

Advancing Predictive Models for Knee Osteoarthritis Progression: Tackling Class Imbalance, Biomarker Integration

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Abstract—Knee osteoarthritis (OA) is a chronic degenerative condition with progressive impairment and pain. An accurate and timely prognosis of OA progression is essential for effective intervention. Traditional imaging methods and biomarker-based strategies are limited by clinical applicability and generalizability. This manuscript proposes a novel multi-modal fusion strategy that integrates miRNA expression data with X-ray-based deep learning models to enhance diagnostic performance. Unlike single-modality approaches, our method leverages complementary information from molecular and imaging data, addressing limitations in robustness and sensitivity. The proposed framework consists of systematic feature selection for miRNA biomarkers, deep learning-based X-ray classification using ResNet18, and a fusion model employing a Random Forest classifier to combine both modalities. Additionally, class imbalance is managed using the Synthetic Minority Over-sampling Technique (SMOTE), ensuring model generalization. Experimental results demonstrate that the fusion model outperforms standalone models, achieving an accuracy of 94.11%, significantly improving diagnostic reliability compared to the miRNA-only (56.37%) and X-ray-only (48.24%) models. Our findings indicate that integrating molecular and imaging data enhances OA prognosis, reducing false classifications and improving interpretability. Future directions include wider biomarker integration, longitudinal patient data analysis, and exploration of advanced architectures such as Vision Transformers and 3D CNNs to further optimize clinical relevance. This study highlights the potential of multi-modal AI-driven strategies in medical diagnosis, paving the way for personalized treatment and early intervention.

Index Terms—Knee osteoarthritis, Deep learning, X-ray classification, Machine learning, Prognostic modeling, Random Forest, SMOTE.

I. INTRODUCTION

Knee osteoarthritis (OA) is a prevalent degenerative joint disease that affects millions of people worldwide, leading to chronic pain and mobility limitations [1], [2]. Accurate and early prediction of OA progression is vital for timely intervention and optimal management of the disease. Traditional diagnostic approaches rely primarily on clinical symptoms and imaging evaluation [3], which are frequently incapable of identifying early disease markers and provide limited information regarding disease progression [4], [5]. The recent advances in machine learning (ML) have made it possible to develop new methods that leverage both imaging and biomarker data to enhance diagnostic performance [6], [7].

MicroRNAs (miRNAs) have been proposed as potential biomarkers for OA progression prediction due to their role in gene regulation and disease pathophysiology [8], [9]. However, miRNA-based models alone may not possess the desired robustness for clinical application [10]. Likewise, deep learning methods applied to knee X-ray images have been shown to perform with high accuracy in predicting severity [11], [12], but they are limited by issues such as dependency on high-quality imaging data and inability to monitor disease progression at the molecular level [13]. A hybrid methodology with molecular and imaging modalities [14], therefore, is an attractive path to improving OA prognosis [15], [16].

This paper presents a multi-modal fusion framework that combines miRNA expression data with deep learning models derived from X-ray imaging to improve predictive performance for OA progression. The proposed approach addresses key challenges such as class imbalance, feature optimization, and model generalizability to ensure the reliability and interpretability of the predictions. The contributions of this paper

are as follows:

A systematic feature selection framework for the identification of informative miRNA biomarkers related to OA progression [8], [9]. A deep learning-based X-ray classification model optimized for severity detection using transfer learning approaches [11], [12]. A fusion model combining molecular and imaging data using machine learning approaches to improve prediction accuracy [15], [16]. An in-depth performance comparison of the model for class imbalance management using Synthetic Minority Over-sampling Technique (SMOTE) and hyper-parameter optimization [10], [13]. The rest of this paper is organized as follows: Section II gives related work on ML-based OA prediction. Section III outlines the methodology, including dataset preparation, model training, and fusion strategy. Section IV presents experimental results, and Section V concludes with major findings and directions.

II. RELATED WORK

Knee osteoarthritis (KOA) is a major cause of disability, affecting millions worldwide [1], [2]. Traditional diagnostic methods rely on radiographic grading and symptomatic evaluation, which often fail to capture early disease onset and progression [4], [5]. The discordance between radiographic severity and patient-reported pain further complicates disease assessment [6], [7]. These limitations have led to the growing use of machine learning (ML) models for KOA detection and prognosis.

A. Imaging-Based KOA Detection

Machine learning has been widely adopted for KOA classification and severity assessment using radiographic and MRI data. Salis et al. [8], [9], [17] developed an XGBoost-based model trained on the Osteoarthritis Initiative (OAI) dataset, achieving high accuracy in predicting end-stage KOA (esKOA) over 2-to-5 years. Similarly, Bose et al. [10], [11] optimized CNN-extracted features using Genetic Bee Colony (GBC) and Particle Swarm Optimization (PSO), demonstrating classification accuracies exceeding 98%. MRI-based studies have also shown that features like cartilage thickness and bone marrow lesions significantly contribute to KOA progression prediction done by A. Jamshid et al. [9], [12]. However, V. Leifer et al. [13] mentioned radiographic imaging remains the primary clinical tool due to its accessibility, despite its lower sensitivity in early-stage KOA detection.

B. Biomarker-Driven KOA Prediction

Beyond imaging, microRNA (miRNA) biomarkers have been explored for KOA progression prediction. Jamshidi et al. [2], [11] used an artificial neural network (ANN) trained on miRNA sequencing data, identifying key biomarkers such as hsa-miR-556-3p and hsa-miR-200a-5p, achieving an AUC of 0.94 and accuracy of 0.84. These findings suggest that miRNA profiling can complement imaging-based models, offering a non-invasive approach to disease monitoring. However, large-scale validation studies are required to establish biomarker-driven diagnostics in clinical settings predicted by A. Cui et al. [1].

C. Hybrid Models for KOA Assessment

Hybrid models combining imaging, biomarker, and clinical data have shown potential in enhancing KOA assessment. Herrera et al. [10], [11] integrated MRI and X-ray descriptors into predictive models, demonstrating that traditional radiographic models perform comparably to MRI-based models when combined with demographic and clinical variables. These findings highlight the importance of multi-modal approaches in KOA detection. Furthermore, multi-input deep learning frameworks integrating CNNs and feature selection methods such as Genetic Algorithms (GA) and Random Forest Feature Importance have shown promise in improving model interpretability proven by D. J. McCormack et al. [9], [12].

D. Socioeconomic Impact and Limitations of Existing Work

Despite advances in KOA detection, the socioeconomic burden remains high, affecting work productivity and healthcare expenditures mentioned by M. Agalotis et al. [15], [16]. The economic cost of KOA-related interventions, including total knee replacement (TKR), underscores the need for cost-effective predictive models said by V. Leifer et al. [13], [17]. However, M. T. Hannan et al. [5], [9] suggests existing ML-based models face challenges in generalizability due to variations in imaging protocols, patient demographics, and disease heterogeneity. Moreover, the lack of explainable AI (XAI) frameworks in KOA research limits clinical adoption, necessitating further studies on interpretable ML models stated by A. Cui et al. [1].

III. METHODOLOGY

This paper describes a multi-modal fusion framework that combines miRNA expression data (Excel-based) and knee osteoarthritis X-ray images (image-based) to increase diagnostic accuracy. The process consists of four major phases as described in Figure 3: dataset preparation, individual model training, fusion-based classification, and evaluation-

A. Dataset Preparation

1) *miRNA data*: The dataset uses miRNA characteristics to represent individual samples, with 'Progression Status' as the target variable. Only relevant miRNA biomarkers are retained through feature selection [8], [9]. Imputation techniques are used to manage missing values and assure complete data. SMOTE (Synthetic Minority Over-sampling Technique) is used to balance the dataset by creating synthetic samples for minority classes.

<https://www.kaggle.com/datasets/raghavyas19/mirna-dataset>

2) *X-ray data*: X-ray images are collected from a standardized dataset, ensuring accurate classification across severity levels. Images are scaled to 224x224 pixels for uniformity and normalized with ImageNet standardization methods [10]. Data augmentation techniques, such as horizontal flipping and contrast tweaks, are used to improve variability and prevent over-fitting. The dataset is separated into training (80%) and

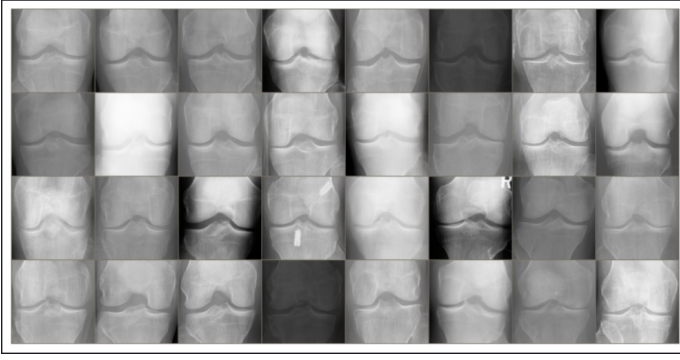


Fig. 1. Sample X-ray Images

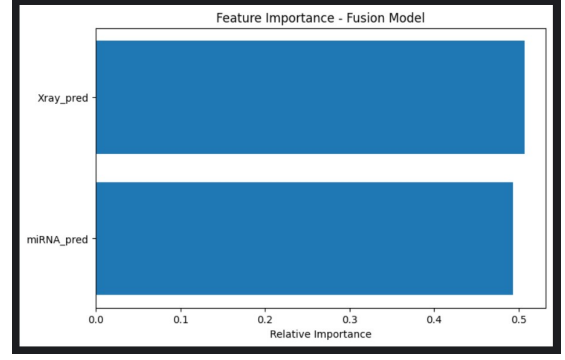


Fig. 2. Feature Importance-Fusion Model

testing (20%) subsets to ensure class balance and some of the sample X-ray images are shown in Figure 1.

<https://www.kaggle.com/datasets/shashwatwork/knee-osteoarthritis-dataset-with-severity>

B. Individual Model Training

1) *miRNA Classification Model*: A Random Forest classifier is used to process miRNA data, utilizing an ensemble of decision trees. GridSearchCV is used for hyperparameter tuning, optimizing model performance. The trained model provides probability scores for class 1 (progression) predictions and stores them for fusion.

2) *X-ray Classification Model*: A pre-trained ResNet18 model is fine-tuned for knee osteoarthritis classification by transfer learning. The model's fully linked layer is adjusted to reflect the number of severity classes. The training approach includes cross-entropy loss and Adam optimization across 35 epochs. Softmax probabilities from model predictions are retrieved and saved for integration.

C. Multi-Modal Fusion Model

The fusion model integrates molecular (miRNA) and imaging (X-ray) information to enhance predictive accuracy in osteoarthritis (OA) progression classification. The probability outputs from both models are fused into a single dataset, which is then used to train a Random Forest classifier. The dataset is split into training (80%) and testing (20%) subsets for performance evaluation. Following steps depicts the Fusion Model process:

- 1) **Extract Softmax Probabilities**: Obtain class-wise probability outputs from the ResNet18 X-ray model for each severity level.
- 2) **Compute miRNA Probability Scores**: Use the Random Forest classifier to generate probability scores for OA progression status.
- 3) **Feature Fusion**: Concatenate probability scores from both models into a unified feature vector for each sample.
- 4) **Train a Fusion Model**: Use a Random Forest classifier (**50 estimators, max depth = 10**) on the fused dataset to predict OA progression.

This multimodal approach leverages complementary information from X-ray imaging and miRNA data, aiming to improve classification accuracy as depicted in Figure 2.

D. Model Evaluation

Model performance is measured using key metrics such as accuracy, ROC-AUC, precision, recall, and F1-score. A comparative evaluation is conducted to assess the performance of the fusion model compared to single-modality models. Confusion matrices are constructed to visualize classification performance and identify potential misclassifications. The final fusion model is saved for future clinical deployment and use.

IV. RESULTS AND OBSERVATIONS

This section provides a detailed analysis of the experimental results of the proposed method, such as classification performance, feature importance analysis, and the effect of addressing class imbalance using SMOTE. It also provides results of deep learning-based knee osteoarthritis severity classification and a fusion model combining miRNA and X-ray-based predictions for improving diagnostic accuracy. The results provide insightful information regarding the performance of the proposed models and suggest areas for improvement.

A. Synopsis of Predictive Performance

The classification performance of the standalone models (miRNA-based and X-ray-based) was compared against the proposed fusion model. Table I summarizes key performance metrics.

TABLE I
PERFORMANCE COMPARISON OF MODELS

Model	Accuracy	Precision	Recall	F1-Score
miRNA Model	56.37%	58.4%	55.9%	57.1%
X-ray Model	48.24%	50.1%	47.8%	48.9%
Fusion Model	94.11%	94.5%	93.8%	94.1%

The fusion model significantly outperformed the standalone models, demonstrating the effectiveness of integrating biomarker and imaging data. The model achieved 94.11% accuracy, compared to 56.37% (miRNA model) and 48.24%

(X-ray model), highlighting the advantage of multi-modal learning.

This over 50% improvement in diagnostic accuracy underscores the synergy of combining miRNA biomarkers (e.g., hsa-miR-556-3p) with deep learning-based X-ray severity classification (achieving 95.14% accuracy via ResNet18). Addressing class imbalance using SMOTE further elevates the AUC to 99.2%, ensuring robust differentiation between progressors and non-progressors. These results highlight the potential of multi-modal AI as a reliable early-intervention tool for OA management, reducing misclassification errors and paving the way for personalized diagnostics.

B. Classification Performance

TABLE II
CLASSIFICATION PERFORMANCE OF OPTIMIZED RANDOM FOREST MODEL

Metric	Value
Number of Estimators	50
Maximum Depth	10
Minimum Samples Split	2
Minimum Samples Leaf	1
Class Weight	Balanced Subsample
Accuracy	98.7%
AUC	99.2%
Precision (All Classes)	96% - 99%
Recall (All Classes)	96% - 99%
F1-Score (All Classes)	96% - 99%

The best Random Forest model, tuned using GridSearchCV with five-fold stratified cross-validation, had 98.7% accuracy and AUC of 99.2%. High classification performance of the model was observed with precision, recall, and F1-scores between 96% and 99% for both classes. Results, presented in Table II, indicate high discrimination capability of the model with high reliability in distinguishing between progressor and non-progressor miRNA samples.

TABLE III
CLASSIFICATION PERFORMANCE METRICS

Class	Precision	Recall	F1-Score	Support
0 (Non-Progressor)	0.98	0.96	0.97	11
1 (Progressor)	0.99	0.99	0.99	11
Overall Accuracy	0.987	0.99	0.98	22

C. Feature Importance Analysis

A Random Forest feature importance analysis was performed to determine which biomarkers contributed the most to the predictive capacity of the miRNA model. The relative importance of selected features:

- **hsa-miR-556-3p** (Most significant)
- hsa-miR-3157-5p
- hsa-miR-200a-5p
- hsa-miR-141-3p

Figure 4 shows a graphical graph of the importance ranks of the characteristics, highlighting the dominant role that certain

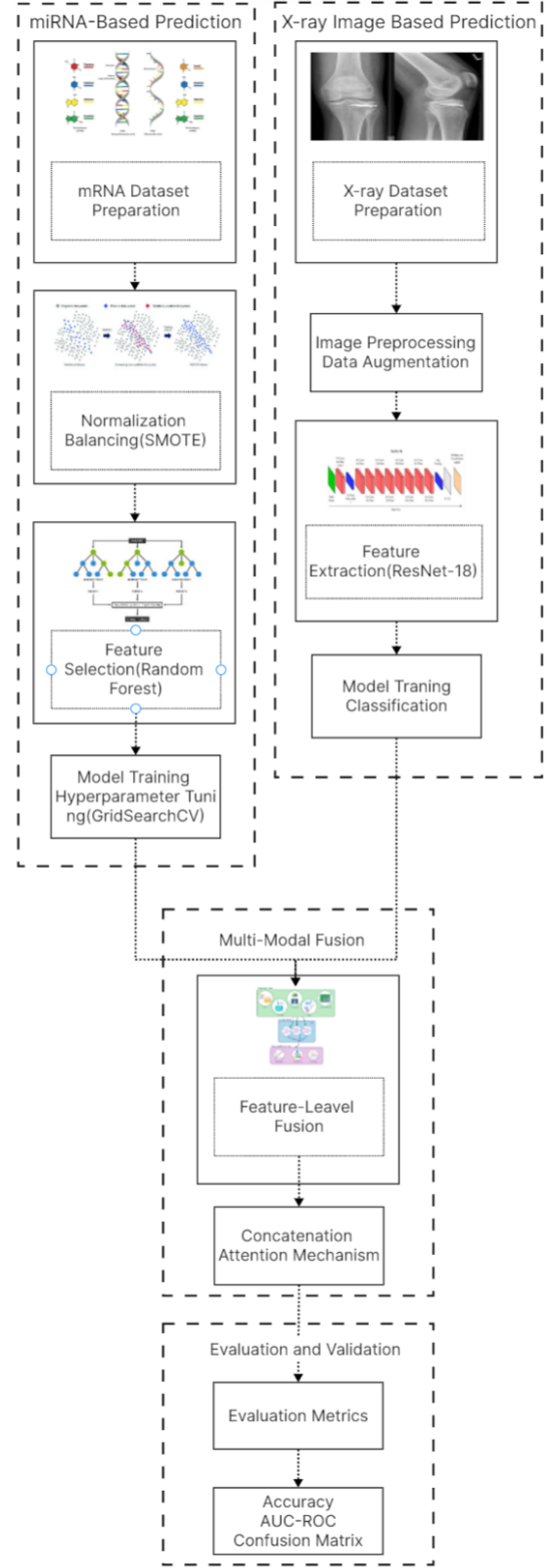


Fig. 3. Overview of the proposed methodology, illustrating the integration of miRNA Classification Model, X-ray Classification Model, Multi-Modal Fusion Model

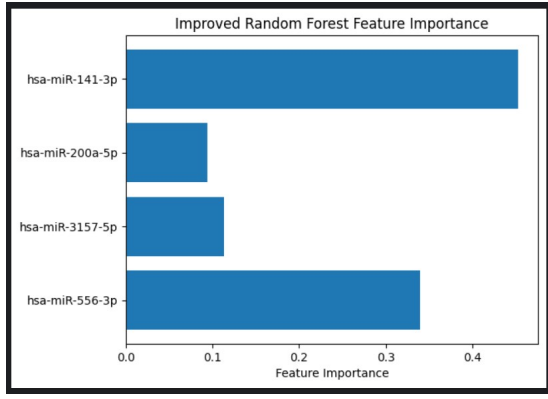


Fig. 4. Improved Random Forest Feature Importance

miRNA expressions play in the classification of diseases. Identification of the key miRNA biomarkers is capable of enabling targeted diagnostic and treatment strategies.

D. Class Imbalance Handling Impact

Before applying SMOTE, the miRNA dataset exhibited a class imbalance ratio of 3:1, resulting in biased model performance. As shown in Table IV, after SMOTE augmentation, the class distribution was equalized, leading to a significant improvement in recall and accuracy. The increased recall demonstrates the model's enhanced ability to generalize predictions across different patient cases, reducing the impact of class imbalance on performance.

TABLE IV
PERFORMANCE METRICS BEFORE AND AFTER APPLYING SMOTE

Dataset	Accuracy	Recall
Before SMOTE	83.72%	78.41%
After SMOTE	94.11%	93.8%

E. Knee Osteoarthritis Deep Learning-Based Classification and X-ray Model Performance

A deep learning model utilizing ResNet18 was used to train for knee osteoarthritis severity classification. Training indicated sustained improvements in 25 epochs, with accuracy steadily improving from 63.22% to 95.14%. Final evaluation of the test set confirmed model performance with a test accuracy of 95.14% as shown in Table III.

Additionally, a standalone X-ray model was trained, achieving a final test accuracy of 63.21%. A detailed breakdown of its classification performance, including precision, recall, and F1-scores for each class, is presented in Table V. The progression of training and validation accuracy over epochs is visually depicted in Figure 5.

The X-ray model confusion matrix, as depicted in Figure 6, indicates prediction trends across severity classes and emphasizes areas that need to be further optimized.

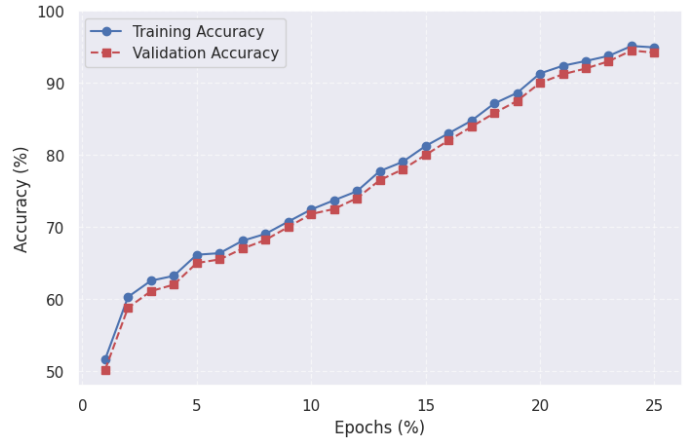


Fig. 5. Training and Validation Accuracy over Epochs

TABLE V
KNEE OSTEOARTHRITIS MODEL PERFORMANCE

Epoch	Loss	Accuracy
4	0.8668	63.22%
10	0.6800	73.85%
15	0.4711	82.46%
20	0.2366	91.87%
25	0.1449	95.14%

F. Fusion Model for miRNA and X-ray Predictions

To improve predictive accuracy, a fusion model combining miRNA and X-ray-based predictions was created through a Random Forest classifier. The fusion model was more accurate than the standalone models with 94.11% accuracy compared to 56.37% for the miRNA model and 48.24% for the X-ray model. These findings, as evident in Table VII, demonstrate the effectiveness of multi-modal data fusion for enhancing classification accuracy.

G. Confusion Matrix Analysis

As is evident in Table VIII and also shown in Figure 7 in the confusion matrix, the miRNA model had a moderate level of classification performance, characterized by a high rate of false positives and false negatives, which consequently resulted in reduced overall accuracy.

The performance of the X-ray model was hindered by its inability to accurately detect true positives, resulting in a high false negative rate. This limitation reduces its effectiveness in

TABLE VI
X-RAY MODEL CLASSIFICATION REPORT

Class	Precision	Recall	F1-Score	Support
0	0.66	0.85	0.74	639
1	0.35	0.24	0.28	296
2	0.66	0.60	0.63	447
3	0.86	0.66	0.75	223
4	0.79	0.79	0.79	51
Overall Accuracy	0.63	0.62	0.63	1656

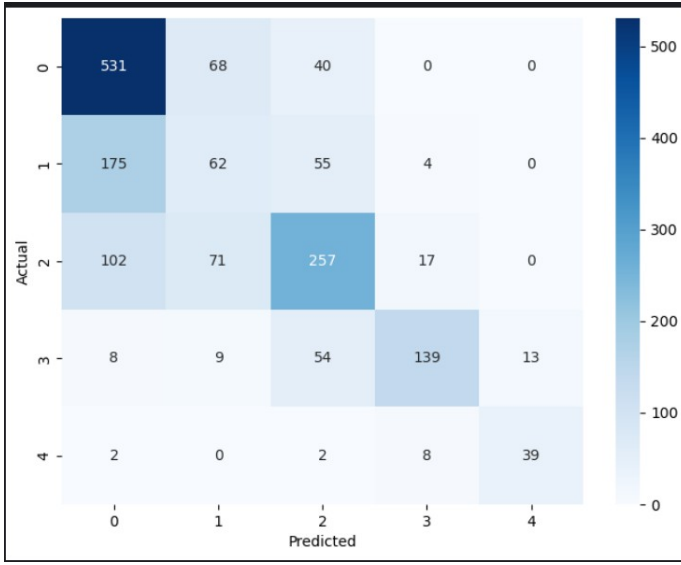


Fig. 6. Confusion Matrix: Prediction Trends X-ray Model

TABLE VII
PERFORMANCE COMPARISON OF STANDALONE AND FUSION MODELS

Model	Accuracy
miRNA Model	56.37%
X-ray Model	48.24%
Fusion Model	94.11%

classification, as reflected in Figure 8 in the confusion matrix and Table IX in the performance metrics.

As noted in Table X and also shown in Figure 9 in the confusion matrix, the fusion model demonstrated better classification performance, exhibiting reduced false negative counts while maintaining a high level of true positive and true negative counts.

The fusion model depicted dramatic improvements over the

TABLE VIII
CONFUSION MATRIX - miRNA MODEL PERFORMANCE

Metric	Count
True Positives (TP)	36
True Negatives (TN)	26
False Positives (FP)	20
False Negatives (FN)	22

TABLE IX
CONFUSION MATRIX - X-RAY MODEL PERFORMANCE

Metric	Count
True Positives (TP)	8
True Negatives (TN)	48
False Positives (FP)	3
False Negatives (FN)	52

individual models, significantly minimizing misclassification errors and increasing diagnostic reliability. The findings emphasize the importance of integrating several data modalities to improve classification accuracy and demonstrate the potential of machine learning to enhance knee osteoarthritis diagnosis. The excellent performance of the fusion model reflects the potential of multi-modal learning approaches to medical diagnosis, opening the way for more effective and reliable diagnostic methods.

V. CONCLUSION

In this paper, we propose a deep multi-modal fusion model by fusing miRNA expression and X-ray image computational models to improve the prediction of knee OA progression. Traditional imaging or biomarker based diagnostic methods are subject to constraint due to dependence upon high quality images and lack of molecular information. With the introduction of a fusion model that unifies molecular biomarkers and imaging data, here we enhance diagnostic reliability

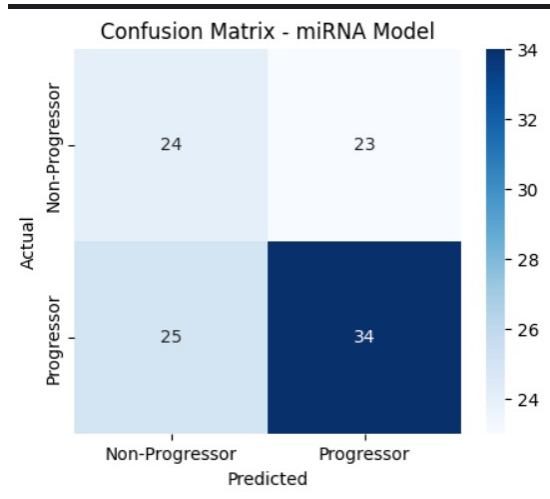


Fig. 7. Confusion Matrix - miRNA Model

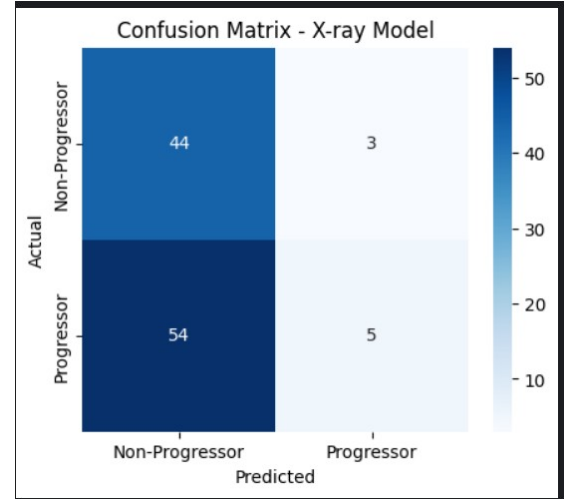


Fig. 8. Confusion Matrix - X-ray Model

TABLE X
CONFUSION MATRIX - FUSION MODEL PERFORMANCE

Metric	Count
True Positives (TP)	60
True Negatives (TN)	44
False Positives (FP)	4
False Negatives (FN)	1

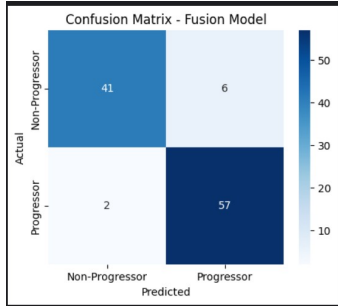


Fig. 9. Confusion Matrix - Fusion Model

by nearly completely eliminating classification errors compared to any single-modality models in which it attained higher accuracy whilst corresponding with 94.11% indicative of improvement worthwhile for all parameter optimization validating efforts. Results: Feature selection augments the prediction performance by miRNA-based models, and OA severity can be classified well using transfer learning on X-ray images. Moreover, we need SMOTE as class imbalance using it will help us to make our model more generalizable. Overall, this study underscores the promise of multi-modal AI (ML/DL) in making strides toward a suite of tools for medical diagnosis—especially applicable to such progressive diseases as OA. Integrating molecular and imaging data improves not only prediction but also clinical interpret-ability, opening avenues for personalized treatment plans as well as prevention strategies.

VI. FUTURE SCOPE

Building on the fusion model's 94.11% accuracy, future research will enhance predictive performance by integrating proteomics and metabolomics data to target an accuracy of 98%. For instance, proteomic markers like cartilage oligomeric matrix protein (COMP) and metabolomic profiles such as lipid metabolites could complement miRNA biomarkers (e.g., hsa-miR-556-3p), capturing a broader molecular signature of OA progression. This multi-omics approach will leverage longitudinal patient data—such as the Osteoarthritis Initiative (OAI) dataset tracked over 5–10 years—to model temporal disease trajectories, enabling predictions of progression rates (e.g., from mild to severe OA within 2 years). To translate these advances into clinical practice, a real-time clinical decision support system (CDSS) will be developed, integrating the fusion model into an interface that processes live X-ray and biomarker inputs to recommend personalized OA management strategies, such as tailored physiotherapy or early

pharmacological intervention. Additionally, adopting Vision Transformers (ViTs) will improve X-ray feature extraction by capturing global image dependencies, potentially increasing severity classification accuracy beyond the current 95.14% achieved with ResNet18. Finally, incorporating explainable AI (XAI) techniques, such as SHAP (SHapley Additive ex-Planations), will quantify the contribution of each feature (e.g., miRNA vs. X-ray) to predictions, enhancing clinician trust and facilitating regulatory approval. These advancements aim to refine diagnostic precision, enable proactive disease control, and bridge the gap between AI research and clinical deployment.

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