Interpretable Graph Learning on Preoperative Biopsy Predicts Pathological Complete Response to Neoadjuvant Therapy in Breast Cancer

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Abstract

Predicting neoadjuvant therapy (NAT) response in breast cancer patients still remains challenging due to the high heterogeneity of tumors and modality differences in medical data. In this paper, we proposed a novel graph learning framework, a clinicopathological-guided spatial-variant network (CSV-Net), which integrates whole-slide images (WSIs) from biopsy samples with clinicopathological (CP) variables to predict pathological complete response (pCR) of patients receiving NAT. CSV-Net incorporates two novel components: (1) a spatial-variant graph convolution (SV-GraphConv) layer, which models the spatial-semantic heterogeneity inherent in whole-slide images (WSIs), and (2) a clinicopathological-guided graph pooling (CG-GraphPool) module that dynamically integrates clinicopathological (CP) variables with WSI features at a fine-grained level, enhancing both performance and interpretability. We evaluated CSV-Net on a retrospective dataset of 950 breast cancer patients from 5 medical centers. CSV-Net achieved ROC-AUCs of 0.845 (95% CI: 0.801-0.886) and 0.815 (95% CI: 0.755-0.873) in predicting pCR on the internal and external validation sets, respectively, outperforming state-of-the-art methods. Notably, subgroup analysis highlighted CSV-Net's robust performance in patients with different molecular subtypes (e.g., Luminal, HER2 overexpression and TNBC), underscoring its clinical utility. Furthermore, disease-free survival relevance and transcriptomic profiling experiments confirmed the model's prognostic value and biological interpretability, suggesting potential applications in personalized treatment planning and biomarker discovery.

Introduction

Background: The accurate prediction of pathological complete response (pCR) prior to NAT holds profound clinical significance. Developing a robust tool for pCR prediction is a critical step towards precision oncology in breast cancer care. Preoperative biopsy can provide a comprehensive cell-level tumor microenvironment by whole slide images and clinicopathological variables.

Challenges: Despite AI's promising potential in preoperative biopsy analysis, its potential to predict NAT response has not yet been fully explored due to two key challenges: (1) lack of exploration into the heterogeneity of the tumor microenvironment and (2) lack of organic fusion between WSI and Clinicopathological variables.

Our Contributions: We propose a clinicopa-thological-guided spatial-variant Network (CSV-Net), a novel graph-based framework that integrates WSIs and CP variables to predict pCR in NAT. Our main contributions including Spatial-semantic heterogeneity modeling, Organic multimodal fusion, Rigorous multi-center validation, Clinical utility verification and Molecular interpretability.

Methods and materials

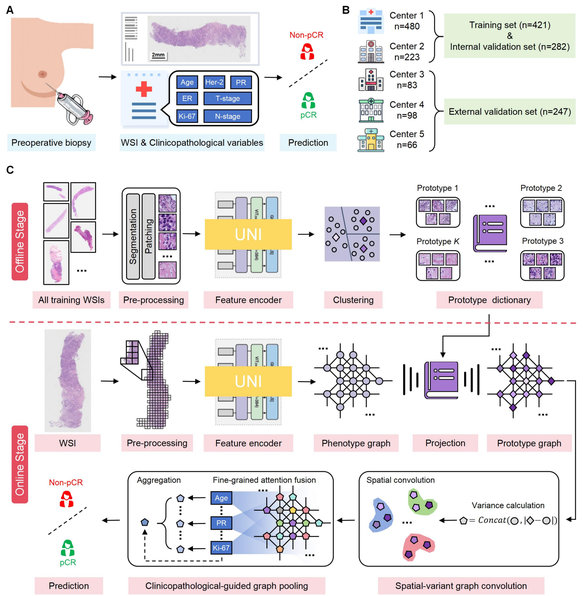


Figure 1. The overall flowchart of this study. A, The biopsy whole-slide image with CP variables (including Age, ER, PR, HER2, Ki67, T-stage and N-stage), served as inputs for the model. **B**, Data collected from 950 patients across 5 centers were used in this study and divided into a training set, an internal validation set, and an external test set. **C**, We propose CSV-Net, which in the offline stage induces biopsy tissue types, and subsequently in the online phase captures cross-patient spatial-semantic heterogeneity via spatial-variant graph convolutional layers. Moreover, a clinicopathological-guided graph pooling module is designed to achieve interpretable multimodal fusion and response prediction.

Results

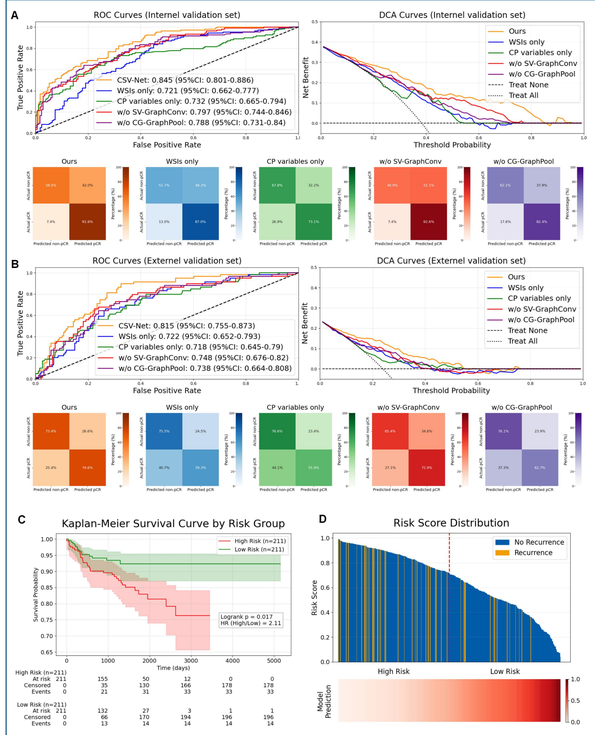


Figure 2. Model performance. A, Performance of CSV-Net and ablation methods in internal validation set. **B,** Performance of CSV-Net and ablation methods in external validation set. **C,** KM curves of high- and low- risk groups stratified by model prediction. **D,** Comparison of recurrence status between high-risk and low-risk groups stratified by model prediction.

Discussion

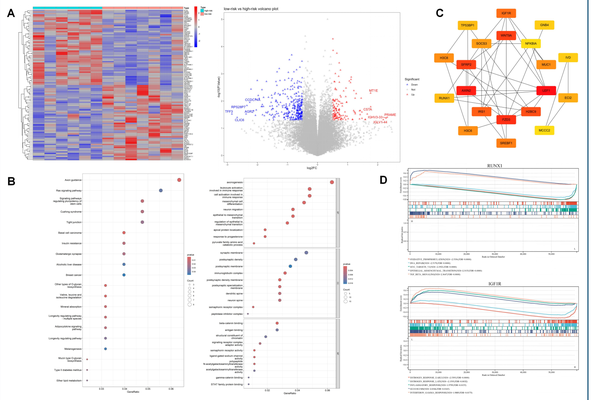


Figure 3. Transcriptomics profiling. A, Heatmap and volcano plot of differential gene expression analysis between high-risk and low-risk groups. **C,** Core gene network. **B,** KEGG and GO enrichment analyses of differentially expressed genes in high-risk vs. low-risk groups. **D,** Single-gene GSEA of RUNX1 and IGF1R.

Conclusions

This study establishes CSV-Net as an interpretable graph learning framework that effectively predicts pathological complete response to neoadjuvant therapy in breast cancer by integrating biopsy whole-slide images with clinicopathological variables. Our novel SV-GraphConv explicitly models tumor heterogeneity while CG-GraphPool enables dynamic multimodal fusion, achieving state-of-the-art performance across multi-center cohorts. The framework's biological interpretability and survival stratification capability demonstrate significant potential for guiding personalized treatment planning in clinical practice.

Future work will focus on prospective validation, incorporation of dynamic MRI biomarkers, and extension to other cancer types where treatment response prediction remains challenging.

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