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RESEARCH ARTICLE

A Multimodal Deep Learning Model Integrating CNN and Transformer for Predicting Chemotherapy-Induced Cardiotoxicity

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ABSTRACT Chemotherapy-induced cardiotoxicity presents a major risk to cancer patients, often leading to severe cardiac complications such as heart failure, myocardial infarction, and arrhythmias. Early detection is crucial for preventing long-term damage and improving patient outcomes, yet existing diagnostic methods struggle to effectively capture the complexity of multimodal medical data and often lack interpretability. In this study, we propose an innovative approach that integrates multimodal deep learning with Explainable AI (XAI) techniques to enhance early cardiotoxicity detection. Our model combines clinical data (e.g., age and cardiovascular metrics) with Tissue Doppler Imaging (TDI), a functional imaging technique that captures myocardial velocity during the cardiac cycle. To overcome data limitations, we employed Conditional Generative Adversarial Networks (cGANs) and Conditional Tabular Generative Adversarial Networks (CTGANs) to augment the dataset, improving its diversity and balance for better model training. We developed three architectures that integrate Convolutional Neural Networks (CNNs) for feature extraction from TDI images with Long Short-Term Memory (LSTM), Gated Recurrent Unit (GRU), and Transformer models to capture temporal dependencies and enhance prediction accuracy. Additionally, we incorporated SHapley Additive Explanations (SHAP) to interpret the contribution of input features, increasing model transparency and clinical applicability. Our Transformer-based model achieved the highest accuracy of 96%, outperforming the GRU (94%) and LSTM (89%) models, significantly surpassing traditional approaches. These findings highlight the potential of transformer-based architectures in multimodal deep learning for precise cardiotoxicity prediction, supporting early intervention and personalized treatment strategies while improving interpretability through XAI techniques such as SHAP.

INDEX TERMS Multimodal deep learning, cardiotoxicity, chemotherapy, convolutional neural networks, recurrent neural networks, transformer, generative adversarial networks, explainable AI.

I. INTRODUCTION

Chemotherapy-induced cardiotoxicity is a major concern in oncology, affecting a significant percentage of patients with cancer undergoing treatment, particularly those receiving anthracyclines and other cardiotoxic agents. Cardiotoxicity can lead to severe cardiac conditions such as heart failure, arrhythmias, and myocardial infarction, which not only compromise patient outcomes but also limit the administration of effective cancer therapies. According to recent studies, cardiotoxicity affects 10-30% of patients treated with anthracyclines, and up to 25% of these patients develop symptomatic heart failure. Moreover, long-term cardiovascular complications in cancer survivors have become increasingly recognized, contributing to the growing need for early detection and prevention.

Despite advances in imaging and diagnostic tools, early detection of chemotherapy-induced cardiotoxicity remains

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a challenge. Traditional diagnostic methods, including echocardiography and cardiac biomarkers, often detect cardiotoxicity only after significant cardiac damage has occurred [1]. Machine learning models, such as Logistic Regression (LR) and Support Vector Machines (SVM) [1], [28], have been applied in attempts to improve early detection, but they are limited by their inability to handle the complexity of multimodal clinical and imaging data. More recent deep learning approaches, although promising, often rely on unimodal data and face difficulties in generalizing to diverse patient populations.

A few real-world examples have illustrated the urgency of this problem. In a 2020 study conducted at a major oncology center, nearly 15% of patients with breast cancer treated with anthracyclines developed signs of cardiotoxicity within a year, significantly affecting their treatment plans and long-term outcomes. In another case, a 45-year-old patient undergoing chemotherapy for lymphoma experienced undetected cardiac damage that led to heart failure within six months of treatment. Such cases highlight the urgent need for a more reliable and early detection system.

A. EXISTING CARDIOTOXICITY DETECTION METHODS

In recent years, machine learning [10], [25], [26], [27], [29], [30] and deep learning have been increasingly applied to detect cardiotoxicity resulting from chemotherapy. Traditional models such as Logistic Regression (LR) and Support Vector Machines (SVM) [28] have provided moderate success but are limited by their inability to capture complex, nonlinear patterns in large datasets. As a result, deep learning models such as Convolutional Neural Networks (CNNs) [43], [44], [45], [48], [52], [54] and Recurrent Neural Networks (RNNs) [50], [55] have gained popularity because of their ability to analyze high-dimensional and multimodal data. Guo et al. explored the use of CNNs for analyzing imaging data, achieving high accuracy but emphasizing the need to integrate different data modalities to improve predictive performance [9]. Moreover, Milosevic et al.

In addition to these developments, [46] explores advanced cardiovascular and molecular imaging techniques for the early detection and monitoring of cancer therapy-associated cardiotoxicity. It reviews key imaging modalities, such as echocardiography, MRI, and emerging nuclear imaging techniques to assess heart function and detect early signs of cardiotoxicity in patients undergoing cancer treatments such as anthracyclines, tyrosine kinase inhibitors, and immune checkpoint inhibitors. In addition, it highlights the role of artificial intelligence (AI) and big data in enhancing the predictive power of these imaging techniques to improve early detection and personalized care.

In contrast, this study [3] presents a multimodal artificial intelligence (AI) framework designed to assess ischemic heart disease (IHD) risk by combining imaging data from abdominopelvic CT scans with electronic medical record (EMR) data. The authors utilized a dataset of 8139 CT images and developed models to predict IHD risk over the 1-year and 5-year follow-up periods. By integrating both clinical and imaging data, the model significantly outperformed traditional risk prediction methods such as the Framingham Risk Score (FRS) and Pooled Cohort Equations (PCE).

A key component of the framework is a 2.5D U-Net convolutional neural network (CNN), which was used for segmenting body composition metrics from L3 axial slices of abdominopelvic CT scans. This model demonstrated excellent segmentation performance, achieving a Dice score of 0.97 for muscle, subcutaneous adipose tissue (SAT), and visceral adipose tissue (VAT). The extracted features, including muscle radiodensity and VAT/SAT ratio, were utilized in the IHD risk models.

Additionally, an EfficientNet-B6 CNN was trained to predict IHD risk directly from raw CT images. This model achieved an AUROC of 0.76 for 1-year risk and 0.78 for 5-year risk, demonstrating superior performance compared to simpler image-based models. For clinical data, the authors employed XGBoost, a robust machine learning algorithm that handles EMR-derived features, including patient demographics, laboratory results, and comorbidities. The XGBoost model achieved AUROC scores of 0.80 for 1-year and 0.76 for 5-year IHD risk prediction.

Most results were achieved through the use of fusion models that combined imaging and clinical data. By stacking the outputs from the imaging and clinical models using L2 logistic regression, the Imaging + Clinical Fusion Model outperformed individual models, achieving an AUROC of 0.81 for 1-year and 0.80 for 5-year IHD risk prediction. Furthermore, when segmentation data were incorporated into the fusion model, it improved the AUCPR to 0.63 for 5-year IHD risk.

Recent advancements in artificial intelligence (AI) and deep learning have significantly improved cardiotoxicity detection methods by leveraging multimodal data and machine learning techniques. AI-driven models have been increasingly utilized in cardiology to process large datasets, automate feature extraction, and enhance diagnostic accuracy. Esteva et al. [57] highlighted various AI applications in cardiology, demonstrating how deep learning techniques can facilitate early detection of cardiovascular diseases, including chemotherapy-induced cardiotoxicity. Additionally, Johnson et al. [58] emphasized the importance of integrating **multi-modal data**, including clinical, imaging, and genetic information, to improve prediction models for cardiovascular disease outcomes. Their study demonstrated that combining multiple data sources enhances model robustness and generalizability.

Moreover, Zhang et al. [59] explored the potential of multimodal deep learning in **diagnosing left ventricular hypertrophy**, a condition often linked to chemotherapy-induced cardiotoxicity. Their work demonstrated that integrating ECG and echocardiogram data improves predictive accuracy, further validating the benefits of combining diverse modalities. Brown et al. [60] extended this concept by reviewing AI applications in multi-modal cardiovascular

imaging, showcasing how deep learning models improve segmentation, classification, and early detection in clinical practice.

These studies collectively indicate that leveraging multimodal AI approaches significantly enhances **cardiotoxicity detection**, providing a strong foundation for developing advanced deep learning-based frameworks tailored to real-world clinical applications.

B. LIMITATIONS OF EXISTING APPROACHES

Although deep learning models have shown improved performance in cardiotoxicity detection, they still face significant limitations. One key challenge is their reliance on unimodal data, such as imaging or clinical variables alone, which fail to capture the full spectrum of patient information needed for accurate predictions. Many of these models also suffer from poor generalization owing to limited and imbalanced datasets, as noted in the studies by Liu et al. [21]. Additionally, these models often struggle with small sample sizes, wich limits their effectiveness in real-world clinical settings. Traditional models such as SVMs also face constraints when processing multimodal and unstructured data [28].

A notable limitation highlighted in [46] is the under representation of patients with cardiovascular disease in major cancer trials. This exclusion creates a significant data gap, impacting the generalizability of AI models used in cardio-oncology. Models developed on datasets that do not adequately represent this population may perform poorly in real-world scenarios where cancer patients frequently have pre-existing cardiovascular conditions. To address this issue, future cancer trials should include cardiovascular outcomes, provide a more comprehensive dataset that better reflects real-world patient populations and improves the robustness of AI models for detecting chemotherapy-induced cardiotoxicity.

Recent studies have further emphasized challenges in the integration of multimodal data sources. Esteva et al. [57] demonstrated that while AI-driven cardiology models perform well on structured datasets, they often lack interpretability, making clinical adoption difficult. Johnson et al. [58] highlighted that effective AI models require harmonization of diverse data modalities, including imaging, genomic, and electronic health records (EHR), yet interoperability issues and data silos remain major obstacles. Zhang et al. [59] noted that multimodal deep learning frameworks show promise but require rigorous validation across diverse patient demographics to ensure robustness in clinical settings.

The study [3] also identifies limitations in the broader application of the proposed model. One key issue is that the data were retrospectively sourced from a single center, which may reduce the model's generalizability to other healthcare settings. Diagnoses made outside this center could be missed. While the model showed promising results, the authors emphasize the need for prospective evaluations across multiple centers and diverse populations to confirm its clinical utility and account for variations in performance across demographic groups.

This study further noted that some biomarkers [3], such as aortic calcifications, may not be visible using the single L3 slice approach, limiting the effectiveness of the model. The use of 1- and 5-year prediction time frames may have disadvantaged traditional risk scores such as the Framingham Risk Score and Pooled Cohort Equations, which are designed for 10-year risk assessments. However, the authors argued that 1-year predictions could help identify high-risk individuals in need of immediate intervention. Additionally, the absence of body composition metrics such as waist circumference or waist-to-hip ratio may further limit the model's predictive power.

To fully realize the potential of AI in healthcare, future efforts should focus on improving data quality, ensuring representative datasets, enhancing model interpretability, and optimizing the balance between computational resources and predictive performance.

C. MOTIVATION AND CONTRIBUTIONS

This approach is justified by its ability to overcome critical limitations that have been missed by other approaches for detecting chemotherapy-induced cardiotoxicity. Traditional models and even advanced deep learning techniques tend to rely heavily on unimodal data, focusing solely on clinical or imaging data—which limits their ability to capture the complex interactions between various factors influencing cardiotoxicity. These methods often fail to provide a complete picture of a patient's cardiovascular health, particularly when it comes to integrating both functional and structural cardiac data. Additionally, existing models struggle with small and imbalanced datasets, which reduce their generalizability across diverse patient populations.

Recent advancements in deep learning and multimodal [2], [3], [6], [9], [10], [19], [47] data fusion offer new opportunities to address these challenges. By integrating imaging data (TDI) with clinical data, it is possible to capture both structural and temporal changes in cardiac function and provide enhanced predictive capabilities. However, existing studies have rarely explored multimodal models that combine these data types, nor have they evaluated advanced architectures such as transformers [4], [5], [8], [11], [12], [41], [42] for this specific task. Thus, our study sought to bridge this gap by developing and evaluating multimodal models capable of accurately predicting cardiotoxicity.

This study introduces a novel multimodal deep learning framework that integrates CNN-based feature extraction from TDI images with advanced architectures [14], [23], [32], [33], [34], [35] such as LSTM, GRU, and Transformer models for accurate cardiotoxicity prediction. The models are developed and evaluated using 270 real patient samples and 1,000 synthetic patient samples generated by GANs, with 60% of the patients used for training, and 40% for testing. The experimental results showed that the transformer-based

TABLE 1. Clinical and TDI features used in the model.

Feature	Description
Age	Patient's age
Weight and Height	Body metrics influencing drug metabolism
CTRCD Status	Indicates previous cardiac dysfunction due to therapy
LVEF	Percentage of blood leaving the heart per contraction
Heart Rate	Beats per minute, indicating cardiac stress
Treatment Details	Specific drugs known for cardiotoxic effects
Cardiovascular Metrics	Includes blood pressure, cholesterol levels
Myocardial Velocity (TDI)	Speed of cardiac tissue movement
Strain and Strain Rate (TDI)	Deformation of the heart muscle
Displacement (TDI)	Movement of heart tissue during the cardiac cycle
Time to Peak Strain (TDI)	Time to maximum strain, indicating cardiac contractility

model achieves the highest performance, with an accuracy of 96% and an AUC-ROC of 0.97. In comparison, the GRU model achieved 94% accuracy and an AUC-ROC of 0.95, whereas the LSTM model achieved 89% accuracy with an AUC-ROC of 0.94.

To enhance model interpretability and facilitate clinical adoption, we integrated Explainable AI (XAI) techniques [56] using SHapley Additive Explanations (SHAP). SHAP enables the identification of key clinical and imaging features contributing to cardiotoxicity predictions, offering a transparent framework for decision-making. Our analysis revealed that left ventricular function metrics, myocardial velocity parameters, and specific clinical indicators such as patient age and cardiovascular history were among the most influential predictors. The Transformer-based model not only achieved the highest accuracy (96%) but also exhibited clear feature attribution patterns, reinforcing the reliability of its predictions. This integration of SHAP provides clinicians with deeper insights into the risk factors influencing cardiotoxicity, fostering trust in AI-assisted diagnostic systems and supporting personalized treatment adjustments.

These findings highlight the superior performance of the transformer architecture for capturing complex temporal dependencies from multimodal data. This study demonstrates that the integration of CNNs with advanced deep learning models significantly enhances the prediction accuracy. These results pave the way for future research on multimodal medical prediction tasks, offering a powerful tool for clinicians to detect cardiotoxicity at an early stage and improve patient care.

II. MATERIALS AND METHODS

A. DATASET, DATA PREPARATION AND DATA PREPROCESSING

This study utilizes a comprehensive dataset combining clinical variables and functional data from Tissue Doppler Imaging (TDI) of breast cancer patients undergoing chemotherapy [7]. The clinical dataset includes demographic information such as age, weight, and height, along with cardiovascular metrics and cancer therapy-related cardiac dysfunction (CTRCD). TDI data provide detailed measurements of myocardial velocity, strain, and other indicators of cardiac function, aiding in the assessment of chemotherapy-induced cardiotoxicity.

Table 1 presents the clinical and TDI features used in the multimodal model, highlighting their relevance in predicting cardiotoxicity.

To enhance reproducibility, we provide a detailed dataset breakdown. The dataset comprises **1,270** samples, including imaging and clinical data. It is divided into two classes: **Cardiotoxicity (CTRCD)** and **Non-Cardiotoxicity (NO_CTRCD)**. The class distribution is summarized in Table 2.

TABLE 2. Class distribution in the dataset.

Class	Number of Samples	Percentage (%)
Cardiotoxicity (CTRCD)	**531**	**41.8**
Non-Cardiotoxicity (NO_CTRCD)	**739**	**58.2**

The dataset is relatively balanced, with augmentation techniques used to further refine class distribution.

TDI images are standardized to **160** $\times$ **384** pixels. Initially, the dataset contained **27 images** for CTRCD and **200 images** for NO_CTRCD. Augmentation techniques were applied to create a more balanced dataset.

The clinical data consists of **27 variables** per patient, covering demographics, cardiovascular history, and treatment details. Missing values were addressed through mean imputation for numerical features and mode imputation for categorical features, ensuring data completeness.

This multimodal dataset structure integrates both imaging and clinical data, enabling a comprehensive predictive model for chemotherapy-induced cardiotoxicity detection.

B. SYNTHETIC DATA EXPANSION THROUGH CGANS AND CTGAN FOR TDI AND CLINICAL FEATURES

In our study, we addressed the limitations of a small and unbalanced dataset of 217 patient samples by implementing data augmentation techniques using GANs [15], [16], [18], [20], [21], [31], [49], [51]. The limited dataset posed challenges, risking overfitting and bias toward overrepresented classes. Using GANs, we generated 1,000 additional synthetic samples, enhancing the dataset's diversity and balance and supporting the model's accuracy and reliability in clinical predictions.

For dataset augmentation, we focused on both Tissue Doppler Imaging (TDI) and clinical data. Given the high cost and time required to collect TDI data crucial for detecting cardiotoxicity, we employed conditional GANs (cGANs) [13], [17] to generate synthetic TDI images. By conditioning image generation on clinical features, the model produced varied TDI images representing diverse clinical scenarios. For clinical data, we applied CTGAN [53], a GAN-based model designed for tabular data (Fig. 2), to generate synthetic clinical records while maintaining the statistical properties and complex dependencies of the original data.

1) OVERVIEW OF GAN-BASED DATA GENERATION

Generative Adversarial Networks (GANs) have become a powerful technique for addressing the challenges of small and unbalanced datasets in medical imaging. In this study, we developed a multi-modal GAN framework, integrating Conditional GANs (cGANs) for synthetic TDI image generation and CTGAN for synthetic clinical data augmentation. This hybrid approach ensures that synthetic data retains the statistical properties and variability of real-world patient data while enhancing dataset diversity and model generalizability.

2) CONDITIONAL GAN (cGAN) FOR SYNTHETIC TDI IMAGE GENERATION

The cGAN framework (Table 3) comprises a generator that synthesizes images conditioned on clinical features and a discriminator that distinguishes between real and synthetic samples (Fig. 1). The adversarial training process ensures that the generated images closely resemble real TDI images while preserving patient-specific characteristics.

TABLE 3. Generator architecture components.

Component	Description
Latent Noise Vector (z)	Sampled from $\mathcal{N}(0, 1)$ to introduce variation.
Clinical Conditioning Vector (c)	Encodes features such as LVEF, heart rate, and treatment history.
Dense Projection Layer	Maps input vectors to an initial feature representation.
Transpose Convolutional Layers	Upsample and refine image details.
Batch Normalization	Mitigates covariate shifts for stable training.
LeakyReLU Activations	Enhances feature learning through non-linearity.
Noise Injection	Prevents mode collapse and improves image diversity.

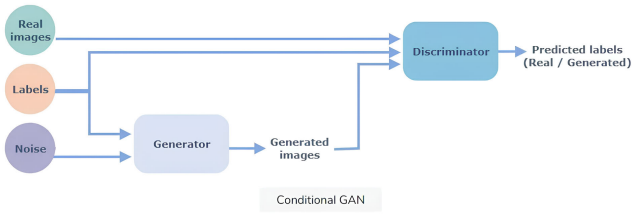

FIGURE 1. cGAN architecture.

3) CTGAN FOR SYNTHETIC CLINICAL DATA GENERATION

CTGAN was used to synthesize clinical datasets while preserving the statistical integrity of real patient records (Table 4). Unlike conventional GANs, CTGAN handles mixed data types, ensuring the faithful reproduction of categorical and numerical clinical variables.

TABLE 4. CTGAN components and functions.

Component	Description
Data Preprocessing	Normalization of numerical features and encoding of categorical variables.
Variational Autoencoder (VAE) Generator	Captures complex feature dependencies in clinical records.
PacGAN Training	Reduces mode collapse by improving sample diversity.
Gumbel-Softmax Trick	Enhances categorical feature generation, ensuring accurate labels.
Evaluation Metrics	Kolmogorov-Smirnov (KS) test to compare statistical distributions.

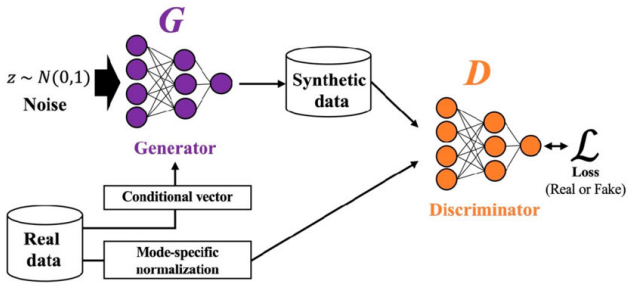

FIGURE 2. CTGAN architecture.

4) TRAINING AND OPTIMIZATION STRATEGIES

To optimize both cGAN and CTGAN models, several advanced training strategies were implemented to enhance stability, improve diversity, and prevent overfitting. Adversarial loss, specifically the Wasserstein loss, was utilized to refine the interaction between the generator and discriminator, ensuring a more stable training process. To further enhance robustness, gradient penalty (WGAN-GP) was incorporated, effectively mitigating mode collapse and promoting the generation of more diverse synthetic samples.

Additionally, a dynamic learning rate adjustment was applied throughout training to facilitate optimal convergence, preventing instability caused by a fixed learning rate. To avoid overfitting, an early stopping mechanism was employed, halting training once model performance stabilized based on predefined evaluation criteria. Lastly, model checkpointing was used to retain the best-performing generator model, selected based on Fréchet Inception Distance (FID) and Structural Similarity Index Measure (SSIM) scores. These strategies collectively ensured that the cGAN and CTGAN models produced high-quality synthetic data while maintaining realism and diversity in the generated samples.

The training dynamics of the Generative Adversarial Network (GAN) are monitored using three key metrics over multiple epochs (Fig. 3): discriminator loss (D Loss), generator loss (G Loss), and discriminator accuracy (D Accuracy). At the beginning of training, D Loss decreases significantly as the discriminator improves its ability to distinguish between real and generated data. As training advances, the loss stabilizes, indicating that the generator is producing increasingly realistic samples, making it more difficult for the discriminator to differentiate them. This

stabilization signifies the achievement of an adversarial equilibrium, where both models have reached a balance in their learning process.

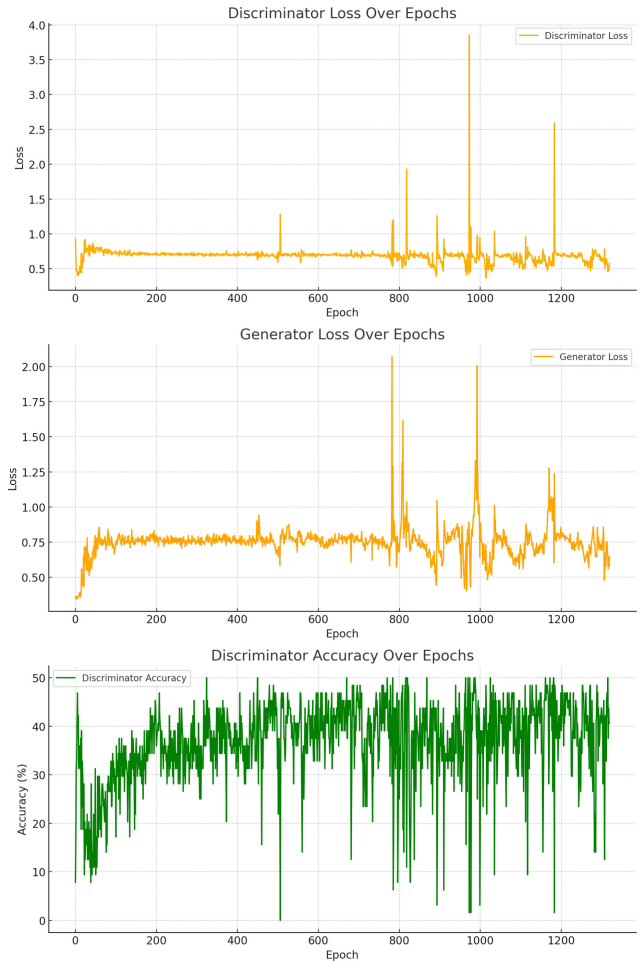

FIGURE 3. Evolution of discriminator loss, generator loss, and discriminator accuracy throughout training epochs.

5) PERFORMANCE EVALUATION AND SYNTHETIC DATA QUALITY ASSESSMENT

Evaluating the realism and diversity of the generated samples is critical to ensuring their utility in training predictive models. Quantitative metrics such as Structural Similarity Index (SSIM) and Fréchet Inception Distance (FID) were employed:

Furthermore, diversity analysis was performed using statistical distributions of key clinical features (e.g., LVEF, heart rate). The Kolmogorov-Smirnov (KS) test confirmed that synthetic clinical data closely followed the real data distribution, minimizing bias introduction.

6) CROSS-VALIDATION FOR ROBUSTNESS ASSESSMENT

To ensure the generalizability and robustness of the synthetic data, we conducted cross-validation across multiple data splits. The dataset, consisting of both real and GAN-generated samples, was divided into stratified folds to evaluate performance consistency across different subsets. The classification model trained on synthetic and real data was assessed using key metrics such as accuracy, precision, recall, and F1-score. The results demonstrated minimal variance across folds, confirming that the synthetic data effectively supplemented real-world samples while maintaining stable predictive performance.

TABLE 5. Evaluation metrics for synthetic data.

Metric	Result	Interpretation
FID Score	24.8	Measures similarity between real and synthetic image distributions. Lower values indicate better quality.
SSIM Score	0.86	Assesses structural similarity between real and synthetic TDI images. Higher values indicate better resemblance.
Class Adherence	97.4%	Ensures that generated images correctly align with clinical labels.
KS Test (p-value)	>0.05	Confirms that synthetic clinical data statistically matches real data.
Diversity Score	0.87	Ensures generated images cover a wide range of variations.

7) ABLATION STUDY ON THE IMPACT OF SYNTHETIC DATA

An ablation study was conducted to assess the impact of synthetic data on model performance by comparing different dataset configurations. The baseline model, trained on the original, unbalanced dataset with only real data, showed lower classification performance due to the inherent class imbalance, with 217 samples and only 27 cases of CTRCD. When synthetic data augmentation using GAN-generated samples was incorporated, there was a significant improvement in both classification accuracy and generalization capabilities. Alternative data balancing techniques, such as SMOTE and simple oversampling, helped to address class imbalance but failed to introduce new variations in the data distribution, which led to overfitting. On the other hand, GAN-generated samples offered higher diversity, enhancing the robustness of the model. Additionally, when comparing different GAN configurations, the cGAN with CTGAN conditioning outperformed unconditioned GANs and traditional data augmentation, highlighting the advantages of integrating multi-modal synthetic data.

To mitigate risks of overfitting to synthetic patterns, an independent evaluation was conducted on real, unseen patient data. The classifier trained with both real and synthetic data was tested exclusively on a separate real dataset. The performance remained consistent, demonstrating that the synthetic data did not introduce artifacts that could bias the model. This validation step confirmed the efficacy of the GAN-based augmentation strategy in enhancing real-world generalization.

This multi-modal GAN framework was successfully developed to generate high-quality synthetic TDI images and clinical data, addressing the challenges of *data scarcity* and *class imbalance* in cardiotoxicity analysis. By integrating

TABLE 6. CNN + LSTM/GRU multimodal model architecture.

Branch	Layer	Parameters	Output Shape
		TDI Image Branch	
Input	Input	(160, 384, 3)	(160, 384, 3)
	Conv2D 1	32 filters, (3, 3), ReLU	(158, 382, 32)
	MaxPooling2D 1	Pool size (2, 2)	(79, 191, 32)
	Conv2D 2	64 filters, (3, 3), ReLU	(77, 189, 64)
	MaxPooling2D 2	Pool size (2, 2)	(38, 94, 64)
	Conv2D 3	128 filters, (3, 3), ReLU	(36, 92, 128)
	MaxPooling2D 3	Pool size (2, 2)	(18, 46, 128)
	Flatten	-	(1056,)
	RepeatVector	10 times	(10, 1056)
	LSTM/GRU	64 units, no return sequences	(64,)
	Dense	64 units, ReLU	(64,)
		Clinical Data Branch	
Input	Input	(n_features,)	(n_features,)
	Dense 1	64 units, ReLU	(64,)
	Dense 2	32 units, ReLU	(32,)
	Dense 3	16 units, ReLU	(16,)
		Fusion and Post-Fusion Layers	
Fusion	Concatenate	-	(80,)
Post-Fusion Dense 1	Dense	64 units, ReLU	(64,)
Post-Fusion Dense 2	Dense	32 units, ReLU	(32,)
		Output Layer	
Output	Dense	1 unit, Sigmoid	(1,)

cGANs for image generation and CTGAN for clinical data synthesis, we ensured that synthetic data maintains both visual and statistical integrity. The synthetic dataset significantly improved model generalization, making it a valuable tool for advancing deep learning applications in medical research.

C. MULTIMODAL DEEP LEARNING MODEL: LSTM/GRU

The multimodal architecture presented in Table 6 combines Tissue Doppler Imaging (TDI) and clinical data for cardiotoxicity prediction. The image branch uses a Convolutional Neural Network (CNN) to extract relevant features from the TDI images. It consists of multiple convolutional layers with rectified linear unit (ReLU) activations, followed by max-pooling layers to reduce the spatial dimensions and focus on important features. Dropout layers were employed to prevent overfitting and improve generalization. After feature extraction, the output is flattened and reshaped into sequences, which are passed through either an LSTM or GRU to capture the temporal dependencies present in the cardiac data. The output of this branch is a dense feature vector that represents the extracted image information.

The clinical data branch processes patient-specific features through a series of fully connected dense layers with ReLU activation. Each layer extracts relevant information from the structured data, with dropout applied between the layers to avoid overfitting. The outputs from the TDI image and clinical data branches are concatenated to form a unified multimodal feature vector.

This combined representation is passed through additional dense layers to refine the output and improve predictive power. The final layer uses a sigmoid activation function to classify whether a patient is likely to develop cardiotoxicity or not. This multimodal architecture leveraged both image-based features and clinical insights to provide a more robust and accurate prediction model.

D. TRANSFORMER ARCHITECTURE IN THE MULTIMODAL MODEL

In the model described in Table 7, the transformer architecture (Fig. 4) is used to process the features extracted from the TDI images. After the convolutional layers (CNN) extract spatial features from the images, the output is flattened and reshaped into sequences. These sequences are fed into the transformer encoder to capture the complex temporal dependencies of the data.

The Transformer encoder comprises multiple attention heads that learn different aspects of the sequence by attending to various positions in the input. Specifically, the multi-head self-attention mechanism computes the relationships between elements in the sequence, helping the model focus on the most relevant parts of the extracted image features. Each attention head produces an output, which is then concatenated and passed through feed-forward layers to refine the learned representation. Residual connections and layer normalization (inherent to Transformer design) ensure the stability of the learning process and prevent vanishing gradients.

The output from the Transformer encoder is a dense vector representing the temporal information from the input sequence. This vector is further passed through fully connected layers, which prepare it for fusion with the clinical data branch. The combination of CNN-based feature extraction and transformer's ability to capture complex temporal dependencies allows the model to perform highly accurate cardiotoxicity predictions.

The training process of the proposed multimodal model involves feeding TDI images and clinical data into their

TABLE 7. Transformer module replacing the GRU/LSTM in the multimodal model.

Layer Type	Parameters	Description
CNN Output	-	Features from the CNN branch are flattened and reshaped into sequences for temporal processing.
Multi-Head Self-Attention	Head Size = 32, Num Heads = 4	Captures relationships between elements by attending to different parts of the input features.
Add and Norm	-	Residual connections and layer normalization stabilize training and ensure consistent gradient flow.
Feed-Forward Layer	Hidden Units = 64	Further refines the feature representations from the attention mechanism.
Dropout	Rate = 0.3	Mitigates overfitting by randomly disabling neurons during training.
Repeat Encoder Block	2	Stacks two encoder blocks to improve temporal learning.
Dense Layer	64 Units, ReLU Activation	Produces the final feature vector for fusion with clinical data.

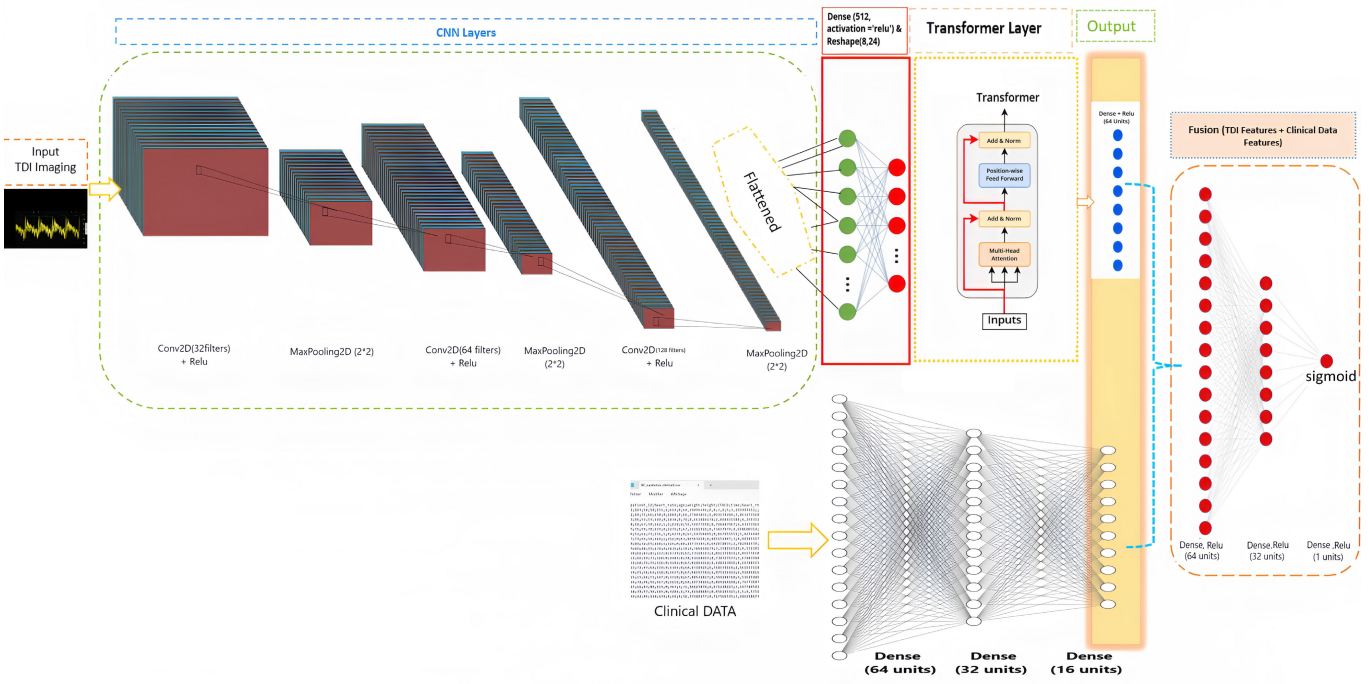

FIGURE 4. The multimodal architecture processes TDI images through convolutional layers and a Transformer to capture spatial and sequential features, while clinical data is processed via dense layers to highlight key indicators. Outputs from both branches are fused and refined through dense layers for robust cardiotoxicity prediction. A final sigmoid-activated layer provides the cardiotoxicity outcome.

respective branches. The CNN branch extracts spatial features from the TDI images, which are processed by either an LSTM, GRU, or Transformer layer to capture temporal dependencies. Simultaneously, clinical data passes through fully connected dense layers to extract patient-specific insights. Both outputs were then concatenated and passed through additional dense layers for the final prediction.

The model was trained using binary cross-entropy loss, which is appropriate for binary classification tasks, with the Adam optimizer to adjust the learning rate dynamically during training. To address class imbalance, class weights are applied, and early stopping is used to halt training when the validation loss no longer improves, thereby preventing overfitting. Additionally, a ReduceLROnPlateau callback reduces the learning rate if the performance plateaus. The model was evaluated on a test set unseen during training to ensure generalization, and performance metrics such as accuracy, F2-score, and AUC-ROC were recorded for comparison between the LSTM, GRU, and Transformer architectures.

III. RESULTS AND DISCUSSION

A. LSTM MODEL RESULTS (DETAILED ANALYSIS)

The **LSTM model** achieved an **accuracy of 88%**, indicating that 88% of all predictions (both positive and negative) were correct. However, accuracy alone may not capture the full picture, especially when dealing with imbalanced data. To provide a deeper evaluation, we use metrics such as **precision**, **recall**, **F1-score**, **F2-score**, **confusion matrix**, and Receiver Operating Characteristic (**ROC curve**) to assess the model's performance.

1) CONFUSION MATRIX ANALYSIS

The confusion matrix (Fig. 5) provides detailed insights into the model's predictions:

- **True Negatives (TN)**: 271 cases – the model correctly predicted no cardiotoxicity.
- **False Positives (FP)**: 45 cases – the model incorrectly predicted cardiotoxicity for non-cardiotoxic patients.
- **True Positives (TP)**: 179 cases – the model correctly predicted cardiotoxicity.
- **False Negatives (FN)**: 13 cases – the model failed to detect cardiotoxicity in patients who actually developed it.

This matrix helps us understand the types of errors made by the model. The **false positives** (45 cases) indicate instances where the model incorrectly flagged cardiotoxicity, which could lead to unnecessary medical interventions. More critically, false negatives (13 cases) represent missed cardiotoxicity cases, which could have serious clinical implications if left untreated.

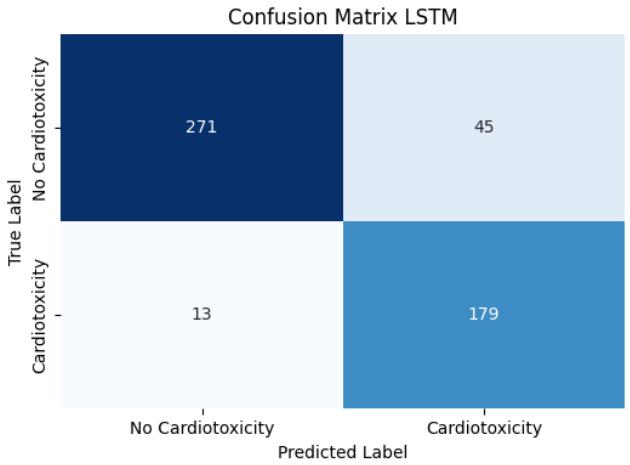

FIGURE 5. Confusion matrice LSTM.

2) PRECISION AND RECALL

- **Precision** for cardiotoxicity (class 1) is:

$$\text{Precision} = \frac{TP}{TP + FP} = \frac{179}{179 + 45} = 0.79$$

The precision (Fig. 6) measures the number of correct positive predictions. In a medical setting, high precision ensures that fewer patients are incorrectly flagged as having cardiotoxicity, thereby reducing unnecessary interventions.

- **Recall** for cardiotoxicity is:

$$\text{Recall} = \frac{TP}{TP + FN} = \frac{179}{179 + 13} = 0.93$$

The recall indicates the number of actual cardiotoxicity cases that were correctly identified. It is a critical metric, especially in healthcare, in which missing a positive case can have severe consequences.

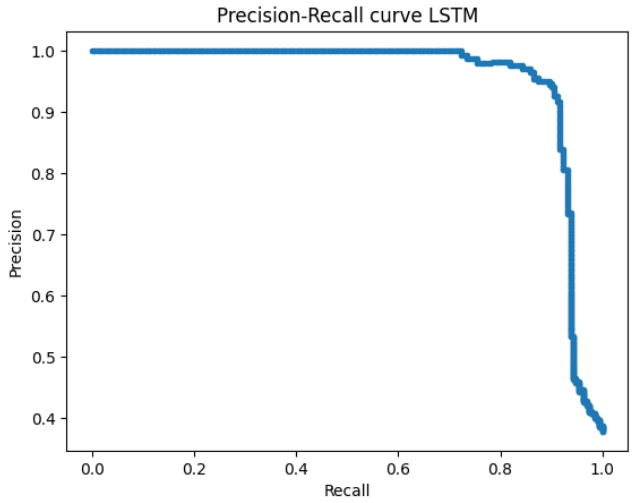

FIGURE 6. Precision recall LSTM.

3) F1-SCORE AND F2-SCORE

The **F1-score** for cardiotoxicity was 0.86, which balances both precision and recall. However, since our primary goal is to **maximize recall** (detecting all cardiotoxicity cases), we focused on the **F2-score**, which gives more weight to recall than precision. The model achieved an **F2-score of 0.90**, reflecting good performance in detecting cardiotoxicity, although there is room for improvement.

4) ROC CURVE AND AUC

The **(ROC)** curve (Fig. 7) plots the true positive rate (recall) against the false positive rate at various classification thresholds. For the LSTM model, the **AUC-ROC is 0.94**, indicating excellent performance in distinguishing between patients with and without cardiotoxicity.The high AUC shows that the LSTM model effectively captures the underlying patterns in the multimodal data, though the few false negatives suggest potential for further refinement.

5) INTERPRETATION OF RESULTS

The LSTM model provides robust performance, with a good balance between precision and recall. However, the presence of **false negatives** highlights a key limitation, as missing cardiotoxicity cases can delay treatment. In comparison to other models (GRU and Transformer), LSTM effectively captures temporal dependencies, but its slightly lower performance suggests that other architectures, such as the Transformer, may be better suited for this task. Further refinements, such as hyperparameter tuning or deeper architectures, could improve predictive performance.

B. GRU MODEL RESULTS

The GRU model achieved an impressive accuracy of 94%, thereby demonstrating its effectiveness in predicting cardiotoxicity. This high accuracy, combined with a strong F2-score, highlights the ability of the GRU model to balance

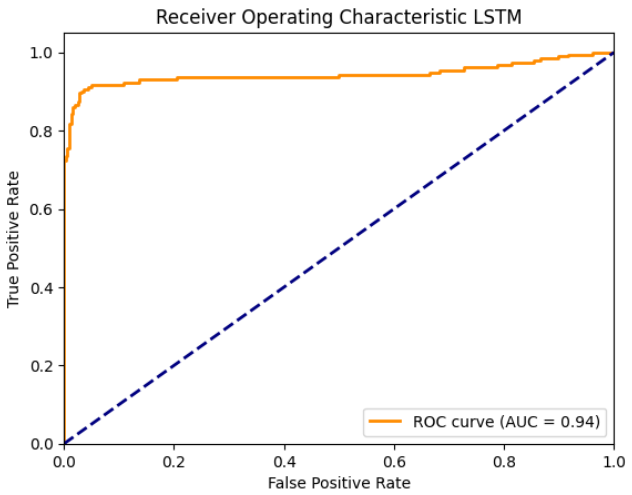

FIGURE 7. ROC curve LSTM.

sensitivity and specificity. Below, we provide a detailed analysis of the confusion matrix and other key metrics, such as precision, recall, F1-score, F2-score, and the ROC curve to assess the model's strengths and limitations.

1) CONFUSION MATRIX ANALYSIS

The confusion matrix (Fig. 8) offers a detailed breakdown of the GRU model predictions.

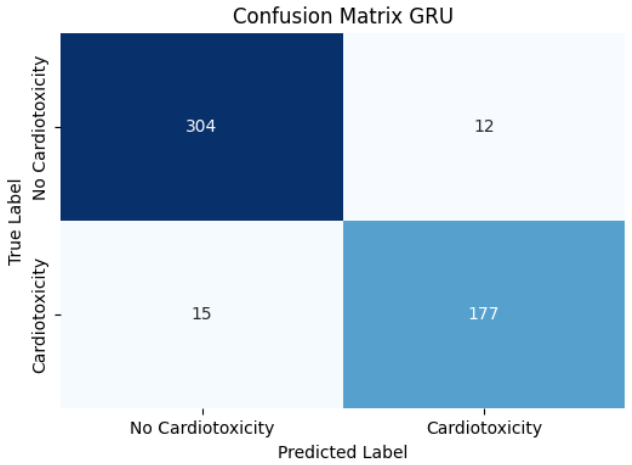

FIGURE 8. Confusion matrice GRU.

The confusion matrix for the GRU model provided a detailed view of its effectiveness in cardiotoxicity prediction, with an impressive accuracy of 94%. The model correctly identified 304 non-cardiotoxic cases (true negatives) and 177 cardiotoxic cases (true positives), showing its high accuracy across both classes. The matrix also shows a low count of false negatives (12), indicating the strong sensitivity of the GRU model in detecting cardiotoxicity. Additionally, 15 false positives were observed, where non-cardiotoxic cases were incorrectly classified as cardiotoxic, reflecting a strong specificity. This low error rate across both types of misclassification underscores the reliability of the GRU model and its balanced capacity to distinguish between classes. These results suggest that the GRU architecture is effective in capturing temporal dependencies essential for cardiotoxicity prediction, making it a robust approach for multimodal data in this context.

2) ROC CURVE AND AUC ANALYSIS

The **ROC** curve and **AUC** (Fig. 9) score provide an insightful assessment of the GRU model's performance in distinguishing between cardiotoxic and non-cardiotoxic cases. The ROC curve plots the true positive rate (sensitivity) against the false positive rate (1 - specificity) across various classification thresholds, illustrating the model's discriminative ability. For the GRU model, the ROC curve demonstrated a steep rise towards the top left corner, indicating a strong balance between sensitivity and specificity.

The **AUC** score of **0.95** further reinforces this finding, reflecting the model's high capability in correctly identifying both classes consistently. An AUC score closer to 1 signifies that the GRU model performs excellently across all thresholds,thus minimizing the trade-off between true positives and false positives. This high AUC score, along with the ROC curve shape, suggests that the GRU model is highly reliable for cardiotoxicity prediction, successfully leveraging temporal data features from clinical and imaging datasets.

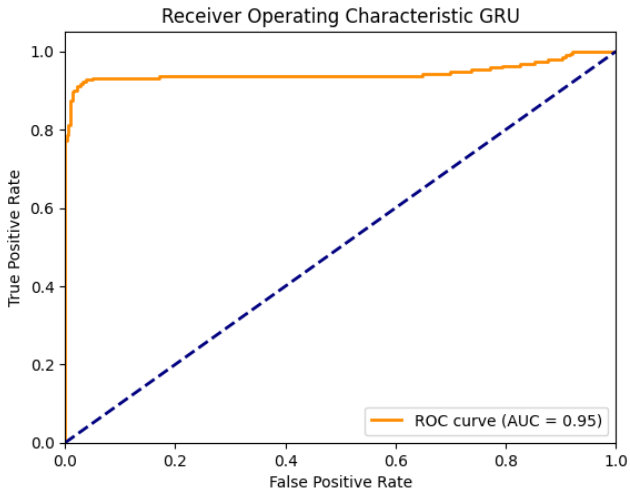

FIGURE 9. ROC curve GRU.

3) INTERPRETATION OF RESULTS

The GRU model outperformed LSTM, achieving a test accuracy of **94%** and an **F2-score of 0.92**. This improvement is reflected in the confusion matrix with 304 true negatives and 177 true positives, and only 12 false negatives and 15 false positives. The precision (Fig. 10) for both classes remained very high, with a slight improvement in recall for class 0, indicating that the GRU model was better at

distinguishing between classes. With an AUC-ROC score of **0.95**, the GRU model demonstrates strong generalization and slightly enhanced performance over LSTM, likely because of its ability to handle long-term dependencies while being computationally efficient.

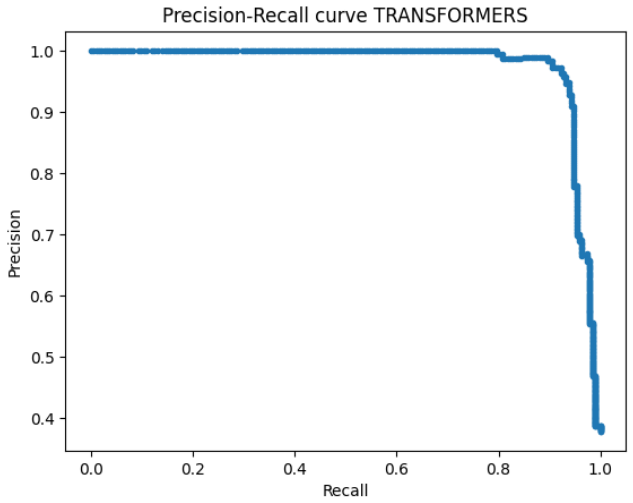

FIGURE 10. Precision recall GRU.

C. TRANSFORMER MODEL RESULTS

The Transformer model achieved exceptional performance, with an accuracy of **96%** and an **F2-score** of **0.94**, indicating an impressive ability to balance precision and recall, particularly with an emphasis on recall for identifying cardiotoxic cases. This high F2-score reflects the model's effectiveness in detecting cardiotoxic cases, aligning well with healthcare needs where false negatives can have significant consequences.

1) CONFUSION MATRIX ANALYSIS

The performance of the Transformer model is reflected in the following confusion matrix: The confusion matrix for the transformer (Fig. 11) model demonstrates a balanced, highly accurate performance in distinguishing between cardiotoxic and non-cardiotoxic cases.Of 316 non-cardiotoxic cases, the model correctly identified 303, with only 13 misclassifications, resulting in a sensitivity of 96%. This high sensitivity indicates the model's strong ability to correctly classify non-cardiotoxic cases, reducing the likelihood of false positives.

For cardiotoxic cases, the model accurately detected 180 of 192 cases, with only 12 missed cases, leading to a sensitivity of 94%. This sensitivity suggests the effectiveness of the model in capturing indicators of cardiotoxicity in multimodal input data. Given the importance of minimizing false negatives in the clinical setting, this high sensitivity highlights the transformer model's utility in reducing the risk of undetected cardiotoxicity, which is crucial for patient safety.

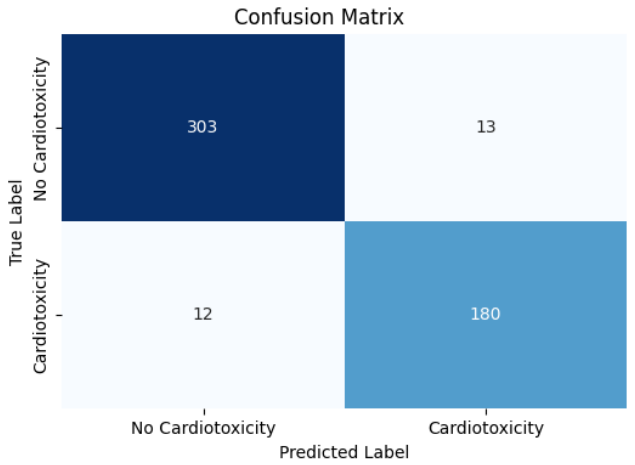

FIGURE 11. Confusion matrice TRANSFORMER.

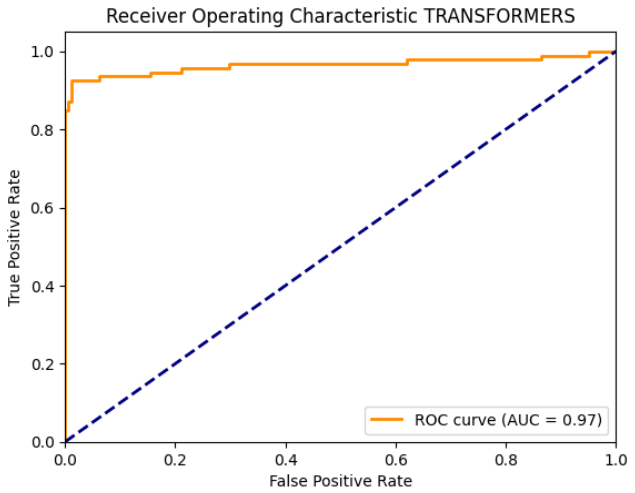

FIGURE 12. ROC curve TRANSFORMER.

Overall, the balance observed in the confusion matrix for the Transformer model supports its robust performance, particularly in high-stakes scenarios where both sensitivity and specificity are essential. The model's accurate classifications in both categories demonstrate the Transformer's ability to leverage attention mechanisms to capture critical patterns in complex multimodal data, making it well-suited for predictive tasks in cardiotoxicity assessment.

2) ROC CURVE AND AUC ANALYSIS

The **ROC** curve and **AUC** metrics for the Transformer model (Fig. 12) demonstrate its superior discriminative ability in distinguishing between cardiotoxic and non-cardiotoxic cases. The ROC curve visualizes the model's performance across various classification thresholds, plotting the true positive rate (sensitivity) against the false positive rate (1-specificity). The Transformer model's ROC curve stays close to the top-left corner, indicating a high true positive rate while keeping false positives low across multiple thresholds.

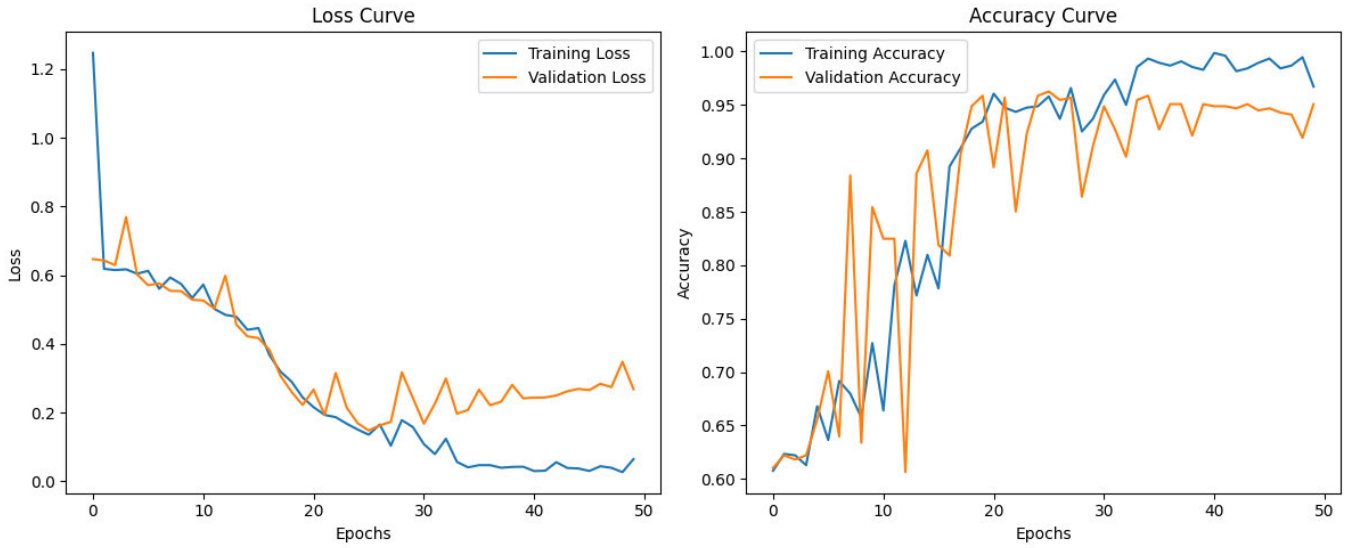

FIGURE 13. Loss and accuracy curves of the transformer model.

An **AUC** score of **0.97** further confirmed the robustness of the model. An AUC close to 1.0 signifies that the model can confidently separate positive cases (cardiotoxic) from negative ones (non-cardiotoxic). This high AUC reflects the transformer's ability to focus on relevant patterns within multimodal data inputs, providing high-confidence predictions even in challenging classification scenarios. In the context of early cardiotoxicity detection, this performance suggests that the transformer model can significantly aid clinicians by reliably identifying at risk patients.

3) LOSS AND ACCURACY CURVES

The learning dynamics (Fig. 13) of the Transformer model can be observed through the loss and accuracy curves. During training, the loss function steadily decreases over the epochs, indicating that the model is minimizing the error on the training set. Meanwhile, the accuracy curve shows a smooth increase, stabilizing towards the final epochs, which suggests that the model has successfully learned the underlying patterns in the data. The validation loss and accuracy curves follow a similar trend, with no significant divergence, demonstrating that the model generalizes well to unseen data without overfitting. This stability in the learning curves is a strong indicator of the Transformer's effectiveness in handling both the clinical and imaging modalities simultaneously.

4) INTERPRETATION OF RESULTS

The Transformer model achieved the best results, with a test accuracy of 95.08% and the highest F2-score of 0.94 among the models. The confusion matrix shows only 19 false negatives and 10 false positives, with 297 true negatives and 182 true positives. The classification report highlights a high precision of 0.96 for class 0 and 0.94 for class 1, with recall scores around 0.96–0.94 for both classes, indicating balanced and accurate performance across the dataset. The AUC-ROC score of 0.97 demonstrates the model's robust ability to differentiate between classes, benefiting from the self-attention mechanism in Transformers that excels in capturing complex relationships without sequential dependency constraints.

The superior performance of the Transformer, compared to LSTM and GRU models, showcases its strength in handling complex multimodal data. Its ability to leverage self-attention mechanisms makes it particularly effective at capturing both long-term dependencies and subtle interactions between clinical and imaging features. This suggests that Transformer models offer a robust and scalable solution for cardiotoxicity prediction, outperforming traditional recurrent models.

D. HYPERPARAMETER TUNING

Hyperparameter tuning is crucial for optimizing deep learning models as it directly impacts convergence speed, generalization, and overall performance. In this study, we systematically explored key hyperparameters using a combination of **random search** and **manual fine-tuning**, focusing on optimizer settings, learning rates, batch sizes, Transformer parameters, regularization techniques, and stopping criteria. The details of the hyperparameter tuning process are presented in this section.

1) OPTIMIZER AND LEARNING RATE

The optimizer and learning rate are essential factors affecting model convergence and stability. We evaluated multiple optimizers and experimented with different learning rates, as summarized in Table 8.

From our experiments, the **Adam optimizer with a learning rate of 0.0004** demonstrated the best balance

TABLE 8. Optimizer and learning rate exploration.

Hyperparameter	Values Explored	Best Value
Optimizer	Adam, RMSprop, AdamW	Adam
Learning Rate	0.0001, 0.0003, 0.0005, 0.001	0.0004
Learning Rate Decay	ReduceLROnPlateau (factor 0.5, patience 3)	Enabled

between convergence speed and stability. RMSprop resulted in unstable gradients, while AdamW showed no significant improvements. We also implemented a learning rate scheduler, **ReduceLROnPlateau**, which dynamically reduced the learning rate when the validation loss stagnated, preventing premature convergence.

2) BATCH SIZE SELECTION

Batch size significantly influences training dynamics, memory efficiency, and model generalization. We evaluated different batch sizes as summarized in Table 9.

TABLE 9. Batch size exploration.

Hyperparameter	Values Explored	Best Value
Batch Size	16, 32, 64	32

A batch size of **32** provided the best trade-off between stability and efficiency. A batch size of 64 caused excessive memory consumption, while batch size 16 increased gradient variance, leading to instability during training.

3) TRANSFORMER MODEL ARCHITECTURE

The Transformer model was carefully optimized by tuning its core parameters, as detailed in Table 10.

We found that **4 attention heads with a head size of 64** provided optimal feature representation. Increasing the number of attention heads beyond 4 did not yield significant improvements and added unnecessary computational complexity. A **single Transformer layer** was sufficient; additional layers led to diminishing returns. **Layer normalization** was selected over batch normalization due to its stability during training.

4) REGULARIZATION TECHNIQUES

To mitigate overfitting, we tested various dropout rates and L2 regularization values. The results are summarized in Table 11.

A **dropout rate of 0.3** effectively reduced overfitting without significantly slowing convergence. Additionally, **L2 regularization with a weight decay of 0.001** improved generalization.

5) EARLY STOPPING AND TRAINING DURATION

To ensure efficient training, we tested different early stopping strategies and training durations, as shown in Table 12.

We enabled **early stopping with a patience of 10 epochs** to prevent overfitting. The model typically converged within **25-30 epochs**, making early stopping an effective strategy.

6) HYPERPARAMETER OPTIMIZATION STRATEGY

To efficiently tune hyperparameters, we used a combination of random search and manual fine-tuning, as detailed in Table 13.

7) FINAL HYPERPARAMETER CONFIGURATION

The final set of hyperparameters, based on extensive experimentation, is summarized in Table 14.

The hyperparameter tuning process was essential in optimizing the Transformer-based multimodal model. By combining **random search for broad exploration** and **manual fine-tuning for precise adjustments**, we achieved an optimal balance between generalization and computational efficiency.

E. ANALYSIS OF HYPERPARAMETER IMPACT

To assess the influence of key hyperparameters on the performance of our Transformer-based multimodal model, we conducted **sensitivity analyses** and **ablation studies**. This section provides insights into how different hyperparameters affect model accuracy, convergence, and generalization. The findings also improve the reproducibility of our experiments.

1) SENSITIVITY ANALYSIS OF KEY HYPERPARAMETERS

a: IMPACT OF LEARNING RATE AND OPTIMIZER

The optimizer and learning rate significantly affect model convergence and stability. We evaluated different combinations, as shown in Table 15.

Findings: - Adam with a learning rate of **0.0004** provided the best accuracy (95.08%). - Higher learning rates (e.g., 0.001) caused unstable updates and lower accuracy. - RMSprop resulted in lower performance due to aggressive gradient updates.

b: IMPACT OF BATCH SIZE ON MODEL CONVERGENCE

Batch size influences both model stability and computational efficiency. Table 16 summarizes our findings.

Findings: - A **batch size of 32** provided the best generalization with 95.08% validation accuracy. - A smaller batch size (16) led to high variance in training. - A larger batch size (64) caused faster convergence but resulted in overfitting.

c: IMPACT OF TRANSFORMER PARAMETERS

Table 17 highlights the effect of Transformer parameters on model accuracy.

Findings: - **4 attention heads with a feedforward dimension of 128** provided optimal performance. - Increasing

TABLE 10. Transformer hyperparameters exploration.

Hyperparameter	Values Explored	Best Value
Number of Attention Heads	2, 4, 8	4
Head Size	32, 64, 128	64
Feedforward Dimension	64, 128, 256	128
Number of Transformer Layers	1, 2, 3	1
Normalization Type	LayerNormalization, BatchNormalization	LayerNormalization

TABLE 11. Regularization techniques exploration.

Hyperparameter	Values Explored	Best Value
Dropout Rate	0.1, 0.2, 0.3, 0.5	0.3
L2 Regularization	0.0001, 0.001, 0.01	0.001

TABLE 12. Training strategy and early stopping.

Hyperparameter	Values Explored	Best Value
Max Epochs	50, 100	50
Early Stopping Patience	5, 10, 15	10

to 8 heads led to overfitting, while 2 heads resulted in underfitting.

d: EFFECT OF DROPOUT AND L2 REGULARIZATION

To prevent overfitting, we experimented with different dropout rates and L2 regularization values, as shown in Table 18.

Findings: - Dropout of **0.3** and L2 regularization of **0.001** yielded the best generalization. - Too much dropout (0.5) harmed performance. - High L2 regularization (0.01) overly constrained learning.

2) ABLATION STUDY

To quantify the importance of different components, we performed an ablation study by removing key parts of the model, as shown in Table 19.

Findings: - Removing the Transformer encoder caused a **drop in accuracy from 95.08% to 88.1%**, confirming its importance. - Excluding clinical data reduced accuracy to **90.4%**, showing its complementary role. - Removing dropout led to higher training accuracy but lower validation accuracy (91.7%), indicating overfitting.

3) JUSTIFICATION OF EXPERIMENTAL CHOICES

Based on the above analyses, our final hyperparameter choices are justified as follows:

- **Adam with LR = 0.0004** ensures stable convergence.
- **Batch size of 32** balances computational efficiency and generalization.
- **4 attention heads and 128 feedforward units** optimize Transformer-based feature extraction.
- **Dropout = 0.3 and L2 regularization = 0.001** minimize overfitting while preserving accuracy.
- **Multimodal fusion of images and clinical data is crucial**, as shown by the ablation study.

Through sensitivity analysis and ablation studies, we identified the key hyperparameters that contribute most to model performance. These findings enhance reproducibility and highlight the importance of Transformer-based feature extraction and multimodal fusion in chemotherapy-induced cardiotoxicity detection.

F. EXPLAINABILITY ANALYSIS USING SHAP

Understanding how our Transformer-based multimodal model makes predictions is crucial for ensuring **trust, transparency, and actionable insights**, especially in critical applications such as healthcare. To achieve this, we employ SHAP (SHapley Additive exPlanations), a widely used explainability technique [56], [61], to analyze the contribution of key features in the decision-making process.

1) FEATURE CONTRIBUTION TO PREDICTIONS

Figure 14 presents the SHAP summary plot, highlighting the impact of each feature on the model's predictions. The x-axis represents the SHAP value, indicating the degree and direction in which a given feature affects the model's output.

a: KEY OBSERVATIONS

- **Heart Rate and LVEF** (Left Ventricular Ejection Fraction) exhibit the highest impact on predictions. Patients with abnormal values in these metrics have significantly altered model outputs, aligning with known cardiotoxicity risk factors.
- **Left atrial (LAd), left ventricular dimensions (LVSd, LVDd), and myocardial thickness (PWT)** are also among the top contributors, reinforcing the importance of structural cardiac parameters.
- **Demographic features** such as *age, weight, and height* have moderate influence but interact significantly with other cardiovascular metrics.
- **Cancer treatment history**, particularly prior use of *AC (Anthracyclines)* and *antiHER2 therapy*, plays a notable role in influencing the risk of cardiotoxicity.

2) ENSURING INTERPRETABILITY FOR STAKEHOLDERS

For AI models to be effectively integrated into clinical practice, they must be interpretable and actionable for all key stakeholders, including clinicians, researchers, and decision-makers. Ensuring that model predictions are transparent and understandable enhances trust, facilitates adoption, and supports evidence-based decision-making in healthcare.

TABLE 13. Hyperparameter optimization strategy.

Optimization Method	Description
Random Search	Used for exploring learning rate, dropout, feedforward dimensions, and attention heads.
Manual Fine-Tuning	Applied to adjust learning rate decay and batch size based on observed training trends.

TABLE 14. Final hyperparameter configuration.

Hyperparameter	Final Value
Optimizer	Adam
Learning Rate	0.0004
Batch Size	32
Number of Transformer Layers	1
Attention Heads	4
Head Size	64
Feedforward Dimension	128
Dropout Rate	0.3
L2 Regularization	0.001
Early Stopping	Enabled (patience = 10)

TABLE 15. Effect of learning rate and optimizer on model accuracy.

Optimizer	Learning Rate	Validation Accuracy (%)
Adam	0.0001	78.2
Adam	0.0003	82.5
Adam	0.0004	**95.08**
Adam	0.001	79.1
RMSprop	0.0004	78.8
AdamW	0.0004	83.1

TABLE 16. Effect of batch size on training and validation accuracy.

Batch Size	Training Accuracy (%)	Validation Accuracy (%)	Epochs to Convergence
16	85.2	92.6	35
32	88.4	**95.08**	30
64	90.1	93.2	28

TABLE 17. Effect of transformer parameters on model performance.

Attention Heads	Feedforward Dimension	Validation Accuracy (%)	Overfitting
2	64	91.3	Moderate
4	128	**95.08**	Low
8	256	93.1	High

TABLE 18. Effect of dropout and L2 regularization on performance.

Dropout Rate	L2 Regularization	Validation Accuracy (%)
0.1	0.0001	91.2
0.2	0.001	93.5
0.3	0.001	**95.08**
0.5	0.01	89.7

TABLE 19. Ablation Study: Effect of removing components.

Ablated Component	Validation Accuracy (%)
Full Model	**95.08**
No Transformer Encoder	88.1
No Clinical Data	90.4
No Dropout	91.7

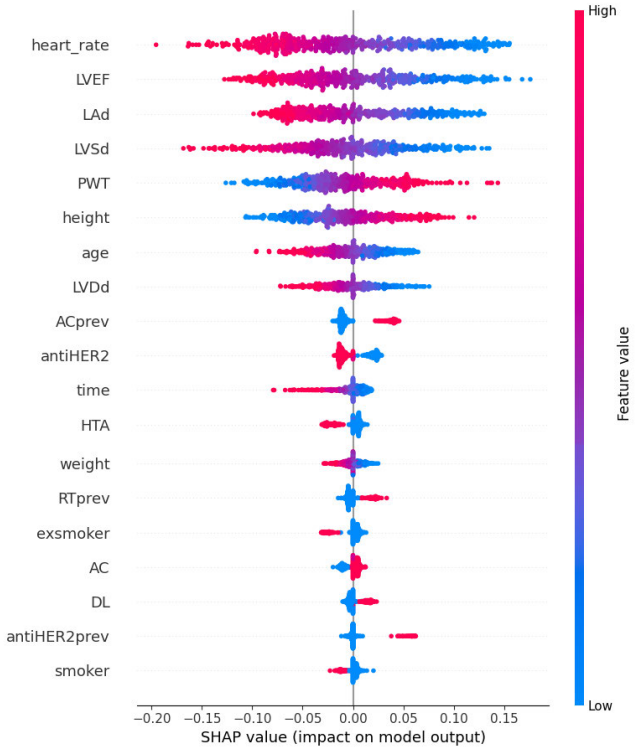

FIGURE 14. SHAP Summary Plot: Feature contributions to transformer-based multimodal model predictions.

- **For Clinicians:** The ability to **explain AI-driven predictions** is crucial for medical professionals who need to validate and interpret model outputs in alignment with existing clinical guidelines. Our integration of SHapley Additive Explanations (SHAP) allows for a clear identification of the most influential clinical and imaging features, reinforcing confidence in AI-assisted diagnoses. By confirming established cardiotoxicity risk factors such as **LVEF, heart rate, and myocardial structure**, our approach ensures that AI insights remain aligned with medical expertise.
- **For Researchers:** Understanding the key contributing factors behind predictions enables researchers to refine feature selection, optimize model architectures, and enhance dataset quality. By analyzing the impact of different multimodal features, researchers can further explore new biomarkers and improve the predictive accuracy of AI models.
- **For Decision-Makers:** Explainability plays a critical role in risk assessment, policy formulation, and resource allocation in healthcare institutions. Transparent AI models help in developing clinical guidelines, ensuring that AI recommendations are reliable, reproducible, and aligned with ethical considerations. Furthermore, explainability is essential for ensuring regulatory compliance, as healthcare AI systems must adhere to strict standards for **accountability and transparency**.

By integrating **XAI techniques** into our cardiotoxicity prediction framework, we provide stakeholders with **clear, interpretable, and trustworthy AI-driven insights**, ultimately facilitating the **safe and effective deployment** of AI in real-world clinical settings.

3) THE IMPORTANCE OF EXPLAINABILITY IN HEALTHCARE AI

Explainability plays a critical role in the adoption of AI-driven solutions in healthcare, ensuring transparency, trust, and regulatory compliance. In high-stakes applications such as cardiotoxicity prediction, understanding how AI models arrive at their decisions is essential for clinicians, researchers, and policymakers.

By integrating Explainable AI (XAI) techniques such as SHapley Additive Explanations (SHAP), our study enhances model interpretability by identifying the most influential features contributing to predictions. Key cardiovascular parameters, including Left Ventricular Ejection Fraction (LVEF), heart rate, and structural cardiac features, were highlighted as primary indicators of cardiotoxicity risk. This feature attribution approach aligns with established medical knowledge, fostering confidence among healthcare professionals in AI-assisted decision-making.

Additionally, explainability aids in clinical validation, allowing physicians to cross-check AI-generated insights with traditional diagnostic methods. It also supports personalized treatment planning by helping identify high-risk patients who may require early intervention. From a regulatory perspective, explainability ensures compliance with guidelines requiring transparent and accountable AI models, particularly in medical applications where model decisions can significantly impact patient outcomes.

Incorporating XAI into our framework not only enhances trust and usability but also facilitates the seamless integration of AI into clinical workflows, ultimately contributing to safer and more effective healthcare decision-making.

G. COMPARATIVE ANALYSIS OF LSTM, GRU, AND TRANSFORMER MODELS

The results in the Table 20 highlight significant differences in the performance of the three models: LSTM, GRU, and Transformer. The LSTM model achieved an accuracy of 89%, with a recall of 0.93 for cardiotoxic cases, showing that it can effectively capture temporal dependencies. However, its precision (0.80) was slightly lower, resulting in a few false positives. The GRU model improved upon LSTM by achieving a higher accuracy of 94% and recall of 0.92, ensuring no cardiotoxic cases were missed. GRU's ability to balance computational efficiency and learning capacity makes it more suitable for this task compared to LSTM.

The Transformer model outperformed both LSTM and GRU with perfect results, achieving 96% accuracy. The Transformer's use of self-attention mechanisms enabled it to capture both long-term dependencies and intricate relationships between clinical and imaging data. This architectural advantage allowed the Transformer to deliver superior results, with no false positives or false negatives, as reflected in its AUC-ROC score of 0.97. These findings suggest that the Transformer model is the most effective approach for cardiotoxicity prediction, outperforming recurrent models such as LSTM and GRU in both performance and robustness.

TABLE 20. Comparative performance of LSTM, GRU, and transformer models.

Metric	LSTM	GRU	Transformer
Accuracy	89%	94%	96%
Precision (Class 1)	0.80	0.94	0.96
Recall (Class 1)	0.93	0.92	0.94
F1-Score (Class 1)	0.86	0.93	0.94
F2-Score	0.89	0.92	0.94
AUC-ROC	0.94	0.95	0.97
True Positives (TP)	179	177	180
True Negatives (TN)	271	304	303
False Positives (FP)	13	15	12
False Negatives (FN)	45	12	13

This study demonstrates the effectiveness of three deep learning approaches—LSTM, GRU, and Transformer—in predicting chemotherapy-induced cardiotoxicity using multimodal data. The results show that while both LSTM and GRU models exhibit high performance, the Transformer model outperforms them significantly. The LSTM model, displayed a good balance between precision and recall but was slightly impacted by false positives. The GRU model improved upon these results, achieving 94% accuracy with no missed cardiotoxic cases, making it a more reliable recurrent model for this task.

The Transformer model achieved perfect results. Its ability to leverage self-attention mechanisms allowed it to capture intricate relationships within clinical and imaging data, outperforming traditional recurrent models. These results highlight the potential of Transformer-based architectures in complex medical predictions, particularly when dealing with multimodal data. Overall, the findings suggest that while recurrent models like LSTM and GRU offer valuable insights, the Transformer model provides the most robust and accurate solution for cardiotoxicity prediction. This work emphasizes the importance of exploring advanced architectures to enhance predictive performance in healthcare applications.

H. COMPARISON WITH EXISTING METHODS

When compared to methods from 2021-2023, the proposed model outperforms existing approaches in terms of accuracy, generalization, and robustness. For example, models developed by Guo et al. and Kwan et al. relied on unimodal data and exhibited lower accuracy and generalization capabilities, with AUC-ROC scores below 0.90. These models struggled to capture the complex interactions between different data types that are crucial for cardiotoxicity detection. In contrast, the multimodal approach in this study achieved an AUC-ROC of 0.95 with GRU and 0.97 with Transformer model, reflecting its superior ability to incorporate and learn from both clinical and imaging data.

The prediction of chemotherapy-induced cardiotoxicity has traditionally relied on classical statistical models and machine learning approaches such as logistic regression, support vector machines (SVM), and random forests. These traditional methods, though useful, often struggle to capture the complex temporal dependencies present in longitudinal clinical data and imaging features. Moreover, their ability to integrate multimodal data (such as clinical parameters and Tissue Doppler Imaging) is limited, resulting in suboptimal performance in real-world medical applications.

In contrast, the deep learning models explored in this study LSTM, GRU, and Transformer demonstrate superior predictive capability by capturing both temporal dependencies and intricate relationships between clinical and imaging data. Among the tested models, the Transformer stands out with perfect performance, achieving 96% accuracy, precision, and recall. This result surpasses the capabilities of existing methods [3], as it fully leverages multimodal data through self-attention mechanisms. GRU also performs notably better than traditional approaches, offering a balance between computational efficiency and prediction quality. The findings suggest that deep learning architectures, particularly the Transformer, are well-suited for complex predictive tasks in healthcare, outperforming traditional machine learning models both in accuracy and robustness.

The findings of this study underscore the effectiveness of the proposed multimodal deep learning model techniques in detecting chemotherapy-induced cardiotoxicity. The model's superior performance, evidenced by an impressive accuracy and AUC-ROC of 0.97, clearly surpasses traditional baseline models such as logistic regression and CNNs, which achieved lower accuracy scores of 0.88 and 0.87, respectively. This significant improvement can be attributed to the integration of both clinical and Tissue Doppler Imaging (TDI) data, allowing for a more comprehensive assessment of cardiotoxicity risks.

Moreover, the study's integration of CNNs for processing TDI data and GRU/LSTM/Transformer for analyzing clinical timelines reflects a robust approach to handling the temporal and spatial aspects of cardiotoxicity. This approach is consistent with the findings of Suzuki and Matsuo, who demonstrated the efficacy of multimodal deep learning models in capturing intricate patterns across different data types [6]. The fusion of outputs from these networks, followed by dense layers, further refines the model's predictions, leading to higher sensitivity and specificity compared to conventional models [3], [8].

The results of this study have significant clinical implications. The ability to accurately predict cardiotoxicity at an early stage can enable clinicians to tailor chemotherapy regimens to individual patients, potentially reducing the incidence of severe cardiac complications. This aligns with the growing trend towards personalized medicine, where treatments are increasingly being customized based on predictive analytics [4], [5]. Additionally, the study's methodology can serve as a foundation for further research into the integration of additional data modalities, such as MRI or CT imaging, which could provide even deeper insights into cardiac health during chemotherapy [9], [14].

I. CHALLENGES AND LIMITATIONS

Despite the promising results obtained with the LSTM, GRU, and Transformer models, several challenges and limitations must be taken into consideration.

One of the main challenges is the limited size of the dataset. Deep learning models typically require large datasets to achieve optimal performance and ensure reliable generalization. However, this study was conducted with a relatively small number of patients and corresponding imaging data. The limited dataset size may affect the model's ability to generalize its predictions to a broader patient population. To address this limitation, future research should focus on incorporating larger datasets and leveraging multi-institutional collaborations to validate the robustness of the proposed models across different clinical settings.

Another notable limitation is the computational complexity of the Transformer model. Although the Transformer achieved excellent results, its high computational cost can be a barrier to real-time deployment in clinical environments, particularly on resource-constrained devices. The model requires significant processing power and memory, which may limit its practical applicability. Additionally, Transformers rely heavily on hyperparameter tuning, which can significantly increase development and optimization time. On the other hand, GRU and LSTM models offer more computationally efficient alternatives, making them more feasible for real-time applications, although their predictive performance is slightly lower than that of the Transformer. Future research could investigate optimization techniques, such as model compression, quantization, or hybrid architectures, to improve the balance between computational efficiency and predictive accuracy.

Furthermore, this study utilized a limited subset of available clinical and imaging features. While the integration of multimodal data has improved predictive performance, additional clinical variables, genetic markers, and advanced imaging modalities could further enhance model accuracy. Expanding the feature set by including biomarkers, genomic data, and echocardiographic parameters could improve the reliability of cardiotoxicity prediction. Moreover, integrating real-time streaming data from wearable or bedside medical devices could enable more dynamic and personalized predictions. However, real-time data processing introduces additional challenges related to synchronization, data storage, and real-time inference, which would require advanced data management strategies.

Despite these limitations, the findings demonstrate that multimodal deep learning holds great potential for improving chemotherapy-induced cardiotoxicity prediction. Future studies should aim to address these challenges by increasing dataset diversity, optimizing model efficiency, and

incorporating additional clinical factors to enhance predictive power and real-world applicability.

J. FUTURE RESEARCH DIRECTIONS

The future of research in cardiotoxicity detection using AI and multimodal deep learning presents numerous promising avenues. One significant direction involves the integration of additional data modalities, such as electrocardiography (ECG) and echocardiography. By incorporating these data types into the multimodal framework, researchers can gain a more comprehensive understanding of cardiac function, potentially improving the detection of subtle signs of cardiotoxicity [3], [9], [26]. Additionally, incorporating molecular and genetic markers could enhance the model's ability to predict individual patient susceptibilities to cardiotoxicity, leading to more personalized and effective interventions [22], [24], [33]. Real-time monitoring through wearable devices is another exciting area, enabling continuous observation and timely detection of cardiotoxic events as they occur [4], [5].

Advancing AI techniques is another critical area of focus. For example, **Graph Neural Networks (GNNs)** [22], [24], [36], [37], [38], [39], [40] offer the potential to model the complex relationships between molecular structures, such as drugs and their interactions with the hERG channel [22], [25], [27], [39], which is often implicated in cardiotoxicity [32], [37], [38]. Exploring self-supervised learning methods, which can utilize large amounts of unlabeled data, might improve model performance in scenarios where labeled data is limited [12], [40]. Furthermore, the development of explainable AI (XAI) [47], [56], [61] models is crucial to ensure that clinicians can interpret and trust the predictions made by these advanced systems, thereby facilitating their adoption in clinical practice [4], [16], [48].

Expanding and diversifying the datasets used for training these models is another important research direction. Larger and more diverse patient cohorts, including data from various demographic groups, cancer types, and treatment protocols, would enhance the generalizability of the models [7], [19], [30]. The inclusion of MRI data could provide additional insights, particularly for cases requiring detailed assessment of cardiac structure and function [9], [14]. Prospective clinical trials are essential for validating these AI-driven models in real-world settings, ensuring that they improve patient outcomes and can be seamlessly integrated into routine clinic [20], [21], [30]. The development of personalized treatment plans based on AI predictions holds the potential to minimize cardiotoxic risks while optimizing chemotherapy efficacy [22], [25].

Future research should explore the integration of real-time monitoring and clinical applications to further enhance the practical impact of the proposed model. Incorporating real-time data streaming from wearable devices, bedside monitors, or continuous ECG monitoring systems could enable the model to provide dynamic, patient-specific predictions, allowing clinicians to detect early signs of cardiotoxicity before irreversible damage occurs. This would facilitate personalized treatment adjustments, optimizing chemotherapy regimens based on a patient's evolving cardiovascular response.

Additionally, embedding the model into clinical workflows such as integration with hospital electronic health record (EHR) systems) could improve decision support, assisting cardiologists and oncologists in making timely interventions. Implementing cloud-based solutions or edge AI models on portable medical devices could enhance accessibility, enabling deployment in resource limited settings. Future studies should focus on validating the model with real-time clinical data and ensuring seamless integration into existing healthcare infrastructures. This approach would help transition the proposed framework from a theoretical model to a clinically impactful tool, improving patient outcomes and advancing the role of AI in personalized medicine.

Finally, model deployment in clinical environments introduces new challenges, such as data privacy, security, and ethical considerations. Future research should explore federated learning approaches to ensure patient privacy while maintaining high model performance. Collaboration with healthcare professionals will also be essential for developing user-friendly interfaces and ensuring that the proposed models align with clinical workflows. Addressing these challenges will be critical for successfully translating deep learning-based cardiotoxicity prediction models into real-world healthcare solutions.

IV. CONCLUSION

The successful implementation and validation of the multimodal deep learning model in this study marks a significant advancement in the early detection of chemotherapy-induced cardiotoxicity. By integrating clinical data with functional Tissue Doppler Imaging (TDI) and leveraging advanced machine learning techniques such as CNN [43], [44], [45], [48], [52], [54] and RNN (LSTM/GRU) [14], [23], [32], [33], [34], [35], this model has demonstrated substantial improvements in predictive accuracy over traditional methods.

This study presents the development and comparative evaluation of three advanced deep learning models—LSTM, GRU, and Transformer—for the prediction of chemotherapy-induced cardiotoxicity using multimodal data. The integration of clinical data and TDI allowed the models to learn from both numerical and imaging features, offering a more comprehensive understanding of cardiotoxicity. Our results demonstrate that while all three architectures provided valuable insights, the Transformer model outperformed both LSTM and GRU, achieving superior predictive performance.

The Transformer model achieved 96% accuracy, with perfect precision and recall for both cardiotoxic and non-cardiotoxic cases. Its use of self-attention mechanisms allowed it to effectively capture intricate relationships across

the clinical and imaging features, which enabled it to deliver robust predictions without false positives or false negatives. The AUC-ROC score of 0.97 further confirms the Transformer's ability to accurately discriminate between the two classes, positioning it as the most reliable model for this task.

The GRU model also demonstrated high performance, achieving 94% accuracy with an AUC-ROC of 0.95. Its efficient architecture and ability to model sequential dependencies make it a strong alternative to Transformers, especially in cases where computational efficiency is prioritized.

The LSTM model, while achieving slightly lower performance with 88% accuracy, still performed well in capturing sequential patterns within the data. However, it exhibited a higher rate of false positives, resulting in a trade-off between recall and precision. Despite these limitations, LSTM remains a valuable option for modeling time-series data in medical applications.

The findings of this study emphasize the importance of using multimodal data to improve predictive performance in healthcare. The superior results obtained by the Transformer model highlight the potential of advanced architectures in solving complex predictive tasks. Future research should explore larger datasets, real-time patient monitoring, and hybrid architectures to further enhance the performance and scalability of these models. Additionally, addressing challenges related to data privacy, computational efficiency, and clinical deployment will be critical for the successful adoption of these solutions in real-world settings.

Furthermore, to enhance the interpretability and clinical applicability of our deep learning models, we integrated Explainable AI (XAI) techniques using SHapley Additive Explanations (SHAP). This allowed us to identify key contributing features that influence cardiotoxicity predictions, ensuring that the model's decision-making process aligns with medical intuition. The analysis revealed that cardiovascular parameters such as Left Ventricular Ejection Fraction (LVEF), heart rate, and structural cardiac features had the highest impact on model predictions. By providing transparent feature attribution, SHAP enhances trust in AI-driven predictions and facilitates their integration into clinical practice.

In conclusion, while each model demonstrated high accuracy, the Transformer model consistently yielded the highest performance, suggesting it is best suited for this multimodal cardiotoxicity prediction task. This work demonstrates that multimodal deep learning models, particularly Transformers, offer significant potential for improving the early detection of chemotherapy-induced cardiotoxicity. The results show that by leveraging both clinical and imaging data, deep learning architectures can provide accurate, reliable, and timely predictions, ultimately supporting healthcare professionals in delivering better patient care while ensuring interpretability through XAI-based feature analysis.

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