewer than 5% of our study population, and so we did not include them in the list of candidate variables for regression analysis. Abdominal pain or tenderness was only retained as a model term during variable selection when no laboratory variables were considered in the full model, showing that this symptom is not very useful for the distinction of dengue versus other febrile illnesses.

When we downsized the models to be more parsimonious, we realised that these models performed only slightly worse than the comprehensive models, while models based on clinical variables only performed notably worse than models based on the combined set of clinical and laboratory variables. The comprehensive models offer the potential to be further developed and included into diagnostic algorithms that could be made available on a handheld device (eg, a mobile phone). Algorithms that are intended to be used directly by clinicians or medical professionals need to be more parsimonious, consisting of a smaller number of variables. Available clinical algorithms that differentiate between dengue and other febrile illnesses[16,22] were not designed on the basis of detailed daily follow-up data of patients or are focused mainly on laboratory predictors.[16] However, in most settings, clinical assessments are almost always done and the inclusion of clinical predictors thus comes without any additional cost. The comparison of the diagnostic performance between the clinical and laboratory parsimonious change model (model 8), the adapted probable dengue plus warning signs model, and the Tuan model showed that, although the Tuan model performed well, the clinical and laboratory parsimonious change model had the highest AUC values, thus performed best with regard to the distinction of dengue versus other febrile illnesses.

Applying the modelling approach to the subgroup of children in Asia resulted in models with a smaller number of variables. However, the association pattern of the selected variables with the outcome remained similar. The parsimonious model for children in Asia (model 3-CH) consisted of two laboratory parameters (platelet count and white blood cell count) and only one clinical variable (cough), highlighting the importance of blood count parameters in this subgroup as well as in the total cohort. With the subanalysis of children in Asia, we aimed to provide much-needed evidence for modifications of the Integrated Management of Childhood Illness guidelines.[30] Local adaptations to the Integrated Management of Childhood Illness algorithms have been evaluated[31] and updated recommendations suggested to include an extension of the age range from 5 years to 15 years.[32]

Our study has several limitations. For instance, a group of patients who could not be reliably diagnosed as having dengue were omitted from the analysis (n=2104), which leads to a smaller sample size and potentially more uncertainty in the probabilities based on our diagnostic models. In addition, if the subgroup of patients who were excluded from the analysis have different characteristics, the performance of the diagnostic models might be worse for them. Additionally, the generalisability of our results is restricted because enrolment numbers differed between regions and countries, reflecting the local epidemiology and the mixture of institutions.

Using a large dataset with daily follow-up from a clinically well characterised prospective study population, we investigated 30 candidate predictors for their ability to distinguish confirmed dengue from other febrile illnesses. Daily full blood count data allowed us to assess the additional diagnostic value of variables that incorporate the change of laboratory results between subsequent days.

Our findings show that a set of 14 clinical and three laboratory predictors in the comprehensive model without interaction terms (model 2) can distinguish between dengue and other febrile illnesses during the early febrile phase of illness, with sensitivity 80–87% and specificity 80–91%. The distinction becomes more accurate over time between day 2 and 5 of illness. Most classic signs and symptoms of severe dengue were not useful for distinguishing dengue from other febrile illnesses. A model that includes laboratory markers that are easy to measure (eg, platelet count and white blood cell count) outperformed the models based on clinical variables only. However, in settings without access to laboratory assessments, the models based on only clinical variables might still be helpful. The granular description of clinical and laboratory features over time helps to inform clinicians in various settings.

Overall, the resulting algorithms performed better than published schemes for distinction of dengue from other febrile illnesses, and they include the dynamic changes over time. We anticipate that the results of our study will be of practical use in endemic settings when translated into locally validated algorithms, resulting both in improved case management and more appropriate use of limited resources.

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Contributors

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Declaration of interests

TJ reports personal fees from the Roche Severe Dengue Advisory Board, Takeda Pharmaceutical Company, Merck Pharmaceuticals, and Emergent Biosolutions, as a member of advisory boards, outside the submitted work. BAW reports personal fees from Takeda Pharmaceutical Company and from the Roche Severe Dengue Advisory Board, outside the submitted work. SY reports personal fees from Roche, outside the submitted work. All other authors declare no competing interests.

Data sharing

Data cannot be shared publicly due to patient confidentiality. The initial ethical approval of the study did not ask for permission to publicly share patients' study data. The dataset used to reach the conclusions in this Article will be made available upon request, for research that fits the remit of the initial study (eg, on the topic of dengue or other arboviruses). The two key objectives of the IDAMS study, the diagnostic characterisation of dengue versus other febrile illness (this Article) and prognostic indicators for severe dengue, both need to be published before the dataset can be made available.

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