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Deep learning for categorizing microsatellite stability in colorectal cancer

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ABSTRACT

Cancer remains a significant global health challenge, with its incidence rising steadily in recent decades. In colorectal cancer (CRC), microsatellite instability (MSI), and microsatellite stability (MSS) are important biomarkers that influence treatment decisions and patient outcomes. Accurate MSI classification is critical but traditional methods can be costly and time-consuming. This study explores the potential of deep learning to classify MSI and MSS in CRC. A large dataset of CRC patients with confirmed MSI and MSS status was utilized, obtained through standard testing images. Deep learning models were applied to histopathological images, analyzing tissue features from digital slides. Convolutional neural network (CNN) and residual network (ResNet)-18 models demonstrated high accuracy in distinguishing between MSI and MSS CRCs. The best-performing model, which integrated genomic and histopathological data, achieved an area under the curve (AUC) receiver operating characteristic (ROC) of 0.85, indicating strong discrimination capability. The findings suggest that deep learning could be a valuable tool for clinical decision-making and personalized medicine in CRC.

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1. INTRODUCTION

Colorectal cancer (CRC) remains a formidable global health challenge, currently ranked as the third most prevalent malignancy and the second leading cause of cancer-related mortality worldwide [1]. Originating within the epithelial cells of the colon or rectum, CRC typically arises from a sequential accumulation of genetic and epigenetic alterations that drive uncontrolled cellular proliferation [2]. These pathological changes often manifest initially as benign polyps which, over time, may transform into malignant neoplasms capable of invading adjacent tissues or metastasizing to distant organs via the lymphatic and circulatory systems, thereby severely compromising patient prognosis [3]. The biological heterogeneity of CRC necessitates precise molecular characterization to guide clinical management. While modifiable lifestyle factors, including sedentary behavior and diets high in processed meats, interact with non-modifiable risks such as aging to influence disease incidence [4], contemporary oncology increasingly relies on genomic biomarkers to navigate the substantial economic and physiological burdens of long-term treatment [5].

A fundamental molecular distinction in CRC is the status of microsatellite stability (MSS). Approximately 15% of cases exhibit microsatellite instability (MSI), a condition resulting from a deficient DNA mismatch repair (dMMR) system [6]. MSI-H tumors are characterized by a high frequency of mutations

in short, repetitive DNA sequences, leading to a "hypermutated" genomic profile. Histologically, these tumors often present with poor differentiation and a dense infiltration of tumor-infiltrating lymphocytes (TILs) [7]. This high tumor mutational burden (TMB) generates immunogenic neoantigens that render MSI-H patients exceptionally responsive to immune checkpoint inhibitors (ICIs), such as pembrolizumab and nivolumab, despite their frequent resistance to conventional chemotherapy [8], [9].

Conversely, MSS tumors often described as "immune-cold", exhibit low mutational profiles and sparse T-cell infiltration, making them intrinsically resistant to single-agent immunotherapy [10]. These tumors are typically driven by chromosomal instability, involving mutations in oncogenes such as KRAS and tumor suppressors like TP53 [11]. For these patients, clinical strategies focus on cytotoxic chemotherapy combined with targeted therapies directed at epidermal growth factor receptor (EGFR) or vascular endothelial growth factor (VEGF) pathways [12], [13]. While the distinction between MSI and MSS is critical for optimizing survival and treatment cost-effectiveness [14], gold-standard diagnostic methods like immunohistochemistry (IHC) or polymerase chain reaction (PCR) are often resource-intensive, time-consuming, and require specialized pathology expertise. Recent breakthroughs in digital pathology suggest that deep learning can potentially predict these molecular biomarkers directly from standard hematoxylin and eosin (H&E) stained slides [15]. Despite these advancements, a significant gap remains in the literature regarding the development of low-cost, automated MSI/MSS classifiers that are rigorously validated on large-scale cohorts such as the Cancer Genome Atlas (TCGA). This study utilizes deep learning over conventional statistical methods due to its superior capacity for hierarchical feature extraction, enabling the detection of subtle morphological patterns in histology images that evade human perception. The primary objectives of this research are to design a customized convolutional neural network (CNN) architecture optimized for CRC screening, conduct a comparative performance evaluation against the established residual network (ResNet)-18 benchmark, and assess the clinical feasibility of these models as automated decision-support tools for oncologists.

2. RELATED WORKS

Although clinically defined by its anatomical origin, CRC is a highly genetically heterogeneous disease. This molecular diversity influences tumor behavior, treatment response, and patient outcomes. Despite this variability, standard chemotherapy protocols, typically FOLFOX or FOLFIRI combined with targeted agents are often applied uniformly, with limited consideration of individual pharmacogenetic variations and molecular characteristics. Adjuvant management remains primarily dictated by tumor stage. The pivotal MOSAIC study established that the addition of oxaliplatin to 5-fluorouracil (5-FU) significantly reduces recurrence risk in stage II and III disease [16], demonstrating that early-stage patients can derive considerable curative benefit. Within this framework, MSI status has emerged as a critical predictive marker for chemotherapy efficacy. While the oxaliplatin/5-FU combination is the established adjuvant standard for resected stage III cancers, the MSI phenotype is historically associated with intrinsic resistance to fluoropyrimidine monotherapy. Pooled analyses of randomized trials confirm that while MSI patients often exhibit prolonged survival, they derive no benefit from adjuvant 5-FU alone; in fact, potential deleterious effects have been observed in stage II disease. However, the integration of oxaliplatin has been shown to overcome this resistance, restoring therapeutic efficacy specifically for stage III tumors [17]-[19]. Furthermore, findings from the IDEA international collaborative study have refined the duration and modalities of these oxaliplatin-based regimens for stage III patients [20].

In the metastatic setting, distinguishing between MSS and MSI phenotypes is a fundamental criterion for therapeutic orientation. Patients with metastatic MSI cancer are now primary candidates for immune checkpoint blockade (ICB) using anti-PD-1 or anti-CTLA-4 antibodies [21]. This immunotherapy protocol is highly effective in MSI-H CRC but remains largely ineffective in MSS cases [22]. Consequently, clinical guidelines, such as the French National Digestive Cancer Thesaurus (TNCD), recommend adjuvant chemotherapy (fluoropyrimidine + oxaliplatin) for stage III MSI tumors, while generally omitting adjuvant treatment for stage II MSI tumors unless high-risk features, such as pT4b status, are present [10]. While the MSI/MSS phenotype can be identified through conventional IHC or genetic analysis [23], these tests are often expensive or unavailable in resource-constrained regions, leading to suboptimal screening. Notably, MSI-H CRCs exhibit distinct histomorphological features compared to MSS counterparts [24]. This morphological divergence has paved the way for deep learning algorithms to analyze histopathological images for survival prediction [25], metastasis detection [26], and precise histological grading [27], [28].

Recent research increasingly demonstrates that deep learning models can bridge the gap between histological patterns and underlying genomic mutations [29]. For instance, Kather *et al*. [30] proved the effectiveness of predicting MSI status directly from H&E-stained slides in gastrointestinal cancers, a finding supported by the interactive HistomicsML system [31] and subsequent studies [32]. Furthermore, Ke *et al*. [33] utilized high-performance computing (NVIDIA Tesla V100) to achieve an MSI prediction accuracy of 87%, while Lee *et al*. [24] estimated that up to 40% of CRC slides could be effectively screened via deep learning without molecular testing.

Advanced models such as MSINet have achieved an area under the curve - receiver operating characteristic (AUC-ROC) of 0.931 [34], and artificial intelligence (AI)-based stratification has shown superior results in cross-validation with an area under the receiver operating characteristic (AUROC) of 0.86 [35]. This progress is mirrored in consensus molecular subtype (CMS) classification [36] and the integration of segment anything model (SAM) with deep learning, which has further refined the segmentation and classification of MSI, unveiling its full clinical significance in contemporary CRC management [37].

3. METHODS

3.1. Dataset

TCGA initiative provides comprehensive molecular portraits of various malignancies, notably including the colon adenocarcinoma (COAD) cohort. These multi-omic datasets enable the prediction of MSI status by integrating molecular profiles, differential gene expression, and DNA methylation patterns [38]. For this study, the dataset consists of high-resolution digital pathology slides processed into standardized JPEG tiles, capturing the distinct morphological features associated with MSI-MUT and MSS phenotypes. The data preprocessing pipeline was engineered to structure and partition these image tiles into three distinct subsets: training (60%), validation (25%), and testing (15%). To mitigate selection bias and ensure statistical representativeness, the allocation process utilizes a randomized shuffling of filenames prior to distribution. The dataset exhibits a class distribution of 39.02% for MSI-MUT_JPEG and 60.98% for MSS_JPEG, reflecting the inherent prevalence variance found in clinical populations. To maintain data integrity during training, these subsets are processed through the torchvision.datasets. ImageFolder class, with images resized and normalized to align with the input requirements of the deep learning architectures. Figure 1 illustrates representative sample images extracted from the dataset, highlighting the textural and cellular diversities between the two molecular subtypes. This figure displaying representative patches for both MSI and MSS classes.

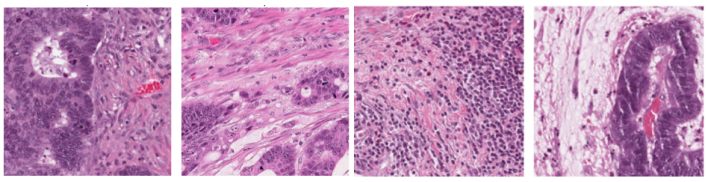

Figure 1. Sample histological images from the dataset

3.2. Deep learning models

CNNs stand tall as a pivotal architecture, particularly in tasks related to image recognition, classification, and even in certain aspects of natural language processing. The efficiency of CNNs can be attributed to their core elements, each playing a distinct role in information extraction and abstraction within the network. Here, this study use the fundamental components of CNNs: input dimension, convolution layer, pooling layer, fully connected layer, and output. The complete architecture of the proposed CNN model is illustrated in Figure 2. ResNet-18 is a pivotal CNN architecture that addresses the vanishing gradient problem through the integration of residual learning [39]. By utilizing shortcut connections, or skip connections, the network effectively performs identity mapping, allowing gradients to bypass intermediate layers and facilitating the optimization of deeper structures. The ResNet-18 variant specifically employs a balanced configuration of 18 deep layers, comprising an initial 7×7 convolution followed by four stages of residual blocks, each containing two 3×3 convolutional layers [40], [41]. This architecture terminates with a global average pooling layer and a fully connected softmax classifier. While deeper iterations like ResNet-50 or ResNet-101 offer higher capacity, ResNet-18 remains a standard benchmark in computer vision due to its

optimal trade-off between representative power and computational efficiency, making it particularly suitable for resource-constrained environments and real-time inference tasks. The detailed structure of the pre-trained ResNet-18 model is illustrated in Figure 3.

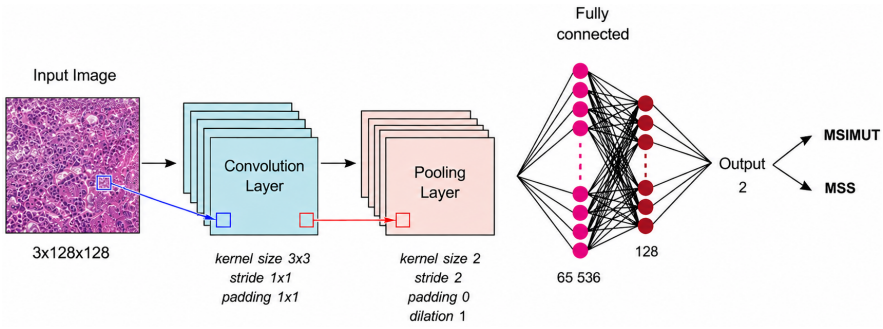

Figure 2. Schematic diagram of the CNN architecture used for MSI/MSS classification

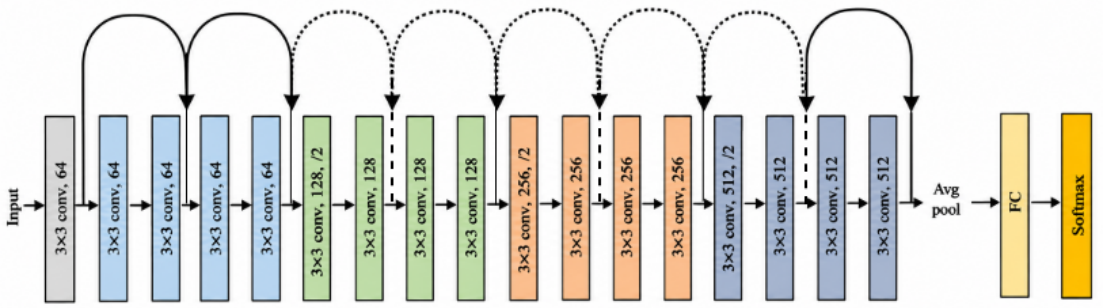

Figure 3. Architecture of the pre-trained ResNet-18 model [39]

For the experimental implementation, the torchvision library in Python is leveraged to preprocess and load the TCGA dataset. Specifically, an organized data structure is established using the ImageFolder class, while the ToTensor transformation standardizes the image inputs. To ensure a balanced representation across all categories, class distributions are rigorously analyzed by iterating over class indices and quantifying image counts for each respective label. The core architecture utilizes the ResNet-18 model tailored for the TCGA data. During experimentation, extensive hyperparameter tuning is performed to optimize model fit; variations include adjustments to the number and type of layers, kernel sizes (ranging from 3×3 to 7×7), padding, and pooling strategies (max and average pooling). Furthermore, the impact of ReLU activation, varying learning rates (0.001 to 0.1), and dropout rates (0.2 to 0.5) is explored alongside several optimizers, including stochastic gradient descent (SGD), adaptive moment estimation (Adam), and root mean square propagation (RMSprop) and regularization techniques (L_1 and L_2).

The TCGA database is partitioned into 60% for training, 25% for validation, and 15% for testing. Performance is quantified using a comprehensive suite of evaluation metrics, including accuracy, precision, recall, F1-score, and the AUC. Additionally, both standard and normalized confusion matrices are analyzed to provide a granular assessment of classification performance and to facilitate comparative benchmarking with existing literature. Computational experiments are conducted on a professional hardware environment featuring an NVIDIA Quadro T2000 mobile GPU with 4 GB GDDR5 memory. This setup is augmented by Google Colab Pro sessions, providing access to cloud-based T4 GPU resources for more intensive processing requirements.

4. RESULTS AND DISCUSSION

The primary objective of this research was to evaluate the efficacy of deep learning architectures in accurately discriminating between MSI and MSS molecular subtypes in CRC histology. The experimental framework compared the performance of a transfer-learning-based ResNet-18 benchmark against a proposed

custom CNN architecture specifically optimized for high-throughput histopathological tile analysis. The empirical results, as detailed in Table 1, demonstrate that the proposed CNN significantly outperforms the ResNet-18 model across all evaluated statistical dimensions. Specifically, the custom architecture achieved an accuracy of 87.51% and an AUC-ROC of 0.8553, representing a substantial improvement over the ResNet-18 baseline, which yielded an accuracy of 69.74% and an AUC of 0.6751. Furthermore, the F1-score of 0.9023 achieved by the proposed model confirms its robust capability to maintain predictive equilibrium, whereas ResNet-18 exhibited a marked susceptibility to the majority class bias inherent in unbalanced histopathological datasets.

Table 1. Evaluation metrics of ResNet-18 and proposed CNN models

Metric	ResNet-18	Proposed CNN
Confusion matrix	$\begin{bmatrix} 29280 & 21846 \\ 17695 & 61886 \end{bmatrix}$	$\begin{bmatrix} 39187 & 12012 \\ 4395 & 75838 \end{bmatrix}$
AUC score	0.6751	0.8553
Accuracy	0.6974	0.8751
Precision	0.7390	0.8632
Recall	0.7776	0.9452
F1-score	0.7578	0.9023

A granular analysis of the confusion matrices, illustrated in Figure 4, reveals critical insights into the clinical reliability and applicability of these models. While ResNet-18 successfully identified 29,280 true positive MSI samples, it was characterized by a high false-negative rate, misclassifying 17,695 MSI cases as MSS. From a clinical perspective, such omissions are highly detrimental, as they could potentially deprive patients of life-saving immunotherapy. In contrast, the proposed CNN model drastically mitigated these errors by correctly identifying 39,187 MSI samples and reducing false negatives to 4,395. This refinement is most evident in the recall (sensitivity) metric, which surged from 77.76% with ResNet-18 to 94.52% with the proposed architecture. Given that high sensitivity is a non-negotiable prerequisite for diagnostic screening tools, these results suggest that the proposed CNN architecture offers a more viable pathway for assisting pathologists in identifying patients who would benefit from immune checkpoint inhibitors, striking a superior balance between representative power and computational efficiency.

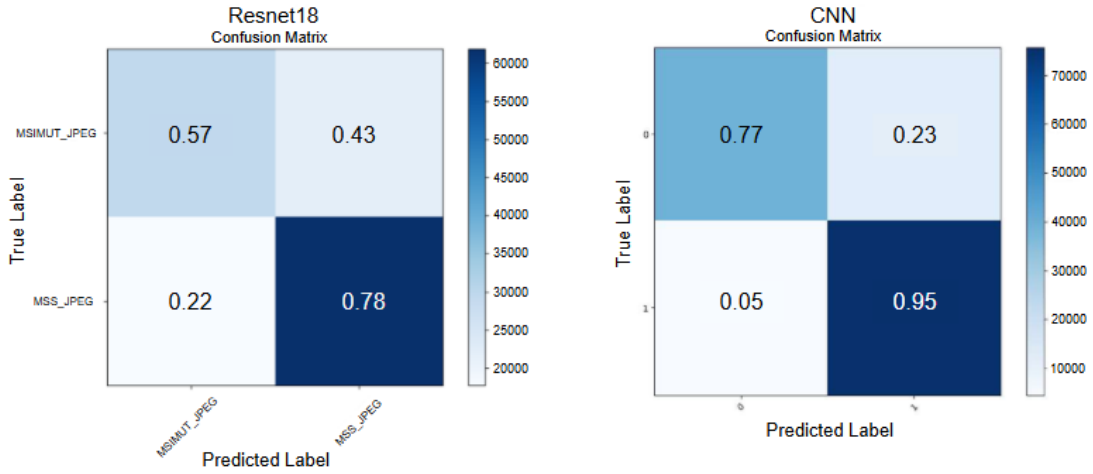

Figure 4. Normalized confusion matrix for MSI/MSS classification, illustrating the prediction accuracy across both classes

To contextualize the findings within the contemporary research landscape, this study conducted a comparative analysis with prominent studies published between 2019 and 2024. The results align closely with the foundational evidence provided by Kather *et al.* [30], who established the baseline feasibility of deep learning for MSI prediction with an AUC of approximately 0.84. Notably, the proposed CNN slightly surpasses this benchmark (AUC 0.855), reinforcing the premise that streamlined, purpose-built architectures can match or exceed the performance of massive pre-trained networks when optimized for specific

histopathological tasks. Recent architectural strategies have further diversified this field. For instance, while Yamashita *et al*. [34] demonstrated the efficacy of MobileNetV2 and ResNet variants, the study highlights that a custom CNN can achieve superior sensitivity without the prohibitive computational overhead associated with deeper networks. Similarly, Du *et al*. [42] introduced a dual-scale information approach to enhance predictive precision. While their multi-scale methodology offers high granularity, our patch-based CNN achieves a highly competitive F1-score (0.90) through a significantly more efficient implementation pipeline.

Furthermore, the methodology offers a distinct contrast to the complex classification techniques described in recent literature. The findings diverge from the two-stage framework presented by Lee *et al*. [43], which necessitates a primary tumor segmentation step followed by an Inception-ResNet-V2 classifier. Although Lee *et al*. [43] reported improved F1-scores at 20× magnification, the model maintains consistent performance across the dataset without the prerequisite of computationally expensive pre-segmentation. Finally, compared to the knowledge distillation model proposed by Ke *et al*. [44], which focuses on intricate patch-level sorting, the end-to-end CNN approach facilitates a more direct and seamless clinical workflow for slide categorization.

5. CONCLUSION

Overall, this study places a particular emphasis on CRC, a leading cause of cancer-related morbidity and mortality, to delve into the epidemiological patterns, risk factors, and advancements in diagnosis and treatment. By exploring the potential of deep learning models for categorizing MSI and MSS in CRC, this study demonstrated the capability of deep learning models to accurately discriminate between MSI and MSS in the case of CRC. This study has limitations, primarily the class imbalance (MSS predominance) and the reliance solely on the TCGA dataset. Consequently, external validation on independent cohorts is required to rule out site-specific biases and confirm generalizability. Future work will also incorporate explainability techniques (e.g., gradient-weighted class activation mapping (Grad-CAM)) to visualize the histological features driving the model's predictions, thereby enhancing clinical trust. Further research is warranted to validate actual findings in large, prospective clinical trials and address potential challenges. Integrating interpretable models and addressing potential biases are crucial next steps. The future works include also: addressing potential biases and enhancing model interpretability are essential for ethical considerations. Exploration of alternative deep learning architectures and data augmentation techniques could further improve performance. Nevertheless, this study provides compelling evidence for the transformative potential of deep learning in enhancing CRC diagnosis and management, ultimately contributing to improved patient outcomes.

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AUTHOR CONTRIBUTIONS STATEMENT

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C : **C**onceptualization
M : **M**ethodology
So : **So**ftware
Va : **Va**lidation
Fo : **Fo**rmal Analysis
I : **I**nvestigation
R : **R**esources
D : **D**ata Curation
O : Writing - **O**riginal Draft
E : Writing - Review & **E**diting
Vi : **Vi**sualization
Su : **Su**pervision
P : **P**roject Administration
Fu : **Fu**nding Acquisition

CONFLICT OF INTEREST STATEMENT

Authors state no conflict of interest.

DATA AVAILABILITY

The data that support the findings of this study are available upon reasonable request to the corresponding author, [SEI].

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