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Scoring systems for prediction of malaria and dengue fever in non-endemic areas among travellers arriving from tropical and subtropical areas

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ABSTRACT

Background Fever is a common symptom among travellers returning from tropical/subtropical areas to Europe, and promptly distinguishing severe illnesses from self-limiting febrile syndromes is important but can be challenging due to non-specific clinical presentation.

Methods A cross-sectional study enrolled adults and children who sought care during 2015–2020 at Karolinska University Hospital, Stockholm, Sweden with fever within 2 months after returning from travel to a tropical/subtropical area. Data on symptoms and laboratory parameters were prospectively and retrospectively collected. Two separate scoring systems for malaria and dengue were developed based on backward elimination regressions.

Results In total, 2113 adults (18–94 years) and 202 children (1–17 years) were included, with 112 (4.8%) confirmed malaria by blood thick smear and 90 (3.9%) PCR/serology dengue-positive cases. Malaria was more likely in a patient who had visited sub-Saharan Africa and presented with combination of thrombocytopenia, anaemia and fever ≥39.5°C. Leucopenia, muscle pain and rash after travelling to Asia or South/Latin America indicated high probability of dengue. Two scoring systems with points between 0 and 7 for prediction of malaria or dengue were created based on the above predictors. Scores ≥3 indicated >80% sensitivity and specificity for malaria and >90% specificity for dengue in children and adults (area under the curve (AUC) for dengue: 0.92 in adults (95% CI 0.90 to 0.95) and 0.95 in children (95% CI 0.88 to 1.0); AUC for malaria: 0.93 in adults (95% CI 0.91 to 0.96) and 0.88 in children (95% CI 0.78 to 0.99)). Internal validation of optimism and overfitting was managed with bootstrap.

Conclusion The presented scoring systems provide novel tools for structured assessment of patients with tropical fever in a non-endemic area and highlight clinical signs associated with a potential severe aetiology to direct the need for microbial investigation.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Malaria and dengue are the most common imported tropical infections in both children and adults in non-endemic areas, where early clinical presentation is non-specific but can rapidly deteriorate to a severe disease requiring intensive care.

WHAT THIS STUDY ADDS

⇒ We have derived two new scoring systems by combinations of symptoms and rapidly available laboratory tests for the early detection of potential malaria and dengue cases. Our approach encourages further microbial testing, particularly in non-endemic settings where tropical infections are infrequent.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The scoring systems may help to make the correct diagnosis in returning travellers in the ED earlier. External validation is needed before the tools can be used in clinical practice.

INTRODUCTION

Travel to tropical destinations and migration from different parts of the world have increased over the past decade, leading to an increased risk of exposure to infections normally not present in the Northern hemisphere.[1–5] Tropical infections are often characterised by non-specific symptoms. As a result, the fever aetiology remains unclear in a large proportion of patients, with many diagnosed with a non-specific viral infection.[6–10] In general, fever is a common symptom in children attending the ED and other symptoms are often unspecific.[11–13] For the ED physician with limited experience of tropical infectious diseases, managing these patients could be challenging.

Malaria and dengue are two of the most common imported tropical infections in both children and adults. Early symptoms are similar to influenza or gastroenteritis, but rapid deterioration to severe disease can lead to multiorgan failure and death if diagnosis is delayed.[14–17] Migrants from sub-Saharan Africa or travellers visiting friends and relatives have an increased risk of tropical infections compared with tourists.[18] Studies have revealed that 10% of children succumb to severe and life-threatening malaria, primarily because of delayed diagnosis or inadequate treatment.[19] In a Swedish study of imported severe malaria cases, 20% were children <5 years who were at higher risk of developing severe malaria than adults.[17] Mortality of malaria is highest in regions where it is seldom managed, and studies suggest the need to raise awareness in settings where doctors are unfamiliar with the diagnosis.[20]

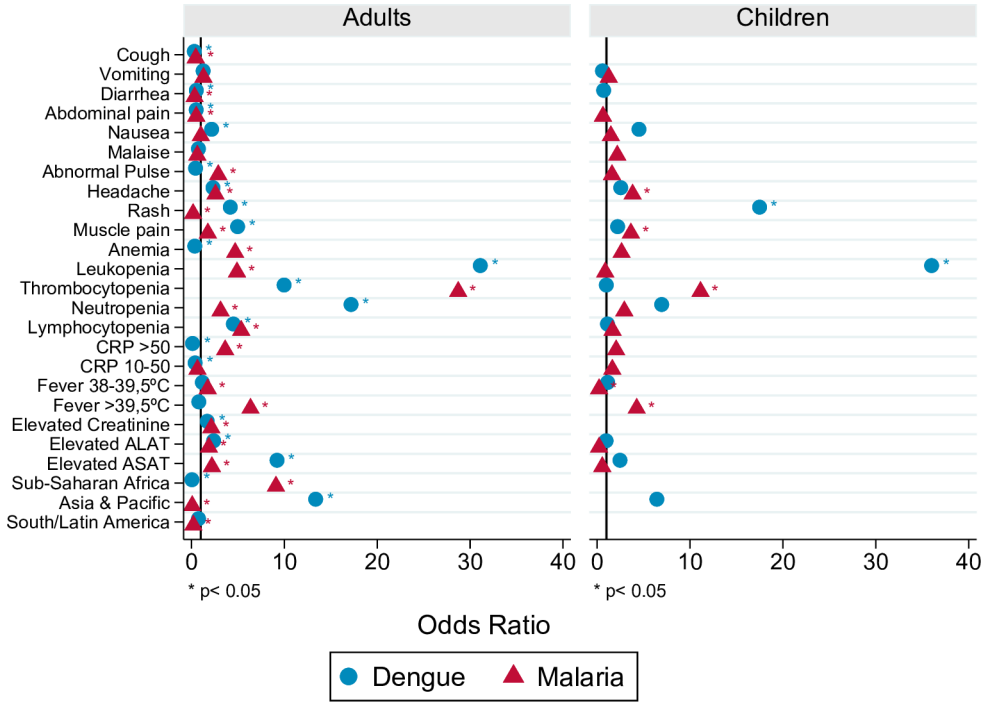

Figure 1 OR of predictors* for malaria and dengue in children and adults estimated by univariate logistic regression. Only the predictors that were statistically significant in any diagnosis and age group are presented (for the 95% CI, see online supplemental table 7). *Total 24 clinical predictors and 6 regions included: cough, vomiting, diarrhoea, abdominal pain, nausea, malaise, pulse, saturation, RR, headache, rash, muscle pain, urinary symptoms, confusion, anaemia, leucocytes, thrombocytes, neutrophils, lymphocytes, CRP, ASAT, ALAT, creatinine and fever measured at the ED. Regions: sub-Saharan Africa, Asia & Pacific, South/Latin America, Middle East/North Africa, South Europe, North America. ALAT, alanine aminotransferase; ASAT, aspartate transaminase; CRP, C reactive protein.

Dengue fever is widely spread throughout the tropical and subtropical regions of the world with 5.2 million cases reported in 2019, out of which 4363 were cases imported into Europe.[21] Dengue presents with a wide spectrum of influenza-like symptoms. Severe cases of dengue suffer from bleeding, organ failure and plasma leakage which can lead to death, predominantly in endemic areas, but has also been reported in travellers.[22]

There are multiple prediction tools to manage different diseases that appear at the ED but there are no specific guidelines except travel history to aid the ED physician in non-tropical areas on when to suspect a tropical disease.[23 24] In this study, we will explore if combinations of specific clinical predictors correlate with malaria or dengue and establish scoring systems to predict the need for a broader investigation of imported infections.

MATERIAL AND METHODS

Patient and public involvement

There was no involvement of patients and the public in this study.

Study design, study population and inclusion criteria

The study is a combined retrospective and prospective observational cross-sectional study. Prospective inclusion of adult patients started in 2017, and children were included from March 2019 to 2020. The retrospective collection of data included a review of medical records from patients assessed from January 2015 to February 2019 prior to the start of the prospective inclusion of patients. We did not perform a formal sample size calculation as we aimed to include all eligible patients. Patients were recruited at the paediatric and adult ED at Karolinska University Hospital Solna/Huddinge in Stockholm, Sweden. Patients included at the paediatric unit were between 1 and 17 years of age, and at the adult emergency unit, patients were ≥18 years. Inclusion criteria were a fever of ≥38.0°C, either measured at the initial examination or self-reported in the last 2 days, and return from a tropical or subtropical destination in the last 60 days.

Data collection

Patients who fulfilled the inclusion criteria at the ED visit were asked to participate. Inclusion occurred after informed consent in the prospective part of the study, whereby patients or their guardians filled in a questionnaire regarding travel details and symptoms. For patients <18 years, informed consent was obtained from caregivers, and children above 8 years were also given age-appropriate patient information. Data provided by the patient were supplemented with information from the medical records from the ED visit. The retrospectively included patients were not asked to give their informed consent. However, only relevant parts of the medical records were retrieved as per ethical permission. Patients included in the retrospective part of the study were identified by screening the ED ledger by cause of seeking care by medical students and infection specialists, and all missing variables were verified for completeness by the first and last authors. Review of medical records included data collection for travel destination (country), presenting symptoms, laboratory values, vital parameters and final diagnosis as determined within 30 days. The final diagnoses were then defined by confirmed positive microbiology findings within 30 days after the inclusion with both positive rapid test and blood thick smear for malaria and PCR or serology for dengue.

Table 1 Observed data on characteristics of the study population and diagnosis

	Adults (%)	Children (%)
Total number of patients	2113	202
Prospective inclusion	426 (20.2)	13 (6.4)
Retrospective inclusion	1687 (79.8)	189 (93.6)
Age		
1–3 years	–	77 (38.1)
4–6 years	–	44 (21.8)
7–12 years	–	51 (25.2)
13–17 years	–	30 (14.9)
18–30 years	695 (32.9)	–
31–45 years	665 (31.5)	–
46–65 years	568 (26.8)	–
≥65 years	182 (8.6)	–
Median age, years	40 (IQR 28–51)	5 (IQR 2–10)
Sex		
Female	1046 (49.5)	94 (46.5)
Region visited*		
Sub-Saharan Africa	769 (36.3)	90 (44.6)
Asia & Pacific	794 (37.5)	66 (32.7)
South/Latin America	187 (8.8)	10 (5.0)
South Europe (subtropical area)	62 (2.9)	8 (4.0)
Middle East/North Africa	233 (11.0)	27 (13.4)
North America (subtropical area)	13 (0.6)	1 (0.5)
Final diagnosis		
Malaria	100 (4.7)	12 (5.9)
Dengue	86 (4.0)	4 (1.9)
Influenza	149 (7.1)	9 (4.4)
Gastroenteritis clinical diagnosis†	209 (9.9)	26 (12.9)
Gastroenteritis confirmed aetiology‡	251 (11.9)	8 (3.9)
URTI	89 (4.2)	22 (10.9)
Pneumonia§	78 (3.7)	6 (2.9)
Pyelonephritis	23 (1.1)	3 (1.5)
Rickettsia	17 (0.8)	0
Typhoid fever	17 (0.8)	3 (1.5)
Other¶	235 (11.1)	32 (15.8)
No diagnosis**	853 (40.5)	67 (33.1)

*Tropical areas defined as regions of earth surrounding the equator. In latitude by the tropic of Cancer in the northern hemisphere at 23°26′11.0″ and the tropic of Capricorn in the Southern hemisphere at 23°26′11.0″. Subtropics defined as 23°26′11.0″ to approximately 45° in the Northern and Southern hemispheres.
†Defined as a clinical diagnosis where no aetiology was found or where no further viral or bacterial analysis was done.
‡Bacterial or viral aetiology identified, that is, *Campylobacter, Salmonella*, *Rotavirus*, other.
§Defined as radiology results.
¶Other non-tropical diseases such as tonsillitis, appendicitis, Kawasaki, etc.
**No clinical or aetiology-defined diagnoses were found such as abdominal pain, non-specific fever, etc.
URTI, upper respiratory tract infection.

Data analysis

Descriptive analyses were performed to calculate the frequency and percentage of variables of interest that were deemed to have a potential role in a scoring system suggested by the literature review.[12 25] The laboratory cut-offs were based on age and gender for both adults and children (online supplemental table 1).[26 27] The association between the diagnosis of malaria or dengue, and the clinical and laboratory characteristics was explored using univariate and multivariate logistic regressions. The ORs, with a 95% CI, were calculated to identify variables associated with the two tropical illnesses.

A total of 24 symptoms, laboratory results and vital parameters that are commonly evaluated at the ED (figure 1) were assessed for their association with malaria or dengue in univariate logistic regression models. Six geographical regions were also defined and assessed. Observed data on variables are described in tables 1 and 2.

The prediction model was developed using backward elimination of the same predictors described in the univariate logistic regressions. To address missing data on clinical chemistry values, 10 datasets were imputed by using the entire dataset. Backward elimination procedures, before and after replacing missing values with multiple imputations, were performed to assess result robustness. Variables with a p value of ≤0.05 in the multivariable prediction model were incorporated into the scoring system. Additionally, to further evaluate the robustness and generalisability of the model while addressing optimism and overfitting, we conducted internal validation with bootstrap analysis with 200 resamples.[25 28]

The final prediction model was transformed into a scoring system by converting the coefficients of the adjusted variables to points. Consequently, the variables with higher coefficients in the prediction model were worth more points in the scoring system since they were stronger predictors of the disease. The ability of the scoring system to predict the diagnosis was assessed using logistic regressions and receiver operating characteristic (ROC) curves. Cut-off points for the scoring system were based on results from ROC curves by prioritising highest possible sensitivity along with sufficient specificity, since the purpose of the scoring system was to identify patients with high risk of possible malaria or dengue fever in both age groups as opposed to ruling them out. Comparing ROC curves for other possible predicting models was based on possible predictors that clinicians use in daily practice such as visited region, symptoms and pathological laboratory values. The area under the curve (AUC) was used to evaluate the performance of the different scoring systems. All analyses were performed with STATA V.17.

RESULTS

Clinical characteristics of children and adults

In total, 2315 patients were included, 2113 adults (91.3%) and 202 (8.7%) children, between 2015 and 2020, the majority (81.1%) as retrospective data. The distribution of age, sex and visited region is presented in table 1. In total, 255 (12.0%) adults and 21 (10.3%) children had a microbiological-confirmed tropical infection. The two most common imported tropical diagnoses were malaria (4.8%) and dengue (3.9%). A total of 1325 (62.7%) adults and 107 (52.9%) children were tested for malaria with rapid tests and microscopy at first assessment at the ED. In addition, 20 adults and 4 children were tested within 30 days of follow-up with negative results. For dengue, both blood serology and PCR were sent from the ED to a laboratory outside the hospital (Public Health Agency) in 788 (37.3%) adults and 11 (5.4%) children. 25 adults and 6 children, who initially did not get tested at the ED, were tested within 30 days, whereby 4 adults and 2 children were confirmed to have dengue.

In the group of patients who were not diagnosed with malaria or dengue, around 10% were diagnosed as gastroenteritis without any microbial aetiology established. Also, 11.1% of adults and 15.8% of children had non-tropical diagnoses (‘other’). In total, 39.7% had a final diagnosis of non-specific fever, abdominal pain or viral infection with no microbiological or clinical diagnosis (‘no diagnosis’, table 1) within 30 days after inclusion.

Table 2 Clinical presentation and clinical chemistry of observed data on the study population

	Adults (%)			Children (%)		
	All N=2113	Malaria N=100	Dengue N=86	All N=202	Malaria N=12	Dengue N=4
Symptoms						
<38°C*	1259 (61.0)	23 (23.0)	51 (60.0)	74 (37.0)	5 (41.7)	2 (50.0)
38–39.5°C	625 (30.3)	42 (42.0)	28 (32.9)	94 (47.0)	2 (16.7)	2 (50.0)
>39.5°C	181 (8.7)	33 (33.0)	6 (7.1)	32 (16.0)	5 (42.7)	0
Cough	577 (27.3)	15 (15.0)	9 (10.5)	57 (28.2)	0	0
Malaise	264 (12.5)	8 (8.0)	10 (11.6)	66 (32.7)	6 (50.0)	0
Headache	734 (34.7)	56 (56.0)	47 (54.7)	58 (28.7)	7 (58.3)	2 (50.0)
Muscle pain	583 (27.6)	39 (39)	55 (63.9)	27 (13.3)	4 (33.3)	1 (25.0)
Rash	209 (9.9)	2 (2.0)	26 (30.2)	32 (15.8)	0	3 (75.0)
Nausea	405 (19.1)	19 (19.0)	28.3 (32.9)	38 (18.8)	3 (25.0)	2 (50.0)
Vomiting	333 (15.8)	20 (20.0)	16 (18.8)	74 (36.6)	5 (41.7)	1 (25.0)
Diarrhoea	714 (33.8)	16 (16.0)	18 (21.1)	65 (32.2)	0	1 (25.0)
Abdominal pain	476 (22.5)	13 (13.0)	11 (12.9)	69 (34.2)	3 (25.0)	0
Confusion	7 (0.3)	0	0	2 (0.9)	0	0
Urinary symptoms	108 (5.1)	5 (5.0)	2 (2.3)	8 (3.9)	1 (8.3)	0
RR†	1545 (76.7)	82 (82.8)	60 (72.3)	56 (38.6)	7 (63.6)	1 (33.3)
Missing	98 (4.6)	1 (1.0)	3 (3.5)	57 (28.2)	1 (8.3)	1 (25.0)
Saturation†	59 (2.9)	5 (5.0)	0 (0)	1 (0.5)	0	0
Missing	60 (2.8)	1 (1.0)	3 (3.5)	0	0	0
Pulse†	400 (20.4)	40 (40.0)	8 (10.3)	78 (39.2)	6 (50.0)	0
Missing	156 (7.4)	1 (1.0)	8 (9.3)	3 (1.5)	0	0
Clinical chemistry‡						
Anaemia	354 (16.7)	47 (47.0)	6 (6.9)	20 (9.9)	3 (25.0)	0
Missing§	117 (5.6)	1 (1.0)	2 (2.3)	39 (19.3)	0	0
Thrombocytosis	93 (4.6)	0 (0)	1 (1.2)	4 (2.5)	0	0
Thrombocytopenia	281 (13.3)	78 (78.0)	49 (57.0)	40 (19.8)	9 (75.0)	1 (25.0)
Missing§	130 (6.1)	3 (3.0)	1 (1.1)	44 (21.7)	0	0
Leucocytosis	687 (33.7)	5 (5.0)	3 (3.6)	33 (20.6)	1 (8.3)	0
Leucopenia	144 (6.8)	24 (24.0)	51 (59.3)	15 (7.4)	1 (8.3)	3 (75.0)
Missing§	121 (5.7)	1 (1.0)	3 (3.4)	42 (20.1)	0	0
Lymphocytosis	19 (1.9)	1 (1.5)	0 (0)	5 (3.7)	1 (8.3)	0
Lymphocytopenia	293 (13.9)	44 (44.0)	34 (39.5)	42 (20.7)	5 (41.7)	1 (25.0)
Missing§	1123 (53.1)	34 (34.0)	31 (36.1)	67 (33.1)	0	1 (25.0)
Neutrophilia	176 (17.5)	1 (1.5)	2 (3.6)	45 (32.8)	1 (8.3)	0
Neutropenia	83 (3.9)	13 (13.0)	28 (32.5)	10 (4.9)	2 (16.7)	1 (25.0)
Missing§	1119 (52.9)	34 (34.0)	30 (34.8)	65 (32.1)	0	1 (25.0)
Elevated ALAT	257 (12.2)	26 (26.0)	25 (29.0)	14 (6.9)	1 (8.3)	1 (25.0)
Missing§	865 (40.9)	19 (19.0)	19 (22.1)	126 (62.4)	3 (25.0)	1 (25.0)
Elevated ASAT	233 (11.0)	26 (26.0)	35 (40.7)	13 (6.4)	1 (8.3)	1 (25.0)
Missing§	1251 (59.2)	40 (40.0)	39 (45.3)	128 (63.3)	3 (25.0)	1 (25.0)
Elevated creatinine	313 (14.8)	26 (26.0)	19 (22.0)	0	–	–
Missing§	130 (6.2)	3 (3.0)	3 (3.4)	129 (63.8)	3 (25.0)	2 (50.0)

*Measured temperature by triage at the ED visit.
†Abnormal vital parameters referred to NEWS or PEWS.
‡Normal range values are presented in online supplemental table 1; age-specific thresholds have been adopted.
§Missing values of continuous variables such as haemoglobin, leucocyte count, etc. Multiple imputations have been used only in clinical chemistry.
ALAT, alanine aminotransferase; ASAT, aspartate transaminase; NEWS, National Early Warning Score; PEWS, Pediatric Early Warning Score.

Relationships between symptoms, clinical chemistry and diagnosis in children and adults

The proportion of symptoms and clinical chemistry in cases with malaria and dengue fever is presented in table 2. For adult patients diagnosed with malaria or dengue, headache and muscle pain were frequently observed, with more than half of the study subjects presenting with at least one of them. The paediatric population presented with a wider variety of symptoms and combinations of symptoms.

Of the 24 different predictors for malaria or dengue, the individual ORs of variables that were significantly associated with malaria or dengue ($p<0.05$) in the univariate analyses were plotted (figure 1 and online supplemental table 7). Thrombocytopenia was the factor with the strongest association with malaria in adults (OR 28.7, 95% CI 17.4 to 47.2) and children (OR 11.1, 95% CI 2.8 to 43.6), and leucopenia with dengue fever in adults (OR 31.1, 95% CI 19.1 to 50.8) and children (OR 36.0, 95% CI 3.5 to 373.1). Rash was also a significant predictor

Table 3 Scoring systems for prediction of dengue and malaria for adults and children

	Malaria scoring system	Adjusted OR	95% CI
1p	Sub-Saharan Africa	16.0	6.4 to 40
2p	Thrombocytopenia	27.2	12.2 to 60.8
1p	Anaemia	4.9	2.3 to 10.2
1p	Lymphocytopenia	3.1	1.5 to 6.6
1p	Neutropenia	4.3	1.5 to 12.3
1p	Fever >39.5°C	5.1	2.1 to 12.6
	Dengue scoring system	**Adjusted OR**	**95% CI**
1p	Asia or South/Latin America	21.3	9.5 to 47.9
2p	Leucopenia	17.8	9.5 to 33.4
1p	Thrombocytopenia	4.3	2.6 to 8.2
1p	Muscle pain	3.6	2.0 to 6.4
1p	Rash	4.0	2.1 to 7.7

of dengue among both children and adults, with high ORs in the univariate analysis for adults (4.2, 95% CI 2.5 to 6.8) and children (17.5, 95% CI 1.75 to 173.8). Furthermore, headache, muscle pain, thrombocytopenia, and high fever had high and statistically significant ORs in both populations. Additionally, in adults, muscle pain, thrombocytopenia, neutropenia and high aspartate transaminase were significant univariate predictors of dengue. Leucocytosis, lymphocytosis, thrombocytosis or neutrophilia was not significantly associated with malaria or dengue in any patient group.

Scoring system for prediction of malaria and dengue fever in children and adults

Two scoring systems were developed based on the results of the prediction model resulting in points between 0 and 6 for dengue fever and 0 and 7 for malaria (table 3). The variables with a negative association with each diagnosis (figure 1) were ruled out in the backward elimination regression because of an absence of statistical association (p>0.05). Cut-off points were set as a minimum of 3 points with 83–85% sensitivity and 86–91% specificity for malaria in both age groups. For dengue, the sensitivity was 75% and 91–92% specificity (online supplemental tables 2 and 3). Higher points indicated a higher probability of having malaria or dengue (online supplemental tables 4 and 5). The internal validation of the results for each scoring

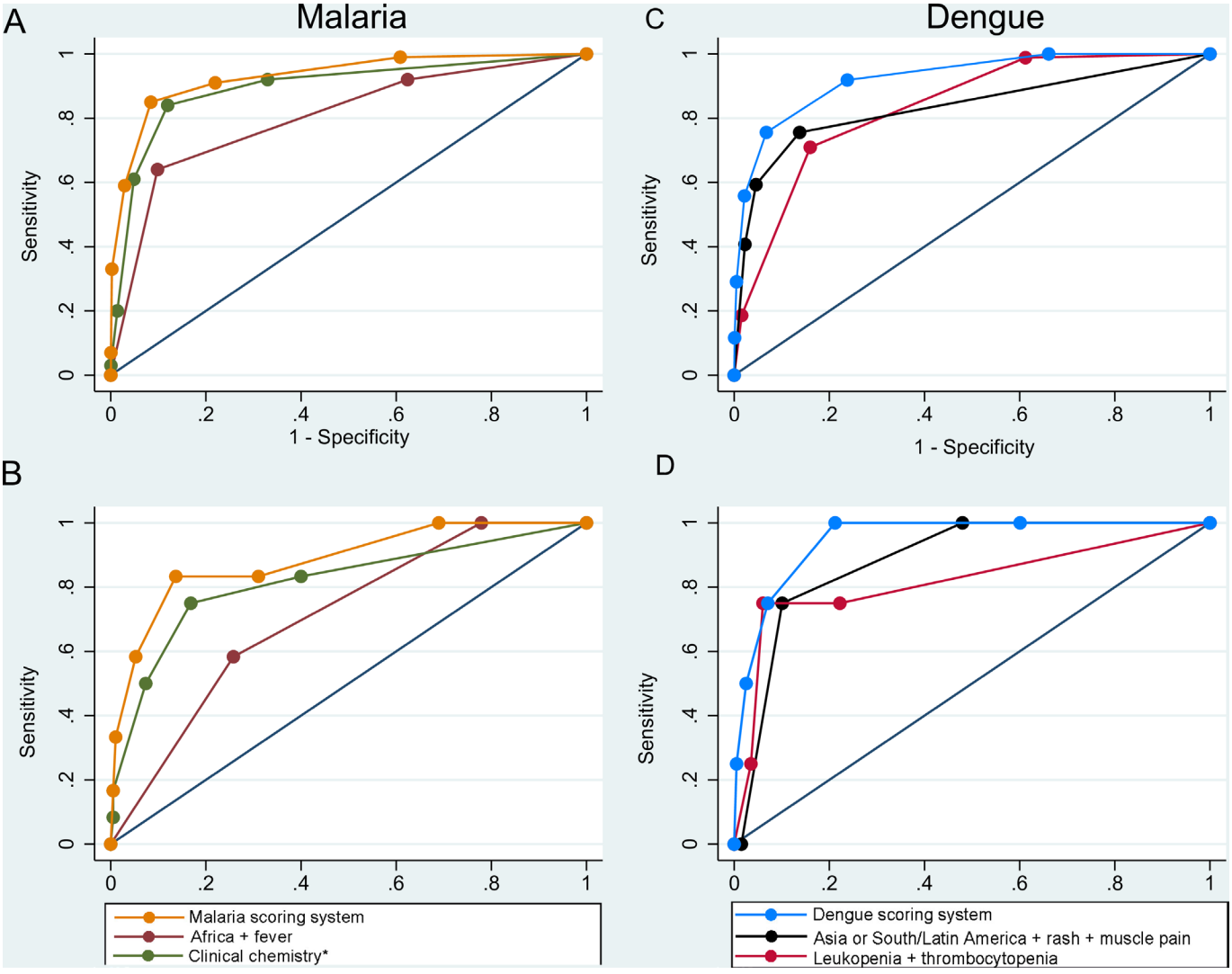

Figure 2 ROC curve of malaria scoring system for adults (A) and children (B) and dengue scoring system for adults (C) and children (D). ROC curves for clinical chemistry and visited region/symptoms as separate comparing curves. *Clinical chemistry=thrombocytopenia, anaemia, lymphocytopenia, neutropenia. ROC, receiver operating characteristic.

Table 4 Area under the curve (AUC) for malaria and dengue and comparison of equality against the scoring systems

	Adults			Children		
	AUC	P value	95% CI	AUC	P value	95% CI
Malaria						
Malaria scoring system	0.93	–	0.91 to 0.96	0.88	–	0.78 to 0.99
Africa+fever	0.80	0.00	0.76 to 0.84	0.71	0.02	0.59 to 0.83
Clinical chemistry*	0.89	0.00	0.86 to 0.93	0.82	0.01	0.67 to 0.96
Dengue						
Dengue scoring system	0.92	–	0.90 to 0.95	0.95	–	0.88 to 1.0
Asia/South Latin America+symptoms†	0.84	0.00	0.80 to 0.87	0.88	0.35	0.76 to 1.0
Clinical chemistry‡	0.84	0.00	0.79 to 0.88	0.82	0.26	0.54 to 1.0

*Thrombocytopenia, anaemia, lymphocytopenia, neutropenia.
†Rash and muscle pain.
‡Leucopenia and thrombocytopenia.

system demonstrated robustness to optimism and overfitting, as assessed through bootstrap analysis of 200 resamples (online supplemental table 6). The AUC for dengue was high in both adults and children which indicated a strong predictive value of the scoring system (figure 2 and table 4). The malaria scoring system had a high predictive value in both groups. The results before and after multiple imputations had no significant difference and the imputed data had similar distribution as the original data (online supplemental figures 1–3). Comparing ROC curves for models including only symptoms/visited regions or only clinical chemistry showed that only symptoms and visited regions were insufficient to indicate the risk of malaria or dengue (figure 2). The AUC for laboratory variables was higher than the AUCs for symptoms/visited regions but not as high as our scoring systems (table 4).

DISCUSSION

We developed two separate scoring models for the prediction of malaria and dengue for patients in all age groups and believe that this is particularly useful at the ED where many junior physicians with limited exposure to the management of imported fevers are on duty. From our results of a Swedish population of travellers, less than 70% were tested for malaria, even though over 90% visited a tropical destination with a risk of malaria (table 1). Children were also less often tested for dengue (5.4%), even though over 50% of both age groups visited a high-endemic area. This reflects the fact that there are no specific guidelines in Sweden on when to investigate malaria, dengue or other tropical infections, and each physician at the ED investigates by individual experience and clinical assessment. In Sweden, there are also some laboratory challenges when suspecting a tropical infection. Rapid test for malaria is available in most hospitals but not all have a physician/laboratory worker available at the hospital 24/7 who can do the microscopic examination with a thick blood smear. It is still gold standard with microscopic analysis, but the scoring system could here be useful by highlighting the patients at higher risk and argued as a support to further microscopic analysis and early treatment if the rapid test is negative or not available. Also, there are difficulties in diagnosing dengue fever since PCR test is not available at all hospitals around the clock. This can lead to missed cases in the early stages that potentially could become severe.[22] The scoring systems broaden differential diagnosis in febrile patients with a travel history based on laboratory and clinical data. This inclusivity applies to individuals with non-typical travel history, such as malaria from Asia or South America, and dengue from Africa. Early suspicion of malaria is crucial for prompt treatment. Hospitals lacking dengue diagnostic tests or having few tropical cases stand to benefit significantly from the scoring system for predicting dengue risk, guiding referral and testing decisions.

Like other studies,[4 8] a large proportion of the included patients did not get any microbial-confirmed diagnosis, and the number of self-limiting cases of dengue is unknown. Establishment of the cause of fever in returning travellers is a big challenge with the variance of aetiological pathogens requiring broad laboratory investigation. It is of importance, not only for the individual patient but also for overall surveillance and characterisation of ongoing transmission of infectious diseases, to confirm aetiology. Details of travel history are important to be able to consider a broader differential diagnosis, and the need for prediction tools for unknown pathogens has been demonstrated by the COVID-19 pandemic as well as the mpox epidemic in 2022.[24]

Our investigations support other studies that suggest prediction models for tropical infections. Our results (figure 2) imply that the optimal scoring system to predict malaria or dengue contains a combination of presenting symptoms, visited regions and clinical chemistry. Similar conclusions were also seen in a smaller study of children after travel to the tropics suggesting elevated liver enzymes, headache, travel to Africa/Asia and thrombocytopenia as predictors for developing severe illness.[12] Furthermore, another study developed a scoring system for dengue fever in adults by combinations of clinical symptoms as significant predictors. No laboratory values or data of children were analysed but as our study implies, adding laboratory values would be useful.[29]

The scoring systems can easily be applied at the ED, triage and primary care for both children and adults to guide the need and urgency for further investigations. This may reduce the risk of delayed diagnostic procedures and overuse of antibiotics, and has the potential to contribute to improved management of common tropical diseases with a high severity potential. The scoring systems were however not designed to rule out dengue or malaria, but rather to indicate increased risk and the need for additional investigation and a need to consult with an infectious disease specialist. We do advise that any febrile patient returning from sub-Saharan Africa should have malaria ruled out already at the first presentation since approximately 90% of imported *Plasmodium falciparum* malaria cases originate from this region.[1] It is a prerequisite for all aspects above that a system for detection of travel history is in place early in the triage process.

This study has some limitations that need to be considered in the interpretation and use of results. First, there are big differences in data size between adults and children; however, similar

results were shown on ROC curves and the paediatric sample size is larger compared with similar studies on children with tropical fever. This could indicate that the scoring systems are valid for children and motivate to include children's data in the final results. Second, the scoring system is mainly based on a healthy and young study population of Swedish travellers which limits the validity in the elderly populations with many comorbidities who may also be common travellers in the future. Information bias could also appear during collection of data from medical charts, since the documentation is not standardised. By double-checking all missing data and confirming the diagnosis with positive microbiology, we have tried to handle this problem as much as possible. It is crucial to note that the scoring tool is in its early stages, and its application should be limited to research settings. To confirm the results, external validation of the scoring systems should be done in a second independently collected cohort.

Early symptoms of tropical diseases, especially the first month, can be challenging for a physician to distinguish from other infections that are more common. In studies, over one-third of the final diagnosis of travellers with fever is of 'unknown origin'.[4 8] Clinicians need to consider a broad spectrum of potentially severe illnesses, and these scoring systems could be a useful guide.

In conclusion, we developed two scoring systems that are valuable tools for improvement of the management of post-travel illness in both adults and children in non-endemic settings. This could lead to earlier treatment and prevention of severe disease of malaria and dengue. Future studies involve external validation of the models in a second larger cohort, before the tools can be used in clinical practice.

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