

Transformer-Based Deep Learning for Preoperative Prediction of Microvascular Invasion in Hepatocellular Carcinoma

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Abstract

Background

Microvascular invasion (MVI) is a critical prognostic factor in hepatocellular carcinoma (HCC), but preoperative three-class prediction remains challenging. Radiomics and clinical biomarkers may enable more accurate and individualized assessment.

Aim

To develop and validate a Transformer-based deep learning framework that integrates radiomic and clinical features for direct three-class MVI classification in HCC patients.

Methods

This retrospective study included 438 patients with pathologically confirmed HCC and MVI status from a single institution. Radiomic features were extracted from preoperative Gd-BOPTA-enhanced MRI, and clinical laboratory data were collected. A two-stage feature selection strategy, combining univariate statistical testing and recursive feature elimination, was applied. A Transformer-based model was built to classify three MVI categories (M0, M1, M2), and its performance was evaluated on internal and external test sets. Results were compared with traditional machine learning models, including Random Forest, Logistic Regression, XGBoost, and LightGBM.

Results

The Transformer-based model achieved an accuracy of 0.733, a weighted F1-score of 0.733, and a macro-average AUC of 0.880 (95% CI: 0.807–0.953) on the internal test set. On the external validation set, it reached an accuracy of 0.758, a weighted F1-score of 0.768, and a macro-average AUC of 0.886 (95% CI: 0.833–0.940). It outperformed traditional classifiers and showed superior ability to identify high-risk M2 cases.

Conclusions

This Transformer-based model enables accurate and objective three-class MVI prediction using multimodal features, supporting individualized surgical planning and improved clinical outcomes.

Key Points

- A Transformer-based deep learning model was developed for direct three-class MVI prediction in HCC.

- The model integrates radiomic features from Gd-BOPTA-enhanced MRI and clinical biomarkers.
- It outperforms traditional machine learning models and shows high performance in identifying high-risk M2 cases.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer globally and the third leading cause of cancer-related mortality[1], [2]. In the Asia–Pacific region, particularly China, chronic hepatitis B virus (HBV) infection accounts for 70–90% of HCC cases [3]. Although surgical resection and liver transplantation offer potential curative options for early-stage HCC, recurrence rates remain high, affecting 40–70% of patients post-resection and 10–15% post-transplantation, with most recurrences occurring within two years [4], [5].

Microvascular invasion (MVI), defined as the presence of tumor cells within microvessels lined by endothelial cells, is a critical pathological feature associated with early recurrence and poor prognosis after surgery [6]. MVI is further classified into three categories based on the number and distribution of invaded vessels: M0 (no invasion), M1 (≤ 5 invaded vessels within 1 cm of the tumor margin), and M2 (> 5 invaded vessels or invasion beyond 1 cm) [6], [7]. Accurate preoperative identification of MVI, particularly M2, is vital for optimizing surgical margins and guiding adjuvant therapies.

Currently, MVI diagnosis relies exclusively on postoperative pathological examination, limiting its utility for preoperative decision-making [8]. To address this limitation, radiomics- and MRI-based predictive models have emerged as promising non-invasive alternatives. However, most existing studies are restricted to binary classification (MVI presence vs. absence) and lack the capacity to differentiate high-risk M2 status[9],[10],[11].

Radiomics enables the extraction of high-throughput, quantitative features from medical images, offering insights into tumor heterogeneity that are imperceptible to the human eye[12]. When combined with clinical laboratory indicators, radiomics can offer a comprehensive characterization of tumor biology. Nevertheless, the high dimensionality, redundancy, and complex interactions among these features pose challenges for conventional machine learning approaches[13].

Transformer models, originally developed for natural language processing (NLP) tasks, have recently demonstrated superior performance in modeling high-dimensional structured data through their self-attention mechanisms[14], [15]. Their ability to capture non-linear and hierarchical feature dependencies makes them particularly suitable for integrating multimodal data sources, such as radiomic features and clinical variables, which traditional models often struggle with.

In this study, we propose a Transformer-based deep learning framework that integrates radiomic features from preoperative MRI and clinical laboratory data for direct three-class MVI classification (M0, M1, M2) in HCC patients. Our approach addresses the limitations of previous studies by enabling fine-

grained risk stratification in a fully automated, objective manner. We hypothesize that this method can provide a valuable, non-invasive tool to support individualized surgical planning and improve long-term survival outcomes.

While previous radiomics-based approaches primarily focused on binary classification, few have explored direct three-class MVI prediction using deep learning. Moreover, most prior methods relied on conventional classifiers such as logistic regression or tree-based models. In this study, we implemented a Transformer-based architecture specifically designed to handle structured radiomic and clinical features. The model leverages self-attention mechanisms to learn feature interactions and dependencies, thereby enhancing predictive capacity for fine-grained MVI stratification.

Materials and methods

1. Patient Enrollment and Clinical Data Collection

This retrospective study was approved by the Ethics Committee of Eastern Hepatobiliary Surgery Hospital, with approval number EHBHKY2022-H-P002. The requirement for written informed consent was waived due to its retrospective nature. Patient privacy was strictly protected through data anonymization procedures.

A total of 653 patients with hepatocellular carcinoma (HCC) and available microvascular invasion (MVI) analysis were initially identified via electronic medical records using targeted keywords such as “liver,” “tumor,” “mass,” “surgical records,” and “pathological diagnosis.” Among them, 458 patients were from Hospital A and 195 patients from Hospital B.

After applying predefined inclusion and exclusion criteria, 438 eligible patients remained, including 305 from Hospital A and 133 from Hospital B.

From Hospital A, 229 patients were randomly allocated to the training set, and 76 patients to the internal test set. The remaining 133 patients from Hospital B were assigned to an independent external validation set to evaluate the generalizability of the model across institutions.

The inclusion criteria were as follows:

1. Patients who underwent liver resection and received Gd-BOPTA-enhanced MRI within two months prior to surgery.
2. Histopathological confirmation of hepatocellular carcinoma (HCC) and microvascular invasion (MVI) status.
3. No prior treatments before surgery, such as radiofrequency ablation or transarterial chemoembolization (TACE).
4. Absence of extrahepatic malignancies.
5. Availability of complete clinical, imaging, and pathological data.

Exclusion criteria included patients who underwent preoperative local therapies, had extrahepatic malignancies, or lacked essential clinical or imaging data.

A detailed patient selection workflow is presented in Fig. 1.

2. MRI Image Acquisition

All participants were required to fast for at least 6 hours and to abstain from water intake for at least 4 hours before the MRI examination. The scanning range extended from the upper edge to the lower edge of the liver.

The contrast agent, 0.1 mmol/kg of Gd-BOPTA (MultiHance, Bracco), was administered through injection into the median vein of the patient's elbow using a high-pressure syringe at a rate of 2.0 mL/s, followed by a 20-mL saline flush lasting approximately 20 seconds.

After contrast agent administration, imaging was performed during specific phases: arterial phase (AP) at 25–45 seconds, portal venous phase (PVP) at 50–70 seconds, and delayed phase (DP) at 100–180 seconds. The MRI protocol also included fat-suppressed T2-weighted imaging (T2WI), T1-weighted imaging (T1WI) and diffusion-weighted imaging (DWI).

3. Imaging Analysis

Manual segmentation of HCC lesions was conducted to construct the radiomics dataset. Two radiologists, each with more than five years of experience in abdominal MRI interpretation, independently delineated the region of interest (ROI) of HCC tumors on MRI. Subsequently, a third senior radiologist with over ten years of experience reviewed and verified these ROIs to ensure accuracy and consistency. Manual segmentation was performed using ITK-SNAP (version 3.6.0; <http://www.itksnap.org>) software.

The delineations were based on the visible tumor boundaries in MRI sequences, including T2WI, T1WI, DWI, AP, PVP, DP. The final consensus ROIs were subsequently used for radiomics feature extraction and statistical analysis.

Importantly, no qualitative assessments assessed by radiologists were included in this study. All data inputs for model development were based solely on objective information, including clinical laboratory parameters and automatically extracted radiomics features from manually delineated ROIs. This approach minimizes potential interobserver variability and enhances the objectivity, the reproducibility, and the generalizability of the predictive model.

4. Pathological evaluation

All hematoxylin and eosin (H&E)-stained sections were retrospectively reviewed for MVI by two board-certified pathologists, each with more than 10 years of experience in hepatopathology. The pathologists were blinded to all clinical and imaging data during the assessment. In cases of disagreement, a senior pathologist with over 20 years of diagnostic experience was consulted to reach a consensus.

MVI status was determined according to standardized pathological criteria. Patients were classified into three groups: M0 (no MVI), M1 (1–5 MVI sites within ≤ 1 cm from the tumor margin), and M2 (> 5 MVI sites or any MVI detected beyond 1 cm from the tumor margin). This grading system has been widely adopted in clinical research for prognostic stratification of HCC[16].

5. Radiomic Feature Extraction

Radiomic feature extraction was conducted following manual segmentation of the region of interest (ROI) by an experienced radiologist using ITK-SNAP software (version 3.6.0)[17], [18]. The delineated ROIs were used to extract quantitative features with the PyRadiomics library. A total of 1,500 radiomic features were obtained, including first-order statistical descriptors (such as mean, skewness, and kurtosis), shape-based metrics (such as sphericity and elongation), and texture features derived from gray-level matrices, including the Gray-Level Co-occurrence Matrix (GLCM) and the Gray-Level Run-Length Matrix (GLRLM)[18]. To better characterize tumor heterogeneity, features were extracted not only from the original images but also from filtered versions processed via wavelet and Laplacian of Gaussian (LoG) transformations[19], [20].

6. Data Preprocessing

Preprocessing involved two major steps:

- **Missing Value Handling:** Samples with more than 10% missing values were excluded. For the remaining samples, missing values were imputed separately for each feature using k-nearest neighbor (KNN) imputation ($k = 3$), based on the Euclidean distance in the feature space[21], [22].
- **Normalization:** Radiomic features were normalized using Z-score transformation. The mean and standard deviation were calculated exclusively from the training set and then applied to the validation and test sets to ensure no information leakage during model evaluation[23].

7. Feature Selection

To mitigate the risk of overfitting and enhance model generalizability, a two-stage feature selection strategy was employed.

In the initial screening phase, features were first evaluated for reproducibility using the intraclass correlation coefficient (ICC)[19], and only those with $ICC > 0.75$ were retained. Subsequently, univariate

statistical tests (t-test or Mann-Whitney U test, depending on data distribution) were performed to exclude features with weak discriminative ability.

In the dimensionality reduction phase, Recursive Feature Elimination (RFE)[24] based on Random Forest classifiers was conducted to further select the most informative subset of features.

To systematically evaluate the impact of different feature selection strategies, sixteen pipelines (4 initial screening methods $\times$ 4 dimensionality reduction methods) were constructed and compared using cross-validation performance within the training set.

Ultimately, the pipeline combining “t-test or Mann-Whitney U test + RFE with Random Forest” was selected for final model training, as it achieved the best balance between feature compactness and model performance.

8. Model Architecture and Training

We developed a Transformer-based deep learning model tailored for three-class MVI prediction. The model architecture was adapted from the Transformer framework, originally introduced for natural language processing tasks[14], and later extended to structured tabular data such as clinical and radiomic features[15]. As illustrated in Fig. 3, the model architecture comprised three main components: an input embedding layer that projected the input features into an 8-dimensional latent space; two stacked Transformer encoder layers, each utilizing 2 attention heads, a feedforward dimension of 16, and a dropout rate of 0.2; and a final output classification layer that generated predictions across three categories.

Following the definition of the model architecture, we proceeded to model training. Cross-entropy loss with class-balanced weights was employed to mitigate class imbalance. Model parameters were optimized using the AdamW optimizer with a learning rate of 0.0005 and a weight decay of 0.02. The mini-batch size was set to 16. Training was conducted for 2000 epochs on an NVIDIA RTX 4090 GPU.

9. Data Augmentation and Balancing

Based on the extracted radiomic features, the overall preprocessing and modeling strategy is summarized in Fig. 3. This includes feature normalization, missing value imputation, two-step feature selection, and Transformer-based classification. To mitigate the issue of class imbalance in the training set, a hybrid resampling strategy was employed. Specifically, the Synthetic Minority Over-sampling Technique combined with Edited Nearest Neighbors (SMOTE-ENN) was utilized to simultaneously oversample minority classes and clean borderline or noisy samples[22]. Following resampling, updated class distributions were computed, and class weights were recalculated and incorporated into the cross-entropy loss function to further mitigate residual imbalance during model training.

This combined approach has been demonstrated to enhance classifier performance in highly imbalanced multiclass medical datasets.

Results

Model Performance Across Datasets

The proposed Transformer-based model demonstrated robust classification performance across training, test, and validation sets.

On the training set, the model achieved a loss of 0.540, an accuracy of 0.759, a weighted F1-score of 0.766, and a macro-average AUC of 0.920.

On the independent test set, the model yielded a loss of 0.816, an accuracy of 0.733, a weighted F1-score of 0.733, and a macro-average AUC of 0.880 (95% CI: 0.807–0.953).

On the external validation set, it reached a loss of 0.948, an accuracy of 0.758, a weighted F1-score of 0.768, and a macro-average AUC of 0.886 (95% CI: 0.833–0.940).

The confusion matrices and corresponding ROC curves for all three datasets are presented in Fig. 4.

The model consistently demonstrated strong discriminative ability for Class 0 across all sets, while Class 1 and Class 2 showed moderate variation in precision and recall.

Summary of Performance Metrics

A comprehensive summary of model performance across the training, validation, and test sets is provided in Table 1.

Table 1
Overall performance of the proposed Transformer-based model.

Dataset	Accuracy	Weighted F1-score	Macro-average Precision	Macro-average Recall	Macro-average AUC (95% CI)
Training Set	0.759	0.766	0.761	0.794	0.920 (0.884–0.955)
Validation Set	0.758	0.769	0.676	0.719	0.886 (0.833–0.940)
Test Set	0.733	0.733	0.635	0.635	0.880 (0.807–0.953)

Ablation Study with Traditional Machine Learning Models

To assess the effectiveness of the Transformer-based model, we compared its performance against several traditional machine learning classifiers, including Random Forest, Logistic Regression, XGBoost, and LightGBM. As summarized in Table 2, the Transformer-based model achieved the highest accuracy, F1-score, and AUC on both the validation and test sets, outperforming all traditional models across all evaluation metrics.

Table 2. Comparison of the proposed Transformer-based model with traditional machine learning models.

Model	Validation Accuracy	Validation score	F1-Validation AUC	Test Accuracy	Test F1-score	Test AUC
Random Forest	0.682	0.694	0.834	0.640	0.660	0.827
Logistic Regression	0.629	0.638	0.837	0.547	0.575	0.802
XGBoost	0.545	0.568	0.807	0.533	0.557	0.804
LightGBM	0.523	0.547	0.800	0.573	0.596	0.823
Transformer (ours)	0.758	0.769	0.886	0.733	0.733	0.880

Discussion

Our adoption of a Transformer-based model in this context constitutes a methodological innovation in MVI classification. While Transformer architecture has been increasingly applied in medical imaging, their application to structured radiomic data for multi-class classification remains underrepresented. By tailoring the model to capture dependencies among quantitative features, our framework extends beyond prior binary MVI classification attempts, offering a more nuanced and clinically useful risk stratification strategy.

This study demonstrated the feasibility and effectiveness of using a Transformer-based deep learning model to perform direct three-class classification of microvascular invasion (MVI) in hepatocellular carcinoma (HCC) patients by integrating radiomic features and clinical laboratory indicators. Compared with conventional machine learning methods such as Random Forest and Logistic Regression, the proposed model consistently achieved superior performance, with a test set AUC of 0.880 (95% CI: 0.807–0.953) and a weighted F1-score of 0.733. These findings highlight the Transformer architecture’s capacity to model complex, high-dimensional, and structured medical data by capturing nonlinear and hierarchical feature dependencies through its self-attention mechanism[14], [15], [25].

Previous radiomics-based studies have primarily focused on binary MVI classification (presence vs. absence), typically reporting AUCs ranging from 0.75 to 0.85[10], [26], [27]. In contrast, our approach enables one-step, three-class prediction (M0, M1, M2), providing a more granular and clinically actionable preoperative risk stratification strategy. This advancement allows for refined surgical planning and supports individualized treatment decisions. Additionally, unlike earlier studies that often relied on subjective imaging features manually assessed by radiologists, our model is entirely based on objectively extracted features, which reduces interobserver variability and improves reproducibility[28].

The key contributions of this study lie in three aspects: proposing a Transformer-based framework for direct MVI three-class classification, demonstrating the benefit of multimodal feature integration from radiomics and clinical data, and ensuring high model reproducibility by using only objective quantitative inputs. Nevertheless, several limitations must be acknowledged. First, although the model performed well on both internal and external validation sets, the dataset was collected from a limited geographic region, which may restrict its generalizability to broader populations and imaging protocols[29]. Second, the proportion of M2 cases remained low (~ 15%), and although SMOTE-ENN[22] and class-weighted loss were applied, the class imbalance still posed challenges in reliably distinguishing M1 from M2. Third, as with most deep learning models, the Transformer lacks interpretability, which may hinder its acceptance in clinical decision-making[30].

Future research should focus on external validation using multi-center and multi-ethnic datasets to improve robustness and generalizability[31]. In addition, incorporating multi-omics data (e.g., genomics, transcriptomics, proteomics) may further enhance the model's predictive capacity and biological interpretability[32]. To address the black-box nature of the Transformer, explainable artificial intelligence (XAI) techniques—such as SHAP value analysis, attention heatmaps, and counterfactual reasoning—should be integrated[33], [34]. Exploring advanced Transformer variants, including sparse attention mechanisms or hybrid CNN-Transformer architectures, may also contribute to improved efficiency and clinical utility[35].

Conclusion

In this study, we proposed a Transformer-based deep learning framework that integrates radiomic features and clinical laboratory indicators for the preoperative three-class classification of MVI in patients with HCC.

The proposed model effectively captured complex high-dimensional feature relationships and achieved competitive performance across training, validation, and independent test sets.

By enabling direct three-class MVI prediction in a single step, our approach provides more granular prognostic information and holds promise for supporting individualized treatment planning and streamlining clinical decision-making.

Despite the encouraging results, further work is needed to enhance the model's clinical applicability.

Future research should focus on expanding validation cohorts to larger, multi-center, and multi-ethnic datasets, improving model interpretability through explainable artificial intelligence (XAI) techniques, and incorporating multi-omics data to enrich biological insights and further boost predictive accuracy.

Abbreviations

HCC

Hepatocellular carcinoma
MVI
Microvascular invasion
MRI
Magnetic resonance imaging
AUC
Area under the curve
Gd-BOPTA
Gadolinium benzyloxypropionictetraacetate
RFE
Recursive feature elimination

Declarations

Author Contribution

JN and WL conceived and designed the study. CH was responsible for data collection, and contributed to ROI segmentation and radiomics processing along with ZW, GM, and ZX. HR developed the model, performed the data analysis, and drafted the manuscript. JN and WL provided supervision and revised the manuscript critically for important intellectual content. All authors read and approved the final version of the manuscript.

Data Availability

The data used in this study were obtained from the Eastern Hepatobiliary Surgery Hospital and are not publicly available due to institutional and ethical restrictions. Access to the data can be requested from the corresponding author and may be granted upon reasonable request and approval from the institutional review board.

Critical Relevance Statement

Accurate preoperative three-class prediction of microvascular invasion (MVI) in hepatocellular carcinoma (HCC) remains unmet in clinical imaging. This study demonstrates the potential of a Transformer-based model for non-invasive and individualized MVI stratification.

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Figures

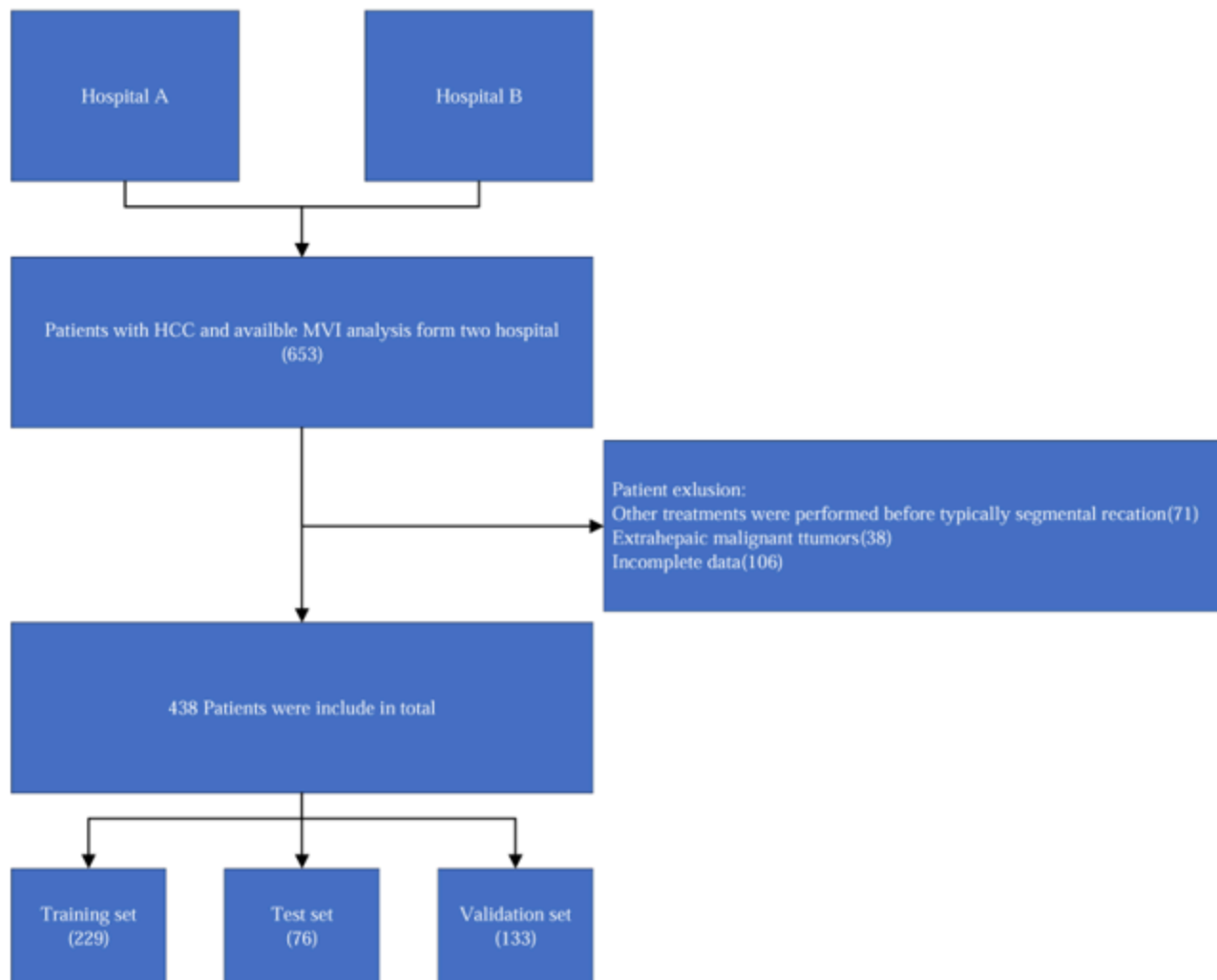


Figure 1

The workflow of patient selection. HCC: hepatocellular carcinoma. MVI: microvascular invasion

Workflow of radiomics-based three-class MVI classification using Transformer model

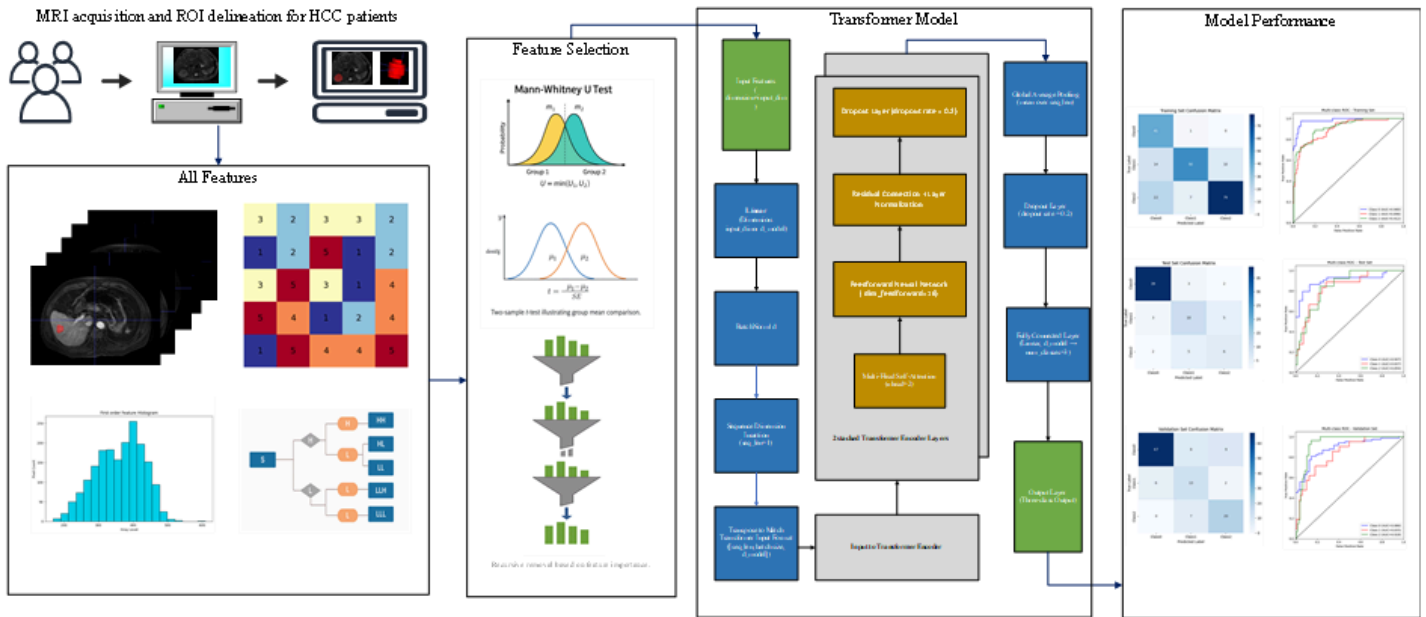


Figure 2

Overall workflow for radiomics-based three-class classification of microvascular invasion (MVI) in hepatocellular carcinoma (HCC). Radiomic features were extracted from Gd-enhanced MRI based on manually delineated regions of interest (ROIs). A two-step feature selection strategy was applied, combining univariate statistical tests (t-test or Mann–Whitney U test) and recursive feature elimination (RFE). A Transformer model was trained for MVI classification (M0, M1, M2), and performance was evaluated using confusion matrices and ROC curves.

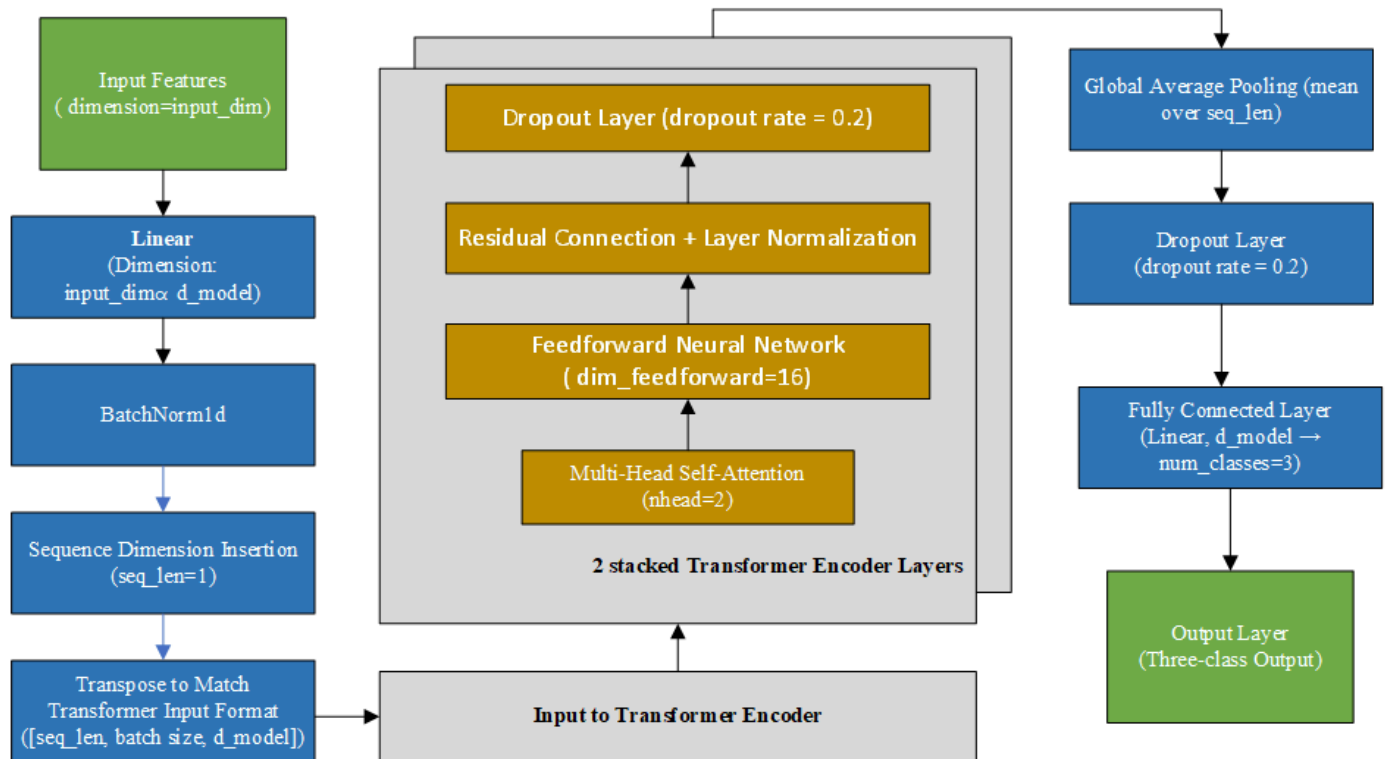


Figure 3

Overview of the Transformer-based model architecture for MVI classification.

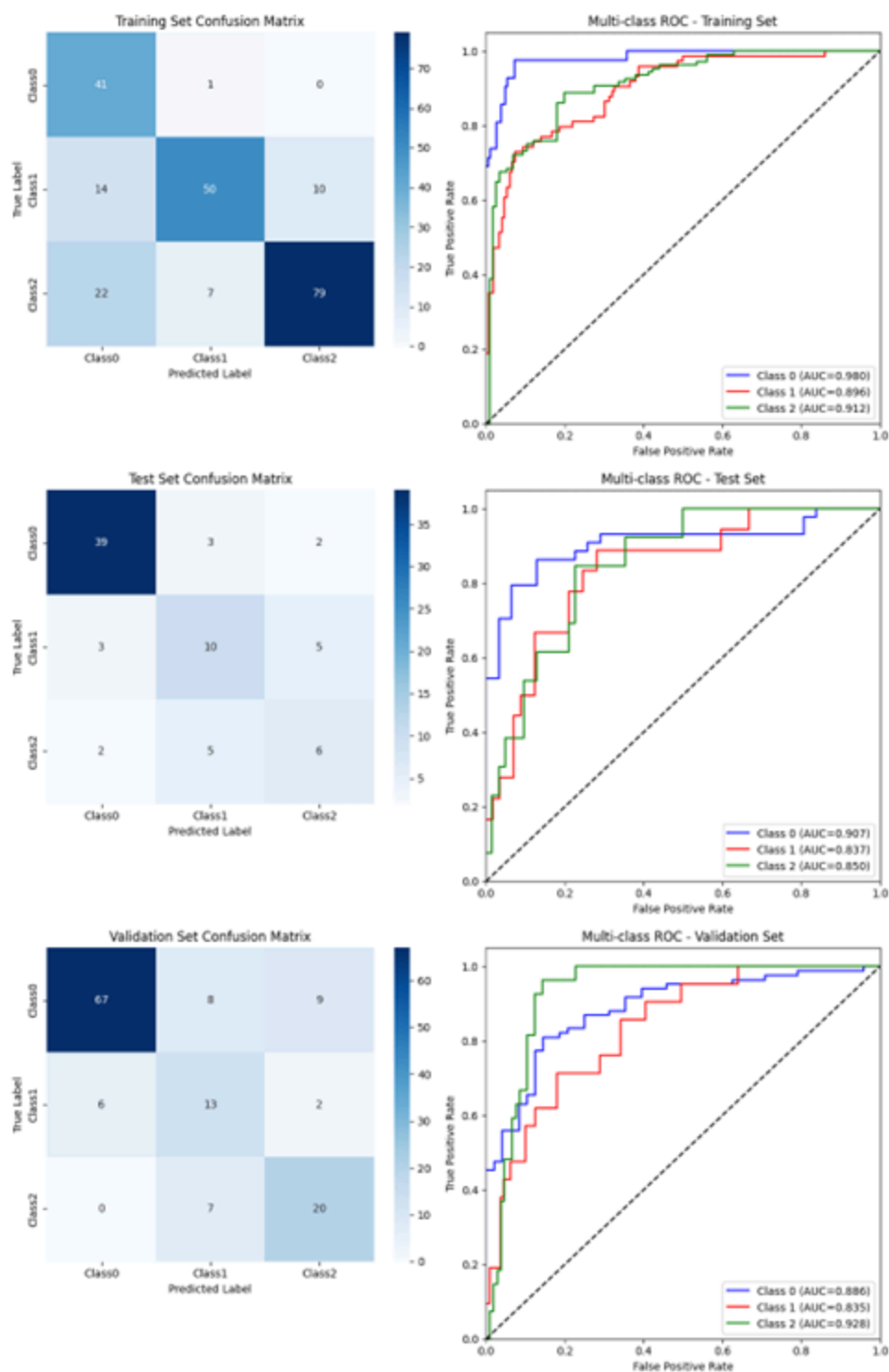


Figure 4

Classification performance of the Transformer-based model across training, test, and validation sets. **Top row:** Training set – Confusion matrix (left) and ROC curves (right). **Middle row:** Test set – Confusion matrix (left) and ROC curves (right). **Bottom row:** External validation set – Confusion matrix (left) and ROC curves (right).