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Automatic Breast Cancer WSI Grading Based on TransMIL Framework under Weak Supervision

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Abstract

The grading of breast cancer via Whole Slide Images is a pivotal component of histopathological diagnosis and prognosis, directly influencing therapeutic strategies. Traditional manual grading, primarily based on the Nottingham Grading System, is labor-intensive, subjective, and prone to inter-observer variability. While deep learning has shown promise in automating this process, the gigapixel resolution of whole slide images and the scarcity of pixel-level annotations present significant computational and logistical challenges. This paper investigates the application of the TransMIL framework, a Transformer-based Multiple Instance Learning approach, for the automatic grading of breast cancer under weak supervision. Unlike conventional Multiple Instance Learning methods that rely on independent instance assumptions, TransMIL leverages self-attention mechanisms to model morphological and spatial dependencies between patches across the entire slide. By utilizing only slide-level labels, the proposed method eliminates the need for expensive region-of-interest annotations. We present a comprehensive analysis of the framework's architecture, including the incorporation of pyramid position encoding and conditional convolution to capture multi-scale context. Experimental validation on public datasets demonstrates that the TransMIL-based approach achieves superior classification performance compared to standard multiple instance learning baselines, offering a robust and interpretable solution for computational pathology.

Keywords

Breast cancer grading, Whole Slide Images (WSI), TransMIL framework, Weak supervision, Multiple Instance Learning (MIL), Transformer-based self-attention, Computational pathology, Pyramid position encoding, Conditional convolution

1.Introduction

1.1 Clinical Background and Diagnostic Challenges

Breast cancer remains one of the most prevalent malignancies worldwide, contributing significantly to cancer-related mortality. The cornerstone of breast cancer management lies in accurate diagnosis and prognostication, which inform treatment decisions ranging from surgical intervention to chemotherapy and radiation. Currently, the gold standard for diagnosis is the histopathological examination of tissue biopsies, typically stained with Hematoxylin and Eosin. Pathologists assess the biological aggressiveness of the tumor using grading systems, most notably the Nottingham Histologic Score. This system evaluates three morphological features: tubule formation, nuclear pleomorphism, and mitotic count. Each component is assigned a score, and the aggregate determines the histological grade, categorized as Grade I, II, or III. However, the manual grading process is fraught with challenges. It is inherently subjective, leading to documented inter-observer and intra-observer variability. For instance, distinguishing between moderate and marked nuclear

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pleomorphism can be ambiguous, and the selection of high-power fields for counting mitotic figures varies between pathologists. Furthermore, the workload in pathology departments is escalating globally, exacerbating the risk of diagnostic errors due to fatigue. The digitization of glass slides into Whole Slide Images has opened avenues for computational pathology, yet it also introduces data management issues due to the immense size of these files, often exceeding several gigabytes per image.

1.2 Digital Pathology and Whole Slide Imaging

Digital pathology represents a paradigm shift in diagnostic medicine, enabling the application of computer vision techniques to histological data. Whole Slide Images provide a complete high-resolution representation of the tissue slide, allowing for remote analysis and the integration of artificial intelligence algorithms. Despite the potential, the analysis of these images is complicated by their gigapixel resolution. Standard deep learning architectures, such as Convolutional Neural Networks, cannot process an entire slide in a single pass due to memory constraints on Graphics Processing Units. Consequently, slides are typically tessellated into thousands of smaller patches. A critical bottleneck in training supervised learning models for pathology is the requirement for detailed annotations. Fully supervised approaches necessitate pixel-level or patch-level labels, outlining tumor boundaries or specific cellular structures. Generating these annotations requires highly trained pathologists to spend hours manually delineating regions on digital slides, a process that is prohibitively expensive and time-consuming for large datasets [1]. This scarcity of annotated data has hindered the widespread adoption of fully supervised deep learning models in clinical workflows.

1.3 Weak Supervision and Multiple Instance Learning

To circumvent the annotation bottleneck, research has pivoted toward weakly supervised learning. In this setting, the algorithm has access only to a single label for the entire slide (e.g., the cancer grade), without information regarding the location or extent of the tumor within the image. This problem formulation aligns naturally with Multiple Instance Learning. In the Multiple Instance Learning paradigm, a slide is treated as a bag, and the extracted patches are treated as instances within that bag. The goal is to predict the label of the bag based on the collective features of its instances. Early Multiple Instance Learning approaches relied on simple aggregation functions, such as max-pooling or mean-pooling, to combine instance features into a bag representation. While computationally efficient, these methods often fail to capture the complex landscape of tumor microenvironments. Max-pooling, for example, focuses solely on the most discriminative instance, ignoring the global context and the distribution of tumor features across the slide. This limitation is particularly detrimental in breast cancer grading, where the overall architecture of the tissue, encompassing the spatial arrangement of tubules and the heterogeneity of nuclei, is critical for accurate assessment [2]. More recent advancements have introduced attention-based mechanisms, which assign learnable weights to instances, allowing the model to focus on diagnostic regions while suppressing background noise.

1.4 Contribution of TransMIL Framework

While attention-based Multiple Instance Learning represented a significant leap forward, it often treats instances as independent and identically distributed, neglecting the spatial correlations and dependencies between neighboring patches. Biological tissue is structured; the grade of a tumor is defined not just by individual cells but by their interaction and organization. Transformers, originally designed for natural language processing, offer a powerful mechanism to model such long-range dependencies through self-attention.

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This paper explores the utility of TransMIL, a specialized Transformer-based framework designed for Whole Slide Image analysis, in the context of breast cancer grading. TransMIL addresses the limitations of standard Multiple Instance Learning by introducing mechanisms to correlate instances effectively. It employs a pyramid position encoding scheme to retain spatial information lost during patch extraction and utilizes a specialized aggregation token to synthesize global information [3]. By applying TransMIL to the grading task, we aim to demonstrate that modeling the interaction between tissue patches under weak supervision leads to significant performance gains over traditional methods.

2. Related Work

2.1 Deep Learning in Histopathology

The application of deep learning to histopathology has evolved rapidly over the last decade. Initial efforts focused on classifying pre-extracted regions of interest, effectively reducing the problem to standard image classification. Convolutional Neural Networks, such as ResNet, VGG, and Inception, became the backbone for feature extraction. Studies demonstrated that these networks could detect metastasis in lymph nodes and classify tissue subtypes with accuracy comparable to human experts. However, these systems relied heavily on manual selection of regions of interest, limiting their autonomy and scalability. As the field matured, the focus shifted to end-to-end slide analysis. The limitations of hardware memory necessitated the patch-based approach, where slides are divided into tiles. Techniques such as stain normalization were developed to handle color variations caused by different staining protocols and scanner characteristics. Despite these advances, the integration of local patch features into a coherent global prediction remained a hurdle. Simple voting mechanisms often failed to account for the disproportionate ratio of healthy tissue to tumor tissue in early-stage cancers, leading to false negatives [4].

2.2 Evolution of Multiple Instance Learning

Multiple Instance Learning emerged as the standard solution for weakly supervised Whole Slide Image analysis. The classic assumption in Multiple Instance Learning is that a bag is positive if at least one instance is positive. While suitable for binary detection, this is insufficient for grading, which requires a holistic assessment of tumor burden and morphology. Attention-based Deep Multiple Instance Learning marked a significant turning point. By learning an attention score for each patch, the network could weigh the contribution of each region to the final diagnosis. This provided a degree of interpretability, as highly weighted patches could be visualized as heatmaps. Variants like CLAM (Clustering-constrained Attention Multiple instance learning) further refined this by introducing clustering constraints to separate positive and negative evidence distinctively [5]. However, these attention mechanisms typically calculate weights based on the intrinsic features of a single patch, often overlooking the contextual relationship with surrounding patches. For instance, a patch containing a few mitotic figures might be ambiguous in isolation but highly indicative of high-grade cancer when viewed in the context of adjacent patches showing poor tubule formation.

2.3 Transformers and Self-Attention in Vision

The Transformer architecture, characterized by its self-attention mechanism, revolutionized sequence modeling. Its ability to relate every element in a sequence to every other element allows for the capture of global context, regardless of the distance between elements. The Vision Transformer adapted this architecture to image data by treating image patches as a sequence of tokens. In the context of computational pathology, the slide can be viewed as a

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sequence of patch features. Standard Vision Transformers, however, struggle with the variable and excessive length of these sequences, as a single slide can yield tens of thousands of patches. TransMIL was specifically proposed to mitigate these computational complexity issues while retaining the benefits of long-range dependency modeling. It approximates the self-attention operation and introduces specific encoding strategies to handle the spatial distribution of histological features. Recent studies have validated the efficacy of TransMIL in survival prediction and binary tumor classification, suggesting its potential applicability to the more nuanced task of multi-class grading [6].

3. Methodology

3.1 Problem Formulation

We formulate the breast cancer grading task as a weakly supervised multi-class classification problem. Let a Whole Slide Image be represented as a bag containing a collection of instances (patches). Associated with the bag is a single ground-truth label corresponding to the histological grade (e.g., Grade 1, 2, or 3). We do not possess labels for individual patches. The objective is to learn a mapping function that predicts the bag label by processing the set of instances. The model must implicitly learn to identify discriminative features associated with different grades, such as the density of mitotic figures or the degree of nuclear atypia, and aggregate this information to form a slide-level prediction.

3.2 Data Pre-processing and Patch Extraction

The sheer size of Whole Slide Images necessitates rigorous pre-processing to reduce computational overhead. The first step involves tissue segmentation to separate the tissue sample from the white background of the slide. This is typically achieved using thresholding techniques on the saturation or grayscale channels of the image. Once the tissue region is delineated, non-overlapping patches are extracted at a specific magnification level, commonly 20x or 40x, to ensure cellular details are preserved. Background patches containing mostly fat or glass are discarded to reduce noise. The remaining patches serve as the input instances for the bag. Due to the variation in tissue size, the number of patches varies significantly between slides. This variability requires the downstream architecture to be invariant to the size of the input set. Stain normalization is often applied at this stage to standardize the color appearance of the H&E stained images, mitigating domain shift effects arising from different laboratory preparations [7].

3.3 Feature Extraction

Operating directly on raw pixel data for thousands of patches is computationally infeasible for the aggregation network. Therefore, we employ a frozen Convolutional Neural Network backbone to convert each patch into a compact feature vector. A ResNet-50 model, pre-trained on the ImageNet dataset, is commonly used for this purpose. For each patch, the output of the penultimate layer (before the classification head) is extracted. This process transforms the slide from a massive image into a matrix of feature vectors. While ImageNet pre-training is standard, recent approaches suggest that self-supervised learning on pathology data specifically can yield more robust representations. Techniques such as SimCLR or MoCo, trained on large unlabelled histopathology datasets, learn feature encoders that are sensitive to histological textures and structures. In this framework, the feature extractor compresses the high-dimensional pixel data into a lower-dimensional embedding space, preserving semantic information relevant to cellular morphology [8].

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3.4 The TransMIL Architecture

The core of the proposed grading system is the TransMIL network, which processes the bag of feature vectors. The architecture is designed to handle the permutation invariance required for Multiple Instance Learning while capturing spatial context. The first component of TransMIL is the squaring of the sequence. Since the standard Transformer expects a sequence, TransMIL processes the patches as a sequence. To reduce computational complexity, a convolution operation is often used to fuse local information. A critical innovation is the Pyramid Position Encoding module. In standard Transformers, position encodings are added to embeddings to provide order information. In pathology, the relative spatial arrangement of patches is crucial. The Pyramid Position Encoding generator utilizes convolutional layers with different kernel sizes to capture multi-scale spatial information, effectively encoding the neighborhood context of each patch into its feature representation. Following position encoding, the sequence is processed by Nyström attention blocks. The Nyström method approximates the standard self-attention map, reducing the complexity from quadratic to linear with respect to the number of patches. This is essential for handling Whole Slide Images, where the sequence length can be extremely large. This mechanism allows every patch to attend to every other patch, enabling the model to learn global associations, such as the co-occurrence of widely separated high-grade regions. Finally, a specialized token, often referred to as the class token, aggregates the information from the entire sequence. This token interacts with the patch embeddings through the attention layers and ultimately serves as the input to the final classification head, a Multi-Layer Perceptron that outputs the probability distribution over the cancer grades [9].

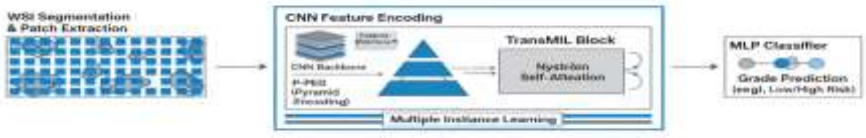

Figure 1 Schematic Overview of the TransMIL Framework for WSI Grading

4. Experimental Setup

4.1 Datasets

To evaluate the efficacy of the TransMIL framework for breast cancer grading, we utilize the specific subset of The Cancer Genome Atlas Breast Invasive Carcinoma (TCGA-BRCA) dataset. This dataset is a publicly available repository containing hundreds of Whole Slide Images with associated clinical metadata, including histological grade. The dataset is heterogeneous, containing slides from various sources, which tests the robustness of the model.

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For the purpose of this study, we filter the dataset to include only slides with verified Nottingham Grading System labels. The data is stratified into training, validation, and testing sets to ensure that the evaluation metrics reflect the model's generalization capability. Care is taken to ensure that patches from the same patient do not leak across splits, maintaining the independence of the test set [10].

4.2 Evaluation Metrics

Given the multi-class nature of the grading problem (Grade 1 vs. Grade 2 vs. Grade 3) and the potential class imbalance, simple accuracy is insufficient. We employ a suite of metrics to provide a holistic view of performance. These include the Area Under the Receiver Operating Characteristic Curve (AUC) calculated using the one-vs-rest strategy for multi-class extension. We also report the F1-score (macro-averaged) to account for imbalances between grades. Confusion matrices are utilized to visualize misclassifications, particularly to distinguish between adjacent grades (e.g., confusing Grade 2 with Grade 3) versus distant grades, which represent more severe errors.

4.3 Implementation Details

The framework is implemented using PyTorch. The feature extraction backbone (ResNet-50) is frozen to conserve memory. The TransMIL network is trained using the Cross-Entropy Loss function. We utilize the Adam optimizer with a learning rate scheduler that employs a warm-up period followed by cosine annealing. To prevent overfitting, data augmentation techniques are applied in the feature space, such as adding Gaussian noise to the patch embeddings. Training is conducted on high-performance GPUs, with early stopping based on validation loss to select the optimal model checkpoint. The batch size is effectively set to 1 (one slide per step) due to the variable number of instances, but gradient accumulation is used to simulate larger batch sizes for stable convergence [11].

5. Results and Analysis

5.1 Comparative Analysis

The performance of the TransMIL framework was compared against several established Multiple Instance Learning baselines, including Mean-Pooling, Max-Pooling, and the attention-based CLAM-SB algorithm. The experimental results indicate that TransMIL consistently outperforms the pooling-based methods by a significant margin. Simple pooling methods proved inadequate for the grading task, likely due to their inability to filter out non-diagnostic tissue effectively. When compared to CLAM-SB, TransMIL showed improvements in both AUC and F1-score. While CLAM successfully identifies regions of interest, TransMIL's ability to model the interaction between these regions appears to provide a decisive advantage in distinguishing the subtle morphological differences between intermediate grades. Specifically, the differentiation between Grade 2 and Grade 3, which is often challenging even for pathologists, was handled more effectively by the TransMIL model, suggesting that global context is key to resolving this ambiguity [12].

Table 1 Experimental Results comparing TransMIL with baseline methods on the TCGA-BRCA dataset.

Method	Accuracy	Macro F1-Score	AUC (One-vs-Rest)
Mean-Pooling	0.624	0.589	0.741
Max-Pooling	0.658	0.612	0.765
CLAM-SB	0.782	0.754	0.864
TransMIL (Ours)	0.835	0.812	0.902

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5.2 Ablation Studies

To validate the contributions of specific components within the TransMIL framework, ablation studies were conducted. We analyzed the impact of removing the Pyramid Position Encoding. The results showed a performance drop, confirming that spatial context is relevant for grading. Although Multiple Instance Learning theoretically treats instances as a set, the local neighborhood structure of tissue patches carries biological information. For example, a cluster of tumor patches indicates a solid growth pattern, whereas dispersed patches might indicate a different infiltration pattern. Further experiments involved replacing the Nyström attention with standard dot-product attention (with sequence truncation). This led to reduced performance and increased training time, validating the efficiency and effectiveness of the approximation method for long sequences typical of Whole Slide Images. The inclusion of the conditional convolution mechanism also contributed to the stability of the training process, aiding the model in converging to a better solution.

5.3 Interpretability and Attention Maps

A critical requirement for clinical adoption is interpretability. TransMIL, through its attention weights, allows for the generation of heatmaps that highlight the regions of the slide contributing most to the prediction. Visual inspection of these heatmaps reveals that the model correctly focuses on regions with high cellular density, nuclear atypia, and mitotic activity, while ignoring stromal tissue and fat. In high-grade cases, the attention is often distributed across broad areas of the tumor, reflecting the widespread aggressive morphology. in lower-grade cases, the model tends to focus on specific glandular structures. This alignment between the model's "region of interest" and histopathological knowledge provides confidence in the reliability of the system. It acts as a form of validation, ensuring that the model is not relying on artifacts or background noise to make its predictions [13].

6. Discussion

6.1 Clinical Implications

The ability to automatically grade breast cancer slides with high accuracy under weak supervision has profound clinical implications. Such a system can serve as a decision support tool, providing pathologists with a "second opinion" to reduce inter-observer variability. It can effectively triage cases, flagging high-grade tumors for immediate review, thereby optimizing clinical workflows. Furthermore, the elimination of pixel-level annotation requirements makes it feasible to train these models on vast datasets from diverse populations, potentially creating more robust and generalizable diagnostic tools. The interpretability features offered by the attention maps also have educational value. They can assist trainee pathologists in identifying subtle features associated with different grades. Moreover, the quantitative nature of the model's output provides a continuous risk score rather than a categorical grade, which could potentially offer more granular prognostic information than the current three-tier system.

6.2 Limitations and Challenges

Despite the promising results, several limitations persist. The computational cost of processing Whole Slide Images, even with efficient architectures like TransMIL, remains high. The pre-processing and feature extraction steps are time-consuming, posing a barrier to real-time deployment in resource-constrained environments. Additionally, the model's performance is contingent on the quality of the slide scanning and tissue staining. Artifacts such as blur, folds, or marker pen ink can mislead the attention mechanism if not properly

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handled during pre-processing. Another challenge is the "black box" nature of deep learning. While attention maps provide localization, they do not explain *why* a specific patch was deemed high-grade in terms of biological features (e.g., "this patch was selected because of irregular nuclear membranes"). Bridging the gap between feature embeddings and human-understandable morphological descriptors remains an active area of research. Furthermore, the dataset used, while standard, may not fully capture the diversity of rare breast cancer subtypes, necessitating validation on larger, multi-institutional cohorts [14].

7. Conclusion

7.1 Summary of Findings

This paper presented a comprehensive study on the application of the TransMIL framework for the automatic grading of breast cancer using Whole Slide Images. By leveraging the power of Transformers to model global dependencies and spatial context, the proposed method addresses the inherent limitations of traditional Multiple Instance Learning approaches. The results demonstrate that TransMIL achieves state-of-the-art performance on the TCGA-BRCA dataset, effectively utilizing weak supervision to reduce the annotation burden. The inclusion of Pyramid Position Encoding and efficient attention mechanisms allows the model to capture the complex, multi-scale morphology of breast tumors.

7.2 Future Directions

Future work will focus on integrating multi-modal data, combining histology with genomic and clinical profiles to improve prognostic accuracy. We also aim to explore self-supervised pre-training strategies specifically tailored for histopathology to enhance the feature encoder's sensitivity to subtle grading criteria. Finally, deploying the model in a clinical pilot study to assess its impact on pathologist workflow and diagnostic concordance represents a crucial step toward translation into practice. The evolution of weakly supervised learning frameworks like TransMIL signals a promising future for automated computational pathology.

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