# Automated detection of retinal whitening in malarial retinopathy

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## ABSTRACT

Cerebral malaria (CM) is a severe neurological complication associated with malarial infection. Malaria affects approximately 200 million people worldwide, and claims 600,000 lives annually, 75% of whom are African children under five years of age. Because most of these mortalities are caused by the high incidence of CM misdiagnosis, there is a need for an accurate diagnostic to confirm the presence of CM. The retinal lesions associated with malarial retinopathy (MR) such as retinal whitening, vessel discoloration, and hemorrhages, are highly specific to CM, and their detection can improve the accuracy of CM diagnosis. This paper will focus on development of an automated method for the detection of retinal whitening which is a unique sign of MR that manifests due to retinal ischemia resulting from CM. We propose to detect the whitening region in retinal color images based on multiple color and textural features. First, we preprocess the image using color and textural features of the CMYK and CIE-XYZ color spaces to minimize camera reflex. Next, we utilize color features of the HSL, CMYK, and CIE-XYZ channels, along with the structural features of difference of Gaussians. A watershed segmentation algorithm is used to assign each image region a probability of being inside the whitening, based on extracted features. The algorithm was applied to a dataset of 54 images (40 with whitening and 14 controls) that resulted in an image-based (binary) classification with an AUC of 0.80. This provides 88% sensitivity at a specificity of 65%. For a clinical application that requires a high specificity setting, the algorithm can be tuned to a specificity of 89% at a sensitivity of 82%. This is the first published method for retinal whitening detection and combining it with the detection methods for vessel discoloration and hemorrhages can further improve the detection accuracy for malarial retinopathy.

**Keywords:** malarial retinopathy, cerebral malaria, retinal whitening, retina, computer-aided diagnosis

## 1. INTRODUCTION

Cerebral malaria (CM) is a life-threatening clinical syndrome associated with malarial infection. In 2013, malaria affected over 198 million people and claimed the lives of 584,000 people worldwide, more than 75% of whom were African children under five years of age [1]. Most of these deaths were thought to be associated with CM. Lewallen [2] and Taylor [3], however, found that nearly a quarter of the children who died following a clinical diagnosis of CM actually had other non-malarial causes of death, in which concurrent non-CM diseases with similar symptoms produced false positive test results. The misdiagnosis of CM with other prevalent diseases such as pneumonia and meningitis results in inaccurate and delayed treatment or a failure to treat other life-threatening diseases [2].

As of today, CM is clinically diagnosed based on physical symptoms as well as *Plasmodium falciparum (PF)* parasite detection using microscopy or rapid diagnostic tests [4]. These tests have reported sensitivity of 98% and specificity of 93% for PF parasite detection [5]. However, because individuals living in malaria-endemic areas can tolerate PF infections without developing symptoms, the presence of the PF parasite alone does not always reflect a causal association with coma in patients who appear to have CM. This leads to incorrect treatment [6].

Thus, a more specific diagnostic to confirm the presence of CM is urgently needed to improve clinical outcomes [7,8,9,10]. Lewallen et al. [11] first reported on malarial retinopathy (MR) [12,13,14], the highly specific retinal lesions associated with CM, which offers an effective means for confirming CM diagnosis. The histological features of MR present as retinal whitening and vessel discoloration, which are unique to MR, and are related to ischemia, which also occurs in the brain [2,15]. The white-centered (Roth spot) hemorrhages [15] correlate with the cerebral hemorrhages in number and size ($\varrho$=0.8) [16,17,18]. Studies have reported 95% sensitivity and 90-100% specificity of MR to the presence of severe CM [3]. Therefore, it is of the utmost importance that the MR presence be determined at high specificity settings, in addition

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to the clinical diagnosis of CM, to triage patients with non-CM diseases that can be investigated for other causes of coma. However, the diagnosis of MR presents a major challenge, due to the unavailability of ophthalmologists and the lack of ophthalmic equipment in the affected regions of Africa [19,20,21].

In order to address this issue, we developed an automated MR detection software system using retinal color images to detect retinal signs of MR: retinal whitening, hemorrhages, and vessel discoloration. This paper focuses on an image processing methodology for detecting retinal whitening, using retinal color images obtained from children clinically diagnosed with CM (Figure 1.a). Retinal whitening (Figure 1) is thought to be a manifestation of hypoxia, the result of oncotic cell swelling of neurons in the inner retinal layer in response to hypoxic stress [22]. The severity and pattern of whitening is highly specific to MR.

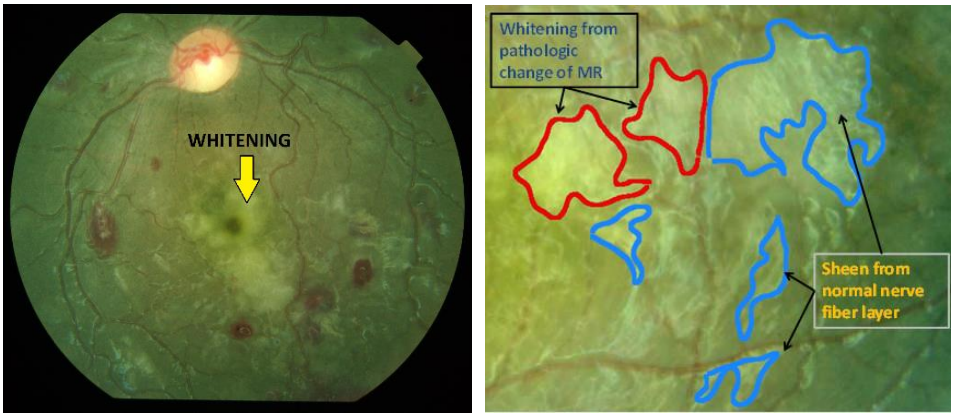


Figure 1. a) Whitening present near the macula; b) whitening and retinal sheen due to nerve fiber reflex.

To the best of our knowledge, no one has implemented an automated method to detect retinal whitening based on retinal color images. Our paper demonstrates a fully automated method to detect regions of whitening and classify retinal images as either with or without retinal whitening. This paper is organized as follows. Section 2 describes the methods and materials, section 3 demonstrates and discusses the results, and section 4 presents our conclusions.

## 2. METHODS AND MATERIALS

### 2.1 Dataset

The retrospective dataset consists of retinal images from N=54 MR cases provided by the University of Liverpool. The images were collected in Malawi, Africa between 2006 and 2014. They were captured using a Topcon 50EX retinal camera with a field of view (FOV) of 50°. Out of N=54 retinal images, 13 were controls (no MR signs) and 41 had signs of MR. Of those with signs of MR, 40 images had retinal whitening, 29 had white-centered hemorrhages, and 31 had vessel discoloration. Figure 2 depicts the number of cases per MR abnormality. For ground truth, VisionQuest's certified ophthalmic medical technologist (COMT) annotated the images for retinal whitening. This database of 54 images with annotations is a valuable resource for future MR investigations. The annotated database was used to develop the whitening detection algorithm, whose image processing flow is shown in Figure 3. Each element of the system is described in the following sections.

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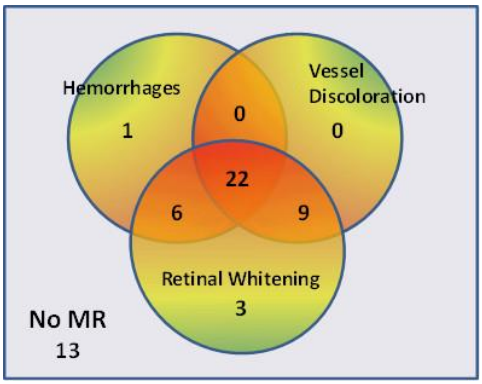


Figure 2. Number of MR cases in the dataset

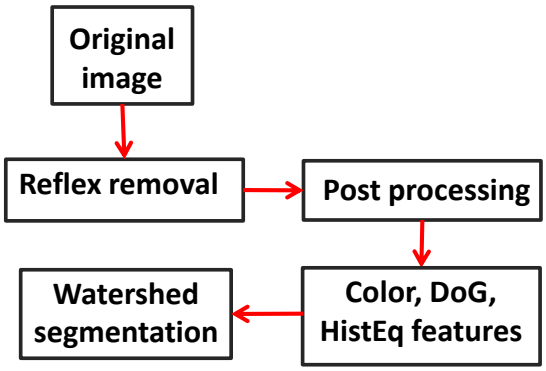


Figure 3. Block diagram of the system to detect retinal whitening

## 2.2 Preprocessing for reflex removal

As shown in Figure 1.b, the color features of whitening have similar characteristics to imaging artifacts such as camera reflex from the internal limiting membrane, which can often cause false positive detections. Thus, the first step is to minimize the effect of camera reflex in the image by using the color channels K (CMYK color space) and X and Z (CIE-XYZ color space) that provide a significant separation between true whitening region and reflex (Figure 4.b). The other differentiating feature is the smooth and fuzzy texture of whitening versus the sharp texture and strong edges of reflex. This difference is detected using a textural filter (Figure 4.c) and highlighted using contrast equalization (Figure 4.d). The equalized image is subtracted from the original image (Figure 5.a) and post-processed to remove noise, the final outcome of which minimizes reflex and preserves true whitening (Figure 5.b).

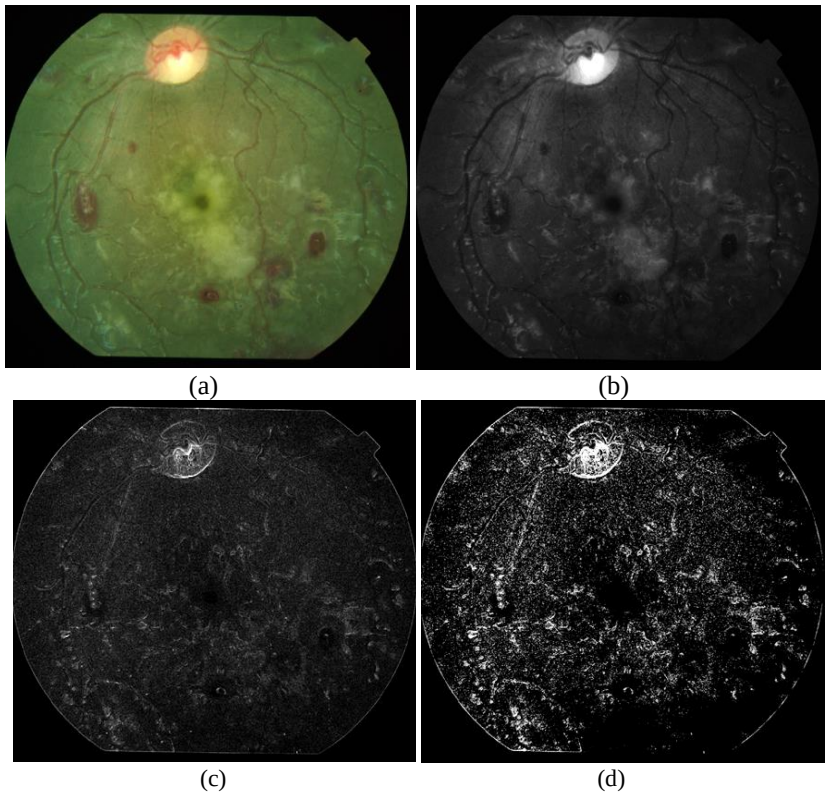


Figure 4. Preprocessing using the 'k, x, z' channels: a) fundus image; b) Z channel (CIE-XYZ); c) texture image; d) contrast equalization of texture image in (c).

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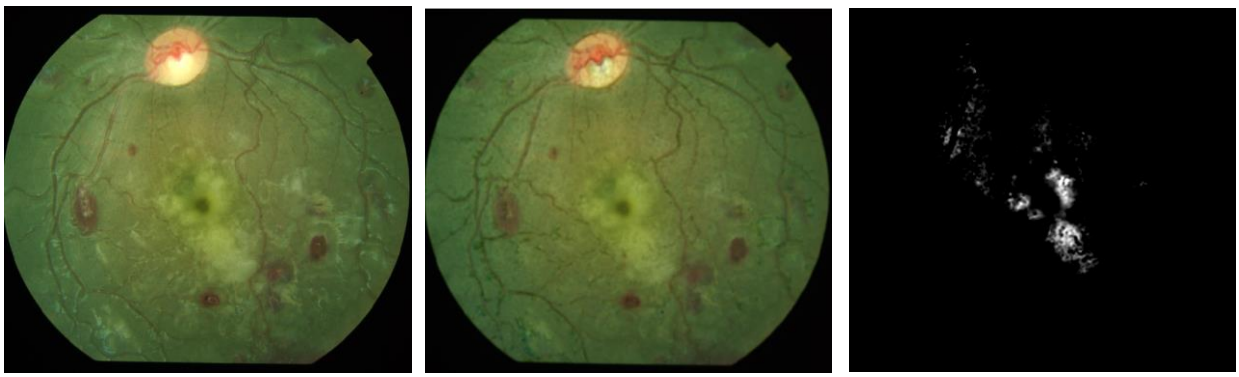
2.3 Feature extraction and whitening segmentation

The color features for detecting whitening were extracted from the above processed image for the CMYK, CIE-XYZ, and HSL color spaces. The feature set also included difference of Gaussians (DoG) at various scales (σ), and adaptive histogram equalization (HistEq) that highlights the textural details due to a local contrast. We then used the Watershed Segmentation [23] method to assign each image region a probability of being inside the whitening (Figure 5.c), which can be thresholded further to detect regions with whitening. The false positives were minimized using morphological features of detected regions, such as size, eccentricity, solidity, and bounding box.



(a) (b) (c)

Figure 5. a) Original image; b) reflex removal; c) whitening probability map.

## 3. RESULTS AND DISCUSSION

The whitening detection algorithm was tested on 54 images (40 with whitening, 14 without) as previously described in the Methods/Dataset section. Because the goal of detecting the whitening is to determine the presence or absence of malarial retinopathy, we classified each patient's image based on the presence or absence of whitening. Figure 6 shows the ROC for image classification that achieved an AUC of 0.80 with optimal sensitivity of 88% at specificity of 65%. However, in clinical practice, the whitening detection method will be used with the ultimate goal of reducing the false positive rate in CM diagnosis based on detection of MR (MR/no-MR). This will require the whitening detection algorithm to perform with high specificity. Therefore, the algorithm can be tuned to a high specificity setting of 89%, while maintaining a sensitivity of 82% (Figure 6).

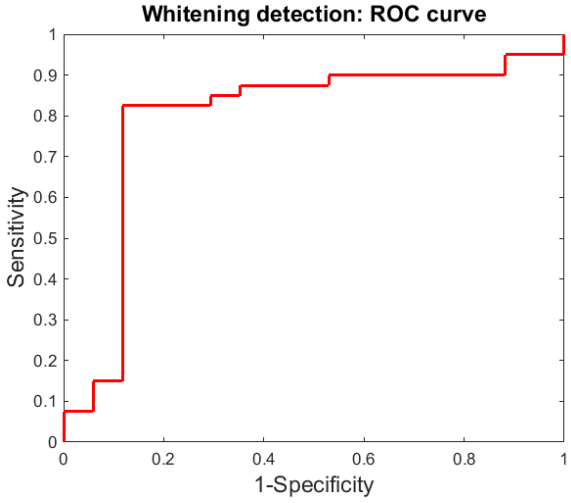



Figure 6. ROC curve for whitening detection

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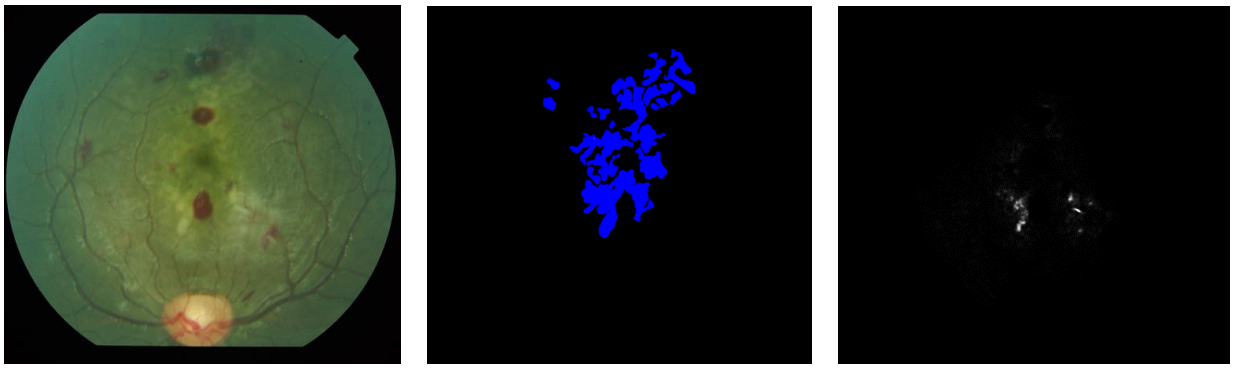
The following images show an example of retinal whitening being not detected adequately using the proposed algorithm. Figures 7 shows (a) the retinal image; (b) ground truth annotated for whitening; and (c) the probability map for whitening. Figure 7.c shows the whitening regions segmented correctly; however, it detected only a portion of the annotated ground truth. This occurred primarily due to a non-uniform illumination across the image, which caused some of the true whitening regions to be assigned a lower probability than others. The uneven illumination can be minimized by using methods designed for intensity normalization [24], or color normalization using a histogram stretching technique that achieves normalized entropy for all images. Furthermore, augmenting the current feature set with more distinguishing features such as Haralick textural features, can improve the detection of whitening. In the current methodology, we used a watershed segmentation to segment the regions occupied with whitening; in future, we will focus our efforts on utilizing more advanced classifiers, such as partial least square, that can enhance the detection performance.



(a) (b) (c)

Figure 7. a) Retinal image; b) whitening ground truth; c) whitening probability map

Determining the presence of MR is essential in the clinical diagnosis of CM. It normally takes 10-14 days from the time of infection for CM to present symptoms, including signs of MR [25]. Neurological disability or death may result if prompt diagnosis and treatment are not available within 24-48 hours of the appearance of symptoms [2]. Considering the urgent need for a timely treatment, patients must be diagnosed using a quick, accurate, and portable system for bedside screening. However, due to the scarcity of ophthalmic experts and unavailability of ophthalmoscopy equipment, the signs of MR are often missed. Therefore, a set of automated methods detecting the retinal signs of MR, such as retinal whitening, can provide this critical piece of diagnostic information irrespective of the availability of ophthalmic experts or equipment.

The research demonstrates an automated method for detection of whitening, a unique retinal feature associated with MR. It classifies the retinal images into those with or without whitening, indicating the presence or absence of MR. When combined with algorithms for detecting the other signs of MR, i.e. hemorrhages and vessel discoloration, which are under development as part of this research project, this automated software system can improve the accuracy of malarial retinopathy detection, and assist the CM diagnostic process.

Apart from its usage in CM diagnosis, automated detection of MR lesions can be an important tool for clinical investigators to quantify and correlate MR severity with the symptoms of CM, as well as for epidemiologists and healthcare policy makers to track the incidence of "true MR and CM." This will help them guide malaria control programs to provide the greatest economic benefit for the delivery of healthcare in Africa.

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## 4. CONCLUSIONS

To the best of our knowledge, we present the first fully automated method for the detection of retinal whitening in retinal color images, which is a unique feature of malarial retinopathy. Our method first minimizes camera reflex in the image and then detects the retinal region with whitening, based on various color and structural features. The proposed method yielded an area under the curve of 0.80, with the high sensitivity point at 88% and 65% specificity for classifying the images as being with or without whitening. In order to reduce false positives in CM diagnostic applications, the algorithm can be tuned to a high specificity setting of 89% at a sensitivity of 82%.

The most important contribution of automated MR detection methods to a clinical practice will be to increase the positive predictive value for detection of CM, thus significantly reducing the current rate of CM misdiagnosis. This can potentially offer a new means of improving CM diagnosis in the presence of other diseases.

## ACKNOWLEDGMENTS

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