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ARTIFICIAL INTELLIGENCE IN BREAST CANCER IMMUNE INFILTRATION PATHOLOGY IMAGING

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Abstract. Breast cancer prognosis and treatment response depend on tumor-infiltrating lymphocytes (TILs) within the tumor microenvironment, but manual assessment of H&E-stained slides suffers from inter-observer variability and labor intensity. This review paper synthesizes current evidence on artificial intelligence (AI), particularly deep learning, for automated TIL quantification in whole slide images (WSIs) of breast cancer pathology. The review examines convolutional neural networks (e.g., U-Net, StarDist) for cell detection and segmentation, foundation models (e.g., ECTIL) for label-efficient learning, open-source pipelines (e.g., QuPath), and multimodal approaches integrating spatial TIL patterns, tertiary lymphoid structures, and multiomics data. AI methods show strong concordance with expert pathologist assessments across multi-center cohorts, provide independent prognostic value for patient survival, and offer improved prediction of neoadjuvant chemotherapy response over manual scoring. Label-efficient foundation models reduce annotation demands while preserving clinical utility, and spatial analyses of TIL distribution and cellular interactions yield additional biological insights. Challenges encompass staining variability, generalization across breast cancer subtypes and populations, and clinical workflow integration. Future directions include standardization efforts, regulatory approval pathways, real-time decision support for pathologists, and broader application to multiplexed immune profiling for immunotherapy guidance. This review highlights AI's potential to standardize TIL assessment and advance precision breast cancer pathology.

Keywords: Breast cancer, tumor-infiltrating lymphocytes (TILs), artificial intelligence, deep learning, computational pathology, whole slide imaging, stromal TILs, foundation models, U-Net, StarDist, QuPath, spatial analysis, digital pathology, neoadjuvant chemotherapy, immunotherapy biomarkers, tumor microenvironment.

1. Introduction.

Breast cancer remains one of the most prevalent malignancies worldwide, with heterogeneous biological behavior and variable responses to treatment. The tumor microenvironment, particularly the presence and spatial distribution of tumor-infiltrating lymphocytes (TILs), has emerged as a critical determinant of prognosis and therapeutic response [1], [2], [3]. TILs represent the host immune response to cancer and serve as important biomarkers, especially in triple-negative breast cancer (TNBC) and HER2-positive subtypes [4], [5].

Traditional pathological assessment of TILs relies on manual evaluation of H&E-stained slides by expert pathologists following standardized guidelines. However, this approach is labor-intensive, time-consuming, and subject to inter-observer variability, limiting its widespread clinical adoption [6], [7]. The advent of digital pathology and whole slide imaging (WSI) has created opportunities for computational analysis of histopathology images at scale [8].

Artificial intelligence, particularly deep learning approaches, has demonstrated remarkable success in medical image analysis tasks. In the context of breast cancer pathology, AI-powered methods offer the potential to automate TIL quantification, improve reproducibility, and extract complex spatial features that may not be readily apparent to human observers [9], [10], [11]. Over the past five years, numerous studies have developed and validated AI algorithms for

automated TIL assessment, with promising results in terms of concordance with pathologists and clinical utility [12], [13], [14].

This comprehensive literature review synthesizes current evidence on AI applications for immune infiltration assessment in breast cancer pathology images. We examine the technical methodologies employed, clinical validation strategies, prognostic and predictive value, and discuss the path toward clinical implementation of these technologies.

2. Background and Theoretical Foundations

2.1 Biological Significance of Tumor-Infiltrating Lymphocytes

Tumor-infiltrating lymphocytes represent a diverse population of immune cells, predominantly T lymphocytes, that migrate into the tumor microenvironment. Their presence reflects active immune surveillance and anti-tumor immune responses. In breast cancer, high TIL levels have been associated with improved survival outcomes, particularly in aggressive subtypes such as TNBC and HER2-positive disease [15], [16]. TILs also predict response to neoadjuvant chemotherapy and immunotherapy, making them valuable biomarkers for treatment selection [3], [17].

The International TILs Working Group has established standardized guidelines for visual TIL assessment, recommending evaluation of stromal TILs (sTILs) as the percentage of tumor stroma occupied by mononuclear inflammatory cells [18]. Despite these guidelines, inter-observer variability remains a significant challenge, with studies reporting moderate agreement between pathologists [6].

2.2 Digital Pathology and Computational Image Analysis

The transition from glass slides to digital whole slide images has enabled computational analysis of histopathology at unprecedented scale and resolution. WSIs typically contain billions of pixels and capture tissue architecture, cellular morphology, and spatial relationships [19]. Computational pathology leverages image processing and machine learning algorithms to extract quantitative features from these images, enabling objective and reproducible tissue analysis [20], [21].

Early computational approaches to TIL quantification relied on traditional image processing techniques, including color deconvolution, thresholding, and hand-crafted feature extraction. While these methods provided some automation, they often required extensive parameter tuning and struggled with the complexity and variability of histopathology images [22].

2.3 Deep Learning in Medical Image Analysis

Deep learning, particularly convolutional neural networks (CNNs), has revolutionized medical image analysis by automatically learning hierarchical feature representations from raw image data. CNNs consist of multiple layers that progressively extract features from low-level edges and textures to high-level semantic concepts [23]. In histopathology, deep learning models have achieved expert-level performance in tasks such as tumor detection, grading, and biomarker prediction [24], [25].

Recent advances include foundation models—large-scale models pre-trained on diverse pathology datasets that can be adapted to specific tasks with minimal additional training. These models learn generalizable representations of tissue morphology, potentially reducing the need for extensive task-specific annotations [1], [26].

3. AI Methodologies and Technical Approaches

3.1 Convolutional Neural Networks for Cell Detection and Classification

The majority of AI-based TIL assessment methods employ CNNs for cell detection, segmentation, and classification. A common pipeline involves tissue segmentation to identify tumor and stromal regions, followed by cell detection and classification to distinguish lymphocytes from other cell types [3], [9], [27].

Several studies have utilized U-Net architectures for tissue segmentation. Rasic et al. developed a supervised deep learning pipeline using a U-Net-based network for tissue segmentation, followed by an MA-Net-based network to classify tissue into tumor, stroma, necrosis, and non-invasive epithelial regions [3]. A multiclassification StarDist network was then employed to detect and classify individual cells into tumor, immune, and stromal categories, enabling precise TIL quantification.

For cell detection, watershed algorithms and specialized architectures like StarDist have been widely adopted. Fanucci et al. employed a convolutional neural network (CNN11) with eight hidden layers, previously trained to assign cells into four categories: tumor cells, lymphocytes, stromal cells, and other cells [29]. This approach achieved superior performance compared to manual pathologist scoring in predicting pathologic complete response (pCR) to neoadjuvant chemotherapy.

3.2 Foundation Models and Label-Efficient Approaches

A significant challenge in developing AI models for pathology is the requirement for large annotated datasets, which are expensive and time-consuming to generate. Recent work has explored foundation models and label-efficient learning strategies to address this limitation [1], [26].

Schirris et al. introduced ECTIL (label-efficient Computational stromal TIL assessment model), which leverages a pathology foundation model to extract morphological features from WSIs and directly regresses TIL scores from these features [1]. Remarkably, ECTIL can be trained in only ten minutes on hundredfold fewer pathologist annotations compared to conventional approaches, while maintaining strong concordance with expert pathologists across multiple external cohorts. This label-efficient approach represents a paradigm shift, making AI-based TIL assessment more accessible and practical for clinical deployment.

3.3 Open-Source Tools and Automated Pipelines

Several studies have developed open-source tools to democratize access to AI-based TIL assessment. Shephard et al. created an automated pipeline for TIL scoring in breast cancer, providing a transparent and accessible solution [9], [14]. Similarly, Tafavvoghi et al. developed a machine learning pipeline using QuPath, an open-source platform for digital pathology analysis, enabling researchers and clinicians to implement automated TIL assessment without proprietary software [24].

Bai et al. contributed an open-source, automated TIL algorithm specifically designed for triple-negative breast cancer, addressing the need for subtype-specific tools [13]. These open-source initiatives are critical for validation, reproducibility, and widespread adoption of AI technologies in clinical practice.

3.4 Multimodal and Multiplexed Approaches

Beyond standard H&E imaging, some studies have explored multimodal approaches integrating immunohistochemistry (IHC) and molecular data. Kobayashi et al. investigated AI-based quantification of TILs using both H&E and IHC-stained slides in TNBC, potentially providing more comprehensive characterization of immune infiltration [6]. Lu et al. integrated deep learning-based TIL characterization with multiomics data, demonstrating the potential for combining imaging and molecular features to improve prognostic models [7].

Zerdes et al. employed machine learning to characterize the tumor-immune microenvironment at spatial and multiplexed resolution in early breast cancer, analyzing data from the EORTC 10994/BIG 1-00 randomized phase III trial with long-term follow-up [19]. This approach enables simultaneous assessment of multiple immune cell types and their spatial relationships, providing a more comprehensive view of the tumor microenvironment.

4. Clinical Validation and Prognostic Value

4.1 Concordance with Expert Pathologists

A critical requirement for clinical adoption of AI-based TIL assessment is demonstrating concordance with expert pathologist scoring. Multiple studies have reported strong correlations between AI-derived and manual TIL scores [1], [2], [3], [29].

Schirris et al. demonstrated that ECTIL achieved concordance with expert pathologists across five heterogeneous external cohorts, with correlation coefficients ranging from r=0.54 to r=0.74 and AUROC values of 0.80 to 0.94 [1]. When trained on all available cohorts (ECTIL-combined), performance improved further on a held-out test set (r=0.69, AUROC=0.85). These results demonstrate robust generalization across diverse patient populations and imaging conditions.

Cho et al. found that assistance with an AI-powered TIL analyzer significantly reduced inter-observer variation in pathologic scoring of TILs in breast cancer, suggesting that AI tools can serve as decision support systems to improve consistency among pathologists [22]. Arab et al. conducted a systematic comparison of machine learning algorithms for TIL scoring using whole slide images, benchmarking performance against pathologists and identifying optimal approaches [25].

4.2 Prognostic Value for Overall Survival

Multiple studies have demonstrated that AI-derived TIL scores provide independent prognostic value for overall survival in breast cancer patients [1], [2], [4], [20].

In the ECTIL study, multivariable Cox regression analyses indicated that every 10% increase in ECTIL scores was associated with improved overall survival independent of

Study	Model/Method	Correlation with Pathologist	Clinical Outcome	Dataset Size
Schirris et al. 2025 [1]	ECTIL (Foundation model)	r=0.54-0.74, AUROC=0.80-0.94	HR 0.86 for OS (p<0.01)	2,340 patients, 6 cohorts
Rasic et al. 2025 [3]	U-Net + MA-Net + StarDist	Matches pathologist scores	Independent predictor of NACT response	200 patients
Fanucci et al. 2023 [29]	CNN11 (QuPath)	r=0.606 (p<0.0001)	AUC 0.709 for pCR prediction	113 patients (SWOG S0800)
González-Farré et al. 2023 [2]	smsTIL (Deep learning)	Validated against experts	Associated with prognosis	Not specified
Xi et al. 2025 [4]	Spatial distribution analysis	Not specified	Prognostic value in luminal BC	Not specified

clinicopathological variables (HR 0.86, p<0.01), similar to the pathologist score (HR 0.87, p<0.001) [1]. This demonstrates that AI-based TIL assessment captures clinically meaningful prognostic information comparable to expert manual evaluation.

González-Farré et al. validated a deep-learning sTIL scoring model (smsTIL) and found that automated quantification of stromal TILs was significantly associated with prognosis in breast cancer [2]. Krijgsman et al. performed quantitative whole slide assessment of tumor-infiltrating CD8-positive lymphocytes in ER-positive breast cancer and demonstrated significant associations with clinical outcomes [20].

Makhlouf et al. specifically evaluated TILs in luminal breast cancer using AI and found prognostic value even in this subtype, which traditionally shows lower TIL levels compared to TNBC [5]. Xi et al. developed a novel computational method for assessing TIL abundance and spatial distribution patterns in luminal breast cancer, demonstrating prognostic value through spatial analysis [4].

4.3 Prediction of Treatment Response

AI-based TIL assessment has shown particular promise in predicting response to neoadjuvant chemotherapy and identifying patients likely to achieve pathologic complete response (pCR) [3], [8], [17], [29].

Rasic et al. demonstrated that higher AI-assessed TIL levels were significantly associated with better response to neoadjuvant therapy and served as independent predictors of treatment response in a real-world study [3]. Lee et al. used AI-powered spatial analysis of TILs to predict response to neoadjuvant chemotherapy in TNBC, showing that spatial features provided additional predictive value beyond simple TIL density [8].

Fanucci et al. analyzed samples from the SWOG S0800 neoadjuvant chemotherapy trial and found that image analysis-based TIL measurement predicted pCR with higher accuracy (AUC 0.709) than pathologist-read sTILs (AUC 0.627) [29]. The mean pretreatment easTILs% was significantly higher in cases with pCR compared to residual disease (median 36.1% vs. 14.8%, p<0.001), and high easTILs% was independently predictive of pCR.

4.4 Multi-Center Validation Studies

Robust validation across multiple centers and diverse patient populations is essential for establishing clinical utility. Several large-scale, multi-center validation studies have been conducted [1], [12], [23].

Schirris et al. performed multi-center validation of ECTIL across 2,340 patients from six cohorts, including three randomized clinical trials [1]. The model demonstrated consistent performance across heterogeneous external cohorts, supporting its generalizability. A separate study by the same group validated an AI-based sTIL% scoring model for breast cancer H&E whole slide images across multiple centers [23].

The TIGER (Tumor InfiltratinG lymphocytes in breast cancER) challenge provided a standardized benchmark for comparing AI algorithms for TIL assessment [12], [15]. Rijthoven et al. analyzed results from the TIGER challenge, demonstrating that multiple AI approaches could achieve clinically relevant performance and serve as biomarkers for prognosis [12].

5. Comparative Analysis of AI Models

5.1 Performance Metrics and Benchmarking

Table 1 summarizes key performance characteristics of selected AI models for TIL assessment in breast cancer:

5.2 Advantages of Foundation Models

Foundation models represent a significant advancement in AI-based pathology analysis. ECTIL's label-efficient approach demonstrates that pre-trained foundation models can achieve clinical-grade performance with minimal task-specific training data [1]. This approach offers

several advantages: reduced annotation burden, faster development cycles, improved generalization across diverse datasets, and lower computational requirements for training. The ability to train ECTIL in only ten minutes on a few hundred samples contrasts sharply with traditional deep learning approaches that require thousands of annotated images and days of training time.

5.3 Comparison with Traditional Image Analysis

Several studies have compared AI-based approaches with traditional image analysis methods. Sun et al. developed a computational TIL assessment method comparable with visual reporting guidelines for TNBC, demonstrating that modern AI approaches can match or exceed the performance of earlier computational methods [21]. The shift from hand-crafted features to learned representations has been a key driver of improved performance and robustness.

6. Spatial Analysis and Tumor Microenvironment

6.1 Spatial Distribution Patterns

Beyond simple TIL density, spatial distribution patterns provide additional prognostic and biological insights. Xi et al. developed a novel computational method for assessing TIL abundance and spatial distribution patterns in luminal breast cancer, demonstrating that spatial features add prognostic value [4]. Lee et al. employed AI-powered spatial analysis to identify focal hotspot and diffuse immune subtypes of TILs in TNBC, showing that spatial clustering patterns correlate with HER2 expression and clinical outcomes [8].

Xie et al. used AI-powered spatial clustering classification to identify focal hotspot and diffuse immune subtypes of TILs in TNBC, demonstrating clinical relevance to HER2 expression [16]. This work highlights the importance of not only quantifying immune infiltration but also characterizing its spatial organization within the tumor microenvironment.

6.2 Interactions Between Immune Cells and Stromal Components

The tumor microenvironment comprises complex interactions between tumor cells, immune cells, and stromal components such as fibroblasts. Nederlof et al. investigated the spatial interplay of lymphocytes and fibroblasts in ER-positive HER2-negative breast cancer using deep neural networks [28]. They found that high TIL levels alone did not significantly improve overall survival (HR=0.76, p=0.212) except in patients who received chemotherapy (HR=0.447). However, spatial mixing of fibroblasts and TILs was associated with good prognosis (HR=0.464, p=0.013), while high fibroblasts without high TILs predicted poorer survival (HR=1.661, p=0.0303). These findings demonstrate that spatial relationships between different cell types provide critical prognostic information beyond simple cell counts.

6.3 Tertiary Lymphoid Structures

Tertiary lymphoid structures (TLS) are organized aggregates of immune cells that form in non-lymphoid tissues and are associated with favorable prognosis in several cancers. Kushnarev et al. developed AI-based methods for predicting TLS and lymphocyte immune infiltration in breast carcinomas [17]. The ability to automatically detect and quantify TLS represents an important extension of AI-based immune profiling, as these structures may indicate particularly effective anti-tumor immune responses.

7. Challenges and Limitations

7.1 Technical Challenges

Despite significant progress, several technical challenges remain. Staining variability across laboratories and scanners can affect model performance, requiring robust normalization strategies [29]. Tissue artifacts, including folds, tears, and processing artifacts, can confound automated analysis and require sophisticated quality control mechanisms [9].

The computational demands of analyzing gigapixel whole slide images remain substantial, requiring specialized hardware and efficient algorithms for clinical deployment [14]. While

foundation models reduce training requirements, inference on WSIs still requires significant computational resources.

7.2 Annotation and Ground Truth Challenges

Establishing reliable ground truth for TIL assessment is challenging due to inter-observer variability among pathologists [6], [22]. Different studies use different annotation strategies, from region-level TIL scores to pixel-level segmentation, making direct comparison difficult [27]. The lack of standardized benchmarks and publicly available annotated datasets has hindered progress, though initiatives like the TIGER challenge are addressing this gap [12].

7.3 Generalization Across Subtypes and Populations

Breast cancer is highly heterogeneous, with distinct molecular subtypes exhibiting different immune profiles. Models trained primarily on TNBC may not generalize well to ER-positive or HER2-positive subtypes [4], [5], [28]. Similarly, most studies have been conducted in Western populations, and generalization to diverse ethnic and geographic populations requires validation [1].

7.4 Clinical Integration and Workflow

Integrating AI tools into clinical pathology workflows presents practical challenges. Pathologists need user-friendly interfaces, clear visualization of AI predictions, and the ability to review and override automated assessments [22]. Regulatory approval, reimbursement, and liability considerations also affect clinical adoption [30].

8. Future Directions and Clinical Implementation

8.1 Standardization and Regulatory Approval

Standardization of AI-based TIL assessment methods is essential for clinical adoption. This includes standardized performance metrics, validation protocols, and reporting guidelines [12]. Regulatory pathways for AI-based diagnostic tools are evolving, with several AI pathology products receiving FDA clearance or CE marking in recent years [30].

8.2 Integration with Molecular and Clinical Data

Future systems will likely integrate AI-derived imaging biomarkers with molecular profiling and clinical data to provide comprehensive patient risk stratification [7], [19]. Lu et al. demonstrated the feasibility of integrating deep learning-based TIL characterization with multiomics data, showing improved prognostic models [7]. Such multimodal approaches may enable more precise treatment selection and personalized therapy.

8.3 Real-Time Clinical Decision Support

AI-based TIL assessment could be deployed as real-time decision support tools to assist pathologists during diagnostic workflows [22]. These tools could flag cases with high or low TIL levels, identify regions of interest for detailed review, and reduce inter-observer variability. The label-efficient approaches like ECTIL make such deployment more feasible by reducing the computational and data requirements [1].

8.4 Immunotherapy Patient Selection

As immunotherapy becomes increasingly important in breast cancer treatment, AI-based immune profiling could help identify patients most likely to benefit from these therapies [3], [17]. TIL levels, spatial patterns, and the presence of tertiary lymphoid structures may serve as predictive biomarkers for immunotherapy response. Prospective clinical trials incorporating AI-based TIL assessment are needed to validate this application.

8.5 Expanding to Other Immune Markers

While most current work focuses on TILs, future research will likely expand to other immune markers, including specific T cell subsets (CD4+, CD8+, regulatory T cells), macrophages, and immune checkpoint proteins [6], [20]. Multiplexed imaging technologies

combined with AI analysis could provide comprehensive immune profiling from routine tissue sections [19].

9. Conclusion

Artificial intelligence has demonstrated remarkable potential for automated, reproducible assessment of immune infiltration in breast cancer pathology images. Current AI methods achieve strong concordance with expert pathologists, provide independent prognostic value for overall survival, and predict treatment response with accuracy comparable to or exceeding manual assessment. Foundation models and label-efficient approaches are reducing the annotation burden and making AI-based TIL assessment more accessible for clinical deployment.

Key findings from this review include: (1) AI-derived TIL scores correlate strongly with expert pathologist assessments (r=0.54-0.74) across diverse cohorts; (2) AI-based TIL quantification provides independent prognostic value for overall survival (HR 0.86-0.87) comparable to manual scoring; (3) AI methods predict pathologic complete response to neoadjuvant chemotherapy with superior performance (AUC 0.709) compared to manual scoring (AUC 0.627); (4) spatial analysis of TIL distribution patterns provides additional prognostic information beyond simple density measurements; and (5) label-efficient foundation models can achieve clinical-grade performance with minimal training data.

Despite these advances, challenges remain in standardization, regulatory approval, and clinical integration. Multi-center validation studies have demonstrated robust generalization, but further work is needed to ensure performance across diverse populations and breast cancer subtypes. The development of open-source tools and standardized benchmarks is facilitating reproducibility and comparison of different approaches.

Looking forward, AI-based immune profiling is poised to become an integral component of breast cancer pathology practice. These tools have the potential to standardize TIL assessment, reduce inter-observer variability, assist pathologists in clinical decision-making, and identify patients who may benefit from immunotherapy. As the field matures, integration with molecular profiling and clinical data will enable comprehensive, multimodal risk stratification and personalized treatment selection. The transition from research to routine clinical practice will require continued collaboration between AI researchers, pathologists, oncologists, and regulatory bodies to ensure these powerful technologies deliver on their promise to improve patient outcomes.

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