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Interpretable Transfer Learning with EfficientNetB0 for Automated Detection of Rare Anemia Morphologies in Peripheral Blood Smears

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Abstract

Accurate diagnosis of rare anemias is challenging primarily due to limited annotated public datasets needed for developing interpretable automated diagnostic tools. We propose a two-stage transfer learning convolutional neural network (CNN) model, EfficientNetB0, for identification of disease-associated patterns in blood smear images.

To create and verify the EfficientNetB0 model, we used a two-part proof of concept method. First, model stability was verified using a binary subset of the TensorFlow Flowers

dataset (n=1539). It gained a validation accuracy of 0.997 and showed stable learning without overfitting. The validated method was applied to a Sickle Cell Peripheral Blood Smear dataset (n=569), to ensure the model would transfer learning to blood smears. The model was highly successful when trained and validated on the Sickle Cell validation set, with an accuracy of 0.992, precision of 1.000, sensitivity of 0.989, and specificity of 1.000, having no false positives and only one false negative.

Gradient-weighted Class Activation Mapping (Grad-CAM) was used to demonstrate the interpretability of the model, showing that attention was focused on characteristic crescent shaped erythrocytes common in sickle cell blood smears (Acharya & Prakasha, 2019; Elendu et al., 2023), rather than background noise. A MobileNetV2 baseline was trained under identical conditions and achieved significantly lower accuracy and specificity, confirming EfficientNetB0 provides substantially better performance for data scarce classification. These findings show that the EfficientNetB0 transfer learning network is highly accurate, interpretable, and generalizable even with limited data, providing a promising method for automated rare anemia diagnoses.

Keywords: Transfer Learning, EfficientNetB0, Peripheral Blood Smears, Rare Anemia Detection, Grad-CAM.

Introduction

Peripheral blood smear analysis can further research for many blood disorders, including various forms of anemia (I & Muhasin T P, 2014). However, rare anemias present a unique challenge, because their infrequency often means limited clinical experience and a severe scarcity of publicly available, well-annotated image datasets (Alzubaidi et al., 2020). That data

scarcity then causes more reliance on manual examination, which is prone to variability and requires specialized hematologists as well as costly specialized equipment that is not available in many countries (Tengshe et al., 2021). Manual examination for rare anemias tends to involve invasive procedures because of limited known biomarkers—most commonly bone marrow biopsies. This lack of accessible diagnostic help for rare anemias can often delay accurate diagnoses and treatment (Fattizzo et al., 2021; Vives Corrons, 2024).

We show that transfer learning with EfficientNetB0 allows for highly accurate classification even with smaller datasets, and Grad-CAM interpretability ensures clinically relevant predictions. Compared to previous models, this method is accurate, data-efficient, generalizable, and interpretable, highlighting structural patterns that correspond to disease pathology.

Convolutional neural networks (CNNs) have revolutionized medical image analysis, presenting new pattern recognition techniques and classification (Carrasco et al., 2025). CNNs excel at learning features directly from raw image data (Anwar et al., 2018). However, training these models typically demands a lot of labeled data, which is again, often difficult to obtain for rarer diseases (Pachetti & Colantonio, 2023; Shu, 2025). Transfer learning is an option to circumvent this issue, using knowledge gained from training on large, general image datasets (for instance, ImageNet) and adapting it to specific, data scarce medical tasks (Alzubaidi et al., 2020). This approach requires significantly less domain specific data for fine tuning, which is far more useful for rare anemias (Ouyang et al., 2022; Pachetti & Colantonio, 2023).

In this study, we propose and validate a transfer learning network using the EfficientNetB0 architecture, a highly efficient and scalable CNN (Tan & Le, 2020), for the automated detection of disease-associated patterns in peripheral blood smears. Recognizing the data accessibility issues with rare anemias, we instead used sickle cell anemia as a proof of concept model. Sickle cell is a severe hereditary disorder characterized by distinct erythrocytes with sickled shapes (Sen et al., 2021), making it useful for demonstrating the model's ability to identify specific features. While sickle cell itself is not a rare anemia, its clear biomarkers and data availability allow us to simulate the conditions of rare disease diagnoses where data is limited.

EfficientNetB0 was also compared to MobileNetV2, a commonly used lightweight CNN (Sandler et al., 2019). This baseline allows for evaluation of whether EfficientNetB0 provides a significant advantage for low data medical imaging tasks such as Sickle Cell diagnoses.

The objectives of this research were to (1) establish the stability of the EfficientNetB0-based model using a flower image dataset; (2) to demonstrate the model's accurate classification disease-associated patterns in blood smears using a sickle cell peripheral blood smear dataset; and (3) to ensure the interpretability of the model's predictions through Grad-CAM, confirming that attention aligns with relevant cellular features. By achieving these objectives, this study aims to further the development of interpretable and data-efficient ML tools that can enhance the diagnostics for rare anemias and increase availability, contributing to earlier treatments and improved outcomes.

We hypothesize that a transfer learning approach using EfficientNetB0, combined with the interpretability of Grad-CAM imaging, can accurately and transparently identify disease-associated patterns in peripheral blood smears, even when training data is limited—providing a practical method for automated rare anemia diagnostics.

Method

Data Sources:

To validate the convolutional neural network EfficientNetB0 model proposed, a two-part proof-of-concept method was used. In the first stage, the publicly available TensorFlow Flowers dataset (Abadi et al., 2016) was used to verify the functionality and configuration of the model in a controlled setting. A binary subset of images of dandelions and roses was extracted, which contained a total of 1539 images (1231 for training and 308 for validation). This dataset was used because it contained visually different classes, which are suitable for observing the behavior of the model in a non-clinical setting. The TensorFlow Flowers dataset consists of five flower species with high interclass variability. A binary subset of dandelions and roses was chosen to minimize class imbalance and enable feature separability.

In the second stage, the model was trained on a Sickle Cell Peripheral Blood Smear dataset from Kaggle (Tushabe et al., 2024) containing a total of 991 images (891 for training and 100 for validation) that were manually re-labeled as Negative (147 images, normal) and Positive (844 images, sickle cell anemia). This dataset was used as a substitute for a rare anemia set due to the limited publicly available peripheral blood smear data for rarer anemias. The objective was to demonstrate the model's ability to identify disease-associated structural patterns from blood

smear images. The Sickle Cell dataset consisted of peripheral blood smear images captured under bright field microscopy with variations in illumination, staining intensity, and density, to provide a realistic test of the robustness of the model to biomedical imaging artifacts.

Preprocessing and Data Partitioning:

All images were resized to the standard size of 256 x 256 pixels and were processed using the *preprocess_input* function from TensorFlow's EfficientNet module to normalize the pixel intensity distribution. Datasets were automatically batched and shuffled, and a fixed train-validation split of 80:20 was applied to both datasets. A random, fixed seed of 1 was used to ensure reproducibility. No additional data augmentation was done to isolate the transfer learning effects.

Versions

All analyses were conducted in Python 3.12.12. Packages Used: TensorFlow (4.9.9), Matplotlib (3.10.0), NumPy (2.0.2), tf-keras-vis (0.8.7), scikit-learn (1.6.1).

Model Architecture:

A transfer learning approach was used for EfficientNetB0, which was pretrained on the ImageNet dataset, as the base convolutional feature extractor (Tan & Le, 2020). The pretrained layers, which were composed of 4,050,852 parameters, were frozen during the initial training to preserve general visual representation. A custom classification was appended, consisting of a Global Average Pooling layer and a single sigmoid-activated Dense layer with 1,281 trainable parameters for binary classification. The model was then compiled using the Adam optimizer, a

binary cross entropy loss function, and accuracy was the primary performance metric. Training was performed for 5 epochs with a batch size of 32.

To assess whether EfficientNetB0 provides architectural advantages in low data environments, MobileNetV2 (which is pretrained on ImageNet as well) was used as a baseline (Sandler et al., 2019). The baseline was trained under identical conditions as EffiicientNetB0 as listed above, and the same training-validation split was used for all experiments, to allow for a fair architectural comparison.

All model code is publicly available on GitHub.

Evaluation and Metrics:

Model performance was assessed on the validation subset using accuracy, precision, sensitivity, false positive rate (FPR), and false negative rate (FNR). These metrics were derived from the confusion matrix by the following standard definitions, where TP is "true positive," TN is "true negative," FP is "false positive," and FN is "false negative":

$$\text{Accuracy} = \frac{TP+TN}{TP+TN+FP+FN}$$

$$\text{Precision} = \frac{TP}{TP+FP}$$

$$\text{Sensitivity} = \frac{TP}{TP+FN}$$

$$\text{Specificity} = \frac{TP}{TN+FP}$$

$$\text{False Positive Rate (FPR)} = \frac{FP}{TN+FP}$$

$$\text{False Negative Rate (FNR)} = \frac{FN}{TP+FN}$$

ROC Curve and AUC:

Classification performance was assessed over various decision thresholds using the Receiver Operating Characteristic (ROC) curve; Predicted probabilities generated by the model on the validation set were compared to true labels to compute the True Positive Rate and the False Positive Rate. The ROC curve was constructed by plotting TPR by FPR and the Area Under the Curve (AUC) was calculated as a threshold-independent metric of distinction ability. These analyses were performed using the scikit learn implementation (Pedregosa et al., 2018).

Interpretability and Visualization:

To assess interpretability, Gradient-weighted Class Activation Mapping (Grad-CAM) (Selvaraju et al., 2020) was applied to the final convolutional block of EfficientNetB0 (*block7a_project_conv*). Grad-CAM heatmaps were normalized between 0 and 1 and overlaid on the corresponding output images using a partially transparent colormap. This allowed for the qualitative visualization of image regions that contributed most strongly to the model's predictions.

Results

Stage 1 (Flowers Classifier, System Validation):

The initial experiment using the dandelion and rose subset of the TensorFlow Flowers dataset (n=1539) confirmed the model's stability (Figure 1). The network achieved rapid

convergence within five epochs (Figure 2). Validation accuracy increased from 0.85 in epoch 1 to 0.997 by epoch 5, as well as a steady decline in validation loss from 0.13 to 0.039 (Table 1).

Figure 1

Sample Dandelion and Rose Images from Tf_flowers Dataset (The TensorFlow Team, 2015).

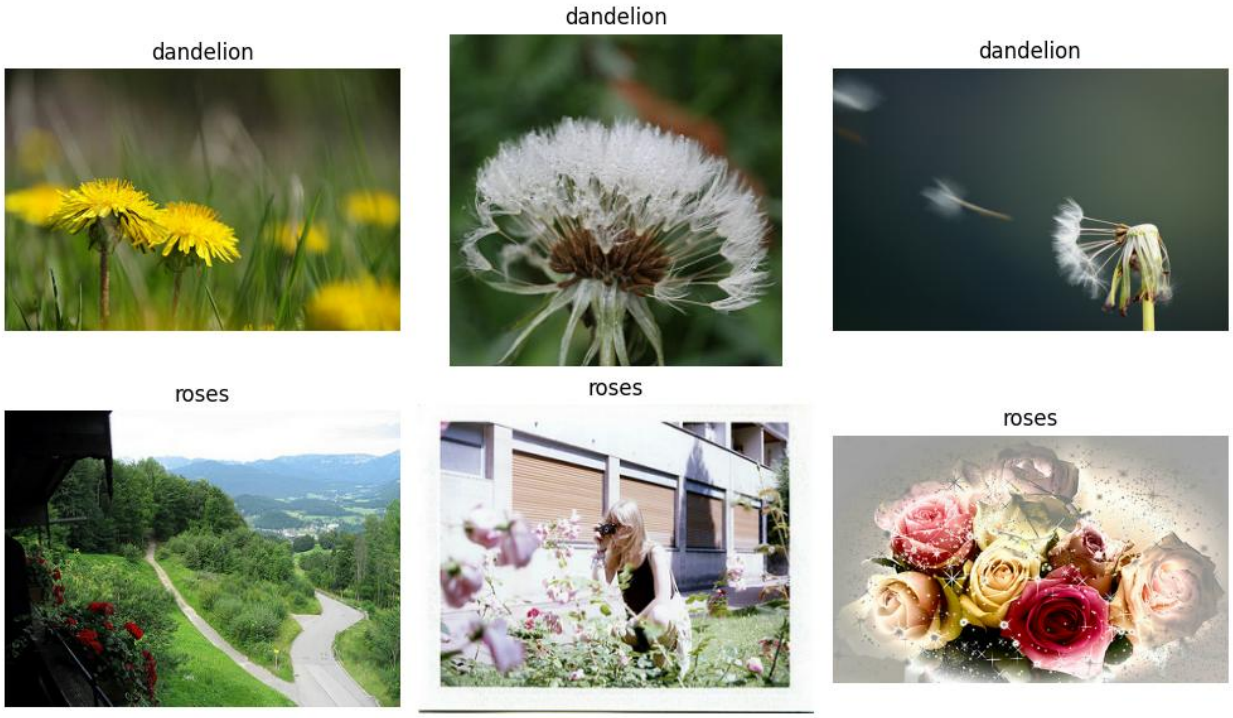


Table 1

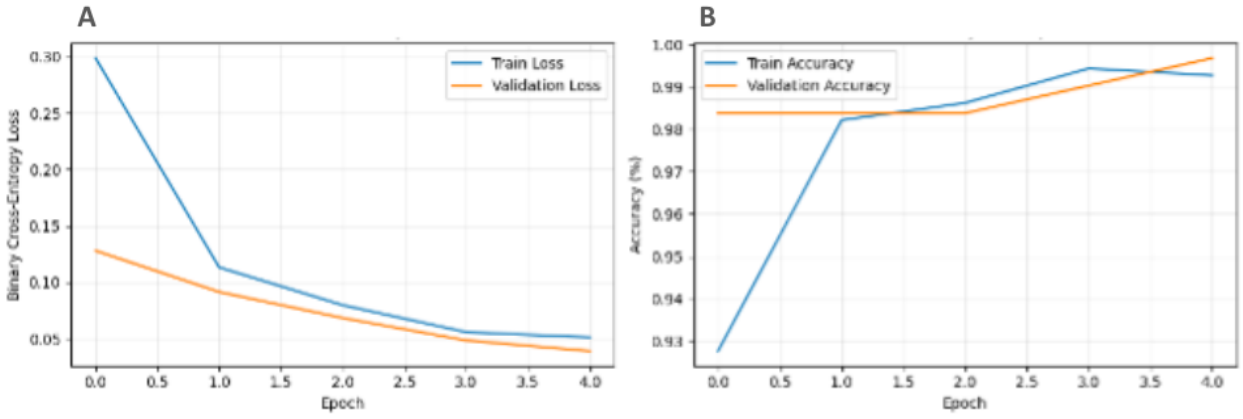
Training Performance (Accuracy and Loss) for Flower Classifier Across 5 Epochs.

Epoch	Training Accuracy	Validation Accuracy	Training Loss	Validation Loss
1	0.8514	0.9838	0.4268	0.1280
2	0.9850	0.9838	0.1255	0.0914
3	0.9846	0.9838	0.0859	0.0683
4	0.9943	0.9903	0.0577	0.0484
5	0.9924	0.9968	0.0529	0.0390

Figure 2

Model Loss and Model Accuracy Graphs for Flower Classifier Across 5 Epochs.

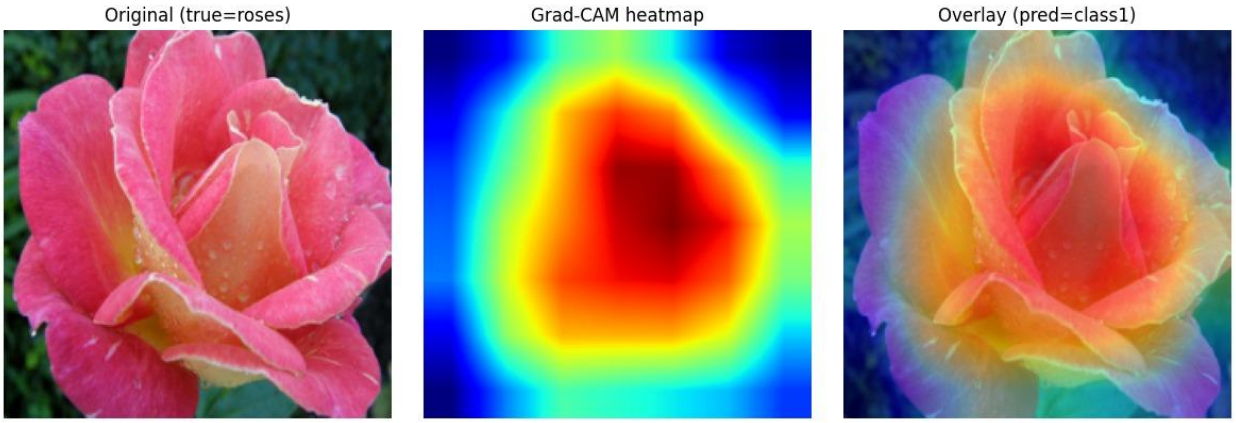
[A] Model loss over 5 epochs. [B] Model accuracy over 5 epochs.



Evaluation on the validation set yielded the confusion matrix [162, 2, 2, 142], where true negatives (TN = 162) and true positives (TP = 142) substantially outnumbered misclassifications (FP = 2, FN=2). Other metrics also confirmed the nearly perfect distinction between dandelions and roses: accuracy = 0.987, precision = 0.986, recall = 0.986, and specificity = 0.988.

Figure 3

Grad-CAM Visualization for Flower Classifier



Grad-CAM visualization revealed that the CNN concentrated on petal regions and central floral structures, while disregarding background elements, confirming biologically plausible attention and successful feature extraction (Figure 3).

Stage 2 (Sickle Cell Classifier)

The validated method was next applied to a Kaggle peripheral blood smear dataset containing 569 images (normal = “Negative”, sickle cell = “Positive”; train ≈ 455, validation ≈ 114). The same EfficientNetB0 backbone was used, pretrained on ImageNet and frozen during training, with a sigmoid-activated dense output layer for binary prediction. Training performance improved consistently over 5 epochs (Figure 4). The model’s validation accuracy increased from 0.70 after epoch 1 to 0.984 by epoch 5, with validation loss decreasing from 0.51. to 0.11 (Table 2, Figure 5).

Figure 4

Sample (Upper Row) Positive and (Lower Row) Negative Images from Peripheral Sickle Cell Dataset.

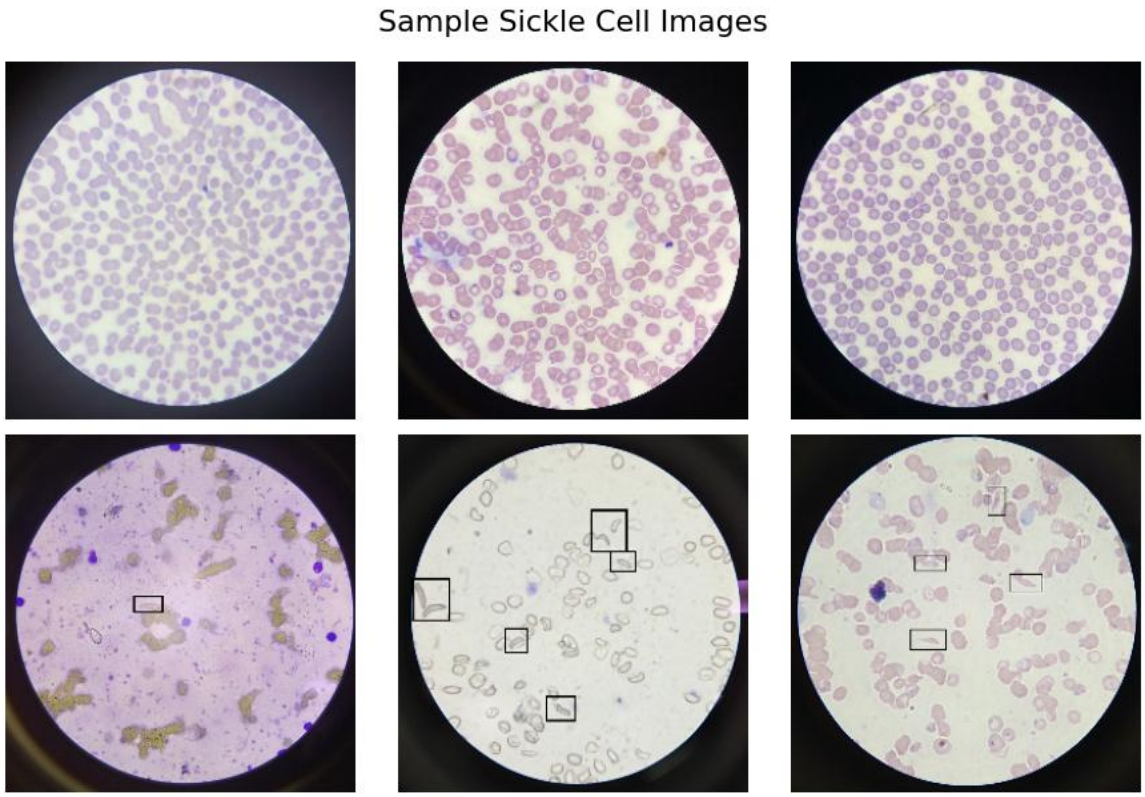


Table 2

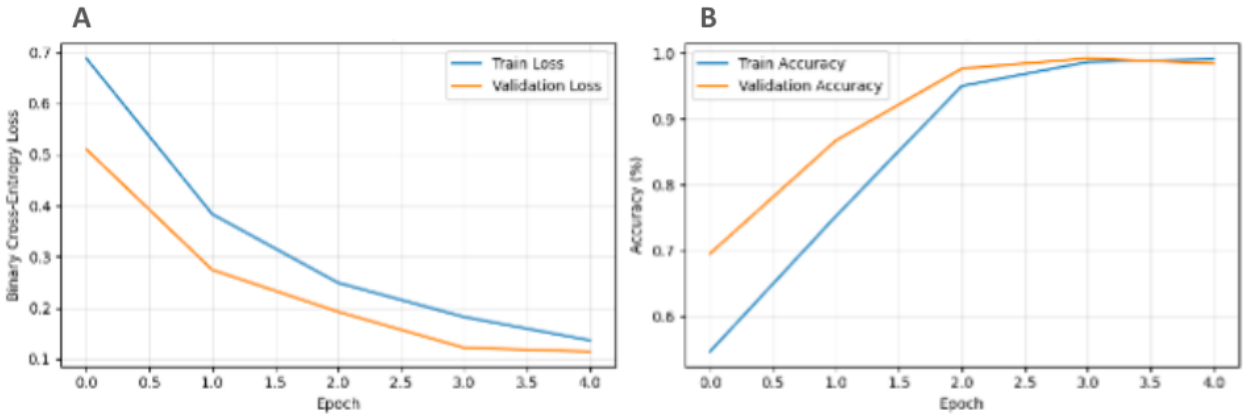
Training Performance (Accuracy and Loss) for Sickle Cell Classifier Across 5 Epochs.

Epoch	Training Accuracy	Validation Accuracy	Training Loss	Validation Loss
1	0.3922	0.6953	0.8574	0.5102
2	0.7534	0.8672	0.4143	0.2743
3	0.9088	0.9766	0.2772	0.1921
4	0.9884	0.9922	0.1949	0.1218
5	0.9900	0.9844	0.1397	0.1142

Figure 5

Model Loss and Model Accuracy Graphs for Sickle Cell Classifier Across 5 Epochs.

[A] Model loss over 5 epochs. [B] Model accuracy over 5 epochs.

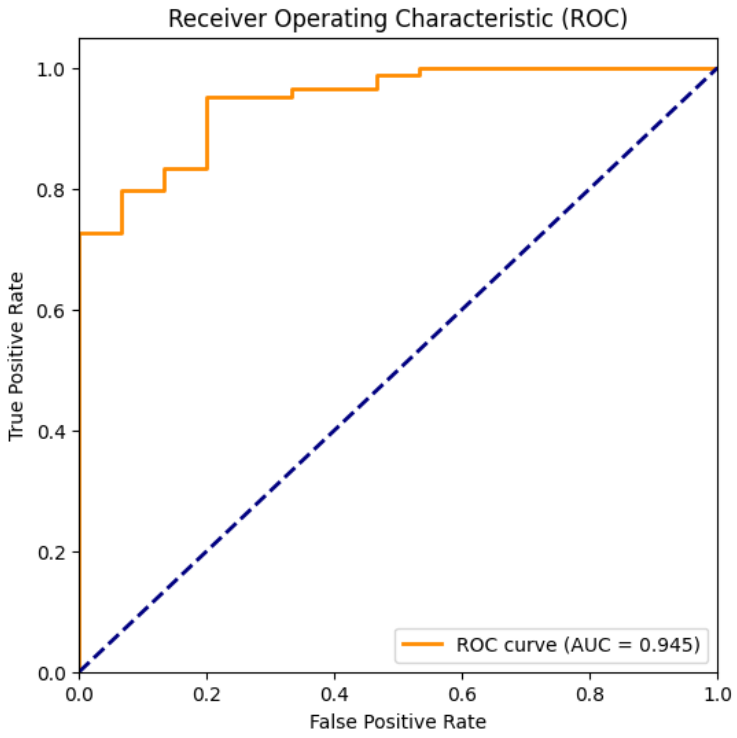


Validation performance yielded the confusion matrix: [34, 0, 1, 93], corresponding to TN = 34, TP = 93, FP = 0, and FN = 1. From these values, the model achieved accuracy = 0.992, precision = 1.000, sensitivity = 0.989, specificity = 1.000, FPR = 0.000, and FNR = 0.011. These results demonstrate excellent performance with no false positives and a single false negative across the entire validation set (Figure A1).

A ROC analysis was also conducted on the validation dataset—reflecting high sensitivity at low false positive rates (Figure 6). The model achieved an AUC of 0.94524, indicating the model's ability to accurately distinguish between sickle cell—positive and negative peripheral smear images.

Figure 6

Receiver Operating Characteristic (ROC) Curve for Sickle Cell Classifier.

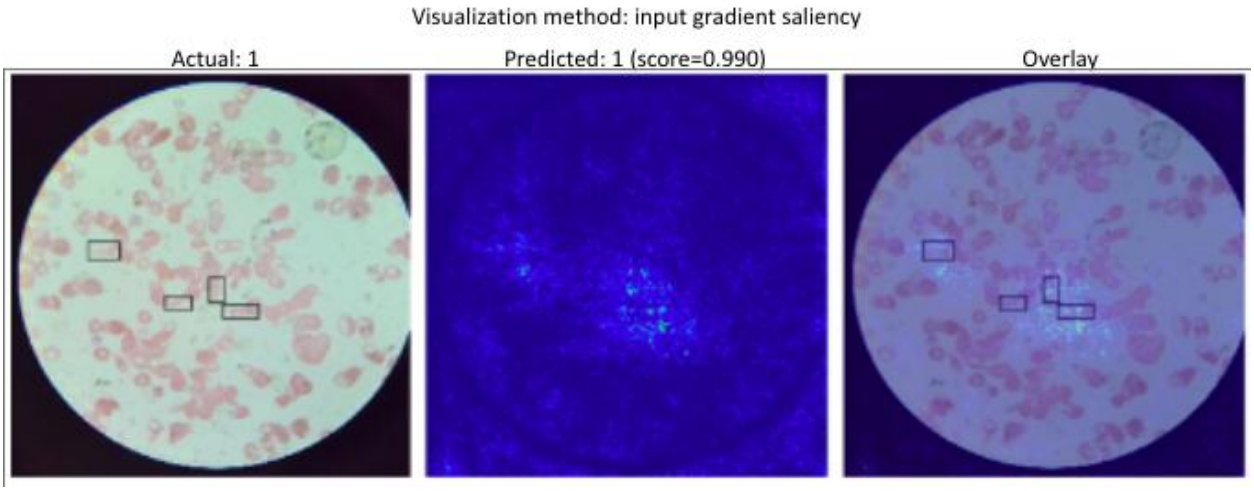


Grad-CAM heatmaps (Figure 7) indicated that the model's attention was concentrated on individual erythrocytes that were elongated and crescent-shaped—characteristic of sickle cell disease (Department of CSE, Manipal Institute of Technology, MAHE, Manipal-576104 et al., 2019; Elendu et al., 2023)—rather than background noise or staining artifacts. In contrast, normal samples produced activations distributed relatively evenly over uniformly circular cells, suggesting the CNN learned clinically meaningful structural features.

Collectively, these findings confirm that the EfficientNetB0-based transfer learning network was successfully generalized from non-medical to medical images, achieving both high quantitative performance and biological interpretability.

Figure 7

Grad-CAM Visualization for Sickle Cell Classifier

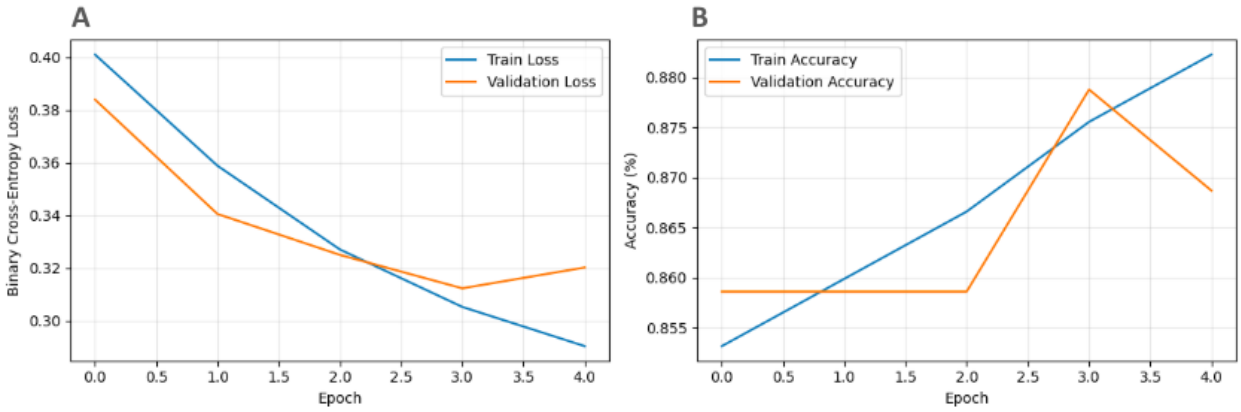


Baseline Architecture Comparison

To evaluate whether EfficientNetB0 provides performance advantage over other commonly used lightweight CNNs, a MobileNetV2 baseline was trained under identical conditions (Sandler et al., 2019). Although it achieved rapid convergence as well, the validation accuracy plateaued and declined after epoch 3, while validation loss began to rise (Figure 8). It achieved accuracy = 0.869, precision = 1.866, sensitivity = 1.000, specificity = 0.133. In contrast, EfficientNetB0 achieved significantly better performance, especially in accuracy and specificity (Table 3).

Figure 8

Model Loss and Model Accuracy Graphs for MobileNetV2 Sickle Cell Classifier Across 5 Epochs.



[A] Model loss over 5 epochs. [B] Model accuracy over 5 epochs.

Table 3

Comparison of EfficientNetB0 and MobileNetV2 Confusion Matrix Values

Model	Accuracy	Precision	Sensitivity	Specificity
EfficientNetB0	0.992	1.000	0.989	1.000
MobileNetV2 (baseline)	0.7534	0.8672	0.4143	0.2743

Discussion

In this study, we presented a two-stage transfer learning approach using EfficientNetB0 that achieved highly accurate and interpretable classification of disease-associated patterns in peripheral blood smears. Stage 1 was conducted on a binary subset of the TensorFlow Flowers

dataset and confirmed the model's stability and ability to generalize from visually distinct classes. The nearly perfect validation accuracy (0.997) confirmed that the model can learn relevant features without overfitting before introducing the model to biomedical images. Stage 2 applied this methodology to a Sickle Cell Peripheral Blood Smear dataset, simulating a rare anemia scenario; The model again achieved excellent performance on the validation set (accuracy = 0.992, precision = 1.000, sensitivity = 0.989, specificity = 1.000), with no false positives and a single false negative. These results indicate that transfer learning enables highly data-efficient classification, even with limited training data (Pachetti & Colantonio, 2023). Generated Grad-CAM heatmaps further showed that the network's attention was concentrated on the sickled, crescent shaped erythrocytes—the main feature of sickle cell disease (Department of CSE, Manipal Institute of Technology, MAHE, Manipal-576104 et al., 2019; Elendu et al., 2023) —rather than background noise or irrelevant staining artifacts. The model also achieved an AUC of 0.94524, indicating the model's excellent ability to distinguish between sickle cell positive and negative blood smears. This threshold-independent metric corroborates the high accuracy, precision, and specificity observed in the confusion matrix, confirming that the classifier maintains successful across a wide range of probability cutoffs.

Compared to other approaches to blood smear analysis that often rely on large annotated datasets or hand engineered features such as ResNet-18, DenseNet121, and VGG16 (Baydargil & Bocklitz, 2025; Houssein et al., 2023; Sandler et al., 2019), this model has clear advantages in both data efficiency and interpretability. The EfficientNetB0 model not only achieves competitive performance, but also has interpretable visual explanation for its predictions, important for clinical use. It was tested against a MobileNetV2 baseline, which demonstrated

extremely low specificity, classifying nearly all samples as positive. This suggests that MobileNetV2 overfit to the majority class and was unable to distinguish sickled from normal erythrocytes in a data limited environment. By focusing on clinically relevant features, EfficientNetB0 offers transparency that other CNN-based classifiers like MobileNetV2*f*mobile lack.

However, there are limitations to this approach. While it was necessary to use a smaller dataset to simulate the data scarce conditions for rare anemias, the small dataset may not have captured the full spectrum of variability that would be observed in clinical practice. Additionally, although the work addresses a binary classification task, the model's high success suggests strong potential for extension to multi-class rare anemia diagnosis. Future work should involve augmenting the datasets with synthetic images, integrating multiple imaging methods, and evaluating generalizability to rare hematologic disorders.

Overall, these findings illustrate that EfficientNetB0-based transfer learning offers a promising strategy for automated, data-efficient, and clinically meaningful analysis of peripheral blood smears. The focus on disease-relevant cellular features and its high classification performance suggests that this approach could improve diagnostic precision and ultimately supplement rare anemia diagnostic methods. This study establishes a method for using non-medical datasets to validate model methodology architectures before clinical application, a strategy that can accelerate development of interpretable ML in low-data environments.

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Appendix

Figure A1

Extracted False Positive for EfficientNet B0 Sickle Cell Classifier