International Journal of Basic and Applied Sciences, 14 (1) (2025) 65-73

International Journal of Basic and Applied Sciences

Website: www.sciencepubco.com/index.php/IJBAS
https://doi.org/10.14419/ms00zj36
Research paper

A non-invasive approach for diagnosing diabetic retinopathy using stacked ensemble deep learning mechanism incidental towards chronic kidney disease

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Received: March 14, 2025, Accepted: April 12, 2025, Published: April 15, 2025

Abstract

Chronic kidney disease (CKD) is progressive in several parts of the world. The prevalence of CKD is rapidly increasing due to dis-eases such as hypertension and diabetes, the two major causes of CKD, and due to the global aging population. Non-invasive methods play an important role in identifying CKD. Retinal photography nowadays is a source that provides vital information related to the eye as well as systemic vasculature and acts as a non-invasive diagnostic test. The physiological, developmental, and pathogenic pathway information shared by the eye and the kidney seems to be similar. With the advent of Deep Learning, the detection of CKD and diabetic retinopathy is taking new horizons. In this paper, a novel mechanism is proposed for identifying Diabetic Retinopathy, which highly influences CKD progression. Also, CKD prediction is done using retina images. To accomplish a notable detection, A lightweight and efficient Transfer Learning based architecture, "RIX Net," has been employed in classifying diabetic retinopathy severity as well as CKD. Five datasets of various sizes with respect to Diabetic Retinopathy and one corresponding retinal dataset to CKD have been used to measure the performance of the proposed architecture. The architecture performed well with around 90% performance in all cases.

Keywords: *Retina-Based CKD Diagnosis; Diabetic Retinopathy Diagnosis; Non-Invasive Techniques in CKD Prediction.*

1. Introduction

Chronic kidney disease is an irreversible kidney disorder that is of serious concern, and it impacts the rise of wide range of ailments that include heart failure, orthopaedic disorders, anaemia, and others. Usually, kidney disease couldcan'tlearly identified at the early stage. The state of the kidney becomes chronic by the time the symptoms are visible. Other diseases also lead to Chronic kidney ailments. As the chronic condition shall be known at a later stage, the disease will be in an irreversible state, consequently treatment becomes difficult, which leads to death. Therefore, an early-stage diagnosis is highly essential for treating such ailments.

The presence of chronic kidney disease is analysed and confirmed with the Filtration Rate -GFR of 60 ml/min/1.73 m^2 and/ or the indication of renal impediments for minimum three months [1]. As per the clinical settings, the blood samples of an individual are tested for the presence of Urinary Albumin to Creatinine Ratio and estimated GFR, in short mentioned as UACR & eGFR respectively. According to the KDIGO guidelines, there are five stages for renal disease in which End-stage kidney disease (ESKD) and Severe CKD are the severe stages that requires kidney replacement or yet times lead to death. The next set of stages namely the moderate CKD or mild CKD in which the CKD is curable if the patients are properly treated. The first stage is Normal CKD, where the kidney dysfunction is in its initial stage. Planned and prompt management increases the quality of life in CKD patients, even those who possess a high risk of ESKD. Morbidity, Mortality, and healthcare-related costs also may be reduced.

The eye is a window to several diseases, most importantly kidney diseases and Diabetes. Fig. 1 represents the similarities between the Eye and Kidney in structure as well as other aspects. Various systemic conditions in the body are often reflected by the eyes. Due to the rising incident of chronic as well long prevailing diseases such as diabetes and hypertension, paralleling trends of the Western world, there is a surge in the incidence of CKD and is expected to continue over time. The normal functionality of the kidneys is disrupted by various health disorders and other medical conditions. Most importantly diabetes mellitus, that leads to microvascular complications such as nephropathy and diabetic retinopathy (DR) deviate the kidney functionality. Due to CKD exerting extensive systemic effects, multiple organs and organ systems become highly impactful.

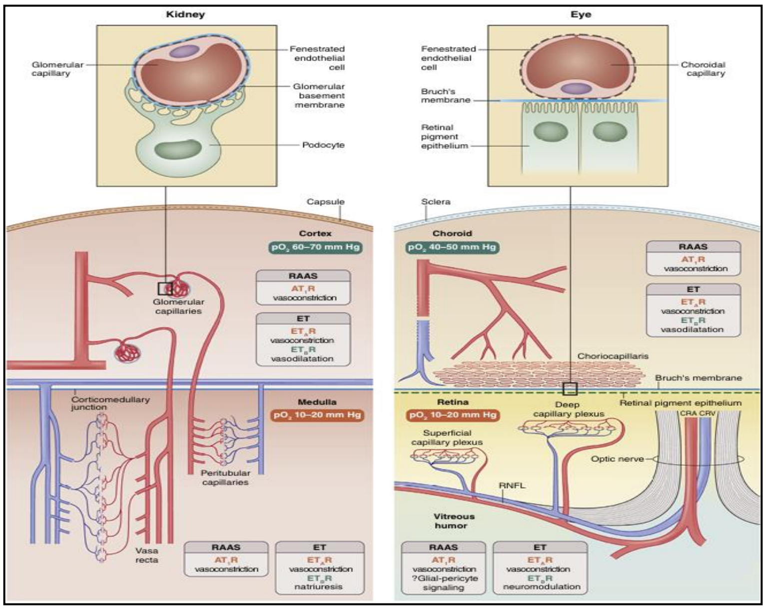

Fig. 1: Eye-Kidney Similarities.

Retinal fundus pictures are highly effective in diagnosing various disorders, including chronic kidney disease (CKD). Fig. 2(a) and 2(b) depict the retinal fundus pictures, vascular structures, and skeleton maps illustrating the fractal dimension of a healthy individual and an individual with chronic kidney disease (CKD), respectively.

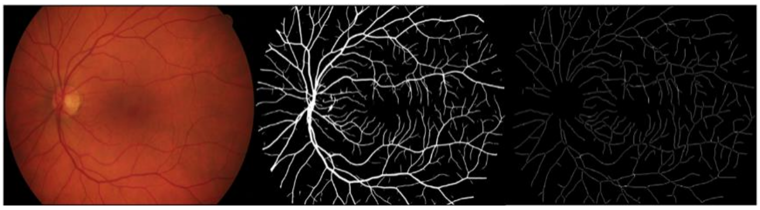

Fig. 2: A) Healthy Volunteer – Retinal Fundus Image – Vascular Structure – Skeleton Maps for Fractal Dimension

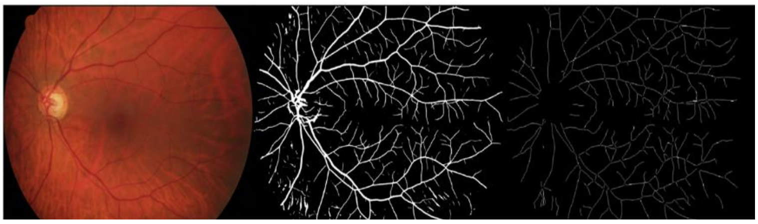

Fig. 2: B) Patient with CKD – Retinal Fundus Image – Vascular Structure – Skeleton Maps for Fractal Dimension (DF) Analysis.

Grzybowski et.al. [2] performed a systematic review on how AI is highly useful in retina image-based applications. It was found that the interpretation of retinal images using AI algorithms offered distinguished performance when compared to expert physicians and clinical data in identifying ophthalmic as well non-non-ophthalmic disorders. According to Mitani et al. [3] retina is a source of subtle indications of various diseases. They investigated that the application of deep learning in retinal image analysis can reveal the risk of CKD. Alongside Wen et al. [4], mentioned that AI reformed the health care due to its commendable capabilities. They affirm that the eye is a non-invasive observation window to identify various diseases that including CKD, T2DM, hypertension, and so on. A detailed analysis of various diseases that could be identified using retinal images is cited in their review. The severity of retinopathy is related to the level of loss of kidney functionality. As the presence of diabetic retinopathy indicates the CKD incidence, it is worthwhile to mention the research exploration on DR. Haq et al. [5] conducted an exhaustive literature review on the deep learning models used in DR detection. Their research highlights specific research questions and presents the taxonomy for DR detection.

In this section, a brief introduction is given on Retinal diagnosis, diabetic retinopathy, and DR-CKD association. The literature review is presented in the succeeding section, while the datasets used, and the deep learning architecture are described in Section 3. In section 4, the results and discussion are presented and then verified. The fifth section concludes the work.

2. Literature survey

Prominent researchers contributed to the fields of Diabetic Retinopathy and retinal-based chronic kidney disease diagnosis. This section presents the literature relevant to their research.

In [6], the systemic biomarkers relevant to retinal images are described in detail, and Deep Learning methods are employed to extract them. The associations between retinal fundus and chronic kidney disease (CKD) were investigated by Hamzah et al. [7]. Using clinical factors and deep learning algorithms applied to retinal photographs, Joo et al. [8] developed a non-invasive technique for stratifying chronic kidney disease. Three DLA models were used to demonstrate the noteworthy findings by Sabanayagam et al. [9] that include a Hybrid Deep Learning Algorithm (DLA) using RF DLA alone, in addition to both Retinal Image and RF.

The kidney and eye typically exhibit analogous structures concerning physiological and pathologic pathways. Patients exhibiting retinal microvascular symptoms are diagnosed with chronic kidney disease (CKD). It would be easier to diagnose CKD if DR screening could determine its prevalence. The study is done on 11,758 images, and the performance is quantified with an Area Under Curve, which is commendable. Betzler et al. [10] devised a CNN architecture for the identification of Diabetic Kidney Disease across three cohorts including 13,284, 1,969, and 712 pictures, achieving ROC-AUC values of 0.826, 0.764, and 0.726, respectively. An et al., [11] created an ensemble model that integrates ResNet and EfficientNet to diagnose chronic kidney disease (CKD) using a dataset of 14,040 retinal fundus images. They achieved an ROC-AUC of 0.798.

In detecting chronic kidney disease (CKD), Zhang et al., [12] performed a groundbreaking work using 115,344 retinal fundus photos for training and testing with a deep Convolutional Neural Network model. Validation of the primary cohort demonstrated enhanced performance, with an AUROC of 0.85–0.93. An external cohort consisting of fundus photos obtained through cell phones and other devices is utilised to validate the work.

A subsequent study by Nadeem et al. [13] was executed systematically, adhering to the PRISMA methodology. The first search in this research report was simple, using only the terms "deep learning" and "Diabetic retinopathy." In their study, authors compared an inclusive range of deep learning models, architectures, and platforms, breaking down each one according to its accuracy, datasets, and image modalities. Their work revealed that the studies that look at the pros and cons of using deep learning models in healthcare are fewer in number.

A comprehensive analysis was conducted in another study on diverse methodologies to diagnose diabetic retinopathy, encompassing detection techniques and methods for picking pertinent variables [14]. The investigation included many computational approaches, such as genetic algorithms, fuzzy logic, and neural networks. Research was performed by combining these techniques as potential tools for identifying diabetic retinopathy. Although their study performed well, their study didn’t seem to be systematic. It seems that the details related to the publicly available DR datasets are limited.

The exhaustive study performed by Vij & Arora, [15] in their research covering the deep learning (DL) methods for early detection of DR using retinal fundus images seems to be systematic. However, the complexity of the models was not addressed in their study. They analysed literature on diabetic retinopathy detection with the articles published till 2021. They mentioned that the earlier Diabetic retinopathy (DR) screening methods seemed to be time-consuming and labour-intensive, which delayed diagnosis and treatment. Using AI to screen for diabetic retinopathy focuses on three main goals: reducing the costs, improving the accuracy, and enabling more patients to afford the screenings. Bosch DR algorithm, Retmarker DR and Eye Art are few examples of the many AI-driven screening tools that use the deep learning technique involving CNN to analyse retinal images to detect and track the development of diabetic retinopathy (DR) [16]. It is proven that using the AI-powered methods in detecting diabetic retinopathy has enhanced the sensitivity and specificity. According to Nanegrungsunk et al., [17], Artificial intelligence-based DR screening has exhibited improved diagnostic sensitivity and accuracy in DR identification, making it to be a promising tool for comprehensive DR screenings. Not only detection, BUT the AI tools are ALSO used in generating images among which a recent AI program generated images with an accuracy of 80.79 to 93.34 percent.

In the contributions of Bermejo et al., [18] and Lee et al., [19], research has shown that DR, which is a common microvascular disorder of diabetes, is significantly correlated with CKD in the people having diabetes. Reduced Filtration rate (eGFR) levels are associated with increased diabetic retinopathy risk. Wang et al., [20] provides a more disease-specific viewpoint. There association between retinal changes and the renal function has been identified and specified in [21] in which they found that diabetic retinopathy was more common in those who also had diabetic nephropathy. The major focus of the study conducted by Nusinovici et al., [22] is on the quantitative relationships between renal function indicators and the retinal vascular characteristics. This research has important implications for diagnosing and treating diabetic kidney disease at an early stage. It is due to the strong associations between renal markers like the albumin to creatinine ratio and the severity of DR. It also shows that higher retinal vascular calibres indicate to a higher risk of developing DKD. Diabetic retinopathy (DR) has been greatly aided by digital fundus photographs, which are a means of non-invasive procedures that suggest the usage of retinal imaging in medical diagnostics in a broader sense and in turn motivate in CKD identification [23].

The study of Kang et al. [24] aimed at detecting renal function impairment at an early stage using 25706 fundus images in which a CNN-based VGG-19 model is used in the process. Their model achieved an AUC of 0.81in the overall sample. L. Zhao et al., [25] characterized the association between diabetic retinopathy and nephropathy to determine if DR severity could predict CKD. The research is performed on 91 T2DM with biopsy-confirmed Nephropathy patients but not in End end-stage renal Disorder stage (ESRD). A deep learning network, Retinal Net is used in their research, and the results were promising. In another research of the same kind, Yamanouchi et al. [26], the study is performed on 232 patients, and the progression of diabetic kidney disease is observed. Examinations were performed to find the relationship between retinopathy progression and renal lesions. Cox regression analysis is used to explore the risk.

In identifying Diabetic Kidney Disease, Shi et al. [27] employed various Machine Learning algorithms using the retinal vascular parameters combined with clinical parameters. Their research resulted in the Random Forest algorithm offering optimum performance when compared to other classifiers. Also, the research indicated that the vascular changes could assist in DKD detection. Zhao et al. [28] performed another study using 26539 ultra-wide fundus eye images. Two deep learning architectures, UNet++ and Efficient Net, are employed in their research for segmentation and CKD screening. The deep learning model offered remarkable performance when compared with other models, such as ResNet50 and so on. Zhang et al. [29] researched on image-based deep learning in kidney diseases. Their major analysis focused on the techniques applied to neoplastic and non-neoplastic renal diseases. They uphold that deep learning increases the accuracy of diagnosis, delineation, and evaluation of kidney-related diseases.

Having gone through the literature by all the illustrious researchers, it can be understood that in identifying CKD-related and also other diseases, non-invasive techniques in association with AI, ML & DL - based approaches are the currently adopted ones. Although there are articles compiling the retinal-based CKD research, very few instances are available in diagnosing CKD associated the Diabetic Retinopathy. Hence, in this article, an effort is made by proposing a non-invasive Retinal image-based CKD diagnostic approach. Diabetic Retinopathy is a serious condition that leads to CKD, and hence DR is also diagnosed by employing a Deep Learning model trained and tested using five DR datasets and one DR-CKD dataset.

3. Methodology

Some of the topics that have been covered in this part include the datasets that were utilized, the stacked ensemble deep learning architecture, modelling parameters, and the algorithm.

Datasets: Diabetes is the illness that is seeing the most rapid expansion in terms of the number of patients, and at the same time, diabetic retinopathy is also experiencing a continuous rise in prevalence. The connection between diabetic retinopathy and chronic renal disease was the subject of several venerable research studies. We first concentrated on the retinal datasets of DR since our primary purpose is to

concentrate on detecting chronic kidney disease (CKD) via the retina as a non-invasive method of identifying the disease, and because DR is strongly connected with CKD.
A robust and lightweight architecture has been designed which is discussed in the next subsection. Hence in this study, firstly five datasets for identifying DR are discussed below and subsequently one dataset which shows the close association between DR and CKD has been explored in identifying the CKD using Retinal images. The five datasets are of various sizes obtained from Kaggle while the last dataset is from [30]. Of datasets are presented in Table 1.

Table 1: Datasets Used in This Research

S. No	Dataset considered	Type of dataset	Size of the dataset (No. of images)	Disease diagnosis	Source of the dataset
1	Retinal Dataset	Image	2802	Diabetic Retinopathy	(RDHMI - DRD, 2024)
2	Retinal Dataset	Image	3590	Diabetic Retinopathy	(Diabetic Retinopathy, 2022)
3	Retinal Dataset	Image	3662	Diabetic Retinopathy	(Diabetic _Retinopathy_Image_Dataset_A1, 2024)
4	Retinal Dataset	Image	9025	Diabetic Retinopathy	(Diabetic Retinopathy, 2024)
5	Retinal Dataset	Image	35126	Diabetic Retinopathy	(Diabetic Retinopathy Dataset 2023, 2024)
6	Retinal Dataset	Image	70	Chronic Kidney Disease	(J & Sharat, 2024)

The number of images with respect to each category of diabetic retinopathy are given in Table 2. Similarly, the CKD-DR dataset is as explored in Table 3.

Table 2: Details of DR-CKD Dataset

Dataset No.	Total No. of images	NoDR		MildDR		ModerateDR		ProliferateDR		SevereDR	
		Training	Testing	Training	Testing	Training	Testing	Training	Testing	Training	Testing
D1	2802	1133	127	295	33	739	83	218	25	134	15
D2	3590	1610	179	318	36	884	99	251	28	166	19
D3	3662	1624	181	333	37	899	100	265	30	173	20
D4	9025	1624	181	1624	181	1624	181	1624	181	1624	181
D5	35126	23229	2581	2198	245	4762	530	785	88	637	71

Table 3: Details of Each DR Dataset

CKD Stage	No. of Patients	Normal (J & Sharat, 2024)	Normal (RIX NET)	NPDR (J & Sharat, 2024)	NPDR (RIX NET)	PDR (J & Sharat, 2024)	PDR [RIX NET]
1	12	10	10	1	1	1	1
2	13	8	8	2	2	3	3
3	15	7	7	3	2	5	5
4	16	5	3	1	1	10	8
5	14	4	2	1	1	9	6
Total	70	34	30	8	7	28	23

Proposed Deep Learning Architecture: A stacked ensemble deep learning classification method using transfer learning is used to identify DR and CKD. The schematic representation of the ensemble model is presented in Fig. 3. The Deep Learning architecture proposed is RIX NET which is a stacked ensemble model combining ResNet18, Inception Net, and Xception Net. Data (Images) are provided as input to each baseline model in the ensemble.

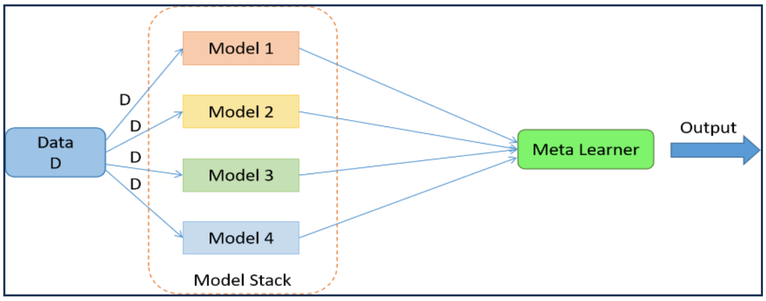

Fig. 3: Outline Diagram of the Stacked Ensemble Model.

The output generated by these models was used as input for the Meta Learner. The categorization result is provided by the Meta model. The performance metrics for each dataset include Accuracy, Precision, Recall, and F1 Score. The results for all datasets are shown in tables 4 to 8 and pictures 5 to 9. The results apply to individual models as well as a stacked ensemble.

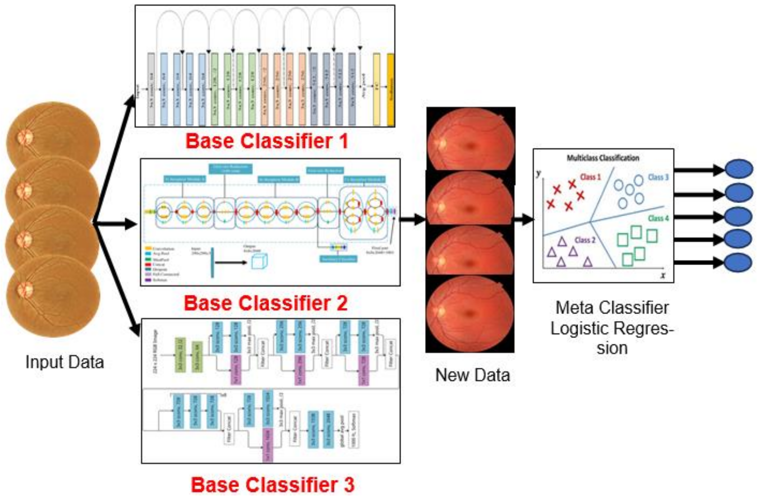

Fig. 4: Proposed Deep Learning Architecture.

The proposed architecture is a lightweight model besides offering remarkable performance. The Base learners are highly effective and suitable for all kinds of datasets. ResNet 18 is a lightweight CNN architecture besides being potential. Inception model is an efficient architecture which can handle datasets of less size to medium size [31]. Exception model, in other words called as Extreme Inception is an excellent model that suits for datasets of large size. Alongside the models being highly efficient, they perform well with limited computational resources and are lightweight. Altogether the models are adaptable, parameters are efficient.
Algorithm:
Step 1: Load images in the Diabetic Retinopathy dataset
Step 2: Divide the data into training and testing data
Step 3: Identify the features and the target variable
Step 4: Perform Image resizing
Step 5: Input the image to the three networks (ResNet, Inception Net, Xception Net)
Step 6: for each model and image Train the ensemble model
Step 7: A new dataset is generated from the predictions of RIX model
Step 8: Train the Meta learning model (classifier)
Step 9: Test the prediction of meta classifier

4. Results and discussion

In this section, the performance measures are evaluated and discussed. For DR datasets, the input is an image whereas the output categories are five namely, NoDR, MildDR, ModerateDR, SevereDR and ProliferateDR. Experimentation is done using Python and the associated libraries viz. Keras and Tensorflow; on Intel i5 machine with 16 GB RAM.
Experimental results on DR Datasets: The sizes of DR datasets range from 2.8K to 35.1K images and each dataset is split in the training and testing ratio of 90:10. The number of layers in the RIXNet architecture is 106. The classification activation function used is sigmoid whereas the loss function is conditional cross entropy and Adam is the optimizer.

Table 4: Performance Measures for Dataset 1

Metric	ResNet18	Inception V3	Xception Net	Stacked ensemble
Accuracy(A)	0.87	0.90	0.91	0.91
Precision(P)	0.86	0.89	0.89	0.92
Recall(R)	0.86	0.89	0.90	0.90
F1-score	0.85	0.90	0.89	0.90
AUC	0.89	0.89	0.90	0.91

The proposed architecture is implemented with all the datasets and the performance comparison has been done with individual RIX Net networks i.e., ResNet, InceptionNet and XceptionNet and finally with the combined architecture stacked ensemble. For all the datasets, the performance metrics are presented in Table 4 to Table 8 and Fig. 5 to Fig. 9. It could be understood that RIX Net performed well in all cases when compared to the individual networks.

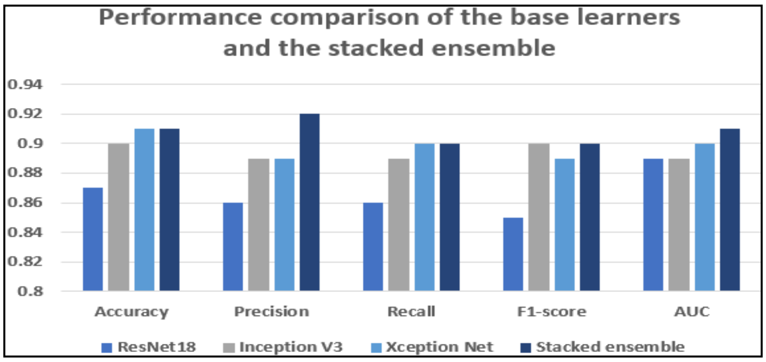

Fig. 5: Performance Comparison for Dataset 1.

Table 5: Performance Measures for Dataset 2

Metric	ResNet18	Inception V3	Xception Net	Stacked ensemble
Accuracy(A)	0.86	0.90	0.90	0.90
Precision(P)	0.86	0.90	0.89	0.89
Recall(R)	0.87	0.90	0.90	0.90
F1-score	0.87	0.88	0.90	0.90
AUC	0.88	0.90	0.90	0.91

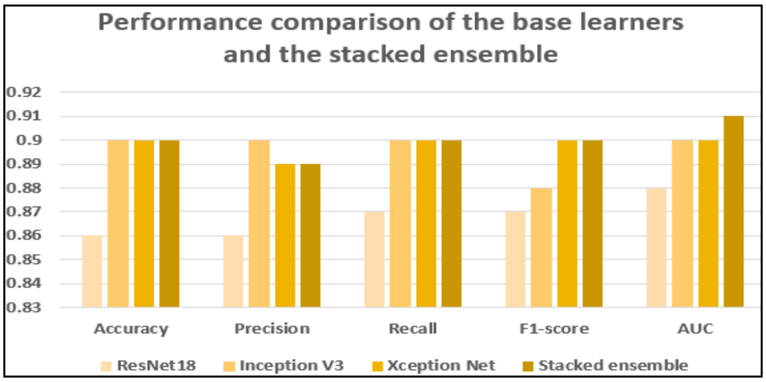

Fig. 6: Performance Comparison for Dataset 2.

Table 6: Performance Measures for Dataset 3

Metric	ResNet18	Inception V3	Xception Net	Stacked ensemble
Accuracy(A)	0.84	0.90	0.90	0.91
Precision(P)	0.83	0.89	0.90	0.91
Recall(R)	0.84	0.90	0.89	0.90
F1-score	0.83	0.89	0.89	0.90
AUC	0.89	0.91	0.92	0.92

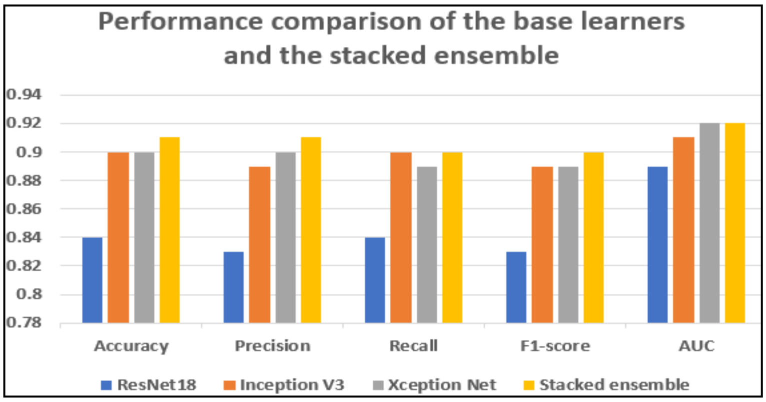

Fig. 7: Performance Comparison for Dataset 3.

Table 7: Performance Measures for Dataset 4

Metric	ResNet18	Inception V3	Xception Net	Stacked ensemble
Accuracy(A)	0.83	0.89	0.89	0.90
Precision(P)	0.84	0.89	0.89	0.90
Recall(R)	0.83	0.90	0.90	0.90
F1-score	0.83	0.88	0.89	0.89
AUC	0.90	0.90	0.90	0.91

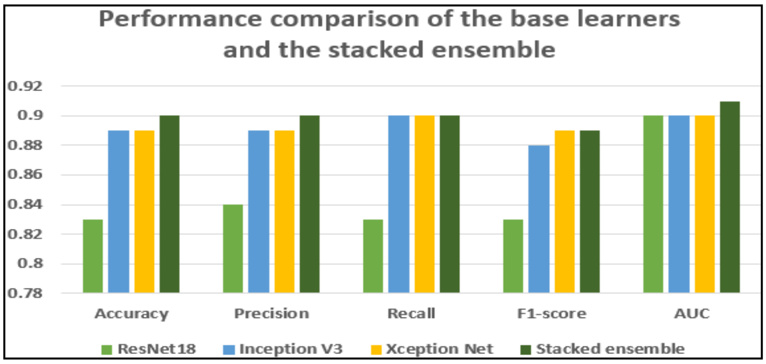

Fig. 8: Performance Comparison for Dataset 4.

Table 8: Performance Measures for Dataset 5

Metric	ResNet18	Inception V3	Xception Net	Stacked ensemble
Accuracy(A)	0.81	0.83	0.85	0.86
Precision(P)	0.82	0.85	0.85	0.87
Recall(R)	0.84	0.84	0.86	0.86
F1-score	0.84	0.85	0.87	0.88
AUC	0.85	0.85	0.87	0.87

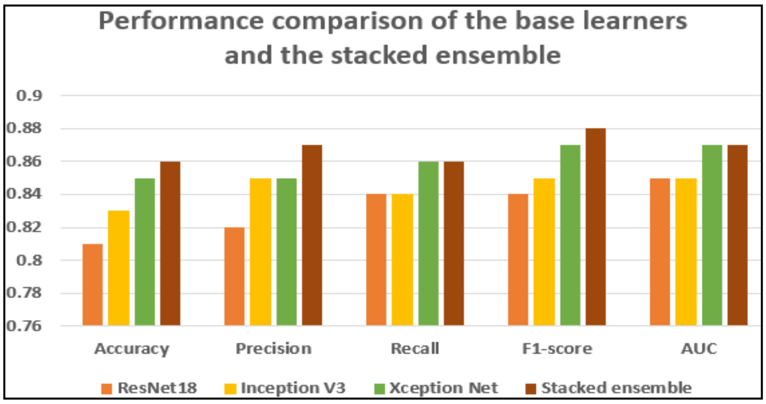

Fig. 9: Performance Comparison for Dataset 5.

Validating the proposed architecture using CKD-DR image dataset: In the earlier section, the proposed stacked ensemble architecture is employed to diagnose DR using five datasets. The performance metrics show that the model is consistent as well robust. In this section, the proposed architecture is used in identifying chronic kidney disease using the retinal images associated with Diabetic Retinopathy. As there is an association between CKD and DR, the dataset is further termed as the CKD-DR dataset. In the CKD-DR dataset, the images are divided into three categories, namely Normal images, Non-Proliferate DR, and Proliferate DR. The total number of images in the dataset is 70, among which the CKD levels and their DR levels are described. The number of images in each category is mentioned in Table 9.

Table 9: CKD-DR Dataset Performance Measures for CKD-DR Dataset

Fundus type	Number of actual images [10]	Number of images identified (RIX NET)	Accuracy
Normal Fundus	34	30	0.88
Non-Proliferative Diabetic Retinopathy	8	7	0.87
Proliferative Diabetic Retinopathy	28	23	0.82
Average accuracy			0.86

The proposed architecture is used in diagnosing the DR category and is successful in identifying the DR level with an average accuracy of 85.99% (0.86), which seems to be promising. The results are also depicted in Fig. 10.

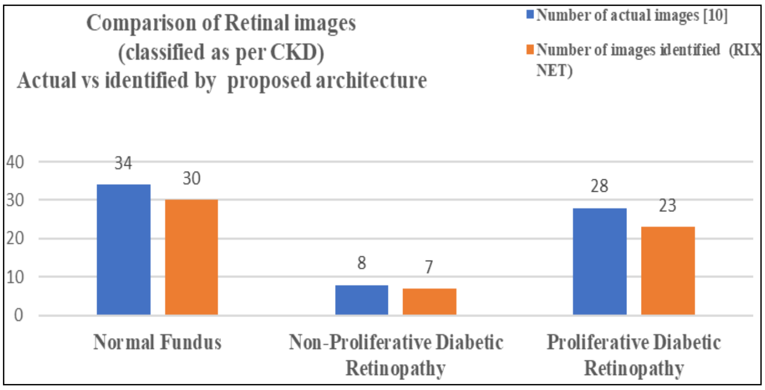

Fig. 10: Performance Comparison for DR-CKD Dataset.

From the preceding experimentation and results, it can be understood that the proposed architecture resulted in consistent performance and the architecture can be employed in further medical image analysis. Also, it is vivid that retinal imaging can be used in identifying CKD, thus attaining the objective of this research

5. Conclusion

In general, blood serum tests are used in diagnosing CKD. Due to the inconvenience faced by the patients and a few other reasons, non-invasive techniques are also effective. In this work, a study has been made to determine the association between retinal characteristics and Chronic renal failure. It is understood that Retinal fundus image examination also gives a provision for estimating ophthalmic conditions, as well as diabetes mellitus. Moreover, Diabetic Retinopathy is also an indicator of chronic kidney disease. A Deep Learning Architecture by the name "RIX Net," which is an ensemble of ResNet18, Inception Net, and Xception Net. Diabetic Retinopathy classification is performed using the ensemble mode. Classification is done using Deep Learning architecture on five datasets, and the results seem to be more promising. The overall accuracies are more than 90% for four datasets and 86% for one dataset. Another CKD dataset comprising 70 patients' data has been taken, and we classified by using a deep learning architecture to improve the accuracy for each category is more than 85%. We can conclude that retinal-based diagnosis is an effective means for detecting chronic kidney disease. Although the results seem noteworthy, there is still a lot of room for improvement, and importantly, advanced Deep Learning models could be applied to huge image datasets of CKD and Diabetic Retinopathy for classification. Further non-invasive methods could also be explored and employed for image classification.

Acknowledgement

I would like to thank my guide, Dr. Bhramaramba Ravi, for her support in my research work, and also thankful to the GITAM University for providing sufficient laboratory support for this work.

Conflict of interest

The authors declare that there is no conflict of Interest.

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