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Retinopathy of Prematurity Disease Diagnosis Using Deep Learning

Elizabeth Ndunge Mutua[1], Bernard Shibwabo Kasamani[2], Christoph Reich[3]

[1] *School of computing & Engineering sciences, Strathmore university, Nairobi, Kenya*
[2] *School of computing & Engineering sciences, Strathmore university, Nairobi, Kenya*
[3]*Institute for Data Science, Cloud Computing and IT Security, Furtwangen university, Furtwangen, Germany*

E-mail address: elizabeth.mutua@strathmore.edu , bshibwabo@strathmore.edu, rch@hs-furtwangen.de

Abstract: Retinopathy of Prematurity (ROP) is a disease affecting infants born preterm, at birth their retina is not well developed and in most times after birth the veins do not develop to full term. Sometimes these veins stop growing and then suddenly start growing to the wrong directions and this abnormally causes retina traction, causing blindness. Each country has its own screening guidelines for the diagnosis. The disease can be categorized as severe or mild and has five stages. Stage one and two is not severe and can develop and heal unnoticed. Stage three should be diagnosed because it is reversable through treatment but when the disease progresses to stage four retina traction occurs and causes blindness at stage five. The emergent of digital imaging support has resulted to having hospitals capturing retina images to determine the presence or absence of severe ROP. These images can be used to determine the presence of retinal detachment or lack of growth of the veins. The disease diagnosis is expensive with few eye specialists available in hospitals and the process of capturing retina images by non-eye specialists and transmitting them to specialists for disease diagnosis pauses many issues. Different cameras produce images of different contrast, image transmission may cause quality reduction depending on the channel of transmission. These challenges call for the development of systems to support both image quality assessment and assistive disease diagnosis. This paper proposes a Deep learning model to assist ophthalmologists to determine the presence or absence of the disease as well as diagnosing the disease at stage three. Data obtained from two databases: Kaggle database and HVDROPDB database were used for model training, testing and validation by having the model achieve an accuracy of 92.8%, sensitivity of 94.9%, and precision of 97.3%.

Keywords: Retina Image Analysis, Retinopathy Classification, Eye Disease Diagnosis, Image Quality, Deep Learning.

1. INTRODUCTION

Retinopathy of prematurity screening in most countries is done for babies of gestational age 28 weeks and or 1500 grams [1]. At gestational age of 16 weeks, retina vessels begin to form and by week 39 they are fully developed [2]. Preterm babies have their retina vessels underdeveloped and, in most cases, they do not grow to full term [3]. As shown in Figure 1, The disease has five stages, stage one and two can develop and heal without any medical examination or treatment but at stage three which is a reversable stage, diagnosis and treatment is required [3]. Stage four and five are severe stages, at stage four retina traction occurs and the baby goes blind at stage five [4-5]. Stage three of the disease has a unique feature of the development of a well visible ridgeline which we used as a key feature for diagnosis [6-7].

When the disease is at stage one, a thin white line begins to form because of the stopping of growth of the vessels [4-7]. This line grows wider and the color changes to pink at stage two [7-8]. For stage three, the demarcation line is very wide and upon screening it can easily be noticed. In stage four, retinal detachment occurs with the baby going blind at stage five with a symptom of a white tinny spot in the eye [8-9].

A. Retinopathy of prematurity in Retina Zones

The retina has three zones as shown in Figure 2, with zone I being the innermost zone which is circular in shape and is surrounded by inner zone II. Zone II is divided into two, inner zone II and outer zone II. Inner zone II is closer to zone I and outer zone II is closer to zone III. Zone III is the outer zone [2]. Retinopathy of Prematurity disease in zone

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I is more aggressive and could rapidly progress from mild stages to severe stages [3].

B. Pre and Plus ROP Disease

Pre-Plus ROP is ROP that is mild and not severe and is characterized by abnormal growth of blood veins with no presence of Plus ROP. Plus ROP is severe stage ROP which most times is found in Zone I and can be diagnosed when the pupil is dilated [6].

C. Aggressive ROP (A-ROP)

Retinopathy of Prematurity disease is aggressive if upon occurrence it has the potential to progress rapidly to stage V. This type is found in zone II and the effects of this type of ROP are severe for regions where disease screening is not common [6]. Most times it is diagnosed while at stage V.

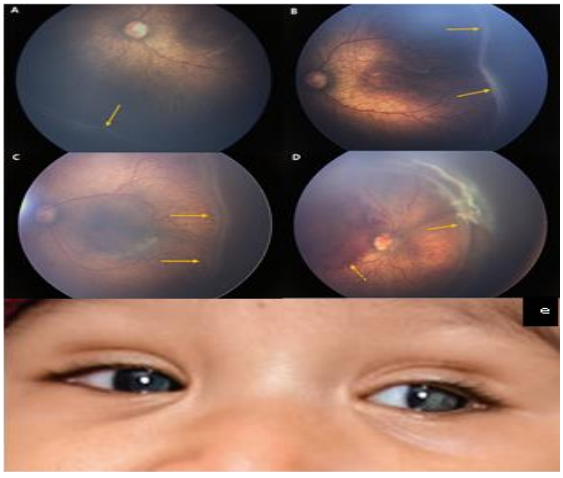

Figure 1. ROP stage Features, stage one (image a), stage two (image b), stage three (image c), stage four (image d)

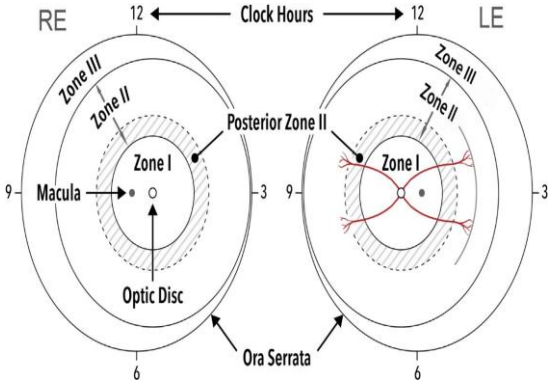

Figure 2. Retina zones [5]

This work first customizes the ResNet-50 model for ROP disease detection, extracted features are fed to a Dee Neural Network to diagnose the disease at stage three. In this paper we first provide a background information of ROP disease, in section two we provide a review of literature for ROP disease diagnosis as well as Deep learning models applicable for ROP disease diagnosis, we use section three to present the developed model and discuss the results in section four and conclude with recommendations for future work under section five.

2. LITERATURE REVIEW

This section presents a review of recent developments and the available architectures for ROP disease diagnosis.

A. Data Preparation

Eighteen studies were first obtained after initial database screening, seven of which used data from China [10-16], [17] got data from North America, [18] from America and Mexico, [19] from America and Nepal and the study [20] had data obtained from a hospital in New Zealand. The eight studies had their data collected between 2011 and 2020. The studies [14-16,17,20]. Sorted their data into two data sets: quality and non-quality.

Ten studies did data augmentation to increase on the datasets for both training and testing [11-12,14-15, 18-20,22-24]. There was a similarity between the following eleven studies where all babies screened were of a gestational age above 30 weeks and or birth weight above 1500 grams [11-13,15-16,19, 20,25-28]. The eleven studies also used databases of a size whose range was between 2668 and 52,249 images. Twelve studies [10-12, 16, 19,22-28] developed models to detect the presence or absence of ROP disease while seven studies [13-15,18,20-21] focused on detecting the severity of the disease, utilizing datasets larger than 5358 images.

B. Architectures design

Eleven studies [11-13,15-16,19, 20,25-28] developed CNN, U-Net, VGG16, VGG19, ResNet and ImageNet. Nine studies [10,12,14-16, 22-25] had datasets for training, testing and validation with images more than 10,000. All studies co-opted one to five image graders as experts to sort quality images to be used for model development. Twelve studies [10,17-20, 22-28] did a comparative analysis of the performance of their models with similar existing architectures. Five studies [10-12,16,19] detected the presence or absence of ROP disease within an average of 0.984 Area Under the ROC Curve (AUC). Six studies [12-15,17,20] detected the Plus disease providing an average of 91.13% sensitivity and 95.92%, specificity. Three studies [10-11,16] had an average sensitivity of 95.72% and average specificity of 98.15%. One study [16] worked closely with an ophthalmologist to prepare a report of their model results with his results for ROP disease diagnosis achieving 94.1% sensitivity and 99.3% specificity. Two studies [13,17] detected the presence of ROP at stage one and two with an average sensitivity of 96.2% and 95.7% specificity.

3. METHODOLOGY

ResNet-50 architecture [37] is a revised advanced version of the ResNet-34 model which utilizes a bottleneck structure while building the blocks. The blocks are built to allow 1*1 convolutions as the bottleneck to reduce model parameters and the multiplication of the matrix. The design of the architecture enhances the speed of the model training providing a three-layered stack. The architecture consists of a 7*7 Kernel convolution which are two sized strides, one maximum pooling layer with a two sized stride, one average pooling layer with one fully connected layer utilizing SoftMax activation function. The implementation follows a function, Output=F(X)+X where x represents an input from a residual block which is an output from the previous layer and F(X) is a function of the convolutional Neural Network Model built in blocks. The model architecture design steps shown in Figure 3 is designed to receive images as inputs, which are preprocessed by the ResNet-50 pipeline. After preprocessing, desired features are extracted and fed into a Deep Neural Network to quickly sort them as with having the disease or not. Those with ROP are further run under a classification module for ROP stage III disease detection.

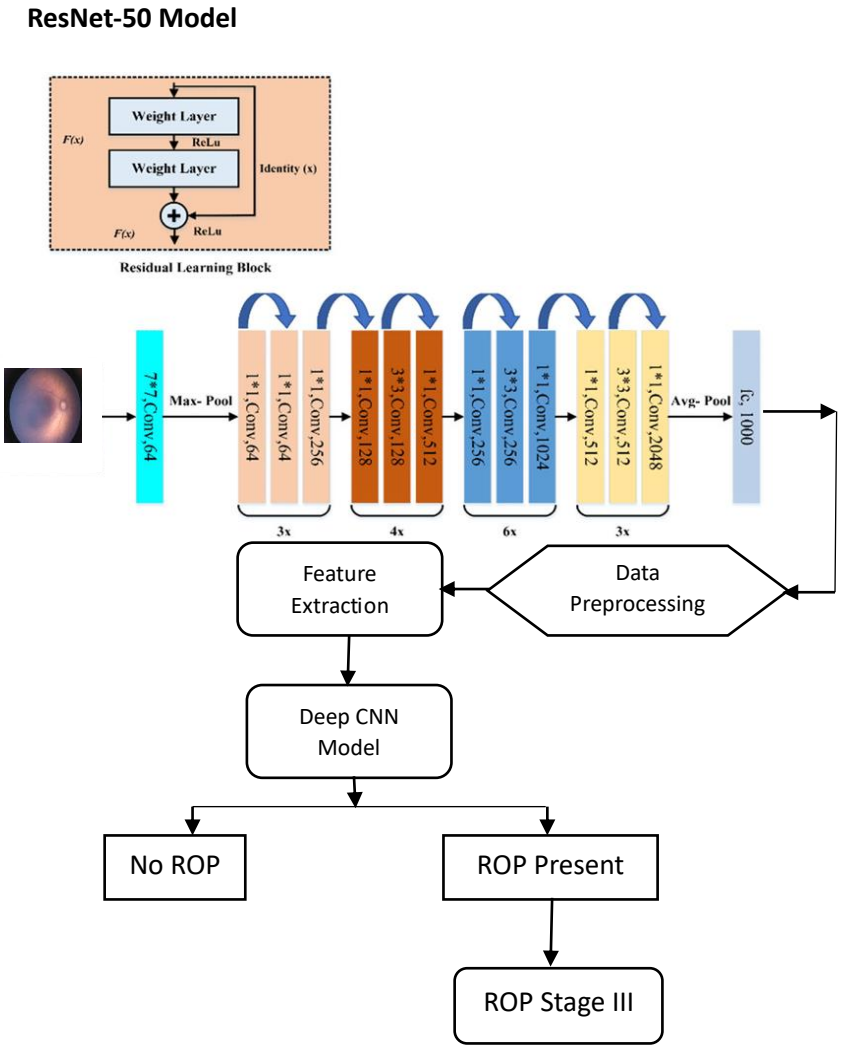

Figure 3. Model Architecture Design Steps

A. *Data Preparation*

A total of ninety-one (91) images were obtained from the Kaggle database [29]. Thirty-nine (39) images had been labeled as not having ROP disease. Nineteen (19) images had been labelled ROP stage one, Twenty-two (22) ROP stage two, eleven (11) images ROP stage three. The database does not contain images of ROP stage four and five. These images are all collected by different eye specialists globally and stored in Kaggle which is an online open-source database for scientific and research use. HVDROPDB database had fifty (50) images with ROP disease and not labeled as per the disease stage. As shown

in Figure 4, Data was split into two smaller datasets: Images with No ROP and images with ROP, those with ROP were then split creating another set of images with ROP stage three. Open CV library was used to preprocess images through reducing their size to 224*224. To increase the volume of the images data was augmented and all images were rotated setting the range of 2, width of 0.05 and height of 0.05, enabling the Zoom range to be [0.85,1.15]. Selection of the images for training, testing and validation was done with a ratio of 0.80 training, 0.10 testing and 0.10 validation.

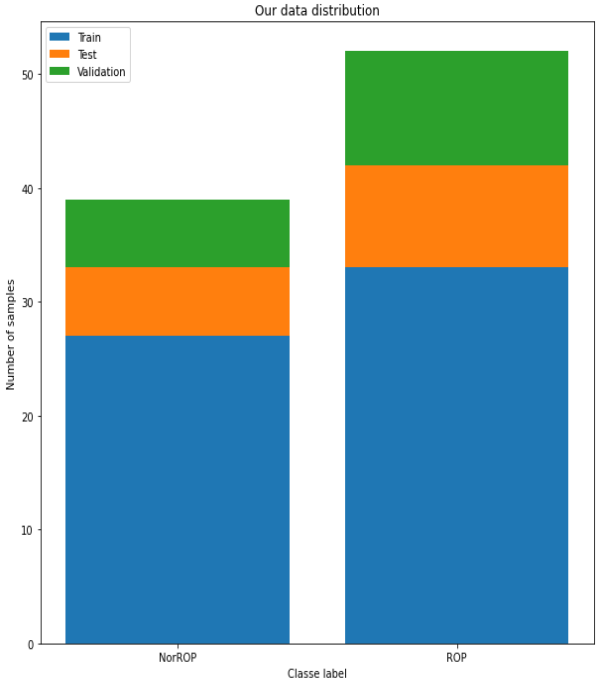

Figure 4. Data Class output

4. RESULTS

Data was first split into two sub classes. Images with ROP and with No ROP.

A. Data Visualization and preprocessing

Before augmentation, we split the data into training, Testing and Validation and as shown by Figure 5, and displayed the images.

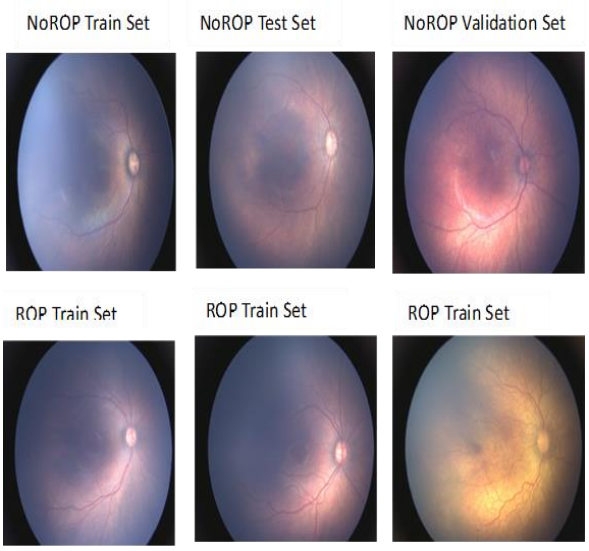

Figure 5. Data Visualization output

We build a list containing indexes for each data set which produced an output of the total number of images per data set with an output summary graph as shown in Figure 6. Images had been captured from both eyes, left and right having the structure of the images different. Images were flipped to obtain a uniform structure. Ninety-one images were also few, so we augmented the data to increase the number of images. The Deep Convolutional Neural Network design consisted of five layers for feature extraction and pretraining, one pooling layer and three fully connected layers with model epochs being 40 epochs. Adam optimizer was used to adjust the learning rate of all parameters reducing the loss function. At epoch 32 we did observe that there were no significant changes shown up to epoch 40 and the model producing stable results of 92.3% accuracy on testing results and the model loss decreased with the increase of each epoch as shown in Figure 7 and 8. The model has a function to predict the labels or class group to which each image belonged to. As shown by Figure 6, a confusion matrix was created to show test labels against predicted test labels.

B. Deep Neural Network Model Training

The model was trained to detect ROP stage three. Features of the images preprocessed by ResNet-50 were input to the model for disease stage three diagnosis. As shown by Figure 8, image grayscale conversion was done to reduce any chance of classification errors as a result of color and CLAHE applied to reduce image contrast as shown in Figure 9. The image vascular structure was extracted and used as the model training features. The distinguishing feature of ROP stage II from Stage III is that the ridge line for ROP stage III is longer than that of Stage II as shown in Figure 10.

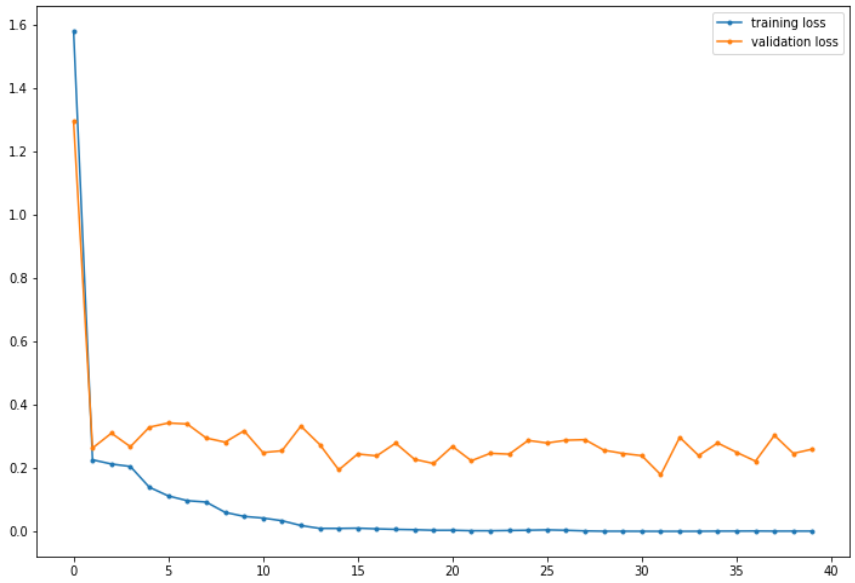

Figure 6. Model Training and Validation Loss

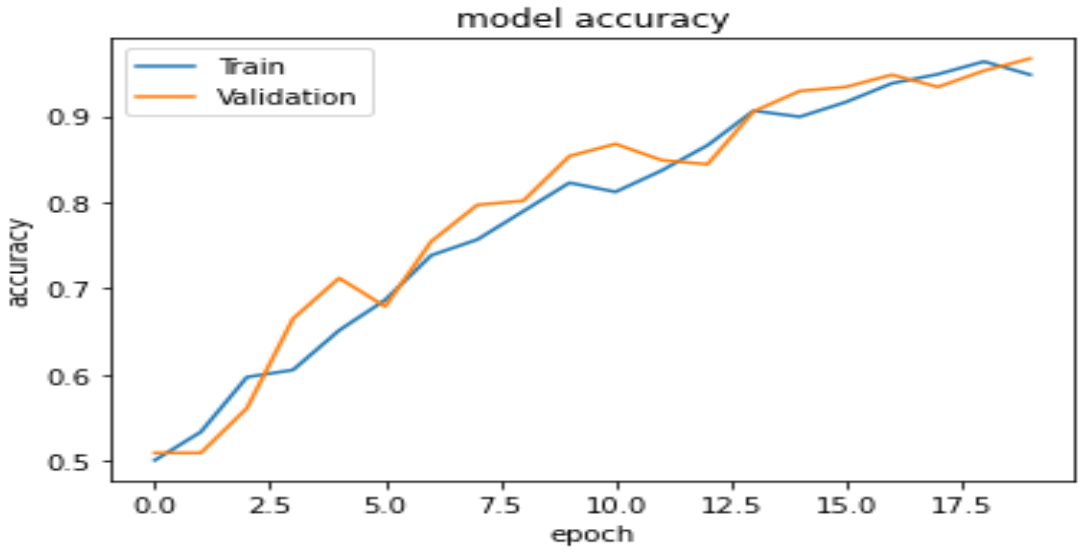

Figure 7. Model accuracy

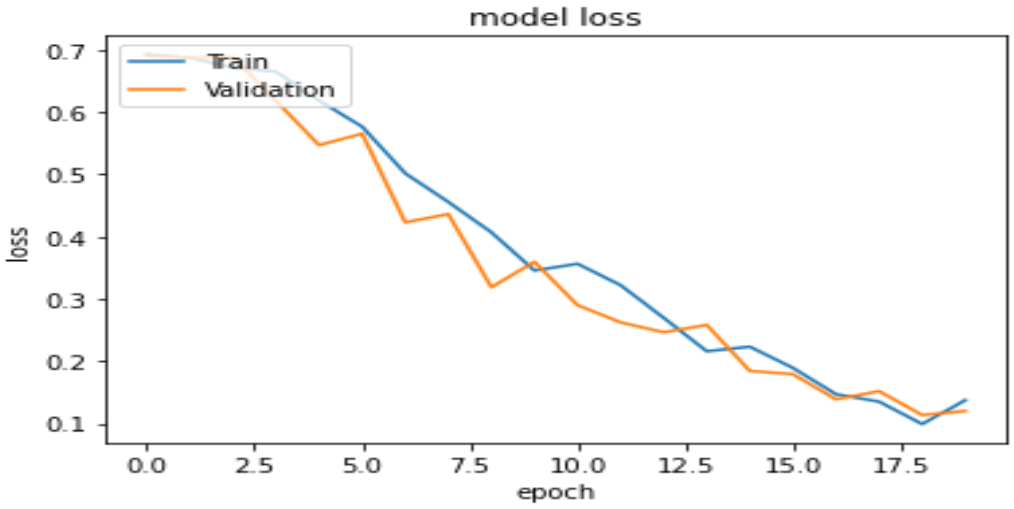

Figure 8. Model loss

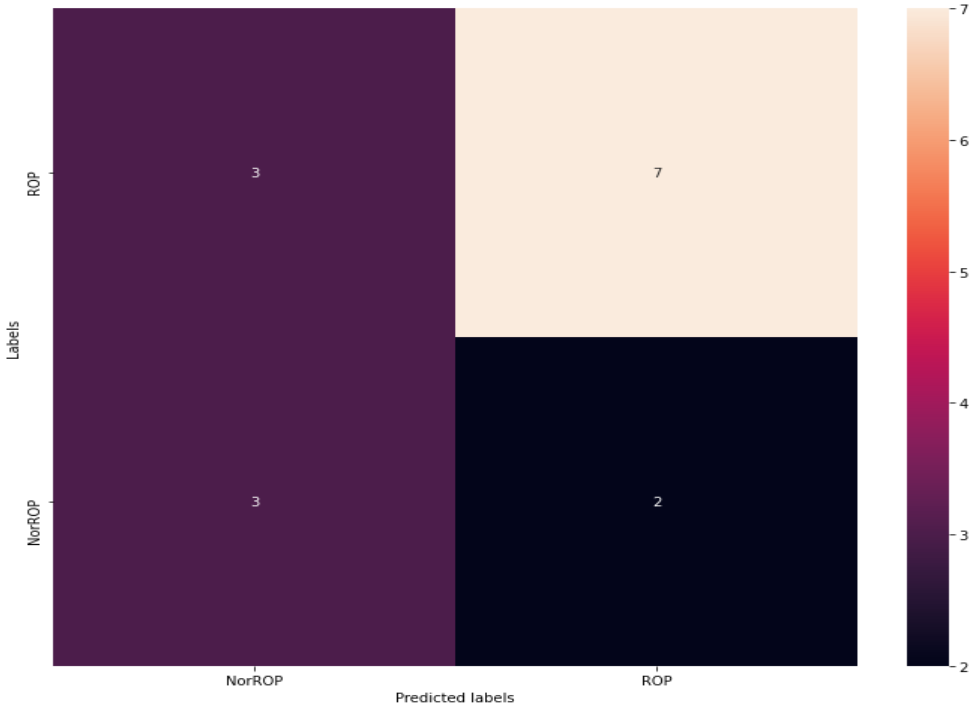

Figure 9. Prediction labels output

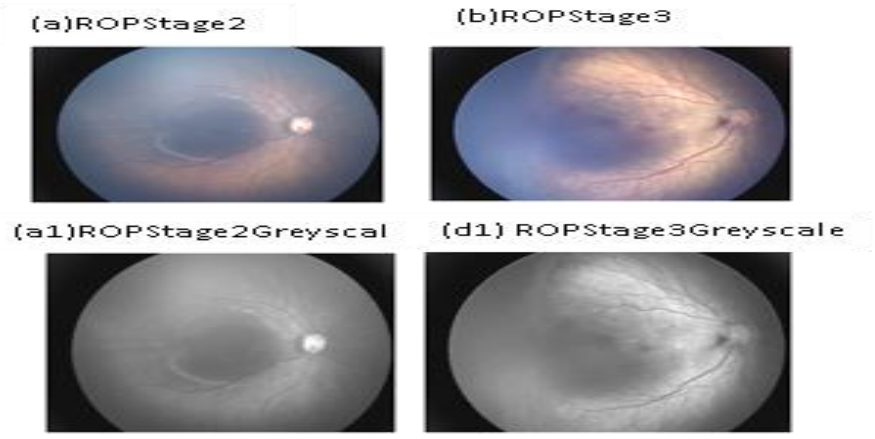

Figure 10. Image colour Normalization

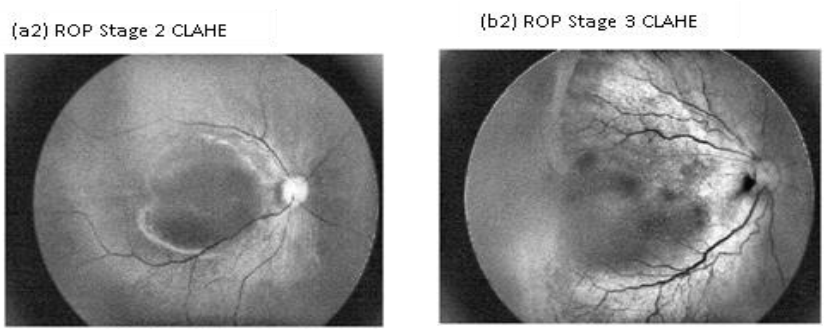

Figure 11. CLAHE output

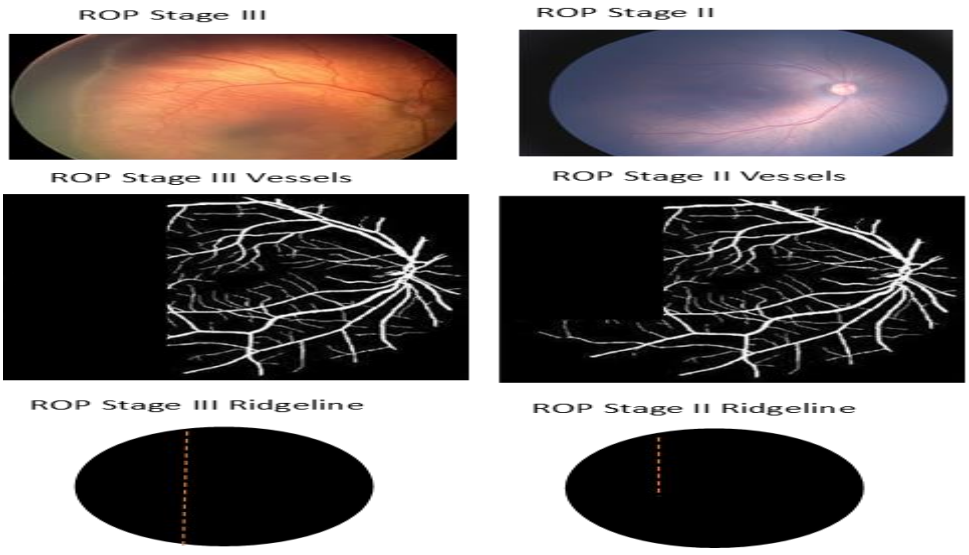

Figure 12. ROP stage III Ridgeline extraction

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Using equation 1-3 we obtained accuracy, sensitivity, and specificity of the Vgg19 and the S-Net models and compared the results of our model with that of an ophthalmologist as guided by the Kappa method [30] used for obtaining inter-rater reliability. The approach helped to allow comparison of the models results with the rating provided by the ophthalmologist [30]. TP (True Positive) is used to denote that ROP disease is present and the model results gives a positive output to confirm the presence of the disease, FN (False Negative) used to denote that ROP disease is present and the model results provides a negative result as disease absent, FP (False Positive) standing for disease absent and the model results showing ROP disease present, TN (True negative) to denote ROP disease absent and the model results showing absence of the disease.

$$Accuracy = \frac{TP + TN}{TP + TN + FP + FN} \quad (1)$$

$$Sensitivity = \frac{TP}{TP + FN} \quad (2)$$

$$Specificity = \frac{TN}{TN + FP} \quad (3)$$

C. Model Design Platforms

Some images classified as not of quality were processed using MATLAB R2023B and were incorporated into the quality database. The computer used for running the deployed model operated under Windows 10 OS with a RAM of 1 Terabyte. With the sponsorship of Google PhD Research Africa Funding, we were able to afford the GeForce RTX 2080 NVIDIA GPU which provided a powerful graphics for better image view. The GPU provides 11GB memory with a 352-bit bus to boost the memory.

D. Model Performance Comparison

The existing Deep Learning architectures have been developed to detect either the presence or absence of ROP disease or the ROP disease severity with no model for ROP stage III disease diagnosis. We configured the design of two models VGG-19 [31] and S-Net [32] ensuring that the same number of images are used for training, testing and validation. These two models had been built to detect presence or absence of ROP disease where we changed the design to have presence of ROP was named ROP stage II and absence ROP stage III. The design architecture for the two models VGG19 and S-Net had four layers [31,33] with the VGG19 having the first two layers of size 200 with a dropout rate of 49.5%, the third layer was lesser in size of 68 and with a drop out rate of 49.7%, the fourth layer was applied to produce disease detection. The S-Net model design was different with all layers of different sizes, having the first layer of size 510 with a dropout rate of 49.6%, second layer of size 202 and a dropout rate of 48.9%, the third layer of size 100 with a dropout rate of 50% and the last layer for disease detection giving no drop out.

As shown in Table I, a confusion matrix was created with 0 representing ROP stage two images and 1 representing ROP stage three images. The models were tested using the same image data sizes of one hundred and eighty-four (184). VGG19 model classified one hundred and seventy-five (175) images to their correct class of ROP stage two (TP) and giving nine images (9) as wrong classifications for ROP stage two (TN). The model also correctly classified one hundred and seventy-eight (178) images containing ROP stage three (TP) and six (6) images wrongly classified (TN) for ROP stage three. S-Net model on the other hand classified one hundred and sixty-eight (168) images to their correct class of ROP stage two (TP) and giving sixteen images (16) as wrong classifications for ROP stage two (TN). The model also correctly classified one hundred and seventy (170) images containing ROP stage three (TP) and fourteen (14) images wrongly classified (TN) for ROP stage three.

As shown in Table II, VGG19 model had the highest accuracy of ROP disease classification, and the results were compared with the results of our model. Five-fold cross validation was performed, and the results of our model was at an accuracy of 95.8, 96.9% sensitivity and 98.3% precision outperforming that of VGG19 model which had an accuracy of 92.8%, 94.9% sensitivity and 97.3% precision as shown in Table III. As shown in Table IV, we did a comparative analysis of the performance of our model with the results of similar recent developments even though most models were not developed to diagnose ROP stage three but for the presence or absence of the disease which was one of our objectives.

TABLE I. VGG19 AND S-NET MODELS CONFUSION MATRIX

VGG19[31]		0	1
	0	175.0	9.0
	1	178.0	6.0
S-NET [32]		0	1
	0	168.0	16.0
	1	170.0	14.0

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TABLE II. S-NET AND VGG19 RESULTS

Model	Accuracy	Specificity	Sensitivity	Precision	AUC
S-NET	86.21%	89.50%	95.63%	93.41%	0.90
VGG19	91.21%	97.52%	97.72%	90.84%	0.97

TABLE III. 5-FOLD CROSS VALIDATION OUTPUT

Fold Number	Accuracy (%)	Sensitivity (%)	Specificity (%)	Precision (%)	AUC
Fold 1	89.30	92.41	93.23	96.72	0.95
Fold 2	89.61	93.20	94.51	96.91	0.96
Fold 3	90.82	93.91	94.92	96.91	0.96
Fold 4	91.73	94.42	95.21	97.12	0.97
Fold 5	92.82	94.90	95.20	97.31	0.98

TABLE IV. RECENT DEVELOPMENTS RESULTS

Citation	Publication year	Classification	No. of Images	Accuracy	Sensitivity	Specificity
Haung et al., [12].	2021	Stage I and II ROP	11,372	99.92	96.12	95.90
Li, P., and Liu, J. [34].	2022	ROP stage I-III	18,827	none	95.91	96.42
Wang et al., [10]	2018	Mild or Severe ROP	20,795	none	96.63	99.32
Hu et al., [11]	2019	Mild or Severe ROP	3017	97.21	none	none
Brown et al., [17]	2018	Plus or Pre Plus ROP	5511	none	88.42	92.32
Camphell et al., [35]	2016	Plus or Pre Plus ROP	77	95.07	none	none
Yildiz et al., [36]	2020	Plus or Pre Plus ROP	1459	none	93.90	94.03

5. CONCLUSION

Retinopathy of Prematurity (ROP) disease affects babies born preterm and characterized with low birthweights. ROP disease is preventable when diagnosed before progressing from stage three to four. The disease which currently is termed as third pandemic has a high contribution to preventable blindness among children. High income countries have national screening guidelines and screening is mandatory to all babies born preterm which reduces the chances of blindness. The disease remains a burden for low-income countries with only two countries in Africa: South Africa and Kenya being the only two countries with national screening guidelines. The screening criteria for countries without screening guidelines is determined through a discussion and agreement of ophthalmologists available for the disease screening. The increase in the cost burden for the disease diagnosis with only few ophthalmologists available for the disease screening creates the need for technological experts to develop Artificial Intelligence systems for assistive diagnosis.

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Deep Learning applications have recently been developed to accurately provide a classification of many disease stages or detection. These systems results accuracy relies mostly on the quantity of data used for training paying attention on the model testing and evaluation by an expert. There exist three key challenges associated with Deep Learning models development which this work managed to overcome.

A. Data Quality

Data from the two databases had labelling on the camera used and we do note that different cameras produced images of different contrast affecting clarity and resolution. Transfer of images in some cases was causing distortion and we managed to overcome this challenge by building a module for image quality assessment then using quality images to train the model.

B. Data Imbalance

The dataset with ROP disease and the one without ROP were not equal in numbers creating imbalance. Imbalanced data increases the chances of misclassification. To avoid these challenges, we were able to augment the data to increase on volume of the images and obtained the Area Under Curve (AUC) to show the model loss results as shown in Figure 8.

C. Model Development

Developing a Deep Learning architecture from scratch is a tedious task and we do appreciate the developers of the existing architectures which can be customized and applied to solve many problems. In this work, we were able to customize ResNet-50 architecture for detecting the presence of ROP disease and a Deep Neural Network model for ROP stage three disease diagnosis. Transfer learning was applied to quickly adapt the training of the customized architectures to use the new available datasets successfully.

This work developed a Deep Learning model to first detect the presence or absence of ROP disease then diagnose ROP stage three which is a critical stage. The ResNet-50 architecture is customized to preprocess the images for ROP disease detection. Features are extracted where the ridgeline for ROP stage three is done for model training.

Extracted features are used to train a Deep Neural Network (DNN) to class ROP stage three. 91 images were obtained from Kaggle database, and 50 images were obtained from a recently published ROP database the HVDROPDB. The data sets were combined and augmented to achieve adequate datasets for training, testing and validation. The performance of our model was compared with the VGG19 and S-Net architectures where our model results had the highest accuracy of 92.8%, 94.9% sensitivity and 97.3% precision. To support future developments, we do recommend that there is need for more population-based research to be done on ROP and allow the data to be public which will support innovative developments for the disease diagnosis.

A. Availability of data and materials

Data used in this work is publicly available on Kaggle database and the HVDROPDB database. No license is required for use or during publication of articles.

B. Funding

This work received funding from Google PhD research in the year 2023.

C. Ethical approval

This study was reviewed and approved by Strathmore University Institutional Scientific and Ethical Review Committee (SU-ISERC), Certificate number (SU-ISERC1534/22) and approved by the Kenya National Commission for Science, Technology and Innovation (NACOSTI), license number (NACOSTI/P/23/23702).

D. Consent to participate

This work did not involve direct participation of human subjects or animals. Data and human images used in this study had been collected by ophthalmologists, properly labelled and stored in databases for research purposes and use.

E. Competing interest

All Authors declare no Competing Interests

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