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ARTICLE

Breast Cancer Prediction Using Machine Learning Models and Digital Pathology: A Systematic Review

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Abstract

Background: Breast cancer (BC) remains a paramount global health challenge, driving the oncology community toward more precise and efficient diagnostic methodologies. The advent of digital pathology has been transformative, creating an unprecedented opportunity to apply computational intelligence to the analysis of tissue samples. In this context, a diverse array of artificial intelligence (AI) techniques including traditional machine learning (ML), data-intensive deep learning (DL), and integrated hybrid learning (HL) models are being actively developed for BC prediction. However, the rapid proliferation of research in this domain has led to a fragmented understanding of their comparative strengths and practical implementation barriers. This systematic review was therefore undertaken to synthesize the existing evidence, critically appraising the distinct capabilities and limitations of ML, DL, and HL in the analysis of digital pathology images. Aim: This study aims to systematically review and analyze the application of ML, DL and HL techniques in BC prediction using digital pathology, highlighting their comparative strengths, limitations, and impact on diagnostic accuracy. Method: Following Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines, a systematic review was conducted using Google Scholar to identify relevant studies. Search terms were formulated to retrieve literature on ML and DL models in digital pathology. Articles were screened based on predefined inclusion and exclusion criteria. Result: A total of 107 articles were reviewed, including 19 on ML models, 76 on DL models, and 12 articles on HL models. The results highlight the strengths and limitations of each model technique, with DL model being the most widely used approach. Conclusion: The assessment of ML, DL, and HL approaches reveals their individual capabilities and shortcomings in predicting BC via digital pathology. DL is the current front-runner, excelling with large image sets, but the slower uptake of ML and HL methods shows room for exploration. This is particularly true for needs like model transparency, combining diverse health records, and ensuring robustness across populations. The conclusions also call for more international partnerships and greater involvement from overlooked areas, especially African nations, to make certain that innovations in computational pathology are universally applicable and address a wide range of medical environments.

Keywords: Breast Cancer, Machine Learning, Deep Learning, Hybrid Learning and Digital Pathology

1.0 Introduction

BC is one of the most prevalent cancers globally, affecting millions of women each year (Zhang *et al.,* 2024). According to GLOBOCAN, there were approximately 2.3 million new cases and 685,000 deaths due to BC in 2020, about 15% of women and 2% of men making it the leading cause of cancer-related mortality among women (Camarillo-Quesada *et al.,* 2021; Sung *et al.,* 2021). No single definitive cause has been pinpointed that explains why the disease develops in every individual (Macaulay *et al.,* 2021).

Many risk factors for BC have been identified such as genetics, hormones, (a long term hormone), age, family history increase the risk (having first degree relative like mother, sister, or daughter), lifestyle factors influence the risk (like obesity, alcohol consumption, physical inactivity) and radiation exposure (Macaulay *et al.,* 2021). Subtype of BC include hormone receptor–positive, HER2+ (human epidermal growth factor receptor 2), and triple negative (TNBC) (Chen *et al.,* 2021).

Early detection and accurate diagnosis are critical for improving treatment outcomes, yet traditional diagnostic methods, which often depend on subjective interpretations by pathologists, can lead to significant variability in diagnosis (Bray *et al.,* 2024). This variability highlights the urgent need for more standardized and objective diagnostic tools, paving the way for the integration of digital pathology and ML in clinical practice.

Digital pathology involves the digitization of traditional glass slides into whole slide images (WSIs), facilitating the application of advanced image analysis algorithms. DL models, especially convolutional neural networks (CNNs), have demonstrated proficiency in analyzing these complex images. For instance, DL has been used in segmentation and classification of epithelial and mesenchyme regions in BC histopathology WSIs with promising accuracy. This approach employs a multi-scale, multi-level network structure that integrates feature maps from various resolutions, effectively modeling both local cellular and global tissue-level features (Huang *et al.,* 2024).

The application of AI in BC diagnosis has been the subject of numerous systematic reviews. A review published in January 2023 shows various AI applications in BC diagnosis, noting that while several studies have demonstrated the value of AI, there remains a lack of systematization, with each study appearing to be conducted uniquely (Uzsahim *et al.,* 2022). Another paper from December 2022 emphasized the importance of DL in BC imaging, discussing how CNNs have become state-of-the-art tools for digital pathology image analysis in BC (Guillén-Rondon *et al.,* 2019).

The availability of public datasets has significantly propelled research in this domain. A systematic review was impactful for cancer diagnosis in the year 2022 and gave an overview of computational and digital pathology in BC and DL. The paper began by reviewing public datasets related to BC diagnosis, highlighting their critical role in developing and validating ML models (Iqbal *et al.,* 2022). New strides in digital pathology technologies have made it possible for the utilization of ML and DL paradigms in the computational analysis and classification of histopathological imagery leading to high potential for improvement of diagnosis accuracy (Gurcan *et al.,* 2009). These models' characteristics make it possible to define previously overlooked patterns of BC histology, which will enhance the rates of early detection.

Despite the significant advancements and potential benefits of integrating DL with digital pathology for BC, several challenges and problems still need to be addressed such as variability in pathology slides due to differences in tissue preparation, staining protocols, and slide scanning processes, obtaining consistent and accurate annotations from expert pathologists can be time-consuming and expensive, scarcity of labeled data hinders the training of DL models that require large amounts of labeled data to achieve high performance, DL models are often criticized for their lack of interpretability and explainability, pathology slides can contain artifacts such as bubbles, folds, and staining inconsistencies, and DL models may inadvertently learn and propagate biases present in the training data (Amgad *et al.,* 2023; Amgad *et al.,* 2024; Liu *et al.,* 2023; McCaffrey *et al.,* 2024; Nigam *et al.,* 2024; Rong *et al.,* 2023; Verdicchio *et al.,* 2023) etc**.** To address these issues, this study undertakes a systematic review to examine the which models applied in digital pathology for BC, highlight which models are most predominant, and analyze where they have been deployed. Furthermore, the review underscores the pressing need for greater regional collaboration and inclusivity in research efforts, to ensure that solutions developed are robust, generalizable, and globally applicable.

2.0 Materials and Methods

The systematic review was conducted using PRISMA steps (Keele 2007; Khan *et al.,* 2008; Sung *et al.,* 2021). Search terms included: BC, DL, ML, digital pathology or combination of BC, ML, DL, and digital pathology. Searches were conducted in Google Scholar database and only relevant articles were identified. In particular, articles were included only if they were carried out on BC as applied to ML, DL and digital pathology, articles that demonstrate

an experiment and show results, article that is either journal or a conference proceeding and article written in English language. Exclusion criteria were based on irrelevant articles i.e. articles that does not have anything to do with search terms, articles with poor study design, articles without experiments i.e. without results and finally articles which are either thesis or dissertation were all excluded. Some of the information were extracted from the articles: title, year, country, articles type, methods, algorithm class, dataset source, dataset types, sample size, features, results, strength and limitation.

3.0 Results

3.1 PRISMA flow chart

As presented in Figure 1, 558 potentially relevant articles were identified using the final search terms. After removing irrelevant studies and perusing titles for uniqueness, the number of studies was reduced to 377. Of these, 181 were screened by title and abstract, and 74 were excluded based on the exclusion criteria. Ultimately, 107 articles met the eligibility criteria and were considered for this study.

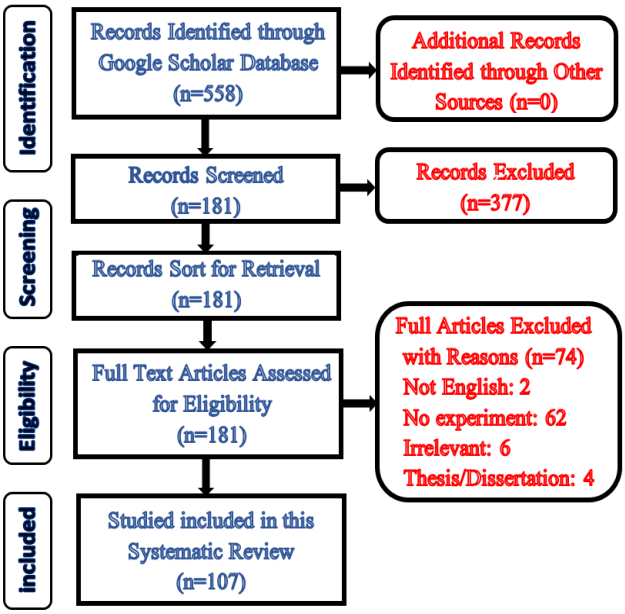

Figure 1: PRISMA flow chart

3.2 Taxonomy of computational models

The taxonomy of computational models in BC digital pathology therefore illustrates not only the evolution from traditional ML to advanced DL methods**,** but also the rising interest in HL that can bridge the gap between interpretability, accuracy, and clinical applicability. Out of the 107 articles reviewed, the distribution of BC digital pathology models shown that 19 articles focused on ML models, 76 articles on DL models, and 12 articles on HL models. A breakdown of the methods used in these models is depicted in Table 1.

3.3 Evaluating BC prediction models

In BC prediction and diagnosis, ML**,** DL**,** and HL approaches have been widely explored, especially with the advancement of digital pathology. Each paradigm offers unique advantages in analyzing clinical and histopathological data, while also presenting notable limitations. Understanding their strengths and weaknesses shown in Table 2 is crucial for identifying suitable models that can improve early detection, diagnosis, and survival prediction in BC patients.

Table 1: Taxonomy computational models used for predicting BC based on digital pathology

Model Techniques	References	Number of Studies	Distribution (%)
ML	(Aloraidi *et al.,* 2014; Beevi *et al.,* 2016; Chen *et al.,* 2023; Cordeiro *et al.,* 2018; Das *et al.,* 2020; Estévez *et al.*, 2002; Filipczuk *et al.,* 2010; Kost *et al.,* 2016; Naik *et al., 2*022; Nguyen *et al.,* 2017; Ortega-Ruiz *et al.,* 2020; Polyakova & Krylov, 2022; Pourakpour &	19	17.76%

	Ghassemian, 2015; Stanitsas *et al.,* 2020; Tashk *et al.,* 2015; Tutac *et al.,* 2009; Veta et *al.,* 2016; Yoder *et al.,* 2022)		
DL	(Ahmad *et al.,* 2022; Amgad *et al.,* 2019; Balkenhol *et al.*, 2019; Bhavsar *et al.,* 2024; Bidart *et al.,* 2018; Boudjelal *et al.* , 2022; Bozdağ & Talu, 2021; Cai *et al.,* 2019; Cano & Cruz-Roa, 2020; Chatterjee & Krishna, 2019; Chen *et al.,* 2016; Dahake & Shinde, 2023; Dai *et al.* 2021; Das *et al.,* 2021; de Bel *et al.,* 2022; Djagba & Mbouobda, 2024; Dong *et al.,* 2014; Gella, 2024; Golatkar *et al.,* 2018; Gulye *et al.,* 2024; Guo *et al.,* 2019; Hadush *et al.,* 2020; He *et al.,* 2018; Hradel *et al.,* 2020; Huang *et al.,* 2024; Jafarbiglo *et al.,* 2018; Jamaluddin *et al.,* 2020; Kasturi *et al.,* 2022; Kate & Shukla, 2021; Kovalev *et al.,* 2016; Lakshmanan *et al.,* 2022; Li & Chen, 2021; Liu *et al.,* 2024; Łowicki *et al.,* 2022; McIntire *et al.,* 2018; Meng *et al.,* 2019; Mercan *et al.,* 2019; Mercan *et al.,* 2020; Mirjahanmardi *et al.,* 2021; Mridha *et al.,* 2021; Munien & Viriri, 2021; Ovtcharov *et al.,* 2018; Paramanandam *et al.,* 2016; Pati *et al.,* 2022; Pedraza *et al.,* 2024; Qian, 2022; Qu *et al.,* 2024; Retamero *et al.,* 2024; Saini & Susan, 2022; Salvi *et al.,* 2019; Sebai *et al.,* 2020; Shahidi, 2021; Sheikh *et al.,* 2020; Singh *et al.,* 2024; Sohail *et al.,* 2020; Subramanian *et al.,* 2020; Subramanian *et al.,* 2022; Subramanian *et al.,* 2022; Sui *et al.,* 2021; Tang & Cai, 2024; Teoh *et al.,* 2024; van Dooijeweert *et al.,* 2024; Vani *et al.,* 2022; Veta *et al.,* 2015; Vo & Trang, 2022; Wetstein *et al.,* 2019; Wollmann *et al.,* 2018; Xu *et al.,* 2014; Żejmo *et al.,* 2017; Zhan *et al.,* 2022; Zhou *et al.,* 2019)	76	71.03%
HL	(Kadhim *et al.,* 2023; Karuppasamy *et al.,* 2022; Liang *et al.,* 2019; Malavade *et al.,* 2018; Pei *et al.,* 2019; Raj & Nair, 2023; Scognamiglio *et al.,* 2021; Wa *et al.*, 2017; Wolf *et al.,* 2024; Yang *et al., 2*023; Zakariapour *et al.,* 2017; Zhu & Lu, 2022)	12	11.21%

Table 2: Strengths and weaknesses of the models (ML, DL, and HL)

Model	**Explanation**	**Examples**	**Strengths**	**Weaknesses**
ML	It is a subset of AI that enables systems to learn patterns from data and make decisions or predictions without being explicitly programmed.	Decision Tree (DT), Extra Tree (ET), Support Vector Machine (SVM), K-Nearest Neighbor (KNN), Random Forest (RF), Logistic Regression (LR), Classification and Regression Tree (CART) etc.	Works well with small to medium-sized datasets. Easier to interpret and explain results. It has faster training time and lower computation cost.	Limited in handling unstructured data. Feature engineering is required. Performance may show diminishing return with complex data
DL	It is a specialized branch of ML that uses ANN with multiple layers to automatically learn hierarchical features from raw data input	Convolutional Neural Networks (CNNs), Recurrent Neural Networks (RNNs).	Excellent at extracting features from complex, high-dimensional data. Performs well with image and text data (e.g., WSI, mammograms). Can model nonlinear and intricate relationships	Requires large labeled datasets. Difficult to interpret ("black box" models). High training time and resource-intensive. Risk of overfitting if not properly regularized.

HL	Combines ML techniques with DL models or integrates two or more AI approaches. Often used to balance feature learning and classification strengths	CNNs +SVM CNN+GNN	Improved prediction accuracy by leveraging strengths of both ML and DL. Adaptable to diverse data types. Enhances model robustness and generalization. Can reduce overfitting by combining complementary models.	Increased model complexity and computational cost. Harder to interpret and debug. Requires expertise in multiple techniques. Model optimization is time-consuming.

3.4 Analysis of contribution of studies by country

To understand the geographical distribution of research efforts in BC digital pathology, the reviewed articles were analyzed based on their country of origin. The contributions reflect the global spread of scientific engagement, with some nations demonstrating higher research output and leadership in the field. The 107 reviewed articles originated from 28 countries. A single paper was contributed by each of the following: Austria, Belarus, Brazil, Canada, Colombia, Delhi, Egypt, Germany, Hong Kong, Iraq, Japan, Jordan, Korea, Pakistan, Romania, and Ukraine. Two (2) papers each came from Italy, Malaysia, Poland, Spain, and Switzerland. Iran, Turkey and the UK contributed four (4) papers each, while the Netherlands contributed six (6). India and China contributed 13 and 18 papers, respectively, and the USA was the largest contributor with 32 papers.

4.0 Discussion

This systematic review examined the application of ML models in predicting BC using digital pathology. The analysis revealed a significant research focus in developed countries where digital pathology tools are widely adopted. Of the reviewed studies, DL emerged as the dominant approach, with 76 studies, followed by traditional ML and HL. DL's prevalence can be attributed to its ability to effectively handle complex histopathological image data, Tradition ML still remains valuable in low resource settings where computational power and large dataset may be limited. An emerging trend is the use of HL that combine the strengths of both ML and DL to balance performance, complexity and generalizability. However, a significant gap was also observed in the geographical distribution of studies with just only one (1) study originating

from Africa, underscoring the need for more inclusive and regionally diverse research.

This study adhered to the PRISMA guidelines, ensuring a rigorous and standardized review process. The classification of ML models based on methodologies provides a clear framework for researchers to identify suitable models for specific applications. The review highlights the importance of refining data augmentation techniques, and exploring hybridized methods to enhance model stability and generalizability across diverse clinical settings. By addressing these limitations, this study offers valuable insights to guide the development of more effective ML models for BC prediction using digital pathology.

5.0 Conclusion

This study's review of ML, DL, and HL techniques underscores their distinct strengths and limitations in BC prediction using digital pathology. While DL currently dominates due to its effectiveness with large-scale histopathological image datasets, the relatively limited adoption of ML and HL indicates opportunities for further research, particularly in areas where interpretability, integration with clinical data, and model generalizability are critical. Importantly, the findings highlight the need for greater collaborative research efforts and increased contributions from underrepresented regions, especially African countries**,** to ensure that advancements in computational pathology are globally inclusive and responsive to diverse healthcare contexts.

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