Assessing Deep Learning Models in Breast Cancer Molecular Marker Prediction: A Systematic Review and Meta-Analysis

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Abstracts: The advancements in artificial intelligence (AI) and its incorporation into clinical care have improved the prognosis, diagnosis and treatment to an extent. Whole slide imaging and multi-omics data analysis sum up into a promising new sub-specialty of computation pathology. Pathology of cancer need quick diagnosis to initiate intervention and AI has gained much importance in this field. This paper aimed to evaluate the diagnostic accuracy of different deep learning models for predicting molecular markers of breast cancer. This study was conducted by following the Preferred Reporting Items for Systematic Review and Meta-Analyses of Diagnostic Test Accuracy Studies (PRISMA-DTA) guidelines. We searched the research articles according to research aims from PubMed, EMBASE and Ovid MEDLINE. For assessment of risk bias, "Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2)" was used that collect application concerns in different areas. The RevMan version 5.4.0 was used for pooled analysis. Sensitivity and specificity were calculated with 95% confidence interval (CIs) for pooling the effect size. The included 9 studies have data of specificity and sensitivity for diagnostic method that help in the detection or interpretation of breast cancer risk or biomarkers through DP model (CNN). The deep learning model showed a generally good accuracy scores for detection of breast cancer through imaging. The area under the SROC curve was 0.940. In contrast to the general detection, DL seems to be more sensitive and specified in diagnosing key molecular biomarkers (PR, ER, HER2 and Ki67) among BC patients. Also, the paper provides links to functional code repositories and ends with the exploration of limitations and potential of deep learning-based diagnostic systems.

Keywords: Artificial Intelligence, Deep Learning, Breast cancer detection, Convolutional Neural Network

1. INTRODUCTION

Breast cancer (BC) is reported as one of prevalent type of cancer diagnosed among women and second most common cause of mortality from cancer globally. In other words, breast cancer accounts for one-third of all female cancer diseases. Approximately 2 million new cases of breast cancer and 0.6 million mortalities were reported in 2018 (1, 2). The majority of types of breast cancers are estrogen and/or progesterone receptor-positive. Thus, biomolecular markers of tumor linked pathogenesis help to diagnose type of breast cancer among patients and their classification (3). On the basis of expression levels of these biomarkers, the breast cancer patients are classified into different subtypes that become possible by molecular biomarker profiling of breast cancer (4). The classification of BC subtypes reported unique therapeutic, prognostic and diagnostic features. Major molecular markers of breast cancer are progesterone receptor (PR), Estrogen receptor (ER), Ki67 and human epidermal growth factor receptor 2 (HER2) (5).

Drugs such as immunotherapeutic drugs interfere with the signaling of these receptors and normally are effective on patients who have receptor-positive tumors. When the patient samples arrive at the microscope slides for staining, pathologists usually render a visual diagnosis by use of H&E staining; although additional staining for molecular markers for confirmation or subtyping may be conducted (6). For determining receptor status, the Immunohistochemistry is used, but IHC staining is both times taking and expensive. In addition, the quality of the tests may differ because of the distinction of the tissue, the tissue-sampling personnel skills and the nature of the specialists. Interpretations made by pathologists are also vulnerable to leading to wrong diagnoses, thereby being a cause of misdiagnosis (7). It was found that about 20% of the current IHC-based receptor and PR test results are false which means that patients are given suboptimal

treatments. The current data based on morphological stains indicate the receptor status of biomarkers or predictors of BC (8).

Computational pathology (CP) assist in rapid diagnosis of breast cancer, optimizing clinical process, and reliability of results due to informational integration provided by complex digital networks such as MRI and CT (9, 10). However, here are some challenges that CP encounters; how to integrate data effectively and in the right manner, how they transform this data, and or process this data given the limited processing power of computers and also the usual ethical parameters that we meet in different fields from economy, law and others (11). Computational pathology is process of applying deep learning algorithms that analyze and interpret the histopathological images. A variety of names are used in pathology, such as "AI," "Computational Pathology," and "Computerized Pathology." The computation pathology is applied to examine the slide images of tissue samples (1). These slides' data can be stored in cloud systems, where pathologists can readily study those with the assistance of artificial intelligence in some cases. Numerous AI algorithms have previously been developed by researchers to aid in ailment diagnosis, particularly in medical imaging (12).

This study aimed to evaluate the role of deep learning (DL) in diagnosis of breast cancer from routine imaging modalities such as MRI and CT. For this purpose, we have characterized the images on basis of modalities used for detection of breast cancer's pathology. This study focused to highlight the role of DP for diagnosis of breast cancer risks and molecular markers through pooled analysis of primary studies.

2. METHODS

2.1 Search Strategy & Eligibility Criteria

This study was conducted by following the Preferred Reporting Items for Systematic Review and Meta-Analyses of Diagnostic Test Accuracy Studies (PRISMA-DTA) guidelines (10).

We searched the research articles according to research aims from PubMed, EMBASE and Ovid MEDLINE by applying PRISMA guidelines. The keywords used for data search were Using AND/OR logic, a combination of keywords was used to conduct the search: (((diagnostic OR malignancy OR tumor OR growth)) OR (deep learning OR machine learning)). The data search was limited to January 2015 to July 2024. We included only those studies for pooled analysis if those met the inclusion criteria on basis of PICO of this study. Only those studies were included having

1. Patient Population diagnosed with breast cancer
2. Index test by using deep learning models to predict the status of BC on basis of key molecular biomarkers (PR, ER, HER2, and Ki67)
3. Comparisons with other biopsies or surgical extraction of sample for biomolecular analysis for prediction of biomarkers
4. Enough data to predict status of BC on basis of images of key molecular biomarkers by staining rather than biopsies.

We excluded the studies that met the following exclusion criteria:

1. Studies having population with other type of cancers or incompatible with the PICO criteria as mentioned above.
2. Already published Narrative Reviews, systematic, and meta-analysis, conference abstracts, case reports, comments, and letters to editors.
3. Studies not using AI based methods for prediction of BC biomarkers.

Two independent reviewers screened the titles and abstracts of selected articles and then full text for data extraction. The information they collected include author's name, year of publication, country, study sample, type of breast cancer patients, type of DL model, and outcomes such as accuracy, specificity and sensitivity. Possible disagreements were discussed and resolved through a consensus.

2.2 Risk Bias Assessment & Statistical analysis

For assessment of risk bias, "Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2)" was used that collect application concerns in different areas. The answer of each domain was given as low risk, high risk and unclear risk to assess the applicability concerns (13). Two reviewers independently assessed the risk bias by using QUADAS-2 tool. The RevMan version 5.4.0 was used for pooled analysis. Sensitivity and specificity were calculated with 95% confidence interval (CIs) for pooling the effect size. To integrate the effect estimates and account for any potential study heterogeneity, a random-effect model was employed. For a meta-analysis, certain studies lacked sufficient data. By hand, we determined the necessary parameters by utilizing each molecular biomarker's sensitivity, specificity, and number of positive and negative classes. The area under the curve (AUC) was determined by plotting the summary receiver operating characteristic curve (SROC). Using a forest plot, we displayed the pooled effect size.

3. RESULTS

3.1 Study Selection

The electronic databases yielded 514 research articles and 213 citations were removed due to duplicates, automation tool rejection and non-full text availability. About 301 research articles were screened. Only 233 research articles were full text and assessed for eligibility criteria. The included studies were published between 2015 and 2020. Among those, only 9 studies met inclusion criteria, as mentioned in figure 1.

3.2 Study Characteristics

The following article presents an overview of nine articles that focus on employment of AI algorithms in breast cancer diagnosis for various subtypes such as HER2 positive, HER2 enriched, and other molecular subtypes. Such studies performed the use of various imaging modalities such as Fine Needle Aspirate (FNA) photographs, ultrasound images and MRI images, with the number of samples ranging from 77 to 6011 images.
Following main types of AI models are discussed in these studies.

1. Research demonstrated 98.25% of accuracy with certain models such as Neural Networks (FNN and CNN)
2. Deep Learning Models (CNN, CLSTM- commonly utilized for HER2 + breast cancer, these models were reported to perform poorly with accuracy ranging from 0.58 ~ 89.7).
3. Lasso Regression Models- Maximum accuracy of 91.53% which includes studies on her2 enriched luminal A and B subtypes.

These models exhibited high true positive rate (TPR) and true negative rate (TNR) depending on the subtype of breast cancer and imaging modality, with the highest TPR reaching 95.61% and TNR of 96.49%

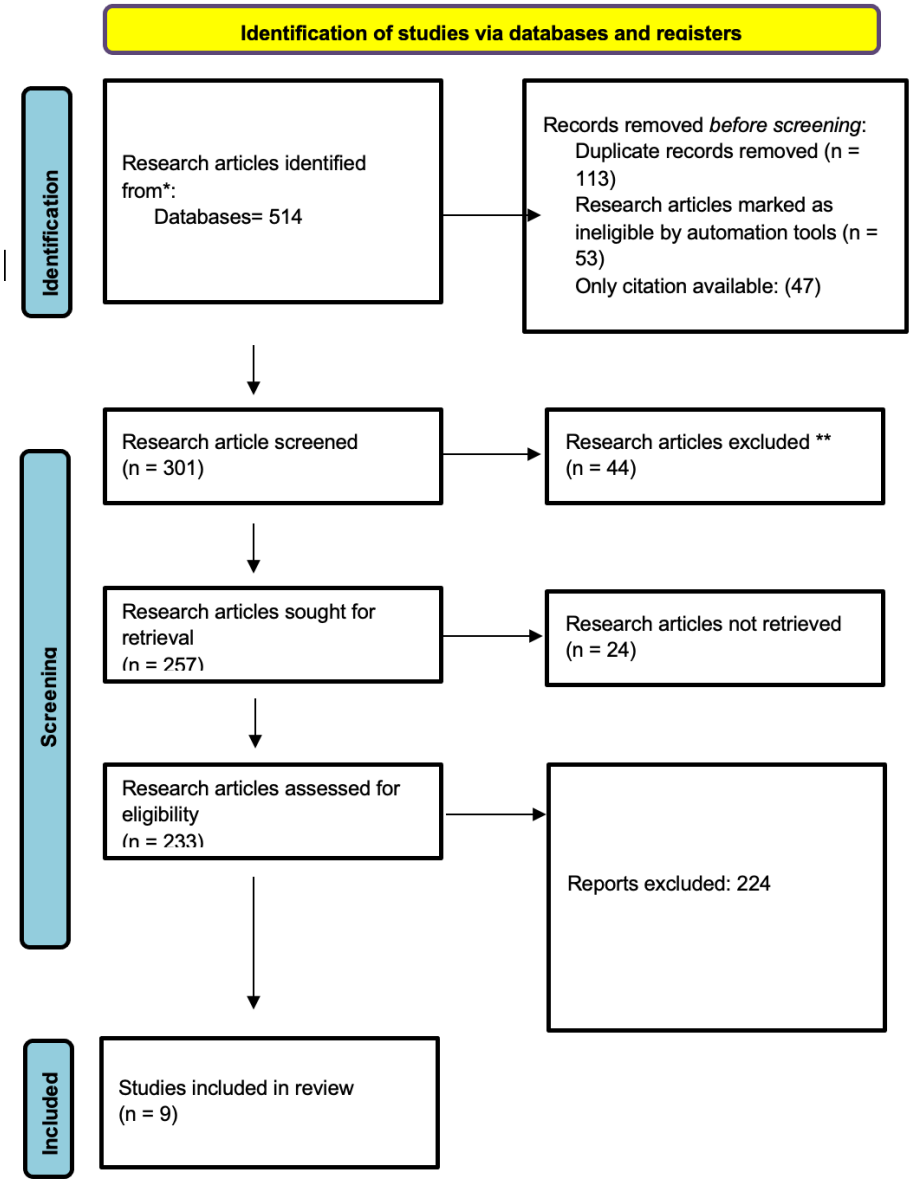

Figure 1: Flow chart of PRISMA for screening and selection of articles for systematic and meta-analysis of deep learning methods for predicting molecular markers for breast cancer study

3.3 Risk bias Assessment

The risk bias assessment of included studies using QUADAS-2 tool were shown in Figure 2 (a) and (b).

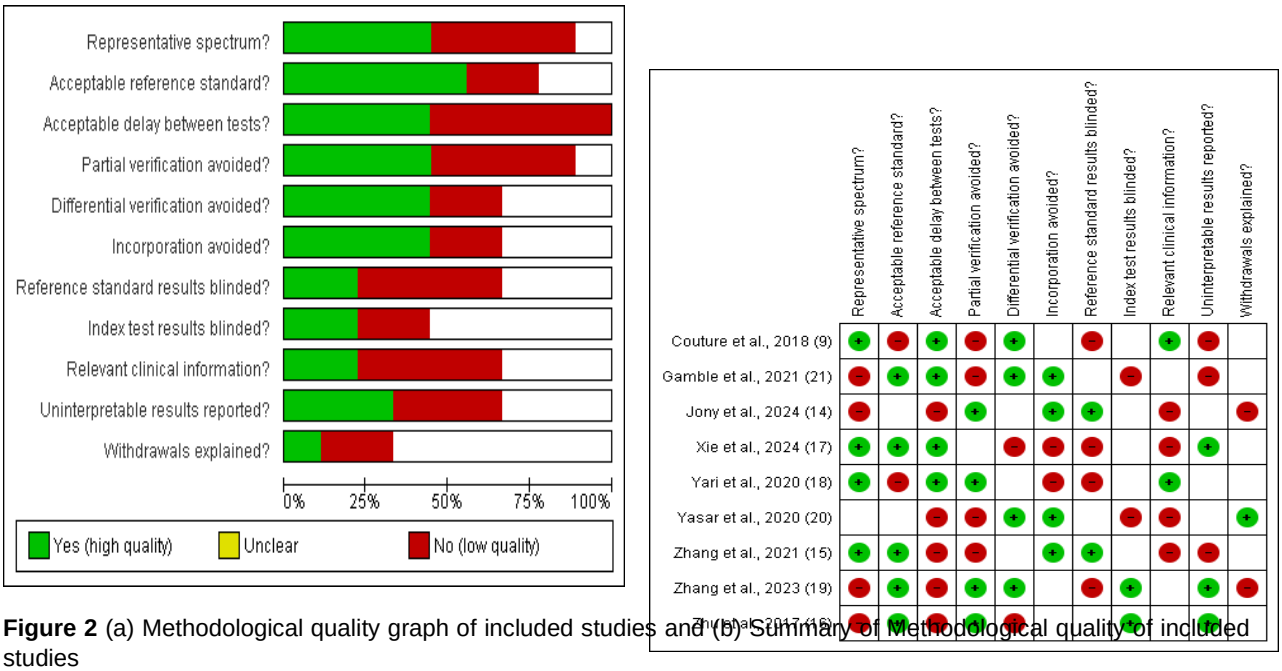

Figure 2 (a) Methodological quality graph of included studies and (b) Summary of Methodological quality of included studies

Table 1: Characteristics of included studies

Author, year	Country	Study sample	Type of breast cancer	Type of model	Accuracy	Specificity	Sensitivity
Jony et al., 2024 (14)	Bangladesh	569 Fine Needle Aspirate (FNA) photographs	Breast cancer	Neural Network (FNN), Convolutional Neural Network (CNN), Long Short-Term Memory (LSTM)	CNN: 98.25%,	96.49%,	95.61%.
Zhang et al., 2021 (15)	China	2,822 ultrasound images	HER2 (+) subtype breast cancer	CNN deep learning model (DLM)	89.7% (false negative: 10.4%)	86.9%	91.3%
Zhu et al., 2017 (16)	USA	270 MRI images	Breast cancer molecular subtypes	Network architectures	0.58	0.78	0.82
Xie et al., 2024 (17)	China	366 MRI images	HER2-positive breast cancer	CNN and convolutional long-short-term-memory (CLSTM)	0.64	0.89	0.84
Couture et al., 2018 (9)	USA	288 images	HER2-positive breast cancer	Convolutional Neural Network (CNN)	84%	76%	88%
Yari et al., 2020 (18)	Norway	6011 images	HER2-positive breast cancer	Convolutional Neural Network (CNN)	98%	85.1	91.3
Zhang et al., 2023 (19)	Netherlands	3360 paired cases	HER2-enriched breast cancer	Multi-modal deep learning	81.1%, TN: 575	75.2%	83.7
Yasar et al., 2020 (20)	Turkey	77 images	HER2-enriched Luminal A, Luminal B subtypes of breast cancer	Lasso Regression Model	91.53		
Gamble et al., 2021 (21)	USA	3274 slides,	ER/PR/HER2 breast cancer	Deep Learning System	0.86	0.89	0.76

3.4 Pooled Analysis

The included 9 studies (Table 1) has data of specificity and sensitivity for diagnostic method that help in the detection or interpretation of breast cancer risk or biomarkers through DP model (CNN) as presented in the forest plot (Figure 4) and SROC plot (Figure 5). As shown in figure 4, the SORC plot with curved area AUC showed the high specificity and sensitivity values for deep learning models, exhibiting it as reliable and quick tool for accurate diagnosis. The deep learning model showed a generally good accuracy scores for detection of breast cancer through imaging. Figure 5's area under the SROC curve was 0.940. In contrast to the general detection, DL seems to be more sensitive and specified in diagnosing key molecular biomarkers (PR, ER, HER2 and Ki67) among BC patients.

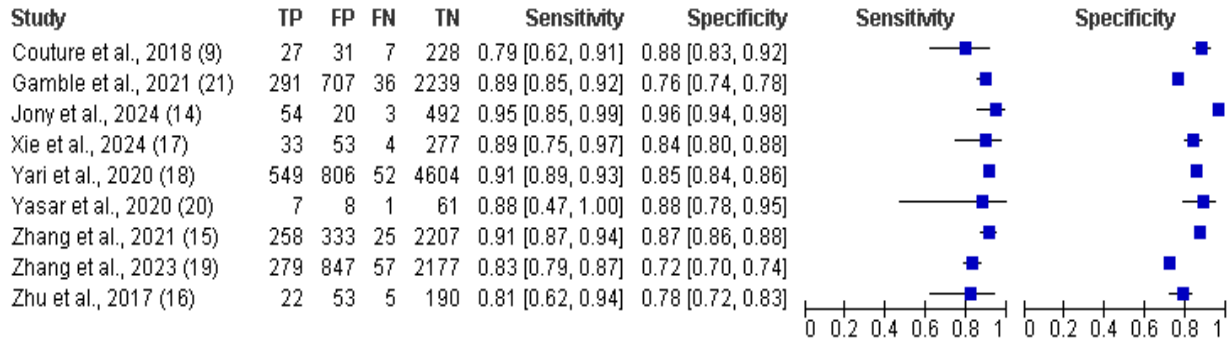

Figure 4: Forest plot of sensitivity and specificity of DL from each included study for diagnosis of BC markers

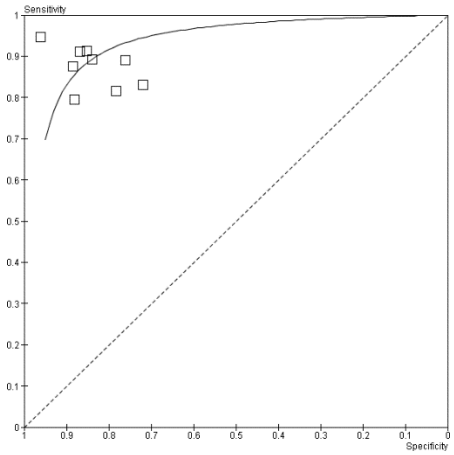

Figure no. 5: SROC plot of included studies

4. DISCUSSION

This study aimed to evaluate the diagnostic accuracy of different deep learning model for predicting molecular markers of breast cancer. Through 9 included studies, the findings reported that AI is effective in providing quick, reliable and robust results related to diagnosis of histological slides images rather than biomolecular analysis. As mentioned above, the strategies that are associated with increased chances of early diagnoses and treatment of breast cancer greatly led to the elevation of patient's life span. Age-standardized breast cancer mortality has reduced from the 1980s to 2020 by 40 percent in developed countries (22). Diagnosis and management approaches of AI have resulted in annual saving of 2 to 4 per cent mortality in several countries. Assuming a 2. 5 percent annual decrease in breast cancer mortality, it is envisaged that an extra 2. About five million patients will live from the year 2020 to the year 2040 (23).

Breast cancer in particular is an ongoing worldwide problem: over 600 thousand women died from it in 2018 (24). Specific on screening mammography, it significantly decreases mortality rate by about 20–40%, and is supported by various health organizations for screening of malignant tumors. Studies based on the cancer surveillance systems of provinces have revealed the trends of breast cancer mortality and survival In North West of Iran. Despite a somewhat superior breast cancer survival rate than one might expect in Iran, survival rates are not up to the level seen in developed world. Breast cancer in the studies done on women from Iran was reported to be the third most frequent cancer. The highest incidence rate is reported from developed countries, particularly the US and western Europe and the lowest from East Asia. Several factors like increase of the aged people, changes in their living styles, late pregnancies and no health facilities and obesity has been considered as causes of cancers and mortality in Iran. On the other hand the agricultural nations are found to report a low rates (2).

Thus, it is vital to discover primary risk indicators to increase the chances of diagnosing BC and containing the disease development. Investigate has directed its attention to risk factors and one of the examples is 17 immune genes that were discovered by Zhang et al. (25) reported the BC biomarkers that have capacity to predict breast cancer. From these genes, they established a survival prediction system with the aid of artificial intelligence. To the identification of the interplay of genetic variants and demographic risk factors for accurate prediction of BRCA and other breast cancers, Behravan et al. (26) used XGBoost. Similar to Liu et al. (27) XGBoost was used to find out the risk factors for menopausal women. Similarly, in a study of risk factors and assessment models for breast cancer by Sharma et al, special focus was given to more frequent examination for high-risk patients. A number of electronic assisted solutions available in the market help to improve examination's speeds and lighten radiologists' burdens. For instance, a commercial AI diagnostic tool was employed for identification of breast cancer using mammograms, to classify patients in such a way to reduce the number of patients referred to radiology. H&E staining and IHC annotated models can be used for multi-instance learning (MIL) where MIL has been recently employed for predicting ML based histopathology.

Another consideration in the design of the models used in the healthcare field is interpretability which helps in winning the confidence of medical experts in the systems that have been developed. In turn, work that makes use of interpretability as a tool can identify areas of interest in an image capturing and is indispensable for understanding and verifying predictions made by a model. The field of interpretable AI is important when it comes to improving the level of interpretability of such opaque models as DNNs. Interpretation methods for black box models are ICE, GS, and Shapley values for interpretation of predictions. The current and future work shall be aimed at establishing what kind of AI methods have the potential of being explained and used effectively in the medical diagnosis with more research continuously being conducted on the subject.AI was spotted to provide high accuracy in automatic diagnosis of breast cancer in the recent past. Of the different AI methods, deep learning (DL) is particularly suitable for analysis of high dimensional patterns like the medical images (28). A number of articles were searched for concerning diagnosis of breast cancer and most of the sourced articles were from Nature database with a special emphasis on breast cancer. Particular emphasis was placed on recent papers, which should also include the source codes for the given problems, made publicly available (29).

However, even getting stunning performances, the use of DL has several significant disadvantages. One important problem is a training data requirement which is usually large and may be difficult to obtain in the medical practice. Preparation of this training data entails labelling by pathologists – an expensive and time-consuming process. Besides, there is often a question of the number of pathologists that can be dedicated to such work. It is also worth mentioning that most of the used DL methods are deterministic. Even though entered well-trained DL models demonstrate satisfactory results when using samples which were not used during training, they may fail with out of distribution (OOD) samples. While the examples given may seem trivial they are highly appropriate in safety critical domains such as the diagnosis of a medical condition

where it is not possible to give wrong information. Hence, there needs to be the creation of DL models that will incorporate uncertainty in measurements of the certainty level of predictions. While using uncertainty-aware DL has been studied in numerous works, it is still a motivating line of research.

However, there are some issues that DL can face and, at the same time, there are some opportunities to use it for solving complex tasks. For instance, in the CAMELYON16 challenge (30), DL-based for diagnosis of disease in hematoxylin and eosin (H&E)-stained whole slide images (WSI), the respective detection rate of cancer reached high level of 92%. 4%, compared to 73.2% by pathologists. International initiatives in computational pathology are intended to increase the efficiency of diagnosis and treatment of diseases as well as to decrease the expenses associated with treatment. Promoting breast cancer diagnosis systems based on DL is an essential part of the same program (31). In breast cancer diagnosis, DL has been the subject of several articles published in the last one and half to two decades. All the same, there is evidence of considerable potential for further development of approaches to teaching. A subfield of ML research, XAI is concerned with the process to break down and better understand how DL models function. Since medical diagnosis is highly sensitive to safety, elaborate assessments of DL-based diagnostic systems are needed. This analysis is based on annotated data, which are scarce and remain the key area of study for researchers. Thus, improving the quantity of labeled data is seen as an area of further development (31, 32)

5. CONCLUSION

In this review, therefore, we sought to review recent studies on breast cancer diagnosis based on DL through image modalities. A plethora of available DL techniques such as the CNNs, RNNs, CNNs, GoogLeNet, ResNet, and ANNs have been used in the literature for this purpose. In addition to a restatement of currently available DL based diagnostic techniques, we presented datasets that belong to the public domain along with sources codes repositories. These advancements points towards an enhanced progress in the use of DL for diagnosing breast cancer. Nevertheless, these findings pointed out that enhancements in the reliability of these automated systems are still needed before they can be implemented almost anywhere. In the years that have passed, DL has evolved to a great extent and model representation capability is not usually an issue. The first is the problem of lack of training samples; it is still a hot topic in the field. There are several strategies that can be undertaken to overcome the difficulty associated with the lack of data. One of them is collection of high-quality public data but it is often unachievable. Another approach is the image composition, where new samples are generated by combining background and foreground images in different techniques. Another technique that can be applied as data restriction solving option is transfer learning. It is efficient to make transfer learning domain-aware because, for example, pre-trained models, trained to process images from ImageNet, can act poorly when dealing with medical ones. For example, in some cases, several feature splits within a certain range corresponding to the target feature distribution are more effective to pre-training on them.

Even relying on the image data for the DL models may not sufficient. There is hope in cases whereby there is a suggestion that a single use case can lead to the enhancement of performance through integrating several types of data. Also, by applying the idea of an ensemble of DL models, the performance and reliability of the decision-making will be significantly improved. However, the main problem is to decrease the complexity of the models which are combined in ensemble-based approaches still keeping the required performance and controlling computational resources. Therefore, making training efficient, knowledge distillation approaches could be helpful in ensemble methods that do not lead to too much loss of performance

Conflict of Interest

I declare that the research presented in this manuscript was not conducted at Amazon, Oklahoma State University and Dr. L.H. Hiranandani Hospital and is not related to any work or interests associated with Amazon, Oklahoma State University and Dr. L.H. Hiranandani Hospital

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