Spatial-Textural Machine Learning for Noninvasive Detection of Malarial Anemia Using Conjunctival Images (Year 2)

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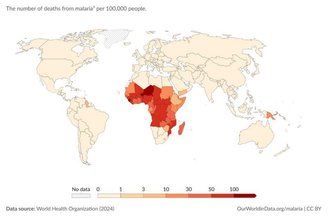
Introduction

Malaria is one of humanity's oldest and deadliest diseases; its deadliest form in humans dates back around 50,000 years [1]. The *Plasmodium* parasite infects red blood cells, causing them to rupture.

Prevalence in sub-Saharan Africa

- 249 million malaria cases occurred in 2022, leading to 608,000 deaths [2]



Challenge:
No noninvasive, rapid, direct test currently exists for fast-track detection of malarial anemia

What is malarial anemia? [3, 4]

- **Malarial anemia is medical emergency** where *Plasmodium* infection destroys red blood cells, causing **severe anemia**
- **Time-critical in resource-limited settings; delays in recognition can be fatal**
- Malaria causes anemia by **destroying red blood cells** and **impairing bone marrow production of new red blood cells**
- **Major driver of malaria morbidity and mortality**; case fatality >30% reported in holoendemic settings
- **Immediate blood transfusion** is a life-saving, time-critical intervention, especially in children
- Linked to long-term **neurocognitive impairment** in children [5]

Direct malarial anemia detection vs. independent malaria + anemia detections

- > half of severe malarial anemia deaths occur within first 24 hours of hospital admission [6]
- Separate malaria and anemia results can **fail to flag malarial anemia as an emergency**, leading to a **missed window** for **life-saving transfusion**.
- Rather than relying on an AND rule to combine outputs from two separate tests (malaria test and anemia test), one-step **malarial anemia** detection enables a clear, fast-track decision that reduces errors and confusion from a two-step link
- **Objective: identify patients who have the dangerous combination that need urgent, rapid escalation of care**

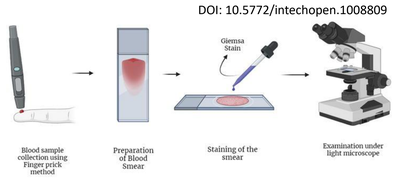
Current Detection Methods

Malaria rapid diagnostic tests (RDT) - point-of-care (POC) [7]

- Capillary blood sampling (invasive)
- Training is required
- WHO recommends RDTs for use in sub-Saharan Africa

Microscopy (blood smear test)

- Drop of blood on a special slide (invasive)
- Laboratory professional examines the slide under a microscope



PCR (Polymerase Chain Reaction) Testing

- Highly sensitive molecular technique
- Training and sophisticated equipment are required

Conventional methods: blood hemoglobin (Hgb) tests or hematocrit tests

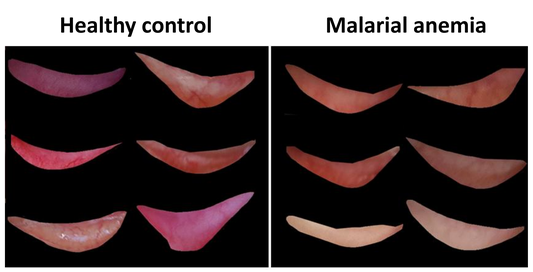
- Blood draws (invasive)
- Iatrogenic blood loss
- Requires clinical laboratory settings (hematology analyzer) and trained personnel

Invasive blood Hgb POC tests [8]

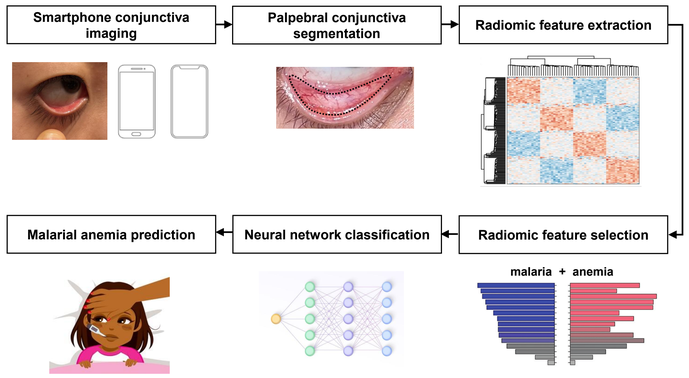
- Capillary blood sampling (invasive)
- Environmentally sensitive
- Short shelf lives
- Less accurate and precise

Manufacturer/Brand Name	Sensing Site
Abbott: i-STATA	Finger prick
HemoCue	Finger prick
VERI-Q	Finger prick
WHO Haemoglobin Colour Scale	Finger prick
Tallquist Haemoglobin Scale	Finger prick
Sanguina: AnemoCheck Home	Finger prick

Hypothesis and Approach



- **A machine learning model can be effectively trained to reliably detect malarial anemia using radiomic (spatial and textural) features extracted from palpebral conjunctiva (inner eyelid) photographs**
- Specific spatial and textural patterns can serve as candidate digital biomarkers of malarial anemia
- Supervised learning model optimized for direct malarial anemia detection achieves superior performance compared with AND gate of independent malaria and anemia detection models



Methods

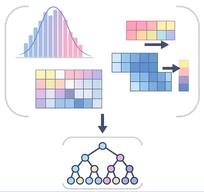
Study design and data

- Cross-sectional study
- Gakoma Hospital, Gisagara District, Rwanda
- Rwanda National Ethics Committee (93/RNEC/2023)
- Publicly available data and additional de-identified data [9]

	Total	Train	Test
Number of images	4,302	3,012	1,290
Number of participants	405	283	122
Age [years] (mean ± standard deviation)	10.5 ± 3.1	10.4 ± 3.1	10.5 ± 3.1
Sex [males] (%)	52.6%	51.9%	54.1%
Malaria RDT [positives] (%)	31.6%	31.8%	31.2%
Blood Hgb [g/dL] (mean ± standard deviation)	10.2 ± 1.6	10.2 ± 1.7	10.3 ± 1.6
Malarial anemia [positives] (%)	13.0%	12.5%	14.4%

Radiomic feature extraction and selection

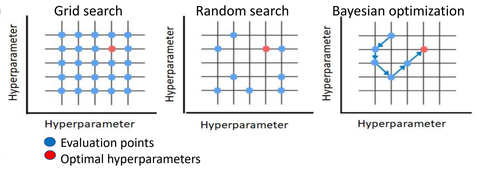
- Predefined parameter set
- Feature extraction followed established radiomics standardization [10]
- Random forest ranking using only the training dataset



Rank	Top radiomic feature associated with malaria	Top radiomic feature associated with anemia
1	First order, root mean squared	Wavelet-H, GLDM, gray level nonuniformity
2	First order, mean	LoG, GLDM, dependence nonuniformity
3	First order, median	Wavelet-L, GLDM, dependence nonuniformity
4	First order, minimum	Wavelet-H, GLCM, informational measure of correction 2
5	First order, 10 percentile	Wavelet-H, GLRLM, short run emphasis
6	First order, 90 percentile	Wavelet-H, GLDM, dependence nonuniformity
7	First order, maximum	Wavelet-H, GLDM, dependence nonuniformity normalized
8	First order, variance	LoG, GLSZM, zone variance
9	First order, energy	LoG, GLDM, dependence nonuniformity
10	First order, mean absolute deviation	LoG, GLSZM, large area high gray level emphasis

Wavelet-H, high-pass wavelet; Wavelet-L, low-pass wavelet; LoG, Laplacian of Gaussian; GLDM, gray level dependence matrix; GLCM, gray level co-occurrence matrix; GLRLM, gray level run length matrix; GLSZM, gray level size zone matrix.

Bayesian optimization of neural network

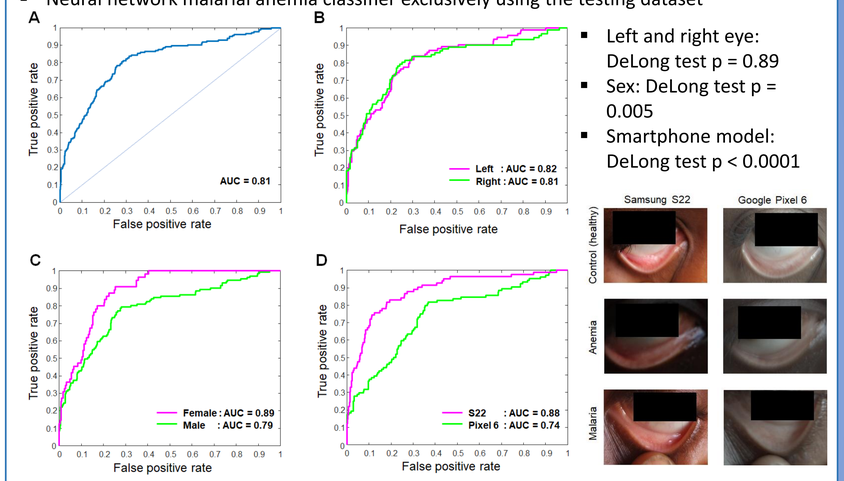


- Combined exploration
- Focus on subspaces that are most promising
- Identify optimal hyperparameters efficiently, reducing evaluation time [11]
- Search space: 1) Hidden layers: 1–5, 2) Units per layer: 1–300, 3) Activation function: ReLU, tanh, or sigmoid, and 4) Optimizer: Limited-memory BFGS
- Final hyperparameters: 2 hidden layers with 118 and 258 neurons, using tanh activation, stochastic gradient descent (SGD) with learning rate 0.001 for 100 epochs

Results

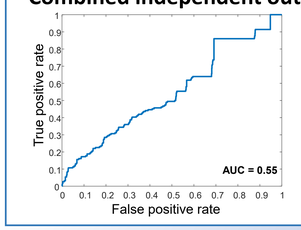
Receiver operating characteristic (ROC) analysis for malarial anemia detection

- Neural network malarial anemia classifier exclusively using the testing dataset



- Left and right eye: DeLong test p = 0.89
- Sex: DeLong test p = 0.005
- Smartphone model: DeLong test p < 0.0001

Combined independent outputs: malaria model + anemia model (soft AND gate)



- AND-gated approach of combining outputs from two separate models (anemia prediction model AND malaria prediction model) substantially reduces performance (AUC = 0.55)
- Instead, **direct model is preferred** as it weighs malaria- and anemia-associated features simultaneously rather than requiring both to cross independent thresholds

Discussion

- Operational definition used: blood Hgb < 9.9 g/dL as detecting clinically meaningful malaria-associated anemia, not strictly guideline-defined severe disease
- Future work should include larger cohorts enriched for very low Hgb, enabling severity-stratified or ordinal prediction (e.g. moderate vs severe)
- No confirmatory malaria testing (e.g. smear microscopy or PCR) to evaluate possible false negatives/positives from malaria RDTs

Conclusion

- The first radiomics-based study using smartphone palpebral conjunctiva images to identify children at elevated risk of malarial anemia in a noninvasive manner
- The malarial anemia model is optimized for the combined target, not for each test independently
- Even if the malaria and anemia models perform well on their own, applying an AND rule does not yield optimal performance for malarial anemia
- Leverages standard built-in smartphone cameras, making the approach portable, low cost, and easy to deploy
- Intended for large-scale prescreening and risk stratification in resource-constrained settings

References

[1] Resurrection of over 50,000-year-old gene reveals how malaria parasite jumped from gorillas to humans. Wellcome Sanger Institute (2019) [2] World malaria report 2024. World Health Organization (2024) [3] What causes malaria anemia? Blood 139:2268 (2022) [4] Malaria-anemia comorbidity prevalence as a measure of malaria-related deaths in sub-Saharan Africa. Scientific Reports, 9:11323 (2019) [5] Severe malarial anemia is associated with long-term neurocognitive impairment. Clinical Infectious Diseases, 59:336 (2014) [6] Estimating the burden of severe malarial anaemia and access to hospital care in East Africa. Nature Communications, 14:5691 (2023) [7] World Health Organization. Rapid diagnostic tests for malaria (2022) [8] Emerging point-of-care technologies for anemia detection. Lab on a Chip 21:1843 (2021) [9] Smartphone conjunctiva photography for malaria risk stratification in asymptomatic school age children. Npj Digital Medicine 8:151 (2025) [10] The image biomarker standardization initiative: Standardized quantitative radiomics for high-throughput image-based phenotyping. Radiology, 295:328 (2020) [11] Hyperparameter optimization: foundations, algorithms, best practices, and open challenges. WIREs Data Mining Knowl Discov. 13:e1484 (2023)