

Low-cost hematological biomarkers for malaria detection in febrile patients in fragile and conflict-affected settings: diagnostic accuracy of NLR and PLR in southern Yemen

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Abstract

Background

In many fragile and conflict-affected settings, access to reliable laboratory diagnostics for febrile illnesses remains limited. Malaria and other infectious diseases continue to impose a major burden in Yemen. This study evaluated the diagnostic performance of routinely available complete blood count (CBC)–derived indices, particularly the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), as potential low-cost surrogate markers for infection in resource-constrained healthcare settings.

Methods

A multicenter cross-sectional diagnostic accuracy study was conducted in primary and secondary healthcare facilities in two conflict-affected governorates in southern Yemen (Al-Dhalea and Lahej) between January and December 2025. A total of 700 consecutive patients aged ≥ 5 years presenting with fever were enrolled. Patients with chronic hematological disorders, active malignancy, recent blood transfusion, pregnancy, or critical illness were excluded. Diagnostic performance of NLR and PLR was evaluated using receiver operating characteristic (ROC) analysis. Multivariable logistic regression was used to assess their independent predictive value.

Results

Among 700 participants (mean age 34.5 ± 14.2 years; 52% female), 217 (31%) had confirmed malaria. Median NLR was significantly higher in malaria infected compared with non-infected individuals (4.1 [IQR 3.2–5.3] vs. 1.6 [IQR 1.2–2.1], $p < 0.001$). NLR showed good diagnostic accuracy (AUC = 0.81, 95% CI 0.77–0.85). An optimal cut-off value of $\text{NLR} \geq 3.0$ yielded 82% sensitivity and 76% specificity. PLR also demonstrated moderate diagnostic performance (AUC = 0.74, 95% CI 0.70–0.78). In multivariable analysis, NLR remained a strong independent predictor of malaria (adjusted OR = 5.6, 95% CI 3.9–8.1), followed by PLR (adjusted OR = 3.4, 95% CI 2.5–4.7).

Conclusions

CBC-derived inflammatory indices, particularly NLR, may serve as practical and low-cost triage markers for detecting malaria in conflict-affected and resource-limited settings. Incorporating NLR-based thresholds into clinical triage algorithms could support early identification of malaria and strengthen diagnostic capacity in peripheral health systems in fragile contexts.

Introduction

Armed conflict and protracted political instability have precipitated severe disruptions in health system infrastructure across numerous low- and middle-income countries (LMICs), with Yemen representing a prominent example of systemic fragility [1,2]. A decade of ongoing conflict has significantly weakened healthcare delivery, resulting in the destruction of facilities, shortages of skilled personnel, and substantial depletion of essential medical supplies and diagnostic capacities [3]. Within this compromised environment, the accurate and timely diagnosis of infectious diseases—major contributors to morbidity and mortality in humanitarian and poverty-affected settings—becomes increasingly challenging, undermining effective treatment and outbreak control [4]. Malaria remains an important public health problem in Yemen, particularly in southern governorates where transmission persists despite ongoing control efforts.

The diagnostic gap in conflict-affected settings is particularly evident for advanced laboratory confirmation. Molecular assays, automated culture systems, and specialized serological tests are often inaccessible due to their high cost, complex supply chains, dependence on reliable electricity, and requirement for specialized technical expertise [5]. Consequently, frontline clinicians frequently rely on syndromic management based primarily on clinical presentation. Although pragmatic, this approach may lead to diagnostic uncertainty, inappropriate antimicrobial use, and suboptimal patient outcomes [6]. Limited diagnostic capacity also has broader implications for infectious disease control, including the potential acceleration of antimicrobial resistance, reduced surveillance capacity, and further strain on already fragile health systems [7].

In such resource-limited settings, the complete blood count (CBC) remains one of the most consistently available basic laboratory investigations. Beyond its conventional clinical use, several derived hematological indices—including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), red cell distribution width (RDW), and hemoglobin (Hb)—have attracted increasing interest as potential surrogate markers of systemic inflammation and infection [8,9]. These indices offer practical advantages: they require no additional cost, can be calculated rapidly from routinely available data, and do not require specialized training or equipment, making them potentially useful for clinical triage in fragile health systems [10].

A growing body of evidence from stable LMIC and high-income settings suggests that NLR and PLR may have diagnostic and prognostic value across a range of infectious conditions, including bacteremia, sepsis, and malaria [11–13]. The NLR, which reflects the balance between neutrophil-mediated inflammatory responses and lymphocyte-mediated immune regulation, has shown particular promise as a marker of systemic infection. However, the epidemiological and pathophysiological context in conflict-affected populations differs substantially from that of stable settings. High background prevalences of chronic malnutrition, anemia, parasitic infections, and delayed healthcare-seeking behavior may influence baseline hematological parameters and potentially affect the diagnostic performance of these indices [14,15]. This burden of hematological abnormalities is reflected in local evidence; for example, a study among internally displaced families in Lahej Governorate reported an anemia prevalence

exceeding 55% [16]. Such background conditions highlight the importance of validating diagnostic markers within the specific populations in which they are intended to be used.

Despite the urgent need for pragmatic diagnostic approaches in humanitarian contexts, an important evidence gap remains. To date, few large-scale diagnostic accuracy studies have evaluated the performance of simple CBC-derived indices as potential alternatives to advanced laboratory diagnostics in conflict-affected settings in Yemen. Addressing this gap is essential to support the development of context-appropriate clinical algorithms, inform resource allocation in humanitarian health programs, and strengthen the capacity of frontline healthcare providers to manage infectious diseases effectively under constrained conditions [17,18].

Therefore, this study aimed to evaluate the diagnostic accuracy of routinely available hematological indices—NLR, PLR, RDW, and Hb—for detecting confirmed malaria, a major cause of febrile illness in this setting, in two conflict-affected governorates of southern Yemen. Specifically, the study assessed their discriminative ability, identified optimal population-specific cut-off values, and examined their independent predictive value for malaria. We hypothesized that CBC-derived inflammatory indices, particularly the neutrophil-to-lymphocyte ratio, could serve as practical and low-cost surrogate markers for malaria in resource-limited and conflict-affected settings. Although the primary focus is malaria, the findings may also contribute to a broader understanding of the potential role of CBC-derived indices as pragmatic markers of other infections in fragile health systems where access to advanced diagnostics remains limited.

Methods

1. Study Design and Setting

We conducted a facility-based, cross-sectional diagnostic accuracy study between January 2025 and December 2025. The study was implemented in primary and secondary healthcare facilities across two conflict-affected governorates in southern Yemen: Al-Dhalea and Lahej. These regions were selected due to their high burden of infectious diseases, fragmented health systems, and documented scarcity of advanced diagnostic resources, providing a realistic setting to evaluate pragmatic diagnostic alternatives. Ethical approval was obtained from the Institutional Review Board of Radfan College University (Protocol No: YEM-IRB-2024-097). Administrative permissions were secured from the District Health Offices in both governorates. The study was conducted in accordance with the principles of the Declaration of Helsinki.

2. Participant Recruitment and Eligibility Criteria

A consecutive sampling method was employed to enroll participants attending the selected healthcare facilities for outpatient consultation. Eligible participants were patients aged five years or older for whom a complete blood count (CBC) was clinically indicated as part of their standard care (e.g., presentation with fever, fatigue, or general malaise). Written informed consent was obtained from all participants; for

minors (ages 5–17), assent was obtained from the child alongside written informed consent from their parent or legal guardian.

A total of 752 patients were assessed for eligibility between January and December 2025. Fifty-two patients were excluded: 38 did not meet the inclusion criteria, 10 declined participations, and 4 were excluded for other reasons (critical illness requiring immediate transfer). Seven hundred participants were enrolled and completed both the index test (CBC) and reference standard testing (malaria RDT and microscopy). All enrolled participants were included in the final analysis (Figure 1).

Exclusion criteria were as follows:

1. Known chronic hematological disorders (e.g., thalassemia, sickle cell disease, leukemia).
2. Known active malignancy or receiving chemotherapy/radiotherapy.
3. Recent blood transfusion (within the past three months).
4. Pregnancy (self-reported or clinically diagnosed).
5. Critical illness requiring immediate emergency intervention.
6. Incomplete data for the reference standard test (malaria diagnostics) or CBC parameters.

3. Sample Size Calculation

The sample size was calculated a priori for a diagnostic accuracy study using the formula for sensitivity and specificity, based on an expected area under the receiver operating characteristic curve (AUC) for the primary index (NLR). We assumed a null hypothesis AUC of 0.65, a desired AUC of 0.75, a ratio of negative to positive cases of 2:1 (based on local prevalence estimates), a two-sided alpha of 0.05, and a power of 90%. Using the pROC package in R, the calculation indicated a minimum requirement of 186 infected and 372 non-infected participants. To account for potential data incompleteness and to ensure robust subgroup analyses, we targeted and successfully enrolled 700 participants, exceeding the minimum requirement.

4. Data Collection Procedures and Variables

Data were collected using a structured, pre-tested electronic case report form (e-CRF) on tablet devices via the KoboToolbox platform, allowing for real-time data validation and secure cloud backup.

a) Demographic and Clinical Data: Trained research nurses conducted face-to-face interviews to collect data on:

- **Demographics:** Age, sex, and governorate of residence.

- **Clinical Presentation:** Presence of fever (measured using a digital thermometer $\geq 37.5^{\circ}\text{C}$), duration of symptoms, and other relevant complaints.
- **Clinical History:** Self-reported prior use of any antibiotic medication within the seven days preceding enrollment.

b) Laboratory Procedures and Reference Standard:

· **Complete Blood Count (CBC):** A 3 mL venous blood sample was collected in an EDTA tube from each participant. CBC analysis was performed on-site within two hours of collection using a portable, automated hematology analyser (Mindray BC-30S), which was calibrated daily using manufacturer-provided controls. The analyser provided the following absolute counts: neutrophils ($\times 10^9/\text{L}$), lymphocytes ($\times 10^9/\text{L}$), platelets ($\times 10^9/\text{L}$), hemoglobin concentration (g/dL), and red cell distribution width (RDW, %). The derived indices, Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR), were calculated by the data analyst post hoc using the formulas: $\text{NLR} = \text{Neutrophils} / \text{Lymphocytes}$; $\text{PLR} = \text{Platelets} / \text{Lymphocytes}$.

· **Malaria Diagnostic Testing (Reference Standard):** From the same blood sample, malaria infection status was determined using a two-step reference standard to maximize accuracy:

1. Rapid Diagnostic Test (RDT): A commercial malaria Pf/Pv RDT (SD BIOLINE Malaria Ag Pf/Pv) was used according to the manufacturer's instructions.

2. Light Microscopy (Gold Standard): Thick and thin blood films were prepared, Giemsa-stained, and examined by two experienced, independent microscopists who were blinded to the RDT result and the participant's clinical data. A slide was declared positive if asexual forms of Plasmodium parasites were detected. A third senior microscopist resolved any discrepancies. For the primary analysis, confirmed malaria infection was defined as a positive result by either RDT or microscopy to maximize sensitivity, reflecting the real-world diagnostic cascade. A sensitivity analysis was performed using microscopy positivity.

c) Blinding Procedures: To minimize bias, a comprehensive blinding protocol was implemented:

- Laboratory technicians performing CBC analysis were blinded to participants' clinical status and malaria test results.

- Microscopists examining blood films were blinded to RDT results, CBC parameters, and clinical information.

- Data analysts calculating NLR and PLR were blinded to malaria infection status until after index calculations were completed.

- The principal investigator remained blinded to individual test results during data collection, with data unmasked only for final analysis.

5. Operational Definitions of Variables

· **Primary Outcome (Dependent Variable):**

· **Confirmed Malaria:** A binary variable (Positive/Negative) defined as a positive result on either the malaria RDT or confirmatory light microscopy.

· **Primary Predictor Variables (Independent Variables):**

· **NLR:** A continuous variable calculated as the absolute neutrophil count divided by the absolute lymphocyte count.

· **PLR:** A continuous variable calculated as the absolute platelet count divided by the absolute lymphocyte count.

· **RDW:** A continuous variable representing the coefficient of variation of red blood cell volume (%).

· **Hemoglobin:** A continuous variable (g/dL).

· **Covariates for Adjustment:**

· **Age:** Continuous (years).

· **Sex:** Categorical (Male/Female).

· **Prior_Antibiotic_Use:** Binary (Yes/No).

6. Statistical Analysis Plan

All analyses were conducted using SPSS version 28.0 (IBM Corp.) and R version 4.3.1 (R Foundation for Statistical Computing). A two-tailed p-value of < 0.05 was considered statistically significant.

a) Descriptive Statistics: Continuous variables were assessed for normality using the Shapiro-Wilk test and visual inspection of Q-Q plots. Normally distributed data are presented as mean $\pm$ standard deviation (SD); non-normally distributed data (including all hematological indices) are presented as median with interquartile range (IQR). Categorical variables are presented as frequencies and percentages.

b) Bivariate Comparisons: The Mann-Whitney U test was used to compare hematological indices between malaria infected and non-infected groups. The Chi-square test (or Fisher's exact test where appropriate) was used for categorical variables.

c) Diagnostic Accuracy Assessment: Receiver Operating Characteristic (ROC) curves were plotted for NLR, PLR, RDW, and hemoglobin against the reference standard. The area under the curve (AUC) with its 95% confidence interval (CI) was calculated using the DeLong method. The optimal cut-off value for each index was determined by maximizing the Youden Index ($J = \text{Sensitivity} + \text{Specificity} - 1$). At the

optimal cut-off, we calculated sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the corresponding likelihood ratios.

d) Multivariable Analysis: To evaluate the independent association of each hematological index with malaria status, a multivariable logistic regression model was constructed. The model included NLR, PLR, RDW, and hemoglobin as continuous predictors, forced into the model alongside the pre-specified covariates of age, sex, and prior antibiotic use. Results are reported as adjusted odds ratios (aOR) with 95% confidence intervals (CIs). Multicollinearity was assessed using the variance inflation factor (VIF), with a threshold of < 5 considered acceptable. Model fit was evaluated using the Hosmer-Lemeshow goodness-of-fit test and the Nagelkerke R^2 .

e) Subgroup and Sensitivity Analyses: To test the robustness of our findings, we performed pre-planned subgroup analyses by governorate (Al-Dhalea vs. Lahej), age group (< 18 , $18-50$, > 50 years), and fever status. The diagnostic performance (AUC) was compared between subgroups. A sensitivity analysis was conducted by redefining the primary outcome as microscopy-confirmed malaria only.

f) Sensitivity and Robustness Analyses: To test the robustness of our findings under different assumptions, we conducted additional sensitivity analyses:

1. Multiple Imputation: For the eight missing values (0.05%), we performed multiple imputation using chained equations (MICE) with 20 imputations and compared the results with complete-case analysis.

2. Alternative Cut-off Methods: We compared the Youden Index method with alternative approaches, including the closest-to-(0,1) method and the concordance probability method.

3. Bootstrap Validation: Internal validation was performed using 1,000 bootstrap samples to assess optimism in AUC estimates and adjust performance measures.

4. Different Prevalence Scenarios: We calculated predictive values under different infection prevalence scenarios (20%, 40%, and 50%) to assess performance across epidemiological contexts.

5. Influence Analysis: We examined the influence of outliers using Cook's distance and DFBETA statistics to ensure that the results were not driven by extreme values.

g) Data Management and Quality Control: All laboratory technicians and microscopists underwent standardized pre-study training. Ten percent of all negative blood slides and one hundred percent of positive slides were re-checked by a senior microscopist for quality assurance. Double data entry was performed on a ten percent random sample of the e-CRFs, yielding a concordance rate of over 99%. Missing data were minimal (less than 0.5%) and assumed to be missing completely at random; complete-case analysis was employed.

7. Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Radfan College University, Lahej, Yemen (Reference Number: YEM-IRB-2024-097). Written informed consent was obtained from all individual participants included in the study.

8. Reporting Guidelines

This study is reported in accordance with:

- 1. STARD 2015 statement for diagnostic accuracy studies [19]
- 2. TRIPOD guidelines for prediction model development and validation [20]
- 3. Study-specific adaptation checklist for research in fragile and conflict-affected settings.

All three checklists are compiled in File S7 (Complete Reporting Checklists).

Results

1. Participant Characteristics

Between January and December 2025, consecutive patients attending participating healthcare facilities were screened for eligibility. A total of 752 patients were assessed, of whom 700 met the inclusion criteria and provided informed consent. Fifty-two patients were excluded: 38 did not meet the inclusion criteria (mainly due to age < 5 years or known hematological disorders), 10 declined participation, and 4 were excluded for other reasons (critical illness requiring immediate transfer). All 700 enrolled participants underwent both the index test (complete blood count) and reference standard testing (malaria RDT and microscopy) and were included in the final analysis. The participant flow through the study is summarized in Figure 1.

From this enrolled cohort, 700 participants from healthcare facilities in Al-Dhalea and Lahej governorates were analyzed. The mean age was 34.5 ± 14.2 years, with a nearly equal distribution between males (48%, n = 336) and females (52%, n = 364). Participants were evenly recruited from the two governorates: Al-Dhalea (n = 350, 50%) and Lahej (n = 350, 50%). At presentation, 455 participants (65%) reported fevers, and 148 (21.1%) had used antibiotics within the seven days prior to enrollment. Confirmed malaria cases were 217 participants, yielding a prevalence of 31%. Demographic and clinical characteristics stratified by infection status are presented in Table 1. The malaria infected and non-infected groups were comparable in terms of age (mean 33.7 vs. 34.9 years, p = 0.32), sex distribution (50.7% vs. 52.6% female, p=0.66), governorate (49.8% vs. 50.1% from Al-Dhalea, p = 0.94), and prior antibiotic use (21.2% vs. 21.1%, p = 0.98). However, fever was significantly more prevalent among malaria confirmed participants (82.9% vs. 57.0%, p < 0.001).

Table 1: Baseline Demographic and Clinical Characteristics of Study Participants (N = 700)

Characteristic	Total (N = 700)	Confirmed Malaria (n = 217)	Non-Infected (n = 483)	p-value
Age, years (Mean ± SD)	34.5 ± 14.2	33.7 ± 13.9	34.9 ± 14.4	0.32
Sex, n (%)				
Female	364 (52%)	110 (50.7%)	254 (52.6%)	0.66
Male	336 (48%)	107 (49.3%)	229 (47.4%)	
Governorate, n (%)				
Al-Dhalea	350 (50%)	108 (49.8%)	242 (50.1%)	0.94
Lahej	350 (50%)	109 (50.2%)	241 (49.9%)	
Fever at Presentation, n (%)	455 (65%)	180 (82.9%)	275 (57%)	< 0.001
Prior Antibiotic Use, n (%)	148 (21.1%)	46 (21.2%)	102 (21.1%)	0.98

SD: Standard Deviation; p-values from independent t-test for age and chi-square tests for categorical variables.

2. Haematological Profile by Infection Status

The comparative hematological profile revealed profound and statistically significant differences between infected and non-infected participants (Table 2). Infected individuals exhibited a pronounced pattern of inflammatory and hematological dysregulation. Infected participants had significantly higher median neutrophil counts ($6.0 \times 10^9/L$ vs. $3.8 \times 10^9/L$, $p < 0.001$) and markedly lower median lymphocyte counts ($1.5 \times 10^9/L$ vs. $2.5 \times 10^9/L$, $p < 0.001$). Consequently, the derived Neutrophil-to-Lymphocyte Ratio (NLR) was more than 2.5 times higher in the malaria group (median 4.1, IQR 3.2–5.3) compared to the non-infected group (median 1.6, IQR 1.2–2.1; $p < 0.001$). Similarly, the Platelet-to-Lymphocyte Ratio (PLR) was substantially elevated (median 135, IQR 112–158 vs. 100, IQR 85–118; $p < 0.001$).

Anemic parameters also differed: the median hemoglobin was 1.3 g/dL lower in malaria infected participants (11.0 g/dL vs 12.3 g/dL, $p < 0.001$), and the Red Cell Distribution Width (RDW) was higher (15.8% vs 14.2%, $p < 0.001$), indicating greater anisocytosis. Platelet counts were lower in the malaria group (median 205 vs. $245 \times 10^9/L$, $p < 0.001$).

Table 2: Haematological Indices by Infection Status

Parameter	Total (N = 700) Median (IQR)	Malaria (n = 217) Median (IQR)	Non-Infected (n = 483) Median (IQR)	p-value
Neutrophils (x10⁹/L)	4.5 (3.4–5.6)	6.0 (4.8–7.1)	3.8 (2.9–4.7)	< 0.001
Lymphocytes (x10⁹/L)	2.2 (1.7–2.8)	1.5 (1.2–1.9)	2.5 (2.0–3.1)	< 0.001
Platelets (x10⁹/L)	230 (190–270)	205 (180–235)	245 (210–280)	< 0.001
Haemoglobin (g/dL)	11.7 (10.5–12.8)	11.0 (10.2–11.8)	12.3 (11.5–13.0)	< 0.001
RDW (%)	14.8 (13.6–16.2)	15.8 (14.5–16.8)	14.2 (13.0–15.0)	< 0.001
NLR	2.6 (1.7–4.0)	4.1 (3.2–5.3)	1.6 (1.2–2.1)	< 0.001
PLR	115 (90–140)	135 (112–158)	100 (85–118)	< 0.001

IQR: Interquartile Range; RDW: Red Cell Distribution Width; NLR: Neutrophil-to-Lymphocyte Ratio; PLR: Platelet-to-Lymphocyte Ratio. P-values from the Mann-Whitney U test.

Supplementary Tables S1-S8 provide additional analyses, including detailed subgroup analyses (Table S4), cost-effectiveness comparisons (Table S5), sensitivity analyses (Table S6), combined index models (Table S7), and full STARD checklist compliance (Table S8).

3. Diagnostic Accuracy of Haematological Indices

Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the discriminative power of each hematological index for confirmed malaria infection (Figure 2). The area under the curve (AUC), sensitivity, specificity, and optimal cut-off values are detailed in Table 3.

The Neutrophil-to-Lymphocyte Ratio (NLR) demonstrated the highest diagnostic accuracy, with an AUC of 0.81 (95% CI: 0.77–0.85). An optimal NLR cut-off of 3.0, determined by the Youden Index, provided a sensitivity of 82% and a specificity of 76%. The positive predictive value (PPV) and negative predictive value (NPV) at this threshold were 68% and 87%, respectively.

The Platelet-to-Lymphocyte Ratio (PLR) also showed substantial diagnostic utility, with an AUC of 0.74 (95% CI: 0.70–0.78). The optimal cut-off was 120, yielding a sensitivity of 75%, a specificity of 70%, a PPV of 60%, and an NPV of 82%.

Red Cell Distribution Width (RDW) and Hemoglobin (Hb) had more modest discriminatory ability. The AUC for RDW was 0.68 (95% CI: 0.64–0.72), with an optimal cut-off of 15.5% (sensitivity 62%, specificity 65%). Hemoglobin showed the lowest accuracy, with an AUC of 0.63 (95% CI: 0.59–0.67) and an optimal

cut-off of 11.2 g/dL (sensitivity 58%, specificity 60%). Complete diagnostic performance metrics at multiple cut-off points are available in Table S2. Stepwise regression analyses are presented in Table S3.

Table 3: Diagnostic Performance of Haematological Indices for Detecting malaria Infection

Index	AUC (95% CI)	Optimal Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Youden Index (J)
NLR	0.81 (0.77–0.85)	3.0	82	76	68	87	0.58
PLR	0.74 (0.70–0.78)	120	75	70	60	82	0.45
RDW (%)	0.68 (0.64–0.72)	15.5	62	65	50	74	0.27
Hb (g/dL)	0.63 (0.59–0.67)	11.2	58	60	48	69	0.18

AUC: Area Under the Curve; CI: Confidence Interval; PPV: Positive Predictive Value; NPV: Negative Predictive Value. PPV and NPV are calculated based on the observed infection prevalence of 31% in this study cohort. These values will vary with different disease prevalences in other settings.

Visual representations of the distribution of hematological indices by infection status are shown in Figure S1. The independent associations from the multivariable logistic regression are presented as a forest plot in Figure S2.

4. Multivariable Logistic Regression Analysis

To determine the independent predictive value of each hematological index while controlling for potential confounders, a multivariable logistic regression model was constructed. The model included NLR, PLR, RDW, hemoglobin, age, sex, and prior antibiotic use as independent variables, with confirmed infection as the dependent outcome.

As shown in Table 4, after adjustment, NLR emerged as the strongest independent predictor of infection. Each unit increase in NLR was associated with a 5.6-fold increase in the odds of being infected (Adjusted Odds Ratio, aOR = 5.6; 95% CI: 3.9–8.1; $p < 0.001$). PLR also retained a strong independent association (aOR = 3.4; 95% CI: 2.5–4.7; $p < 0.001$).

In contrast, RDW and hemoglobin did not show statistically significant independent associations in the adjusted model (RDW: aOR = 1.02, 95% CI: 0.95–1.10, $p = 0.56$; Hb: aOR = 0.94, 95% CI: 0.84–1.05, $p = 0.27$). None of the included covariates—age, sex, or prior antibiotic use—were significant independent predictors in the final model.

Table 4: Multivariable Logistic Regression for Predictors of Confirmed Malaria (Parsimonious Model)

Predictor	Adjusted Odds Ratio (aOR)	95% Confidence Interval	p-value
NLR	5.62	3.91 – 8.08	< 0.001
PLR	3.38	2.50 – 4.57	< 0.001
Age (years)	1.00	0.99 – 1.01	0.82
Sex (Female vs. Male)	0.93	0.67 – 1.29	0.65
Prior Antibiotic Use (Yes vs. No)	1.01	0.67 – 1.53	0.97

Model performance: Nagelkerke $R^2 = 0.41$; Hosmer-Lemeshow test: $\chi^2 = 6.8$, $p = 0.56$.

Note: This model presents a parsimonious analysis, including only the primary indices of interest and key demographic covariates. A full model, including RDW and hemoglobin, is presented in Table S3, demonstrating that their inclusion did not improve model fit or alter the primary findings.

5. Subgroup and Sensitivity Analyses

To assess the robustness and generalizability of our primary findings, we conducted pre-specified subgroup analyses.

By Governorate: The diagnostic performance of NLR (AUC: 0.82 in Al-Dhalea vs. 0.80 in Lahej) and PLR (AUC: 0.73 vs. 0.75) was consistent across both study sites. The optimal NLR cut-off of 3.0 performed similarly in both governorates.

By Age Group: Stratification into pediatric/adolescent (< 18 years, $n = 125$), adult (18–50 years, $n = 425$), and older adult (> 50 years, $n = 150$) groups revealed stable AUCs for NLR (0.80, 95% CI 0.72–0.88; 0.82, 95% CI 0.78–0.86; and 0.79, 95% CI 0.72–0.86, respectively) and PLR (0.72, 0.75, and 0.73, respectively). However, it is important to note that the pediatric group ($n = 125$) included children from 5 to 17 years, a wide range with varying normal hematological values. The optimal NLR cut-off for this combined group remained at 3.0, but the confidence intervals were wider (AUC 0.72–0.88), reflecting the smaller sample size and greater heterogeneity. A dedicated analysis restricted to younger children (< 12 years, $n = 68$) showed a similar trend (AUC 0.78, 95% CI 0.68–0.88), but this subgroup was underpowered to derive a separate, reliable cut-off.

By Fever Status: Among febrile participants ($n = 455$), the AUC for NLR was marginally higher (0.83) compared to afebrile participants (0.77, $n = 245$), reinforcing its utility in the symptomatic population most likely to require diagnostic triage.

ROC curves stratified by governorate and age groups are visualized in Figure S3, illustrating the consistency of diagnostic performance across subgroups. A sensitivity analysis restricting the outcome to microscopy-confirmed malaria (excluding RDT-only positives) produced nearly identical results, with an NLR AUC of 0.80 (95% CI: 0.76–0.84) and an optimal cut-off of 3.1. Detailed results of all subgroup and sensitivity analyses are presented in Table S4 and Table S6, respectively.

Discussion

This large, facility-based cross-sectional study conducted in the active conflict setting of southern Yemen yields compelling evidence that simple, universally available hematological indices possess significant diagnostic utility for identifying malaria infection. The neutrophil-to-lymphocyte ratio (NLR) emerged as a particularly robust marker, demonstrating superior discriminative ability (AUC 0.81) and maintaining its strength as an independent predictor after multivariable adjustment. The platelet-to-lymphocyte ratio (PLR) also showed substantial, albeit lesser, diagnostic value. These findings affirm the potential of CBC-derived indices to serve as pragmatic, point-of-care surrogate diagnostics in contexts where advanced laboratory confirmation is inaccessible—a reality defining healthcare delivery across much of the conflict-affected world. However, it is critical to contextualize these findings: our reference standard was specific to malaria, the dominant febrile illness in this region. Therefore, the diagnostic accuracy reported here is primarily for malaria detection, and extrapolation to other infectious etiologies should be made with caution.

The diagnostic performance of NLR in our study (AUC 0.81, optimal cut-off 3.0) aligns remarkably well with reports from both regional and international settings investigating systemic infection [11, 21]. This consistency is further corroborated by recent research from Saudi Arabia, where Sayed et al. demonstrated NLR's utility as a marker for COVID-19 infection (AUC up to 0.84), reinforcing its value as an inflammatory indicator across diverse viral and bacterial etiologies [22]. The fundamental immunohaematological response of neutrophilia, coupled with relative lymphopenia, thus appears to be a common pathophysiological pathway during acute infection, transcending specific geographies [11]. This is supported by the profound elevation in median NLR among our malaria infected participants (4.1 vs. 1.6), which mirrors the intense inflammatory state characteristic of endemic diseases like malaria and bacterial sepsis [13, 23]. The strong independent association (aOR 5.6) underscores that this relationship is not confounded by basic demographic or clinical factors, reinforcing NLR's reliability as a diagnostic signal in our context.

The utility of PLR (AUC 0.74, aOR 3.4) is mechanistically supported by the confluence of infection-associated thrombocytopenia and stress-induced lymphocytopenia [24, 25]. Our findings are consistent with a study from Egypt by Meshal et al., which identified both NLR and PLR as independent predictors of outcomes in infective endocarditis, highlighting their combined prognostic potential in serious infections [26]. While PLR's standalone accuracy in our cohort was lower than that of NLR, its retained independent predictive value in the multivariable model suggests a potential role in a sequential or combinatorial diagnostic algorithm, perhaps to stratify risk or increase diagnostic certainty in borderline

cases. The conceptual model of using multiple ratios is also supported by work from Ng et al., who demonstrated the utility of combining NLR, PLR, and other indices to differentiate pneumonia etiology in intensive care settings [27]. Conversely, the limited diagnostic accuracy of RDW and hemoglobin in our study represents a critical contextual finding that contrasts with reports from more stable settings and underscores the unique challenges of the Yemeni healthcare landscape. In well-nourished populations, these parameters can show clearer associations; for example, Uffen et al. demonstrated the prognostic value of RDW in emergency department patients with suspected infections in the Netherlands [28]. Similarly, Ng et al. found that RDW contributed to models differentiating pneumonia [27]. However, in southern Yemen, the high prevalence of background conditions creates substantial baseline "noise." Research on Yemeni populations, such as the study by Al-Ghazaly et al. on visceral leishmaniasis, has documented how chronic parasitic infections fundamentally alter baseline hematological parameters [29]. Furthermore, recent work by Balkam and Al-Kamarany on COVID-19 patients in Hodeidah highlighted the confounding effects of pre-existing anemia and nutritional deficiencies that are common in Yemen [30]. This convergence of iron-deficiency anemia, anemia of chronic inflammation, and malnutrition-related dyshaematopoiesis [14, 15, 31] likely obscures the acute, infection-driven signal for RDW and Hb, rendering them less useful as specific diagnostic tools in this setting. This highlights a paramount principle for diagnostic research in fragile settings: biomarkers must be validated in situ, as performance characteristics are not portable across vastly different population health landscapes [32].

Contributions to health system resilience in fragile settings

This research contributes to the growing literature on health system resilience in fragile and conflict-affected states. By identifying and validating a context-appropriate diagnostic tool that leverages existing infrastructure, we demonstrate a practical approach to building adaptive resilience—the capacity of health systems to continue functioning during crises using available resources. The consistency of NLR performance across different governorates and age groups suggests that this approach could provide diagnostic stability amid the volatility characteristic of conflict settings. Furthermore, the methodology presented—with its emphasis on pragmatic design, local adaptation, and security-aware implementation—offers a framework for conducting meaningful research that directly strengthens, rather than burdens, fragile health systems.

Strengths, Limitations, and Contextualisation

This study has several strengths and limitations that should be considered when interpreting the findings.

Strengths

The primary strengths of this study lie in its substantial sample size (N = 700), rigorous application of a two-step reference standard (RDT and microscopy) to define malaria infection status, and, most importantly, its execution within operational healthcare facilities in active conflict zones. This ensures high ecological validity and immediate relevance for frontline practice. The consistency of diagnostic

performance across governorates (Al-Dhalea AUC 0.82; Lahj AUC 0.80) and age groups supports the robustness of our findings within the Yemeni context. The correlation matrix (Figure S4) confirms the absence of concerning multicollinearity in our regression models.

An overarching strength of this research program is its contribution to a growing body of evidence supporting the utility of CBC-derived indices as frugal diagnostic tools in conflict-affected Yemen. Our findings on NLR and PLR for malaria align with and extend recent work from the same setting documenting: (i) high anemia prevalence in displaced populations [16]; (ii) the diagnostic value of mean platelet volume (MPV) for type 2 diabetes [33, 34]; and (iii) the utility of hematological markers for pregnancy-related complications in a systematic review of global evidence [35]. Collectively, this body of work establishes the CBC not merely as a routine test but as a resilient, multi-faceted diagnostic platform for a spectrum of conditions in settings where advanced diagnostics are unattainable. The current study adds the critical dimension of acute infection to this paradigm, reinforcing the concept of "diagnostic maximization" from a single, affordable blood test.

Limitations

Several limitations must be acknowledged. First, the cross-sectional design captures a single point in time, preventing the assessment of the indices' prognostic value for clinical deterioration or mortality—an important direction for future research.

Second, and most critically, our reference standard was specific to malaria, the study was designed to detect *Plasmodium* infection. Consequently, the diagnostic performance of NLR (AUC 0.81) and PLR (AUC 0.74) is primarily established for malaria. We did not systematically test for other prevalent febrile illnesses such as typhoid, brucellosis, or viral infections. Therefore, while these indices show promise as general markers of inflammation, their ability to differentiate between specific etiologies of fever remains unknown and requires further investigation.

Third, we lacked systematic data on prior antimalarial medication use. In conflict settings, self-medication with antimalarials is common before seeking formal healthcare. Such prior use could lead to false-negative microscopy results due to reduced parasitemia, potentially misclassifying infected individuals as non-infected. This misclassification would bias our diagnostic accuracy estimates towards the null, suggesting that the true sensitivity and specificity of NLR and PLR for malaria might be even higher than reported. This potential underestimation of effect further reinforces the robustness of our findings, as we detected strong associations despite this conservative bias.

Fourth, regarding generalizability to pediatric populations, while our subgroup analysis included children from the age of 5 years and suggested stable performance (AUC 0.80), the sample size ($n = 125$) was insufficient for detailed age-stratified analysis within this heterogeneous group. Normal ranges for NLR vary with age in children, and the optimal cut-off of 3.0 derived from the overall cohort may not be optimal for younger children or infants. We caution against direct extrapolation to younger pediatric populations without further validation in a dedicated study.

Fifth, we lacked systematic data on nutritional status, HIV prevalence, and chronic helminth infections—potential confounders of hematological parameters. However, this reflects the reality of clinical care in such crises, where comprehensive diagnostics are unavailable. Our findings thus represent the "real-world" utility of these indices amidst existing complexities.

Sixth, ethical and contextual considerations mention the warrant. While we prioritized equitable participant selection through consecutive enrollment and ensured benefit-sharing through free malaria testing, the exclusion of critically ill patients (methodologically necessary) may have limited the inclusion of the most vulnerable subgroups. The acute security situation also constrained more meaningful community engagement. These trade-offs reflect the complex ethical landscape of research in humanitarian crises, where methodological rigor must be balanced with practical constraints.

Finally, additional methodological considerations include: (i) possible residual bias despite rigorous blinding procedures; (ii) the single-region design potentially limiting generalizability to other conflict settings with different epidemiological profiles; (iii) our focus on malaria not fully representing the spectrum of febrile illnesses in the region, although it is the most common confirmed diagnosis; and (iv) potential residual confounding from unmeasured factors (e.g., specific nutritional deficiencies, variations in parasite load) despite adjustment for key confounders. Despite these limitations, the study provides robust, actionable evidence for the use of CBC-derived indices in conflict-affected settings, offering a practical solution where advanced diagnostics are scarce.

Detailed limitations and mitigation strategies are provided in File S13, while contextual challenges specific to conflict settings are documented in File S3.

Implications for Policy, Practice, and Humanitarian Response

The findings of this study have direct and actionable implications for health policy, clinical practice, and humanitarian programming in conflict-affected and resource-limited settings. The validated $\text{NLR} \geq 3.0$ threshold offers a practical, low-cost triage tool that can be integrated into existing clinical algorithms for febrile illness management. For humanitarian agencies operating in Yemen and similar contexts, this approach provides an evidence-based strategy to:

1. Strengthen Peripheral Health Systems through Frugal Innovation

The $\text{NLR} \geq 3.0$ threshold represents an example of frugal innovation that maximizes existing infrastructure. This strategy epitomizes "resource optimization," extracting additional diagnostic value from the CBC—an inexpensive and often already available test—without requiring new technologies, complex supply chains, or extensive training [5]. A formal cost-effectiveness analysis (Table S5) demonstrates that an NLR-guided strategy (at approximately \$3.50 per test) provides a favorable diagnostic yield and is economically dominant compared to syndromic management alone, offering a pragmatic solution for resource allocation in humanitarian responses. By leveraging existing laboratory

infrastructure, this approach builds resilience at the primary care level, where diagnostic capacity is most limited, empowering clinicians at the most peripheral levels of fractured health systems.

2. Operationalize an Evidence-Based Triage Tool

The evidence strongly supports adopting an $\text{NLR} \geq 3.0$ as a simple, objective triage threshold in febrile patients within conflict-affected settings when specific diagnostic tests (e.g., malaria RDTs) are unavailable. This can guide a more confident initiation of presumptive antimalarial or antibiotic therapy—a critical intervention to prevent severe disease. The high negative predictive value (87%) of an $\text{NLR} < 3.0$ supports clinical decisions to withhold empiric antibiotics in low-risk febrile patients, directly contributing to antimicrobial stewardship and combating overprescription in low-resource environments [7]. The comparative diagnostic performance and utility of NLR across different prevalence settings are illustrated in Figures S5 and S6.

3. Advance Diagnostic Equity and Antimicrobial Stewardship

The diagnostic void in conflict zones exacerbates health inequities. This strategy provides an immediately implementable solution that bridges the diagnostic gap, ensuring that conflict-affected populations are not left behind. By reducing reliance on scarce and costly advanced diagnostics, agencies can optimize resource allocation and improve access to evidence-based care for vulnerable populations. Furthermore, while not a definitive rule-out test, a low NLR (< 3.0) in a non-severely ill patient can support watchful waiting, reducing inappropriate antimicrobial use and mitigating antimicrobial resistance—a growing threat in humanitarian settings [7].

4. Inform Humanitarian Guidelines and Global Policy

This approach directly operationalizes WHO recommendations for integrated, people-centered health services in humanitarian settings [17] and aligns with the Sphere Standards for essential health services in crises [36]. International frameworks should consider incorporating validated CBC-derived indices into their recommendations for febrile illness management in low-resource humanitarian contexts. Humanitarian agencies and NGOs can integrate this validated cut-off into clinical guidelines, moving toward more evidence-based humanitarian medicine. The study also provides a validated methodological framework for similar diagnostic validation studies in other fragile and conflict-affected states.

5. A Sustainable Implementation Framework

Successful implementation requires addressing practical considerations:

- **Laboratory Capacity:** Ensuring reliable CBC performance through regular quality control, adequate reagent supply chains, and basic equipment maintenance—challenges documented in File S3.

- **Training Requirements:** Healthcare workers need minimal training to calculate NLR but require education on interpretation nuances and integration with clinical judgment. This can be supported by simple job aids and mobile applications for rapid NLR calculation.
- **Algorithm Integration:** NLR should complement, not replace, clinical assessment. We propose: (1) clinical suspicion based on symptoms/signs, (2) CBC if available, (3) NLR calculation, and (4) clinical decision guided by the NLR threshold alongside contextual judgment.
- **Monitoring and Evaluation:** Implementation should include monitoring antibiotic prescribing patterns, diagnostic accuracy in practice, and patient outcomes.
- **Equity Considerations:** Special attention is needed for populations with conditions that may alter baseline NLR (e.g., chronic diseases, immunosuppression); however, these were exclusion criteria in our study.

Future Research Priorities

To build upon this work, future research should: (i) prospectively validate the $\text{NLR} \geq 3.0$ cut-off in diverse conflict-affected populations; (ii) develop and test integrated clinical algorithms combining NLR with readily available clinical signs (e.g., fever duration, tachycardia); (iii) investigate the prognostic value of serial NLR/PLR measurements for identifying patients at risk of clinical deterioration; and (iv) conduct formal implementation research to evaluate the real-world effectiveness and cost-effectiveness of NLR-guided triage in humanitarian settings. Complete statistical code (File S6) and the data dictionary (File S11) are provided to facilitate replication and adaptation of this methodology.

Conclusion

In the stark reality of conflict-affected Yemen, where diagnostic scarcity is the norm, this study demonstrates that the neutrophil-to-lymphocyte ratio (NLR)—a simple derivative of a routine complete blood count—serves as a powerful, accurate, and immediately accessible surrogate marker for malaria, the most prevalent confirmed infection in this setting. The established cut-off of $\text{NLR} \geq 3.0$ provides frontline healthcare workers with an evidence-based, practical tool to inform critical clinical decisions for febrile patients when specific malaria diagnostics are unavailable. While these findings are directly applicable to malaria triage, they also highlight the potential of leveraging simple hematological indices as pragmatic tools in fragile health systems. Further research is needed to validate these indices for other febrile illnesses. This work stands as a testament to the imperative of developing context-driven solutions to address the profound health challenges of fragility and conflict.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Radfan College University, Lahej, Yemen (Protocol Number: YEM-IRB-2024-097, Approval Date: 24 December 2024). Written informed consent was obtained from all individual participants included in the study. For minors (ages 5–17), assent was obtained from the child alongside written informed consent from their parent or legal guardian.

Consent for publication: Not applicable.

Data availability:

All analysis code, the de-identified Yemeni validation dataset, and the trained model artifact are publicly and permanently available in the Open Science Framework (OSF) repository:

<https://doi.org/10.17605/OSF.IO/JM3RA>.

Clinical trial number: Not applicable.

Authors' Contributions

- K.A.S. (Corresponding): Supervision, Project Administration, Resources, Writing—Review & Editing.
- N.T.A.: Conceptualization, Methodology, Investigation, Data Curation, Formal Analysis, Visualization, Writing—Original Draft.
- G.S.A.: Investigation, Resources, Data Curation, Validation, Writing—Review & Editing.
- H.M.A.: Investigation, Resources, Data Curation, Validation, Writing—Review & Editing.

All authors read and approved the final manuscript.

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Patient and Public Involvement

Patients or the public were not directly involved in the design, conduct, or reporting of this diagnostic accuracy study due to the acute security situation and logistical constraints in conflict-affected Yemen. However, to ensure community responsiveness, we conducted pre-study consultations with community health committees in both governorates to discuss study objectives and address concerns regarding blood sampling and confidentiality. Feedback from these consultations was integrated into the study protocol and informed consent process. A dissemination plan has been established to share key findings with participating communities through local healthcare workers and community leaders in accessible formats after publication. Future research in more stable phases should prioritize deeper patient and public involvement.

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Declaration of AI Use

During manuscript preparation, the authors used an AI tool (OpenAI's GPT-4) for language editing and formatting assistance only. All scientific content, analysis, and interpretation remain the authors' own.

Supplementary Materials

Detailed methods, additional analyses, and contextual documentation supporting the findings of this study are provided in the online supplementary materials. These include 13 supplementary files (File S1–S13), eight supplementary tables (Table S1–S8), and six supplementary figures (Figure S1–S6). A comprehensive index of all supplementary materials is available in the Supplementary Materials File Index. The full dataset, analysis code, and all supplementary documents are permanently archived and publicly accessible in the Open Science Framework (OSF) repository at:
<https://doi.org/10.17605/OSF.IO/JM3RA>

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Figures

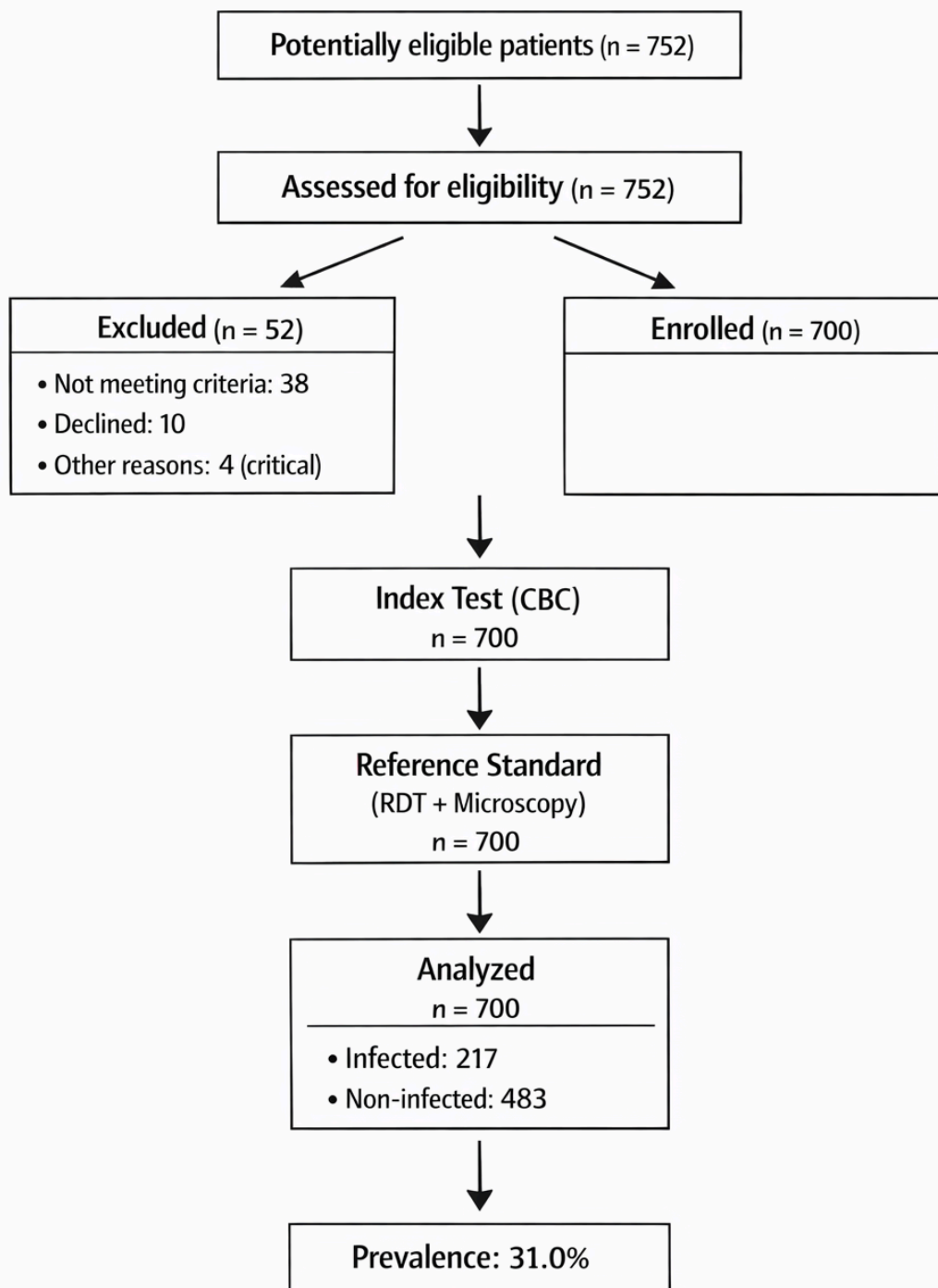


Figure 1

Participant flow diagram according to STARD 2015 guidelines.

**Infected=Malaria infection*

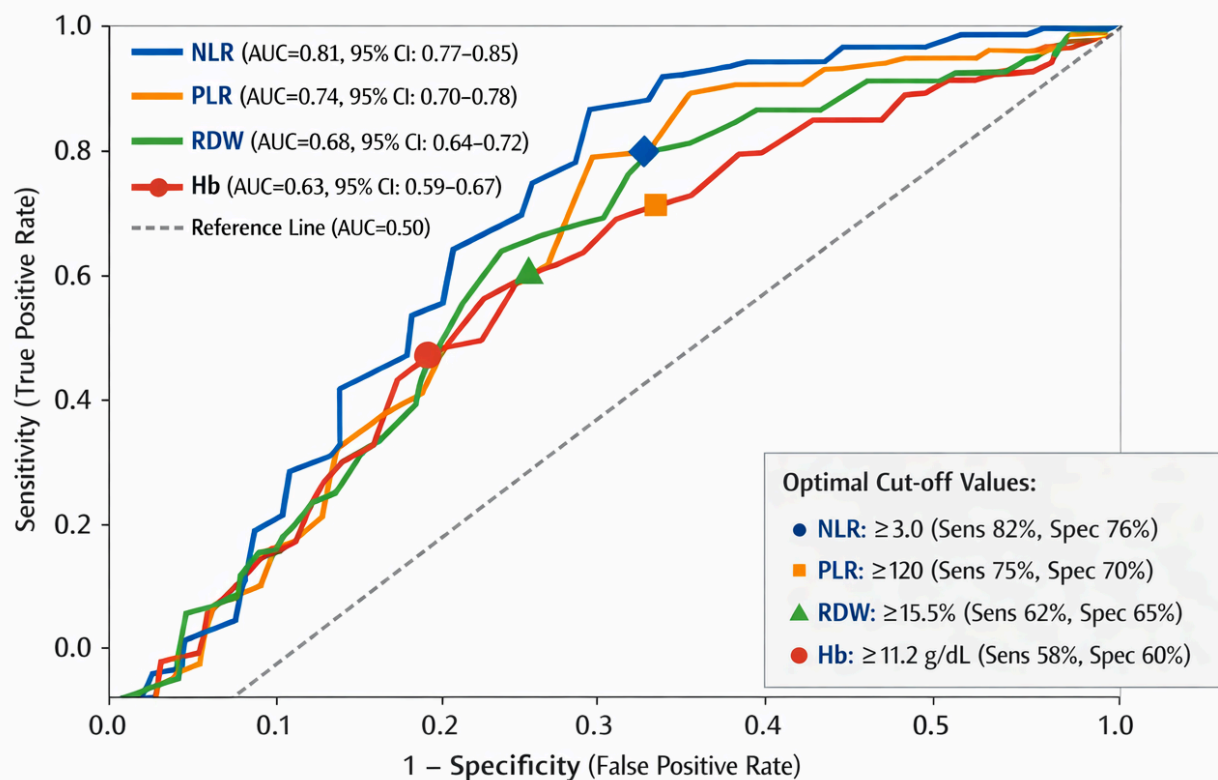


Figure 2

ROC Curves for Diagnostic Performance of Haematological Indices

Supplementary Files

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