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

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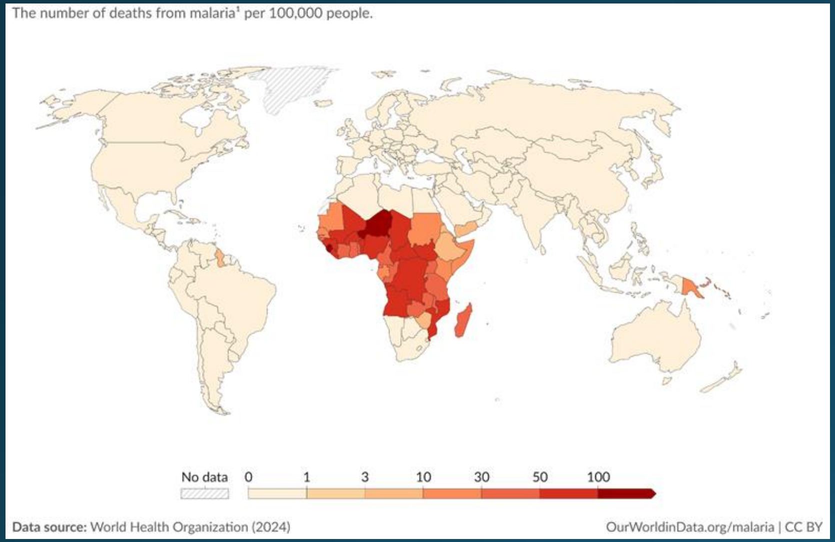
Malarial Anemia: Global Health Challenge

- Malaria is one of humanity's oldest and deadliest diseases; its deadliest form in humans dates back around 50,000 years [1].
- 249 million malaria cases occurred in 2022, leading to 608,000 deaths [2]



- **Malarial anemia is medical emergency** where *Plasmodium* infection destroys red blood cells, causing **severe anemia** [3, 4]
- Malaria causes anemia by **destroying red blood cells** and **impairing bone marrow production of new red blood cells**
- **Time-critical in resource-limited settings; delays in recognition can be fatal**
- **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

Main Challenge: ***No noninvasive, rapid, direct test currently exists for fast-track detection of malarial anemia***
Objective: ***identify patients who have the dangerous combination that need urgent, rapid escalation of care***

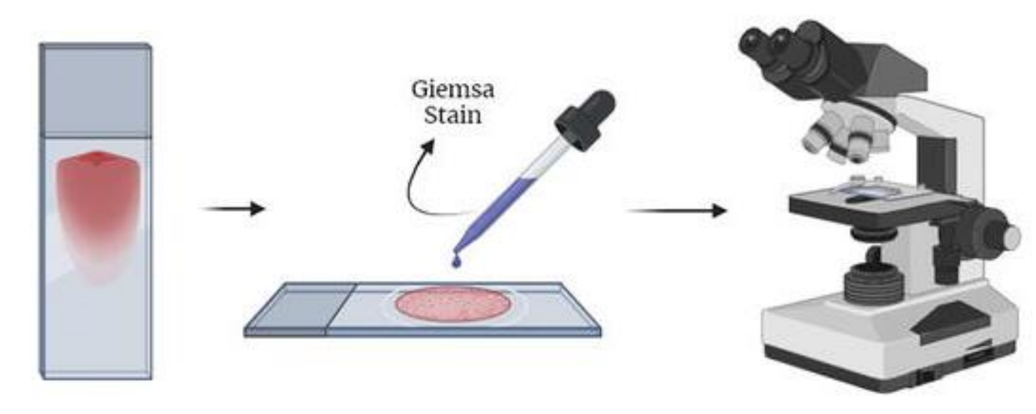
Direct malarial anemia detection vs. independent malaria + anemia detections

- Separate malaria and anemia results can **fail to flag malarial anemia as an emergency**, leading to a **missed window** for **life-saving transfusion**.

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

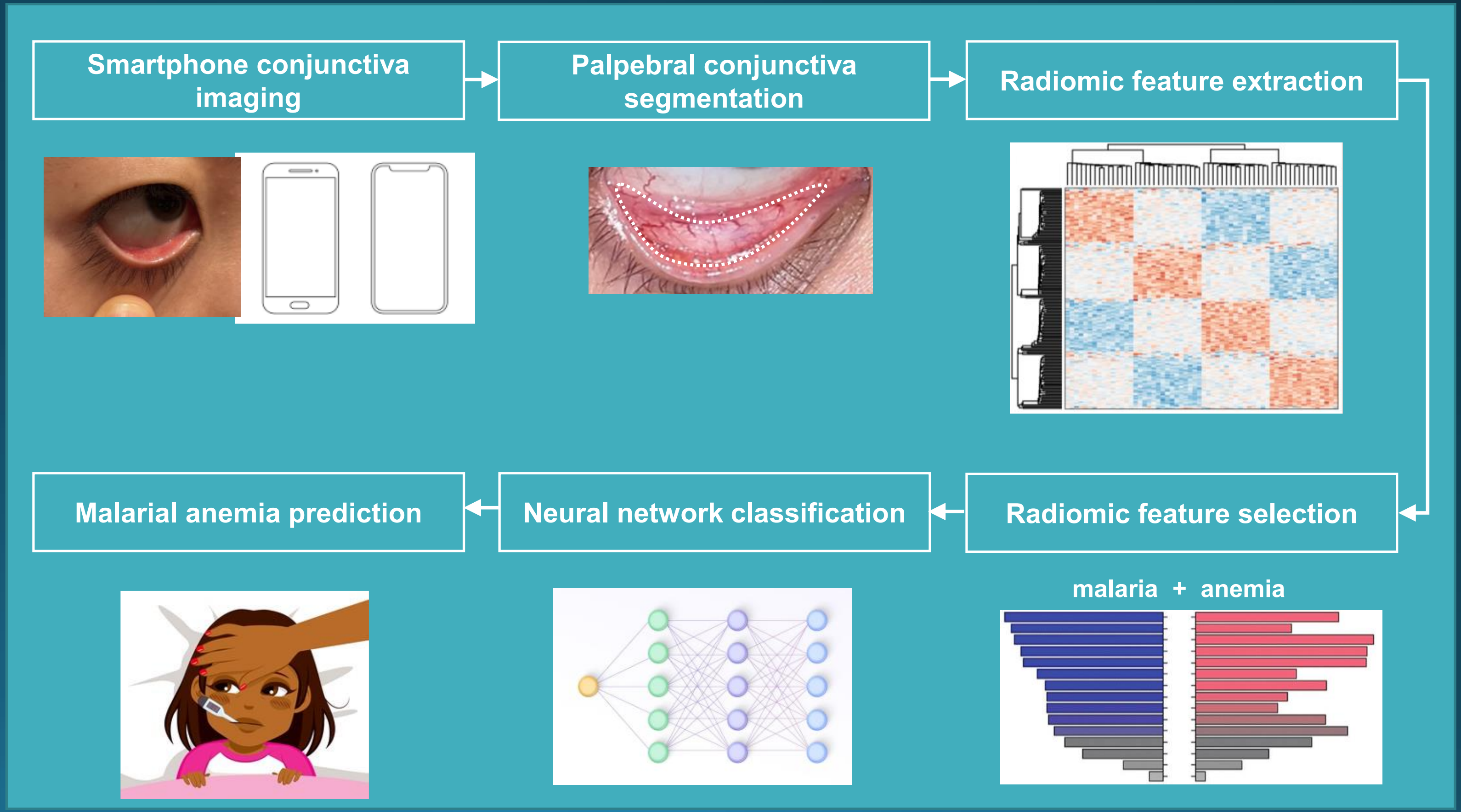
Conventional methods: blood hemoglobin (Hgb) tests or hematocrit tests

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

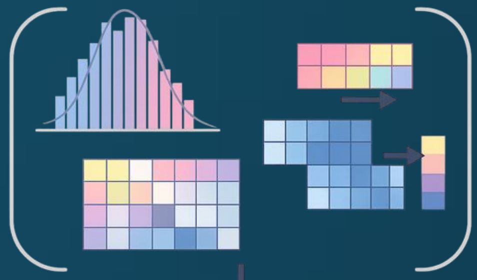
Hypothesis and Approach

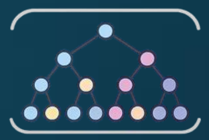
- A machine learning model can be effectively trained to reliably detect malarial anemia using radiomic (spatial and textural) features extracted from palpebral conjunctiva (inner eyelid) photographs
- Supervised learning model optimized for direct malarial anemia detection achieves superior performance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

Healthy control   Malarial anemia



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

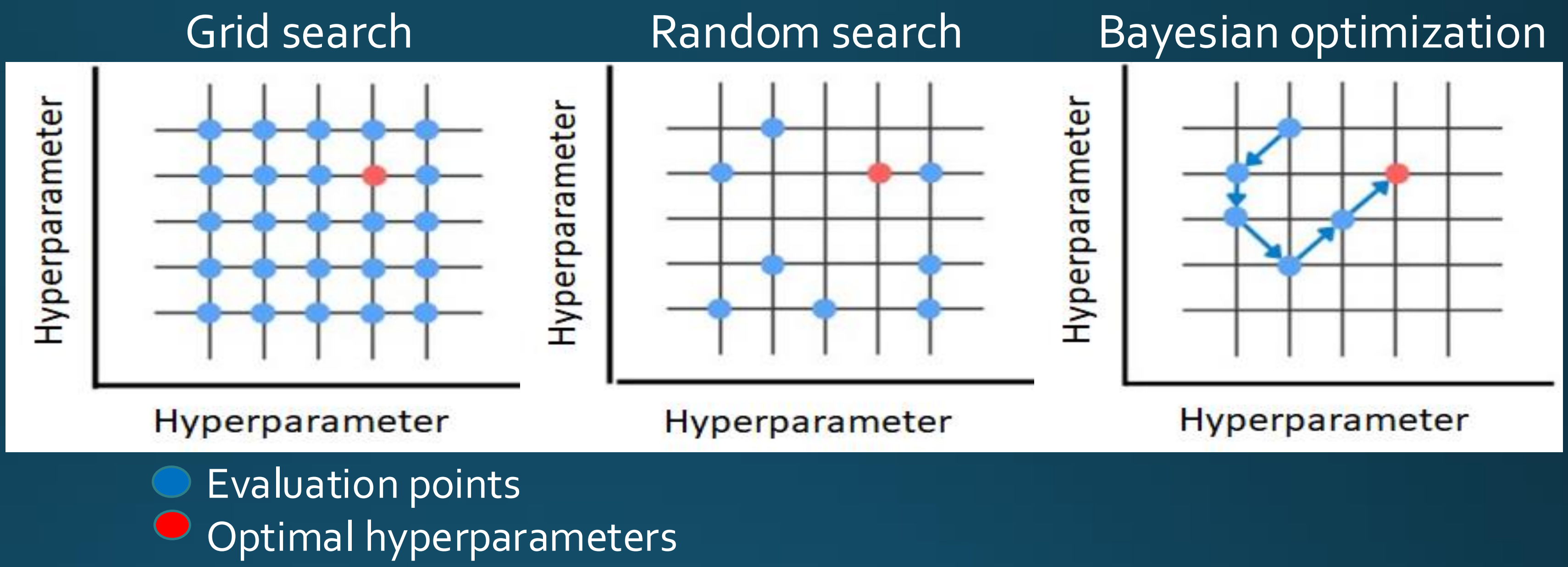
Rank	Top radiomic feature associated with malaria
1	First order, root mean squared
2	First order, mean
3	First order, median
4	First order, minimum
5	First order, 10 percentile
6	First order, 90 percentile
7	First order, maximum
8	First order, variance
9	First order, energy
10	First order, mean absolute deviation

Rank	Top radiomic feature associated with anemia
1	Wavelet-H, GLDM, gray level nonuniformity
2	LoG, GLDM, dependence nonuniformity
3	Wavelet-L, GLDM, dependence nonuniformity
4	Wavelet-H, GLCM, informational measure of correction 2
5	Wavelet-H, GLRLM, short run emphasis
6	Wavelet-H, GLDM, dependence nonuniformity
7	Wavelet-H, GLDM, dependence nonuniformity normalized
8	LoG, GLSZM, zone variance
9	LoG, GLDM, dependence nonuniformity
10	LoG, GLSZM, large area high gray level emphasis

Methods (continued)

Bayesian optimization of neural networks

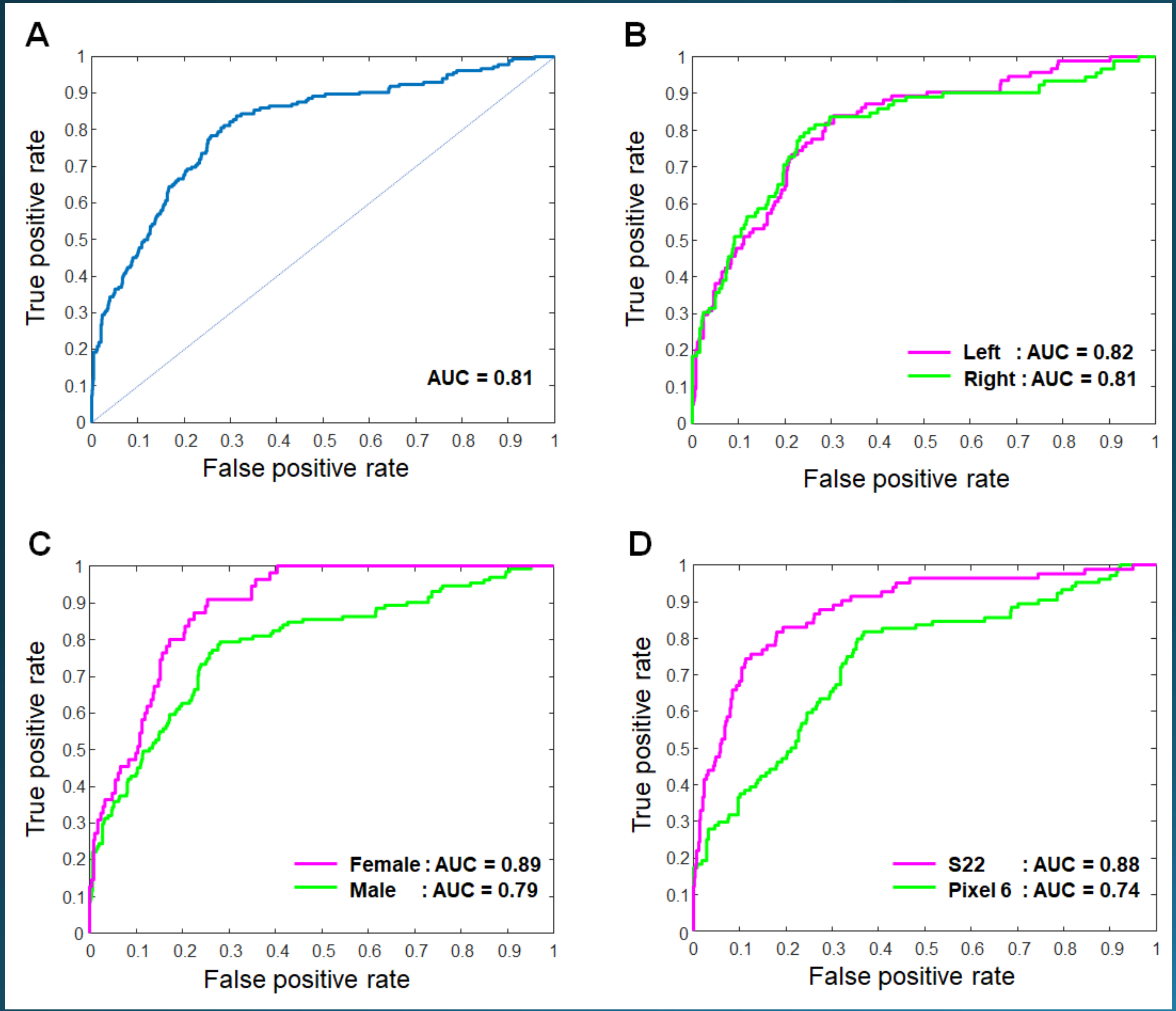
- Combined exploration
- Focus on subspaces that are most promising
- Identify optimal hyperparameters efficiently, reducing evaluation time [11]



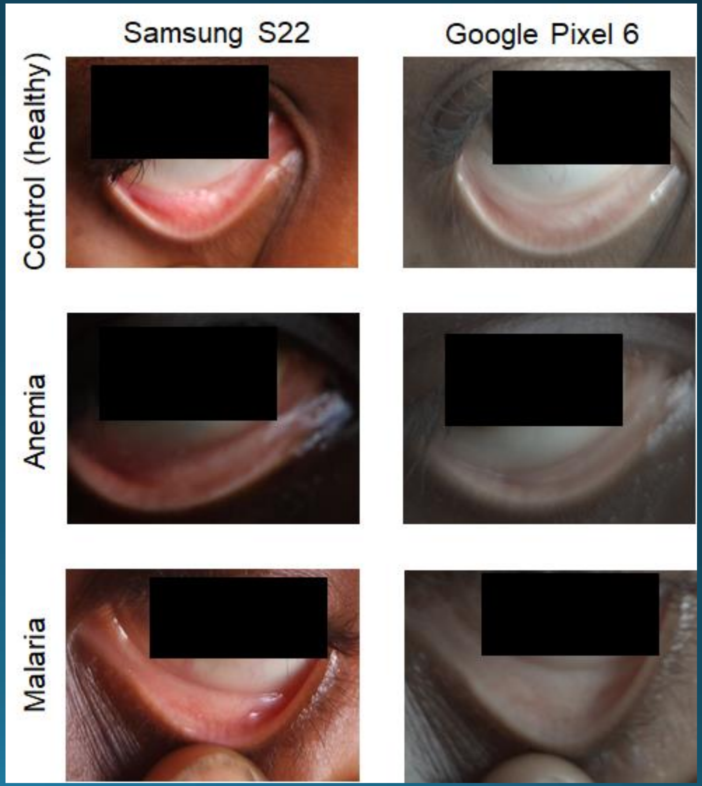
Neural network models

- 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

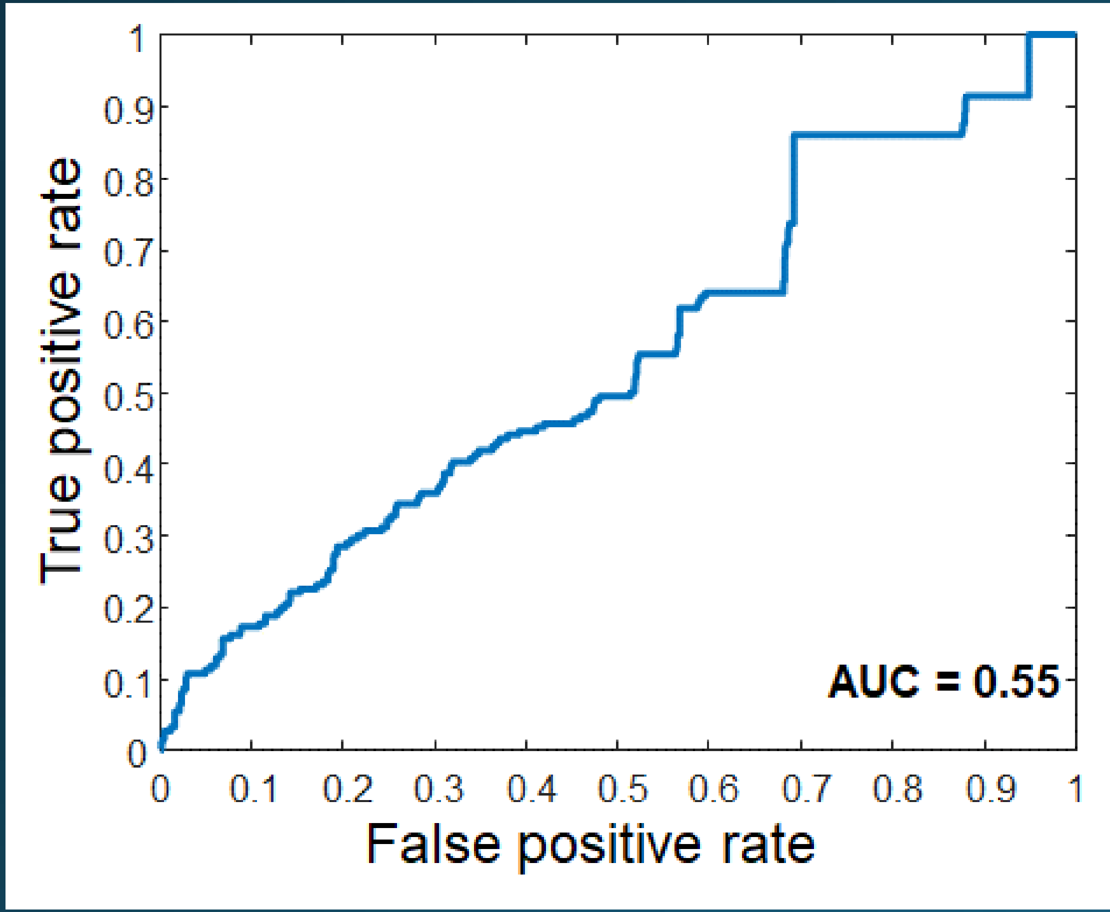
Results: Receiver operating characteristic (ROC) analysis



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



Results: 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 and Conclusion

- 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
- **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

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