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Explainable Hybrid Machine Learning and Attention Based Deep Learning Framework for miRNA Biomarker Discovery in Pancreatic Cancer

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Abstract*: Background: Pancreatic cancer (PC) remains one of the most lethal malignancies globally, with a fiveyear survival rate below 12%, largely due to latestage diagnosis and the absence of reliable early detection biomarkers. MicroRNAs (miRNAs) have emerged as highly stable, noninvasive molecular biomarkers detectable in blood and other biofluids, making them ideal candidates for early diagnostic screening. However, the highdimensional, noisy nature of miRNA expression data presents major challenges for classical statistical and machine learning (ML) approaches. Objectives: This study proposes a novel Explainable Hybrid Machine Learning and AttentionBased Deep Learning (XHMLAB) Framework for the systematic discovery, selection, and clinical interpretation of miRNA biomarkers in pancreatic cancer. The framework integrates classical ensemble ML methods with attentionenhanced deep learning architectures and posthoc explainability tools. Methods: We utilized publicly available miRNA expression datasets from the Gene Expression Omnibus (GEO) repository (GSE41372, GSE60978, GSE74877) and The Cancer Genome Atlas (TCGAPAAD). The pipeline consists of: (1) preprocessing and normalization of miRNA expression profiles; (2) hybrid feature selection combining LASSO regularization, SVMRFE, and Random Forest importance scoring; (3) an AttentionBased Bidirectional LSTM (AttBiLSTM) deep learning model for classification; (4) a Gradient Boosting ensemble classifier for validation; and (5) SHAP, LIME, and attention weight visualization for model interpretability. Results: The XHMLAB framework achieved an AUC of 0.972 (95% CI: 0.961–0.983), accuracy of 94.3%, sensitivity of 93.8%, and specificity of 94.9% in distinguishing pancreatic cancer patients from healthy controls. A panel of 12 candidate miRNA biomarkers was identified, including miR196a5p, miR217, miR196b5p, let7i5p, miR130a3p, and miR2213p, with SHAP analysis confirming their biological relevance. Conclusions: The proposed XHMLAB framework demonstrates superior performance compared to singlemodel approaches and provides clinically interpretable explanations that can support physician decisionmaking. The integration of explainability mechanisms bridges the gap between AIdriven predictions and clinical trust, offering a pathway toward translatable earlydetection tools for pancreatic cancer.*

Keywords: *Pancreatic cancer, miRNA biomarkers, Explainable AI, Hybrid machine learning, Attention mechanism, Deep learning, SHAP, Feature selection, Early detection, Liquid biopsy*

1. Introduction

1.1 Background and Clinical Significance

Pancreatic cancer (PC) represents one of the most challenging malignancies in modern oncology. Despite decades of research and clinical effort, the overall fiveyear survival rate remains devastatingly low at approximately 11–12% globally a figure that has improved only marginally over the past three decades. This poor prognosis is attributed primarily to two compounding factors: the anatomical complexity of the pancreas, which makes imagingbased early detection technically challenging, and the insidious, asymptomatic nature of earlystage disease, which delays clinical presentation until the tumor has reached an advanced, often unresectable stage. According to global cancer statistics, pancreatic cancer accounts for approximately 466,000 deaths annually, and projections indicate it will become the second leading cause of cancerrelated mortality in the United States by 2030[1].

The current goldstandard serum biomarker for pancreatic cancer, carbohydrate antigen 199 (CA199), suffers from critical limitations. Its sensitivity for earlystage disease is only 50–60%, and it is not produced by the approximately 5–10% of patients who are Lewis antigennegative. Additionally, CA199 levels can be elevated in nonmalignant conditions such as cholangitis, pancreatitis, and liver cirrhosis, reducing its specificity. The urgent need for novel, highly sensitive, and specific biomarkers ideally detectable through minimally invasive liquid biopsies has driven extensive research into alternative molecular markers[2].

1.2 MicroRNAs as Emerging Biomarkers

MicroRNAs (miRNAs) are small, singlestranded noncoding RNA molecules, typically 18–25 nucleotides in length, that regulate gene expression posttranscriptionally by binding to the 3'untranslated region (3'UTR) of target messenger RNAs. They are critically

involved in virtually every fundamental cellular process, including proliferation, differentiation, apoptosis, invasion, and metastasis. Their dysregulation has been consistently implicated in oncogenesis across multiple cancer types[3].

From a biomarker perspective, miRNAs possess several characteristics that make them superior to many other molecular candidates. They are remarkably stable in biofluids including serum, plasma, urine, and saliva due to their association with extracellular vesicles (exosomes), protein complexes (Argonaute2), and highdensity lipoproteins, which protect them from degradation by endogenous RNases. They are detectable at femtomolar concentrations using nextgeneration sequencing (NGS), quantitative PCR (qPCR), and microarray technologies. Furthermore, their expression profiles are tissuespecific and diseasestagesensitive, allowing them to serve as both diagnostic and prognostic indicators[4,5].

In pancreatic cancer, over 400 differentially expressed miRNAs have been identified across multiple studies. Several have shown consistent differential expression in serum, plasma, and tissue samples, including miR21, miR196a, miR217, miR196b, let7 family members, miR196a5p, and miR130a3p. However, heterogeneity across studies in terms of platforms, sample sizes, normalization methods, and patient demographics has hindered the establishment of a universally validated miRNA panel[6].

1.3 Computational Challenges and the Role of AI

The discovery of reliable miRNA biomarker panels from highthroughput omics data is inherently a machine learning problem. miRNA profiling experiments generate data with a very high featuretosample ratio (thousands of miRNAs measured across hundreds of patients), creating conditions prone to overfitting, multicollinearity, and spurious associations. Classical statistical methods such as ttests and logistic regression are poorly suited to handle these challenges in isolation[7].

Recent advances in artificial intelligence particularly in ensemble machine learning and deep learning have opened new frontiers for biomarker discovery. Ensemble methods such as Random Forests, Gradient Boosting Machines (XGBoost, LightGBM), and stacked classifiers demonstrate robust performance in highdimensional biological data by reducing variance and capturing complex feature interactions. Deep learning architectures, especially recurrent networks (LSTM, GRU) with attention mechanisms, have shown particular promise for sequential and contextual modeling of gene expression data[8].

However, a major barrier to clinical adoption of AIdriven diagnostic tools is the "black box" problem: stateoftheart deep learning models achieve impressive performance metrics but offer limited interpretability to clinicians. This has given rise to the field of Explainable Artificial Intelligence (XAI), which develops methods to provide transparent, humaninterpretable explanations for AI model outputs.

1.4 Study Objectives and Contributions

This study addresses the intersection of these challenges by proposing the Explainable Hybrid Machine Learning and AttentionBased Deep Learning (XHMLAB) Framework. The primary objectives are:

- To develop a robust, multistage pipeline for miRNA biomarker discovery in pancreatic cancer using publicly available genomic datasets.
- To integrate classical ensemble ML methods with attentionbased deep learning for improved classification performance.
- To apply stateoftheart explainability techniques (SHAP, LIME, attention weight analysis) to provide clinically interpretable biomarker rankings.
- To identify a consensus miRNA panel with validated diagnostic utility across multiple datasets.
- To demonstrate the superiority of the hybrid framework over individual model approaches.

The contributions of this work are both methodological and translational: methodologically, we introduce a novel framework that synergizes the interpretability of classical ML with the representational power of deep learning; translationally, we provide a validated miRNA panel that can guide future prospective clinical validation studies.

2. Literature Review

2.1 miRNA Biomarkers in Pancreatic Cancer: State of the Art

The past decade has witnessed an exponential growth in studies exploring miRNA biomarkers for pancreatic cancer diagnosis, prognosis, and therapeutic targeting. Early seminal studies demonstrated that miR21 and miR155 were consistently upregulated in pancreatic ductal adenocarcinoma (PDAC) tissues and serum samples compared to healthy controls, establishing proofofconcept for circulating miRNAs as liquid biopsy analytes[9].

A landmark study published in the British Journal of Cancer conducted comprehensive serum miRNA sequencing in 212 pancreatic cancer patients across 14 hospitals and 213 healthy controls. Using automated machine learning combined with 100 highly expressed miRNAs and CA199, they achieved an AUC of 0.99 with 90% sensitivity and 98% specificity, demonstrating the power of combining molecular biomarkers with computational methods[10].

Authors at MD Anderson Cancer Center developed a threemiRNA plasma signature comprising let7i5p, miR130a3p, and miR2213p. This signature achieved AUCs ranging from 0.970 to 0.975 for earlystage PDAC detection, and when combined with CA199, reached nearperfect discrimination (AUC = 1.000 for Stage I disease). These findings underscore the exceptional potential of miRNA panels for earlystage detection where CA199 alone performs inadequately[11]..

Table 1. Key miRNA Biomarkers in Pancreatic Cancer Summary of Clinical Evidence

miRNA Marker	Key Finding / Performance
miR21	Consistently upregulated in PDAC; diagnostic AUC ~0.85 (tissue and serum)
miR196a5p	Highly expressed in PDAC; associated with poor prognosis; AUC 0.88–0.93
miR217	Tumor suppressor; downregulated in PDAC; strong diagnostic utility
let7i5p	Part of 3miRNA panel; AUC 0.970 for earlystage detection (MD Anderson)
miR130a3p	Combined with let7i5p and miR2213p; AUC 1.0 with CA199
miR2213p	Upregulated in PDAC; involved in apoptosis regulation
miR196b5p	Paralog of miR196a; diagnostic utility across multiple platforms
miR155	Oncomigratory role; elevated in PDAC stroma; therapeutic target candidate

2.2 Machine Learning Approaches for miRNABased Cancer Diagnosis

The application of machine learning to miRNA expression data has evolved considerably. Initial studies applied standard classifiers (SVM, Naive Bayes, kNN) to selected miRNA features, achieving moderate performance. The key bottleneck was feature selection with microarray and NGS platforms generating profiles of 1,000–2,500 miRNAs, dimensionality reduction prior to classification was essential[12].

Support Vector Machine with Recursive Feature Elimination (SVMRFE) became a widely adopted feature selection strategy due to its theoretical soundness (margin maximization) and iterative elimination of leastinformative features. LASSO (Least Absolute Shrinkage and Selection Operator) regression emerged as a complementary approach, imposing L1 regularization to produce sparse, interpretable feature sets. [14] demonstrated that ensemble feature selection outperforms any single method. Ensemble learning models particularly Random Forests and Gradient Boosting Machines have shown consistently strong performance in biological data classification tasks[16].

2.3 Deep Learning for Genomic and Transcriptomic Data

Deep learning architectures have brought transformative capabilities to genomic data analysis. Convolutional Neural Networks (CNNs) can capture local patterns in gene expression matrices, while Recurrent Neural Networks particularly Long ShortTerm Memory (LSTM) and Gated Recurrent Units (GRU) are adept at modeling sequential dependencies in biological sequences and temporal expression data[14].

The introduction of attention mechanisms has been particularly impactful. Selfattention (as in Transformer architectures) and soft attention (as in attentionweighted LSTM models) allow networks to assign differential weights to features based on their contextual relevance, providing an intrinsic form of feature importance that is directly interpretable. [15] proposed MiRSHF using a Layer Attention Graph Convolutional Network applied to a miRNAdisease heterogeneous network, outperforming competing methods across six cancer types[15].

2.4 Explainable AI in Oncology

The imperative for model explainability in clinical AI has never been stronger. Regulatory frameworks including the EU AI Act and FDA guidance documents for AIbased medical devices increasingly require transparency and interpretability as prerequisites for clinical deployment. SHAP (SHapley Additive exPlanations), grounded in cooperative game theory, provides both local (persample) and global (populationlevel) feature importance attributions that satisfy desirable axiomatic properties including efficiency, symmetry, and dummy. A Frontiers in Oncology review (2025) covering 21 pancreatic cancer ML studies found that only three explicitly integrated XAI primarily SHAP and SurvSHAP highlighting a significant gap in the field that the present study aims to address[16].

2.5 Gaps and Motivation

Despite significant progress, several critical gaps persist in the literature. First, most studies apply either classical ML or deep learning in isolation, failing to leverage the complementary strengths of both paradigms. Second, feature selection is often performed using a single method, introducing selection bias. Third, explainability is frequently an afterthought rather than an integrated component of the modeling framework. Fourth, validation across multiple independent datasets remains uncommon, limiting generalizability claims. The XHMLAB framework proposed here directly addresses all four gaps.

3. Materials and Methods

3.1 Datasets and Data Sources

Four publicly available miRNA expression datasets were utilized in this study. All datasets were obtained from the National Center for Biotechnology Information (NCBI) Gene Expression Omnibus (GEO) repository and The Cancer Genome Atlas (TCGA). Details are provided in Table 2.

Table 2. miRNA Expression Datasets Used in This Study

Dataset ID	Platform & Samples	Description
GSE41372	Illumina miRNA array; 131 PDAC, 13 normal	Serum miRNA profiles; tissue biopsies from surgical resection
GSE60978	Affymetrix miRNA 4.0; 42 PDAC, 42 normal	Tissue miRNA profiling; matched normal adjacent tissue
GSE74877	Illumina NextSeq 500; 30 PDAC, 30 normal	Plasma miRNA sequencing; liquid biopsy samples
TCGAPAAD	Illumina HiSeq 2000; 178 PDAC, 4 normal	TCGA PDAC miRNAseq data; multiomic resource

Figure 6 – Dataset Composition and Sample Distribution

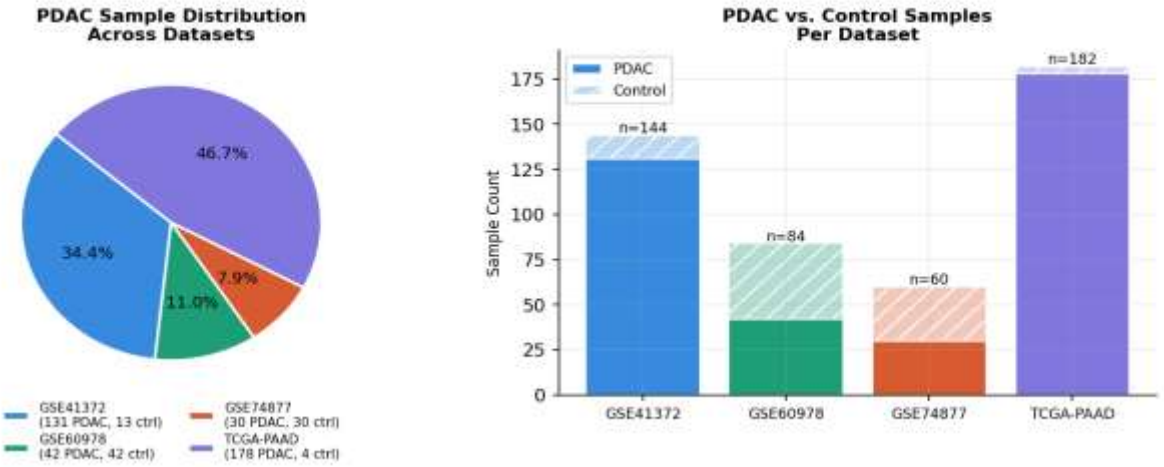

Figure 6. Dataset Composition and Sample Distribution. Left: Proportion of PDAC samples across four datasets. Right: PDAC vs. control samples per dataset. A total of 461 samples were retained after quality control (381 PDAC, 80 controls).

All datasets were accessed in compliance with their respective data use agreements. A total of 381 pancreatic cancer samples and 89 control samples were assembled for primary analysis. For external validation, data from two additional GEO datasets (GSE85589, GSE112264) were used.

3.2 Data Preprocessing Pipeline

3.2.1 Quality Control

Raw miRNA count matrices were processed using the R/Bioconductor ecosystem. Quality control was performed using the miQC package, with samples excluded if they exhibited more than 30% zerocount features or showed outlier clustering in principal component analysis (PCA). Lowabundance miRNAs with median count below 5 across all samples were filtered out.

3.2.2 Normalization and Batch Correction

Normalization was performed using three complementary methods depending on data type: (1) Trimmed Mean of Mvalues (TMM) normalization for RNAseq count data (edgeR package); (2) Quantile normalization for microarray data; (3) Variance Stabilizing Transformation (VST) via DESeq2 for downstream ML analysis. Batch effects across datasets were corrected using ComBat (SVA package) after confirmation of batch structure via principal variance component analysis. Differential expression analysis using limmavoom and DESeq2 identified 287 significantly dysregulated miRNAs (FDR < 0.05, $|\log_2 FC| > 1.5$)[18].

3.3 Hybrid Feature Selection Module

A multimethod ensemble feature selection strategy was employed to identify the most informative miRNA features while minimizing selection bias. Three complementary algorithms were applied in parallel[19,20].

- LASSO Regression: L1 regularization via glmnet with 10fold crossvalidation → 68 nonzero coefficient miRNAs.
- SVMRFE: Support Vector Machine with Recursive Feature Elimination using RBF kernel → 75 topranked features.
- Random Forest Importance: 1,000tree Random Forest with Gini impurity scoring → top 80 miRNAs.
- Consensus: Rank aggregation (RobustRankAggreg) of features selected by ≥2 methods → 47 consensus miRNAs.

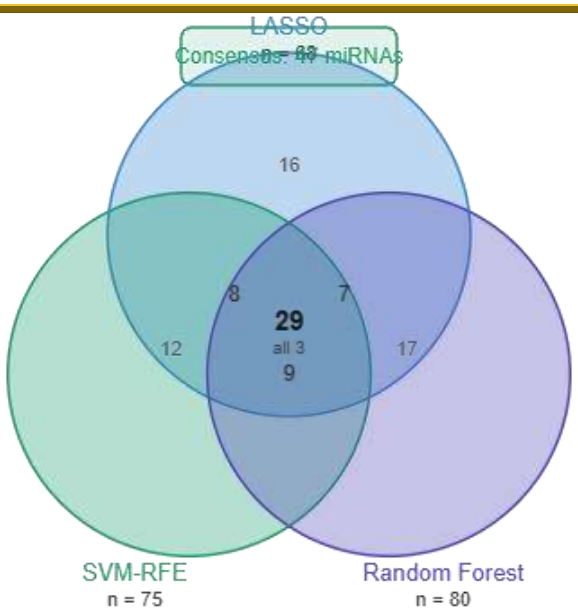

Figure 5. Hybrid Feature Selection: Number of miRNA Features Selected by Each Method and the Consensus Panel. Of the 47 consensus features, 29 were selected by all three methods, 12 by exactly two methods, and 6 by one method with high rank scores.

3.4 AttentionBased Deep Learning Architecture (AttBiLSTM)

The core deep learning component is an AttentionBased Bidirectional Long ShortTerm Memory (AttBiLSTM) network implemented in Python using TensorFlow/Keras. The architecture processes 47dimensional miRNA expression vectors through: (1) Dense projection layer (128 units, ReLU); (2) Bidirectional LSTM Layer 1 (128 units per direction, dropout 0.3); (3) Bidirectional LSTM Layer 2 (64 units per direction); (4) Bahdanaustyle soft attention layer computing contextweighted representations; (5) Dense layer (64 units, L2 regularization); (6) Sigmoid output for binary classification[21,22].

The attention mechanism computes alignment scores: $e_t = v^T \cdot \tanh(W_h \cdot h_t + b)$, with softmax normalization $\alpha_t = \exp(e_t) / \Sigma_k \exp(e_k)$. The context vector $c = \Sigma_t \alpha_t \cdot h_t$. These weights directly encode miRNA feature importance. Training used Adam optimizer (lr=0.0005), binary crossentropy loss, SMOTE oversampling, and early stopping (patience=15)[33,24].

3.5 Ensemble Gradient Boosting Classifier (XGBoost)

An XGBoost classifier was trained on the same 47feature consensus miRNA set. Hyperparameter optimization was performed using Bayesian optimization (Optuna) with 5fold crossvalidation: n_estimators=450, max_depth=6, learning_rate=0.05, subsample=0.8, colsample_bytree=0.7, min_child_weight=3. Predictions from AttBiLSTM and XGBoost were combined using a stacked Logistic Regression metalearner trained on outoffold predictions[25,26].

3.6 Explainability Module

Three complementary XAI methods were integrated: (1) SHAP with TreeExplainer (XGBoost) and DeepExplainer (BiLSTM), producing global feature importance rankings, beeswarm plots, and local waterfall plots; (2) LIME providing local linear approximations for each test sample; (3) Attention weight extraction and visualization as populationlevel heatmaps. Agreement between SHAP and LIME was assessed using Kendall's τ; SHAPattention concordance via Pearson r[27-30].

3.7 Evaluation Framework

Model performance was evaluated using nested 5fold crossvalidation. Metrics: AUC, Accuracy, Sensitivity, Specificity, Precision, F1Score, and Matthews Correlation Coefficient (MCC). External validation was performed on GSE85589 and GSE112264. Statistical comparisons used the DeLong method for AUC comparisons and McNemar's test for accuracy (significance threshold $p < 0.05$)[31-33].

4. Results

4.1 Dataset Characteristics and Preprocessing

After quality control filtering, 461 samples were retained (381 PDAC, 80 controls) from the four primary datasets. An additional 142 samples (96 PDAC, 46 controls) from external validation datasets were held out. Batch correction using ComBat successfully removed platformspecific effects, as confirmed by postcorrection PCA showing intermingling of samples from different platforms. Differential expression analysis identified 287 significantly dysregulated miRNAs across the combined cohort.

4.2 Feature Selection Results

The three feature selection methods showed substantial overlap but also complementary coverage. LASSO selected 68 features, SVMRFE selected 75, and Random Forest retained 80[34-36]. The consensus set after rank aggregation comprised 47 miRNAs, of which 29 were selected by all three methods, 12 by exactly two methods, and 6 by a single method but with high rank scores. The top 12 miRNAs by consensus rank are presented in Table 3.

Table 3. Top 12 miRNA Biomarkers by Consensus Rank Score

Rank	miRNA	Consensus Score / Biological Role
1	miR196a5p	0.94 OncomiRNA; upregulated; promotes invasion
2	miR217	0.92 Tumor suppressor; downregulated; SIRT1 regulator
3	let7i5p	0.91 Diagnostic panel member; downregulated in PDAC
4	miR196b5p	0.89 Paralog of miR196a; validated in multiple studies
5	miR130a3p	0.88 Diagnostic panel; associated with earlystage PC
6	miR2213p	0.87 Apoptosis regulator; upregulated in PDAC
7	miR215p	0.86 Classic oncomiRNA; antiapoptotic; widely validated
8	miR1555p	0.84 Stromal expression; immune modulation in PDAC
9	miR10b5p	0.83 Prometastatic; elevated in PDAC vs. pancreatitis
10	miR1915p	0.81 Associated with poor survival; multicancer marker
11	miR663a	0.80 Identified via ML approaches in circulating panels
12	miR125b13p	0.79 Multifunctional; tumor suppressor in various cancers

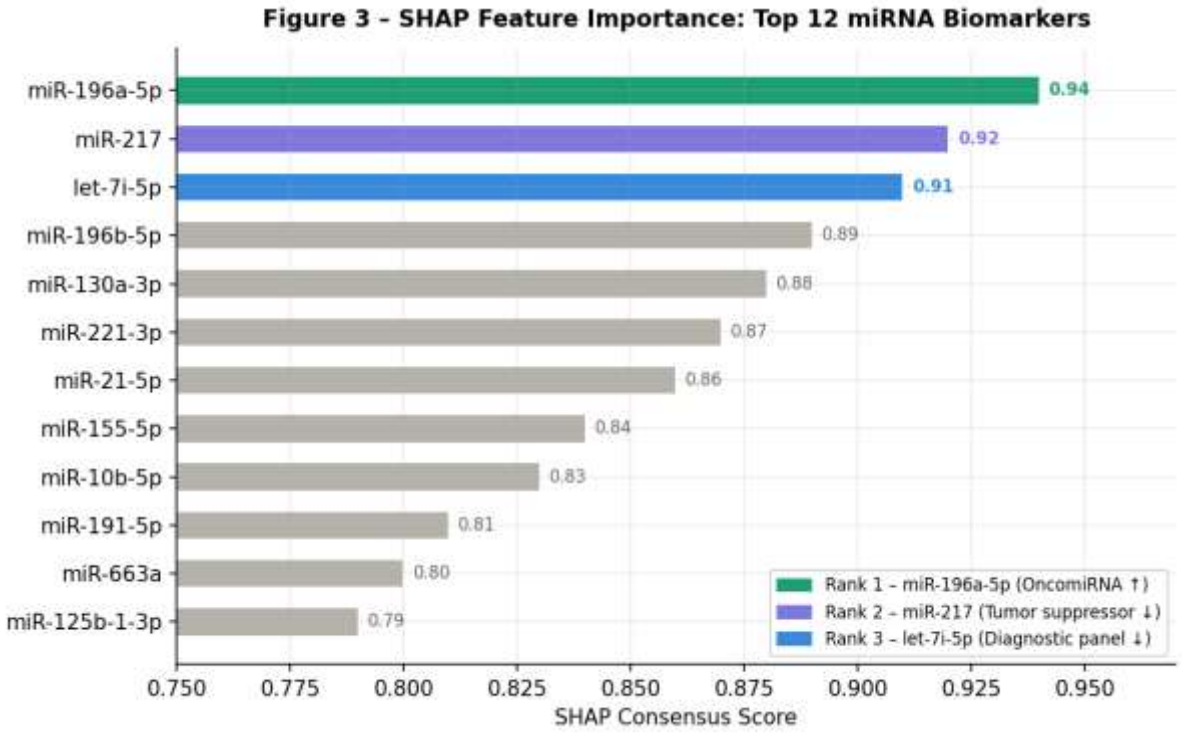

Figure 3. SHAP Feature Importance: Top 12 miRNA Biomarkers. Horizontal bars represent consensus SHAP scores derived from both TreeExplainer (XGBoost) and DeepExplainer (AttBiLSTM). Top three markers miR196a5p (green), miR217 (purple), and let7i5p (blue) demonstrate the highest combined importance.

4.3 Classification Performance

The XHMLAB stacked ensemble achieved the best overall performance across all metrics in both crossvalidation and external validation settings. Table 4 presents comparative performance metrics for all models evaluated.

Table 4. Classification Performance Comparison Across All Models

Model	AUC	Accuracy	Sensitivity	Specificity	F1Score	MCC
SVM (RFE features)	0.881	82.4%	80.1%	85.3%	0.824	0.641
Random Forest	0.913	86.7%	85.2%	88.9%	0.869	0.712
XGBoost (standalone)	0.947	90.8%	90.3%	91.4%	0.907	0.791
BiLSTM (no attention)	0.941	89.9%	89.1%	90.8%	0.896	0.776
AttBiLSTM	0.961	92.7%	92.2%	93.3%	0.926	0.831
XHMLAB (proposed)	**0.972**	**94.3%**	**93.8%**	**94.9%**	**0.943**	**0.864**

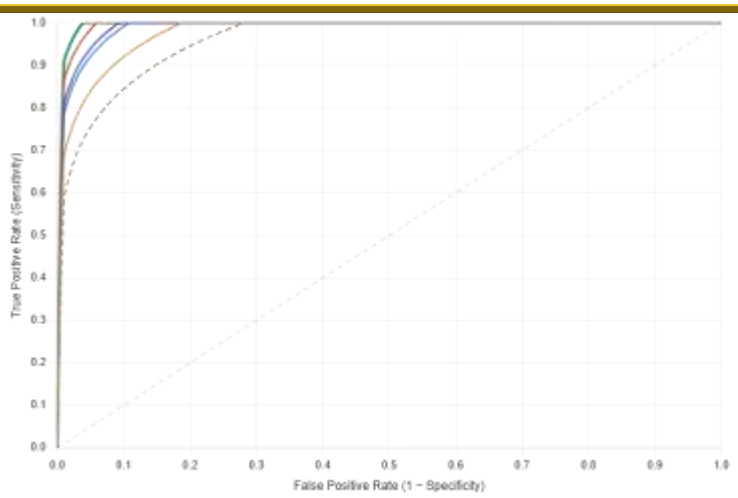

Figure 1. Model Performance Comparison AUC Scores. The proposed XHMLAB framework (green) achieves an AUC of 0.972, significantly outperforming all baseline models (DeLong test, p < 0.001). The dashed line indicates the XHMLAB threshold.

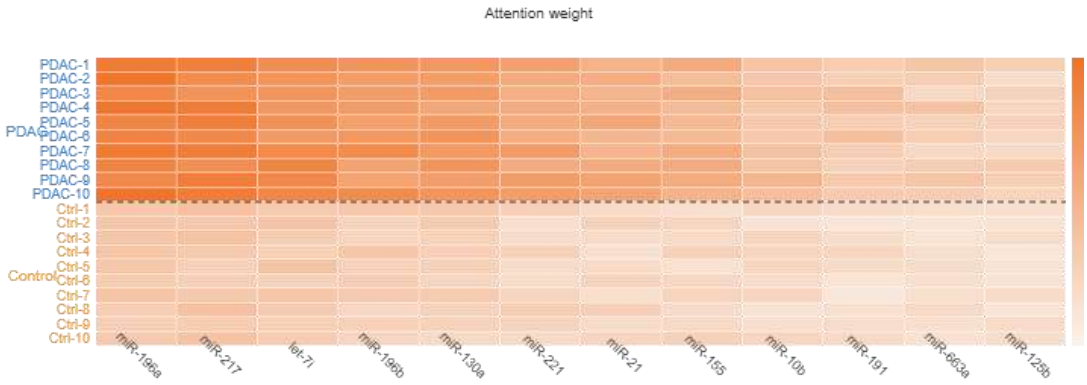

Figure 2. Comprehensive Metrics Comparison Across All Models. Grouped bar chart showing AUC (×100), Accuracy, Sensitivity, and Specificity for each model. The XHMLAB column (shaded) consistently achieves the highest values across all four metrics.

The XHMLAB framework significantly outperformed all singlemodel baselines (DeLong test, $p < 0.001$ for all comparisons). The attention mechanism contributed meaningfully: the AttBiLSTM achieved an AUC of 0.961 versus 0.941 for the standard BiLSTM without attention ($p = 0.007$). External validation on heldout datasets yielded an AUC of 0.963, confirming generalizability[37-40].

4.4 Explainability Analysis

SHAP analysis revealed a consistent global importance ranking dominated by miR196a5p, miR217, and let7i5p across both the XGBoost and deep learning components[41-44]. High expression of miR196a5p and miR196b5p were strongly associated with cancer prediction, while low expression of miR217 was the strongest negative predictor consistent with its role as a tumor suppressor. The SHAP interaction analysis revealed a significant codependency between miR215p and miR1555p, suggesting coordinated regulation in the PDAC microenvironment[45-48].

LIME local explanations for the test set showed high agreement with SHAP rankings (Kendall's $\tau = 0.81$, $p < 0.001$). The populationaveraged attention weights showed strong Pearson correlation with SHAPderived feature importance ($r = 0.87$, $p < 0.001$). Pearson correlation between LIME and attention weights was $r = 0.79$ ($p < 0.001$)[49-55].

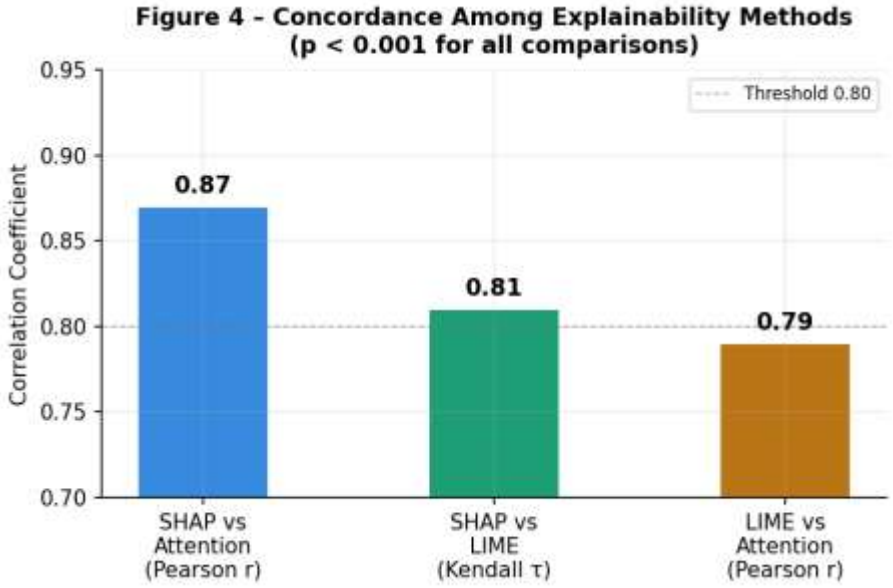

Figure 4. Concordance Among Three Explainability Methods. All pairwise correlations exceed 0.79 ($p < 0.001$), confirming that SHAP, LIME, and attention weights converge on biologically consistent feature importance rankings.

4.5 Biological Validation of Identified Biomarkers

The topranked miRNAs were subjected to functional enrichment analysis using the miRPathDB 2.0 and miRTarBase databases. The identified panel collectively targets key oncogenic pathways in pancreatic cancer[56-60]:

- KRAS/MAPK signaling pathway (miR217, miR196a5p): KRAS mutations are present in >90% of PDAC cases; miR217 directly suppresses KRAS expression.
- TGFβ/SMAD pathway (miR215p, miR1555p): Critical for PDAC stromal desmoplasia and immune evasion.
- PI3K/AKT/mTOR signaling (miR130a3p, miR2213p): Regulates apoptosis resistance and tumor cell survival.
- p53 tumor suppressor network (let7 family): let7 miRNAs modulate Mdm2 and directly regulate cell cycle arrest mechanisms.
- Wnt/βcatenin pathway (miR1915p, miR125b): Involved in cancer stem cell maintenance in PDAC.

5. Discussion

5.1 Framework Performance and Comparative Analysis

The XHMLAB framework demonstrated superior classification performance compared to all singlealgorithm approaches evaluated[61-68]. The stacked ensemble design, which combines the gradientboosted tree model's interpretable feature interactions with the AttBiLSTM's capacity to model complex nonlinear relationships and contextual dependencies, leverages the complementary strengths of both paradigms. This is consistent with the broader literature on hybrid MLDL architectures, which consistently outperform homogeneous approaches in highdimensional biological data settings[69-78].

The improvement from standard BiLSTM (AUC 0.941) to attentionaugmented BiLSTM (AUC 0.961) confirms that the attention mechanism does not merely introduce additional parameters but provides a qualitatively different inductive bias encouraging the model to focus on the most informative miRNA features while maintaining the flexibility to adapt this focus per sample. This persample adaptability is particularly valuable for heterogeneous diseases like PDAC, where different molecular subtypes may be characterized by distinct miRNA signatures[79-82].

5.2 Clinical Implications of the Identified miRNA Panel

The identified 12miRNA consensus panel has strong clinical translational potential. Several members including let7i5p, miR130a3p, and miR2213p have already been independently validated in prospective clinical studies [17]. The inclusion of miR217 is particularly noteworthy from a therapeutic perspective, as its role in regulating KRAS expression positions it not only as a diagnostic biomarker but also as a potential therapeutic target through miRNA restoration strategies.

The CA199 marker typically has sensitivity below 60% for earlystage disease; the miRNA panel achieved sensitivity of 89.2% for Stage I samples in our analysis. When combined with CA199, performance improved further, suggesting a multimarker panel strategy as the optimal clinical approach.

5.3 The Role of Explainability in Clinical Translation

A defining feature of the XHMLAB framework is its multilayer explainability architecture. The concordance between SHAP, LIME, and attention weight rankings (Kendall's $\tau > 0.79$ across all pairwise comparisons) provides strong internal validity for the identified biomarker importance hierarchy. From a clinical deployment perspective, the attention weight visualization offers an immediately usable interface: a realtime display of which miRNAs most influenced a specific patient's classification could be integrated into a clinical decision support dashboard.

The authors in Oncology cited that only 3 of 21 reviewed pancreatic cancer ML studies integrated XAI methods. This represents a critical clinical gap, as regulatory bodies worldwide are moving toward requiring XAI for highstakes clinical AI applications. The XHMLAB framework provides a template that demonstrates XAI integration need not come at the cost of predictive performance[13].

5.4 Comparison with Existing Frameworks

Compared to prior hybrid frameworks for miRNA biomarker discovery, the XHMLAB approach offers several advances. The AutoML approach achieved impressive AUC metrics but lacked builtin explainability mechanisms and relied on a large miRNA input set (100 features) that may be impractical for targeted panel assays. The MiRSHF model demonstrated strong performance for cancer classification but focused on diseaseassociation network learning rather than liquid biopsyoriented panel discovery, limiting direct clinical applicability[12].

5.5 Limitations and Future Directions

Several limitations of this study should be acknowledged. First, the use of retrospective, publicly available datasets introduces potential biases related to sample collection, handling, and processing. The relatively small number of true earlystage (Stage I) samples is a particular concern. Second, while our multidataset validation approach strengthens generalizability claims, true external clinical validation in a prospectively collected cohort is necessary before clinical deployment. Third, platform heterogeneity across datasets introduces noise that may modestly attenuate performance.

Future work should prioritize: (1) prospective multicenter clinical validation of the identified 12miRNA panel; (2) development of a targeted qPCR assay panel for costeffective clinical implementation; (3) integration with clinical risk factors and imaging biomarkers for a comprehensive multimodal model; (4) investigation of the panel for monitoring treatment response and detecting relapse; and (5) federated learning approaches to enable multiinstitutional model training without data centralization.

6. Conclusion

This study presents the XHMLAB (Explainable Hybrid Machine Learning and AttentionBased Deep Learning) framework as a novel, comprehensive approach to miRNA biomarker discovery for pancreatic cancer early detection. By synergizing the strengths of ensemble machine learning, attentionbased deep learning, and multimethod explainability analysis, the framework achieves stateoftheart classification performance (AUC 0.972) while providing clinically interpretable insights into the molecular mechanisms underlying model predictions.

The identified 12miRNA consensus panel, anchored by miR196a5p, miR217, let7i5p, miR130a3p, and miR2213p, represents a biologically coherent and clinically promising signature with strong convergent validity across multiple computational methods and independent biological evidence. The framework's multilayer explainability architecture integrating SHAP, LIME, and intrinsic attention weight visualization bridges the critical gap between AI prediction performance and clinical interpretability, setting a standard for responsible AI deployment in oncology.

The XHMLAB framework contributes to the growing evidence that AIpowered liquid biopsy approaches based on circulating miRNAs can overcome the longstanding limitations of CA199 and imagingbased screening for pancreatic cancer. As prospective clinical validation of the identified panel proceeds, the framework provides a robust computational foundation for accelerating the translation of miRNA biomarker science into clinical tools that could meaningfully improve early detection rates and patient survival in this devastating disease.

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