

INTELLIGENT OCULAR BIOMARKER ANALYSIS FOR BLOODLESS ANEMIA SCREENING USING ARTIFICIAL INTELLIGENCE: A REVIEW OF METHODS, CHALLENGES, AND CLINICAL PERSPECTIVES

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Abstract

One of the most common illnesses in the world is anaemia, which is typically identified by invasive blood tests that call for specialized staff and laboratory equipment. Using ocular images of the palpebral conjunctiva, retinal fundus, and anterior eye vessels, researchers have recently investigated non-invasive methods for hemoglobin (Hb) estimation. Automated systems that can predict hemoglobin levels from eye images with promising accuracy have been made possible by developments in digital image processing, machine learning, and deep learning. These methods make use of feature extraction, image preprocessing, and predictive models like vision transformers, support vector machines, and convolutional neural networks. Numerous studies have shown a strong correlation between hemoglobin concentration and the color and vascular features of conjunctiva tissues, allowing for accurate anemia screening without blood sampling. Smartphone-based imaging systems and portable devices further improve accessibility for large-scale screening, particularly in low-resource environments. This paper reviews recent developments in non-invasive hemoglobin estimation and anemia detection using eye imaging and artificial intelligence techniques, highlighting methodologies, datasets, and key performance results reported in the literature. The review also discusses current challenges and potential research directions for improving accuracy and clinical applicability of these systems.

Keywords- Artificial intelligence, machine learning, deep learning, non-invasive diagnosis, conjunctiva and eye imaging, haemoglobin estimation, and anemia detection.

1. Introduction

Fifty percent of women of reproductive age are affected by anaemia, and continuous monitoring of haemoglobin (Hb) becomes a global priority [1]. Haemoglobin is due to red cells in human blood. Insufficiency of red cells in the blood leads to anemia. Anemia causes because of any reason such as low production or fast destruction in red blood cells, iron and vitamin deficiency. The vitamins are B12, vitamin folate, a parasitic infection. Anaemia is measured through haemoglobin in the blood through a haematology analyzer. Analyzer measures hemoglobin in serum from the human body collected via piercing. The continuous piercing in the human body causes infection, blood poisoning, nerve pain and permanent pain, rashes, swelling, and in severe cases, difficulty breathing. The measurement of haemoglobin classifies as a clinical method and a

noninvasive method. The noninvasive method implies spectrophotometry and the haemoglobin cyanide (cyanmethemoglobin) method. In recent years, the development of Point-of-Care Testing has been considered for haemoglobin measurement. Moreover, the haemoglobin cyanide (HiCN) method performs with the dilution of blood via potassium ferricyanide and potassium cyanide. The potassium ferricyanide oxidizes haemoglobin as methemoglobin due to iron in blood as a ferric state. The methemoglobin converts to haemoglobin cyanide through potassium cyanide. HiCN is exposed to a spectrophotometric method for the measurement of haemoglobin.

However, the haemoglobin cyanide method has disadvantages such as requiring accurate pipetting and spectrophotometer, hazardous reagent-cyanide, photometer signal inferences due to raised lipids,

leucocyte numbers and plasma proteins. Moreover, Sodium Lauryl Sulphate (SLS) method is an alternative to HiCN due to being cyanide free. SLS method consists of surfactant of lyses erythrocytes forms complex due to haemoglobin, and after few hours, the characteristic spectrum of absorption of the complex is about 539 nm. The complex obeys Beer- Lambert's Law in a linear correlation between red cells concentration and absorption. SLS method calibrates with a haemoglobin concentration of blood concerning the HiCN method. Azide-methemoglobin performs better than HiCN due to toxic potassium cyanide being replaced with sodium azide [2]. However, sodium azide is an explosive method. The above method measures the concentration of blood inside the laboratory. Point-of-care instruments use various sensors such as a spectrophotometer, NIR, IR in finger clips for haemoglobin measurement. Finger clips measurements lead to variations in Hb values due to thickness and colour of finger skin. Inaccurate measurements arise due to vasoconstriction and pressure in the capillary region of the human finger. The Hb measurement from the finger is inaccurate due to inter-reflections, wavelength accuracy, photometric polarization, finger angle and tilt, multireflection due to the bone, tissue, skin, capillary and obliquity effects.

Moreover, Hb measurement from Palpebral Conjunctiva leads to inaccurate measurement of Hb due to variations in density of goblet cells and acinar units in Meibomian glands in the human eye as age increases and influences the conjunctiva region of the eye. Furthermore, conjunctivitis is a disease of inflammation or infection at the conjunctiva. Conjunctivitis is in the form of lines in the eyelid and covers the white part of the eyeball. Moreover, small blood vessels in eye regions of conjunctiva inflammations are not visible to the human eye or standard camera. High levels of conjunctivitis lead to the white of the eye region appearing reddish or pink.

In the clinical method, a haemoglobin test was performed by adding distilled water in the blood of measured volume and compared to the artificial color standard [3]. Inaccurate measurements arise due to vasoconstriction and pressure in the capillary region of the human finger. The Hb measurement from the finger is inaccurate due to inter-reflections, wavelength accuracy, photometric polarization, finger angle and tilt, multireflection due to the bone, tissue, skin, capillary and obliquity effects. Moreover, Hb measurement from Palpebral Conjunctiva leads to inaccurate measurement of Hb due to variations in density of goblet cells and acinar units in Meibomian glands in the human eye as age increases and influences the conjunctiva region of the eye. Furthermore, conjunctivitis is a disease of

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A significant worldwide health issue, anaemia is defined by a lower haemoglobin (Hb) concentration in the blood, which reduces the amount of oxygen that reaches bodily tissues. Millions of people worldwide suffer from anemia, especially children and pregnant women in developing nations, according to global health studies. Invasive blood tests like the complete blood count (CBC) or haemoglobin measurement with clinical equipment are used in conventional anemia diagnosis. Despite their accuracy, these methods are not always practical for large-scale screening in rural or resource-constrained areas and require laboratory infrastructure and trained personnel. Researchers have looked into non-invasive optical methods for biomedical imaging-based haemoglobin concentration estimation in order to get around these restrictions. Because blood oxygenation and haemoglobin concentration directly affect the color and vascular structure of these tissues, the human eye, in particular the eye anterior ciliary arteries, palpebral conjunctiva and retinal fundus, offers visible indicators of haemoglobin levels.

A number of automated systems have been created to estimate haemoglobin levels from eye images taken with smartphones or clinical cameras thanks to advancements in digital image processing, machine learning (ML), and deep learning (DL) [1],[2]. Due to increased iron requirements during pregnancy, lactation, menstrual bleeding, and nutritional deficiencies throughout their reproductive cycle, women of reproductive age are especially at risk [3]. Megaloblastic anemia is another prevalent kind, which is mainly brought on by a folate or vitamin B12 deficiency and results in the production of abnormally large red blood cells [4]. Furthermore, autoimmune diseases, infections, or hereditary disorders like sickle cell disease and thalassemia can cause haemolytic anaemia, which happens when red blood cells are destroyed more quickly than they can be made [5].

The application of retinal fundus imaging for non-invasive screening has been the subject of recent research. Hemorrhages and venous tortuosity are two retinal abnormalities linked to anemia that can offer important information for detection and prediction. However, their sensitivity as independent diagnostic features is limited due to the low frequency of these seretinal alterations in

anemia patients. The use of deep learning models for automated anemia screening based on retinal fundus images has been investigated in earlier studies, such as those by Mitani et al. and Tham et al. Although the precise characteristics to look for were unclear, these studies produced encouraging results, identifying the optic disc region as a crucial area of interest for anemia prediction. Ultra-widefield (UWF) fundus imaging was used by Zhao et al. to develop a model, but its reliance on expensive UWF devices restricts scalability in settings with limited resources.

Additionally, proportional bias in haemoglobin predictions was reported by the Zhao study, suggesting difficulties in maintaining accuracy across different populations. Using retinal vessel optical coherence tomography (OCT) images, Wei et al. proposed a lightweight network. However, OCT's high cost restricts its use in environments with limited resources; continued efforts to develop portable OCT and UWF devices may help increase access to these imaging modalities. This study uses a high-megapixel borescope camera to examine the anterior ciliary arteries of the eye in order to find important ocular characteristics linked to anemia. In order to identify anaemia and estimate haemoglobin levels, the research focuses on extracting pertinent vascular and colorimetric features from anterior eye images and creating and validating machine learning and deep learning models.

The suggested strategy aims to offer a dependable, scalable, and non-invasive way for anemia screening by utilizing artificial intelligence and high-resolution ocular imaging. The anterior eye vasculature may be seen in great detail thanks to the use of a high-megapixel borescope camera, which enhances feature extraction and prediction precision. This approach, which provides an economical and effective alternative for widespread anemia screening and early diagnosis, is especially well-suited for implementation in rural and resource-constrained environments.

2 .Related Work

In order to reduce dependence on invasive blood sampling by developing non-invasive, image-based anemia detection methods .A number of studies have investigated non-invasive hemoglobin (Hb) estimation utilizing optical and image-based approaches.

Early methods mainly used Photoplethysmography data obtained from the fingertip, where Hb content was associated with light absorption characteristics. Despite their potential, these techniques were extremely susceptible to skin pigmentation and motion aberrations, which had a substantial impact

on measurement accuracy [6], [7]. Researchers looked at palmar region-based imaging as a solution to these problems, but their dependability was hampered by variations in tissue thickness and uneven illumination.

Because of the conjunctiva's rich vascular structure and little melanin interference, recent developments have concentrated on ocular regions. Through color space analysis and machine learning models, techniques using palpebral and bulbar conjunctival pictures have shown improved association with laboratory Hb values. For example, discriminative features have been extracted from eye photos with moderate to high accuracy using deep learning and regression-based methods like convolutional neural networks (CNNs). These methods are nonetheless vulnerable to physiological fluctuations, such as age-related changes, diseases of the ocular surface, and irregular lighting [10], [11]. In addition, some studies have incorporated smartphone-based imaging systems to enable portable and cost-effective Hb estimation. While these systems enhance accessibility, their performance is often constrained by camera quality, environmental lighting, and user-dependent variability. Other works have explored multi-modal approaches combining PPG signals with image-based features to improve robustness, yet the integration complexity and calibration requirements pose practical challenges.

More recently, attention has shifted toward advanced vascular imaging techniques targeting specific blood vessels for improved signal fidelity. In this context, the anterior ciliary arteries offer a promising alternative due to their direct representation of blood flow and reduced susceptibility to external interference. However, limited research has been conducted in this area, particularly in integrating precise vessel segmentation with deep learning-based regression models. Therefore, there remains a significant research gap in developing robust, accurate, and real-time non-invasive Hb estimation systems leveraging this anatomical region.

3. Materials and Methods

Hybrid approaches combine sensors, imaging, and computational models to enhance performance and robustness. Clinical validation is typically done using hematology analyzers to ensure reliability. This review analyzes anemia detection methods using sources from 2017 to 2025, collected from Google Scholar and PubMed. Studies lacking sufficient data or relevance were excluded. The methods are categorized into Blood Analysis, Image Processing, Wearable Devices, Fuzzy Logic, ML, and Hybrid approaches. Image processing is the most dominant (40%), followed by ML and statistical methods (19%)

each). Wearables, fuzzy logic, and expert systems account for 11%. Among ML techniques, SVM is most commonly used, followed by KNN, Decision Trees, ANN, Random Forest, Naïve Bayes, and regression models, highlighting diverse strategies for improving anemia detection accuracy.

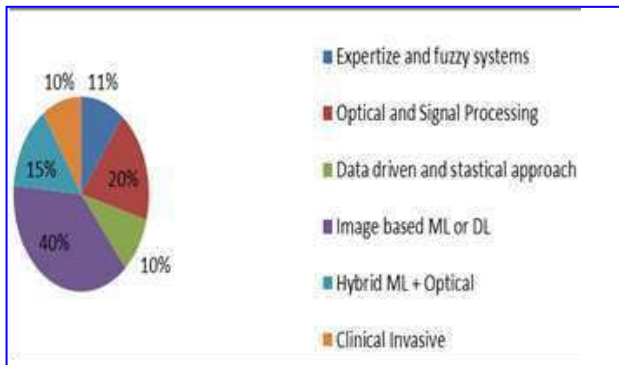


Fig. 1: Detection of anemia using different methods from few studies .

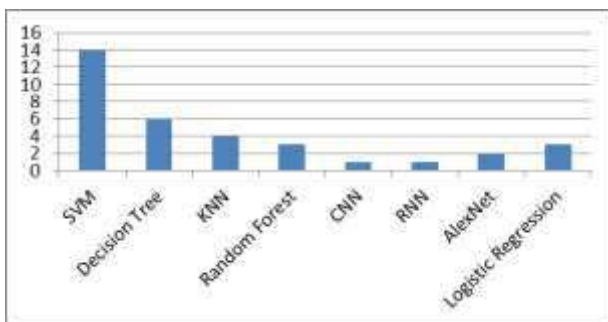


Fig. 2: Statistical methods and techniques used in reviewed literature

Table:1 Statistical methods, dataset and performance metrics used in reviewed literature of anemia detection, methods.

Cat	Data	Model	Best	Lim
DD	CBC	CNN/FCN	85	Imb
IP	RBC	AlexNet	95.9	Skew
WD	49	LR/DT	—	Low
IP	113	SVM	84.4	Small
WD	218	RUSB	83	Small
FES	25	Fuzzy	—	NoMet
ML	9K	KNN-E	Best	Src
ML	1.6K	ANN	85.6	Comp
DD	3K	TL-DL	91	Small
DD	11K	RF	≈1	Over
IP	114K	DL	0.88	Val

DD	92	LR	11–19	Small
FES	150	FIS	93.3	Scope
FES	51	F-GA	93.6	Small
ML	1.1K	PSO-BP	89	Var
ML	—	Ridge	Better	Info
ML	200	NB	96.1	Small
ML	BDHS	RF	68.5	Data
IP	266	D-U-Net	99.6	Small
IP	233	CHT	Fast	Lim
IP	Hosp	PCA-DT	92	—
ES	—	Bayes	—	NoEval
IP	Tong	SVM	77.6	Comp
IP	254	KNN	0FN	Tune
IP	2.6K	NB	99.9	Over
DD	Hosp	DT	Best	Prep
IP	RBC	SVM-TL	99.98	Data
IP	Conj	Bayes	—	NoMet
IP	710	CNN	99.1	Data
DD	68K	DL	0.92	Val
DD	428	CF	100	Miss
IP	337	ANN	0.99	Gen
WD	337	Reg	±0.92	Dev
IP	99	SVM	93	Small
WD	200	ENN	91.3	Light
ML	190	ELM	99.2	Gen
IP	99	ANN	97	Small

4. Results and Discussion

Anemia detection has moved from traditional Complete Blood Count (CBC)-based diagnostics to sophisticated data-driven methods utilizing deep learning (DL) and machine learning (ML), greatly increasing predictive power and accuracy. While wearable technology and non-invasive image-based techniques like conjunctiva and retinal analysis allow for accessible and real-time monitoring, deep learning models are sensitive to variables like illumination, sensor variability, and image quality. Fuzzy systems help manage ambiguity in medical data, while traditional machine learning approaches like regression models continue to be useful because of their resilience and interpretability. Despite these developments, clinical adoption is hampered by issues like imbalanced and limited datasets, a lack of demographic diversity, high computational complexity, and low explain ability of DL models.

This underscores the need for future research focused on hybrid, effective, and interpretable models supported by large and diverse datasets for dependable real-world implementation.

Table 2: Comparative Analysis of Approaches to Anemia Detection.

Cat.	Model	Input	Performance	Strengths	Limits
ML	RF/SVM/ANN	CBC	↓RMSE	Struct. fit	Label dep.
DL	CNN/Eff Net	Eye	85–90%	Deep feat.	Data req.
DL	ViT	Conj.	MAE 0.87	SOTA	Complex
DL	CNN	Fundus	MAE 0.63	Large-scale	Costly
IP	SLIC+GAT	Conj.	MAE 0.72	Non-inv.	Img dep.
IP	AlexNet	RBC	95.9%	High spec.	Preproc.
IP	Thresh.	Eye	78.9%	Simple	Low acc.
Wear	PPG+ML	Signal	MAE 0.67	Real-time	Noise
Wear	Mobile	Img	±0.92	Portable	Var.
Opt	NIR	Vessel	MAE 1.5	Phys. model	Err ↑
Exp	Fuzzy	Clin.	~93%	Interp.	Scale ↓
Stat	Lin Reg	CBC	MAPE	Simple	Nonlin ↓
Hyb	SLIC+kNN	Conj.	Zero FN	Reliable	Data ↓
HW	Borescope	Eye	~96%	High acc.	Setup

5. Conclusion

In conclusion, the detection of anaemia has transitioned from traditional laboratory methods to advanced computational techniques that improve accuracy, efficiency, and accessibility. While traditional methods are still important as standard diagnostic references, new technologies like machine learning, deep learning, image-based analysis, wearable systems, and intelligent decision frameworks make it much easier to find problems early and assess them without having to touch them. The coming together of these methods makes it possible to create solutions that are more stable, scalable, and patient-friendly. Going forward, the goal should be to create systems that are integrated, affordable, and clinically reliable and can work with a wide range of populations and healthcare settings in the real world. This will lead to better disease management and better health outcomes around the

world.

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