Value of genomics- and radiomics-based machine learning models in the identification of breast cancer molecular subtypes: a systematic review and meta-analysis

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Background: In the era of precision therapy, early classification of breast cancer (BRCA) molecular subtypes has clinical significance for disease management and prognosis. We explored the accuracy of machine learning (ML) models for early classification of BRCA molecular subtypes through a systematic review of the literature currently available.

Methods: We retrieved relevant studies published in PubMed, EMBASE, Cochrane, and Web of Science until 15 April 2022. A prediction model risk of bias assessment tool (PROBAST) was applied for the assessment of risk of bias of a genomics-based ML model, and the Radiomics Quality Score (RQS) was simultaneously used to evaluate the quality of this radiomics-based ML model. A random effects model was adopted to analyze the predictive accuracy of genomics-based ML and radiomics-based ML for Luminal A, Luminal B, Basal-like or triple-negative breast cancer (TNBC), and human epidermal growth factor receptor 2 (HER2). The PROSPERO of our study was prospectively registered (CRD42022333611).

Results: Of the 38 studies were selected for analysis, 14 ML models were based on gene-transcriptomic, with only 4 external validations; and 43 ML models were based on radiomics, with only 14 external validations. Meta-analysis results showed that c-statistic values of the ML based on radiomics for the identification of BRCA molecular subtypes Luminal A, Luminal B, Basal-like or TNBC, and HER2 were 0.76 [95% confidence interval (CI): 0.60–0.96], 0.78 (95% CI: 0.69–0.87), 0.89 (95% CI: 0.83–0.91), and 0.83 (95% CI: 0.81–0.86), respectively. The c-statistic values of ML based on the gene-transcriptomic analysis cohort for the identification of the previously described BRCA molecular subtypes were 0.96 (95% CI: 0.93–0.99), 0.96 (95% CI: 0.93–0.99), 0.98 (95% CI: 0.95–1.00), and 0.97 (95% CI: 0.96–0.98) respectively. Additionally, the sensitivity of the ML model based on radiomics for each molecular subtype ranged from 0.79 to 0.85, while the sensitivity of the ML model based on gene-transcriptomic was between 0.92 and 0.99.

Conclusions: Both radiomics and gene transcriptomics produced ideal effects on BRCA molecular subtype prediction. Compared with radiomics, gene transcriptomics yielded better prediction results, but radiomics was simpler and more convenient from a clinical point of view.

Keywords: Breast cancer (BRCA); gene transcriptomics; machine learning (ML); molecular typing; radiomics

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Introduction

Breast cancer (BRCA) has overtaken lung cancer to become the world's most prevalent malignant tumor and the top cause of death for women; the number of deaths accounts for 6.6% of all cancer deaths (1). Statistically, the number of BRCA cases constituted one-third of the total female cancer victims in 2022 (2). With increasing populations and increased risk factors, the burden of BRCA is rising substantially worldwide. Based on the incidence trend of BRCA predicted by the GLOBOCAN database, there will be an estimated 9.1 million new cases by 2070 (3). Early screening and accurate diagnosis are currently regarded as the most effective management of BRCA (4). Core needle biopsy or fine-needle aspiration biopsy is extensively used to detect BRCA, and for suspicious cases, tissue biopsy is used to confirm relevant features. However, as high as 31% of BRCA cases are misdiagnosed using the described methods (4). The heterogeneity in the molecular characteristics and cellular composition of BRCA is well known, and increasingly studies have indicated the significance of BRCA molecular subtypes in the diagnosis, treatment, and prognosis of the disease (5-7). The establishment of molecular profiles of adenocarcinomas has generated common molecular subtypes [Luminal A, Luminal B, Basal-like, and human epidermal growth factor receptor 2 (HER2)], which has enabled the phenotypic

heterogeneity of BRCA subtypes to be determined and also personalized management regimens using subtype-specific indications (8). Luminal A and B are two relatively mild molecular subtypes of BRCA with better prognoses, and both are sensitive to endocrine therapy. The level of Ki67-labeled standardized proliferation is the most significant feature to distinguish the two (9). HER2-positive BRCA is characterized by its high invasiveness and high recurrence, with increased incidence year by year. Studies have indicated an association of its high recurrence with activation of the PI3K-Akt-mTOR signaling pathway and the stimulation of glycolysis (10). Immunohistochemistry and FISH are widely applied in HER2 molecular subtyping, and new detection assays are emerging. Among them, the more applicable methods include quantum dot-based probes, mass spectrometry, and next-generation sequencing (11).

Heterogeneity is associated with shorter disease-free survival and overall survival outcomes (12). Recent studies have reported that BRCA also presents metastatic heterogeneity, which is inseparable from its receptor status (13), and the receptor status determines the molecular subtype of BRCA. Single-cell gene expression analysis (14), genome and transcriptome analyses (15), and lineage tracing (16) can all be utilized to explore the underlying molecular mechanisms, allowing more systematic and in-depth research on the molecular heterogeneity of BRCA. Parker *et al.* have developed five intrinsic subtypes using 50 genes (PAM50), which are consistent with the molecular subtypes of BRCA predicted by hierarchical clustering and microarray analyses (17), and they are of great significance in clinical diagnosis and prognostic prediction. Achieving more accurate predictive performance with fewer but more representative genes is also the goal of researchers. Interestingly, the molecular characteristics of each subtype can also be dynamically changed. For example, triple-negative BRCA itself is multi-heterogeneous, with basal-like characteristics in one of its four specific subtypes (18). This indicates that being able to predict changes in the BRCA molecular subtype will assist in identifying novel therapeutic targets and the transformation of refractory BRCA to treatable BRCA. Despite intrinsic molecular subtypes providing the principle biological classifications of BRCA, the subtype assignment of individuals is influenced by the techniques used, as well as the study cohort composition. How to efficiently and precisely predict molecular subtypes of BRCA has emerged as an ongoing focus of study of BRCA

Highlight box

Key findings
- Data from this systematic review and meta-analysis support radiomics and gene-transcriptomic ML model analyses, which have ideal predictive accuracy in determining early the BRCA molecular subtypes.

What is known and what is new?
- Machine learning models are increasingly being used to predict the molecular subtypes of breast cancer. However, its application is still controversial.
- This paper comprehensively analyzes the application value of the machine learning prediction model based on radiomics and gene transcriptomics in predicting the molecular subtypes of breast cancer.

What is the implication, and what should change now?
- Our study confirmed the application value of machine learning in predicting the molecular subtypes of breast cancer and providing favorable evidence for finding new ways to improve the clinical treatment of breast cancer, also promoting the development of modern precision medicine.

at the molecular level.

Specific treatment for different tumor types has always been a challenge, and great efforts have been made to maximize efficacy and minimize the toxicity of therapies. Therefore, improvement in cancer classification is key to advances in cancer treatment. Progress has been achieved in classification prediction technology through the use of machine learning (ML), which integrates computer science, statistics, and biomedical research (19). ML based on the algorithm of the input data as the premise applies computer analysis to identify data attributes and trends, and learns from previous experience to predict output values with a certain degree of accuracy, and as a semi-automated process is both cost- and labor-saving. It is classified into supervised learning and unsupervised learning. The former finds a pattern in the training set to perform known classification and regression of the data set, and the latter clusters and reduces the dimensionality with the data set only (20). ML can handle large-scale, complex, and diverse data, which is attributed to the formulation of algorithms. The algorithms used for ML in the medical field include support vector machine (SVM), neural network (NN), deep learning, and latent variable models (21). ML has been applied in drug research and development (22), robotic surgery and decision-making (23), and imaging diagnosis (24), and multiple current studies have pointed out that ML is vitally significant in cancer research, especially cancers of the lung, colorectum, and prostate (14,25-27). ML has also attracted widespread attention for BRCA diagnosis and management, such as BRCA tumor identification (28), BRCA neoadjuvant efficacy prediction (29), and BRCA medical imaging analyses (radiomics analysis and histopathological image analysis) (30,31).

Radiomics is an emerging field of medical imaging, based on extracting and quantifying high-throughput feature information from medical images that fail in identification using traditional imaging examination methods. It builds a bridge between medical imaging and personalized diagnosis and treatment, and it has the potential to become an alternative to invasive biopsy (32). However, genetic expression evaluation remains the gold standard (32). How to efficiently extract differentially expressed genes from gene databases and assess their impact on prognosis remain to be solved. Meanwhile, exploring more convenient, noninvasive, and accurate genetic detection methods and tumor markers is also a current research focus, leading to various ML models of gene transcriptomics for BRCA being developed. Such models have the potential to improve biomarker identification of the diverse BRCA molecular subtypes, thereby offering novel insight into the differential pathogenesis of these subtypes and the selection and research of more targeted personalized and systemic treatment regimens. Hence, for clinicians, ML models based on radiomics and gene transcriptomics are helpful and significant in improving diagnostic performance and developing reasonable diagnosis and treatment protocols. Nevertheless, the predictive accuracy of current ML models in identifying BRCA molecular subtypes differs due to their diverse mathematical algorithms and the differences in the classifications of modeling variables. Many studies have shown that meta-analysis is of great significant in determining the prediction accuracy of ML models (33,34). Therefore, we conducted this systematic review to analyze the accuracy of various ML models in the identification of BRCA molecular subtypes based on the same classification of modeling variables.

Given the potential of ML in BRCA molecular subtype prediction, this meta-analysis was conducted to explore its application significance of ML, and to provide some practical reference for accurate diagnostic auxiliary system and medically intelligent diagnosis of BRCA. Furthermore, we also compared the prediction accuracy between radiomics-based and genomics-based ML. We present the article in accordance with the MOOSE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5986/rc).

Methods

This project was prospectively registered with PROSPERO (CRD42022333611).

Literature search

We searched the PubMed, Embase, Cochrane, and Web of Science databases from inception to April 15, 2022. No restrictions were set on region or language, and the retrieval method used subject headings plus free words. Subject headings included Breast Neoplasms and Machine Learning. More search strategies are shown in Table S1.

Inclusion and exclusion criteria

We formulated the criteria for inclusion and exclusion of studies according to the PICO principle. Inclusion criteria included: (I) subjects had pathologically confirmed BRCA

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with relevant molecular subtypes as previously described [Luminal A, Luminal B, HER2 overexpression (Basal-like) and normal]; (II) interventions: (i) ML studies for classifying BRCA molecular subtypes based on radiomics [i.e., mammography (MMG), digital breast tomosynthesis (DBT), ultrasound (US), computed tomography, and magnetic resonance imaging (MRI)], genometrics or other pathological data; (ii) original research designs were cohort studies, case-control and nested case-control studies, or case–cohort studies; (III) the comparison is between different molecular subtypes; (IV) outcomes: the classification performance of the constructed ML model was assessed, and the assessment indicators included one of the following: c-statistic, sensitivity, specificity, calibration curve, accuracy, F1 score, and confusion matrix.

Exclusion criteria were: (I) subjects did not have any of the molecular subtypes as stated in the inclusion criterion; (II) interventions: (i) only difference analysis was performed rather than the construction of an integrated ML model, (ii) studies with small overall samples; (III) outcomes: classification performance of the constructed ML model was not evaluated.

Literature screening and data extraction

We imported the retrieved literature into Endnote, and after ruling out duplicate articles, the original studies that satisfied the criteria were initially screened using titles and abstracts. Selected studies were downloaded for subsequent analysis by intensive reading, and the final included studies for this research were determined.

A standard information extraction spreadsheet was created prior to data extraction, which included article title, author names, publication year, countries of authors, research type, sample source, molecular subtypes, number of samples for training set subtype detection, the total number of samples for the training set, external validation, samples for testing set subtype detection, overall samples for external validation, model types, model overfitting considerations (bootstrap/k-fold cross-validation), and outcome indicators.

Literature screening and data extraction were performed independently by Yiwen Zhang and Guofeng Li, and post-technical cross-validation was performed. Two investigators, Yuzhuo Bai and Wenqing Bian, assisted when there were discrepancies between the first two reviewers.

Quality assessment

Because we adopted gene-transcriptomic and radiomics ML models, we used the Radiomics Quality Score (RQS) [28975929] and PROBAST [PMID: 31585960] for quality assessment of the ML models.

The RQS assesses the quality from the image extraction process to the ML construction process, with 16 assessment items and 36 points in total. The items of the Prospective study registered in a trial database and the Validation are very strict, with 7 and 5 points at most, respectively. If there was no external validation, a penalty of 5 points was given plus no points awarded, which was very severe for radiometrics. Additionally, due to the extraction process of radiomics generating a large number of predictor variables, the assessment of the Feature reduction or adjustment for multiple testing was also very severe. If neither measure was implemented, a penalty of 3 points was given plus no points awarded.

We assessed the quality of the gene- transcriptome ML model using PROBAST, which contains a large number of items involving four distinct aspects: subjects, predictors, outcomes, and statistical analysis, reflecting the overall risk of bias and overall usability. The four domains consisted of 2, 3, 6, and 9 questions with specificity, respectively, each with 3 responses (yes/maybe yes, no/maybe no, and no information). A domain is considered to be at high risk if it contains at ≥1 question with a response of no or maybe no. A low-risk domain is determined when it contains all responses with yes or maybe yes. If each aspect is determined as low risk, the overall risk of bias is rated as low, whereas ≥1 domain is considered as high risk, and the overall risk of bias is judged as high.

Risk of bias assessment/quality assessment was performed by two independent investigators, with post-technical cross-validation. A third investigator assisted in judgment when discrepancies arose between the first two reviewers.

Outcome indicators

In our systematic review, the outcome indicators were c-statistic, reflecting the accuracy of the ML model, and the sensitivity and specificity summed by true positive (TP), false positive (FP), false negative (FN), and true negative (TN). Of these, TP, FP, FN and TN in the original studies can be extracted using the following methods: Method 1—

direct report of the original studies (e.g., multi-classification confusion matrix); Method 2—extract the sensitivity and specificity of the original studies, and combine the number of cases with corresponding molecular subtypes and the total number of samples; Method 3—original research provided receiver operating characteristic (ROC) curves, in light of the principle of the optimal Youden index, the sensitivity and specificity were extracted using Origin 2020 software as per Method 2.

Statistical analysis

A meta-analysis was conducted on the indicators (c-statistic, sensitivity, and specificity) to assess the ML models. If c-statistic was depleted 95% confidence interval (CI) and standard error (SE), we referred to the study of Debray *et al.* (35) to estimate its SE. Given the differences among the variables included in each ML model and inconsistent parameters, For the c-statistic, the random effects model was preferred for meta-analyses. A bi-variable mixed-effect model was used for meta-analysis of sensitivity and specificity. The current meta-analysis was implemented using R4.2.0 (R development Core Team, Vienna, http://www.R-project.org).

Results

Literature search

Our literature search initially identified 3,421 articles from the PubMed, Embase, Cochrane, and Web of Science databases. After deleting 1,093 duplicate articles, 2,328 articles were screened out based on their titles and abstracts, leaving 98 potentially eligible articles. Of them, 10 did not have full text available. No eligible articles were found after searching the references of the remaining 88 articles. After a full-text review of the provisionally eligible articles, 50 were excluded either due to the lack of BRCA molecular subtype or unclear sample size, and so 38 articles were finally included in this study for subsequent systematic review and meta-analysis (*Table 1* and *Table 2*). The screening processes are shown in *Figure 1*.

Characteristics of the included studies

The 38 included studies recruited 17,913 BRCA patients, with 57 ML models, which were mainly multi-classification models, covering molecular subtypes Luminal A, Luminal B, HER2 overexpression, triple negative, and normal. In 28 studies (43 ML models) the BRCA molecular subtypes were identified based on a radiomics ML, and the remaining 11 studies (14 ML models) identified the molecular subtypes by gene transcriptomics ML. There were 22 case-control studies, 3 cohort studies, and 13 retrospective studies. Among all studies, the training sets of 7 studies adopted ≥2 tools for validation, there were 9 articles covering the 4 molecular subtypes, 5 articles classified HER2 subtype only, 5 classified the triple-negative breast cancer (TNBC) subtype, and 5 covered the HER2 + TNBC subtypes. The testing sets of 3 articles used dual-tool analysis, there were 4 articles covering the 4 molecular subtypes, 3 articles classified the HER2 subtype only, and 1 for the TNBC subtype. The number of registrations in the training set of the validation gene transcriptomics group was 3,019; 4 studies performed external validation, and the total sample size for external validation was 2,849. The number of registrations in the training set of the radiomics group was 4,048; 13 studies conducted external validation, and the total sample size was 2,610. In the training set, 9 studies used the logistic regression (LR) model, 7 used the SVM model, 3 used the Naive Bayes (NB) model, 5 used the random forest (RF) model, and 4 used the artificial neural network (ANN) model; in the testing set, 4 studies used the LR model, 2 used the ANN model, 4 used the SVM model, and 1 used the RF model.

Quality assessment

Among the 14 ML models based on genomics, we assessed the quality of studies as per PROBAST. The assessment results revealed that the risk of bias was mostly caused by the lack of external validation and the small number of modeling samples, which was reflected in the statistical analysis of PROBAST assessment (*Figure 2*). Among the 43 ML models based on radiomics, only 14 (32.56%) models conducted external validation, and there was no clearly described Prospective study registered in a trial database. Comprehensive assessment results of other items showed an average score of 14.6 for 43 models (standard deviation: 5.3).

Value of ML for predicting BRCA molecular subtype

C-statistic

Meta-analyses of the c-statistic were conducted using a random effects model, which revealed that the c-statistic values by radiomics ML for Luminal A, Luminal B, Basal-

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Table 1 Basic characteristics of included articles

First author	Publication year	Country/ Region	Study design	Molecular subtype	Type of model	Model evaluation metric
Ma M (36)	2022	China	Cohort	TNBC, HER2	Support vector machines, random forest	Radiomics
Leithner D (37)	2020	USA	Database research	HER2, luminal A, luminal B, TN	Artificial neural network	Radiomics
Chen L (38)	2019	China	Database research	Basal, HER2, luminal A, luminal B	Support vector machines, random forest	Gene
Zhao Y (39)	2020	USA	Database research	Basal, HER2, luminal A, luminal B	Random forest	Gene
Huang CC (40)	2013	Taiwan	UNC Microarray database research	Basal, HER2, luminal A, luminal B	Logistic regression, least square method	Gene
Yu Z (41)	2020	China	TCGA database research	Basal, HER2, luminal A, luminal B, Normal-like	Naive Bayes, random forest, support vector machines	Gene
Liu T (42)	2022	China	TCGA-BRCA database research	Basal, HER2, luminal A, luminal B	Logistic regression, fusion model, CNN, DNN	Gene
Adabor ES (43)	2019	USA	Case-control	HER2	Naive Bayes, random forest	Gene
Huang Y (44)	2021	China	Database research	HER2	Support vector machines, logistic regression	Radiomics
Lopez-Rincon A (45)	2020	Netherlands	Database research	TN	Gradient boosting, random forest, logistic regression, passive aggressive, SGDClassifier, support vector machines (linear), ridge regression	Gene
Wu J (46)	2021	USA	Database research	TNBC	K-Nearest neighbors, Naive Bayes, deep learning, support vector machines	Gene
Mohaiminul Islam M (47)	2020	Canada	METABRIC database research	Basal, HER2, luminal A, luminal B	Support vector machines, random forest	Gene
Wilson TR (48)	2014	USA	Database research	HER2	Random forest	Gene
Seo MK (49)	2020	Korea	Database research	Basal, HER2, luminal A, luminal B	Random forest	Gene
Couture HD (50)	2018	USA	Case-control	Basal, HER2, luminal A, luminal B Normal-like	Deep learning	Radiomics
Fan M (51)	2017	China	Cohort	HER2, luminal A, luminal B Basal-like	Logistic regression	Radiomics
Jiang M (52)	2021	China	Database research	TN, HER2, luminal A, luminal B	Artificial neural network	Radiomics
Moon WK (53)	2015	South Korea	Case-control	TNBC	Support vector machines	Radiomics
Talari ACS (54)	2019	UK	Case-control	TNBC, HER2, luminal A, luminal B	Linear discriminant method	Radiomics
Nie Z (55)	2021	China	Case-control	HER2		Radiomics
Zhou J (56)	2019	China	Case-control	HER2	Logistic regression	Radiomics

Table 1 (*continued*)

Table 1 (*continued*)

First author	Publication year	Country/ Region	Study design	Molecular subtype	Type of model	Model evaluation metric
Fan M (57)	2019	China	Case-control	Basal, HER2, luminal A, luminal B	Random forest	Radiomics
Wu M (58)	2011	China	Case-control	Basal, HER2, luminal A, luminal B	Deep learning	Radiomics
Zhou J (59)	2021	China	Case-control	HER2	Support vector machines	Radiomics
Wu T (60)	2019	China	Case-control	TN	Logistic regression	Radiomics
Ma W (61)	2019	China	Case-control	TNBC, HER2, Lum	Naive Bayes	Radiomics
Wang W (62)	2022	China	Case-control	TN, luminal A + B	Logistic regression	Radiomics
Wu J (63)	2017	China	Case-control	Basal, luminal A, luminal B	Logistic regression	Radiomics
Wu M (64)	2019	China	Case-control	Basal, HER2, luminal A, luminal B	Deep learning	Radiomics
Xie T (65)	2019	China	Case-control	TN	Support vector machines	Radiomics
Yang X (66)	2020	China	Case-control	HER2	Logistic regression	Radiomics
Zhang X (67)	2021	China	Case-control	HER2, TN	Artificial neural network	Radiomics
Zhang Y (68)	2021	USA	Case-control	HER2, TN	Artificial neural network	Radiomics
Zhou J (69)	2019	China	Case-control	HER2	Support vector machines	Radiomics
Saha A (70)	2018	USA	Case-control	TN, HER2, luminal A, luminal B	Random forest	Radiomics
Sutton EJ (71)	2016	USA	Case-control	TN	Support vector machines	Radiomics
Wang F (72)	2022	China	Case-control	luminal A+B	Support vector machines	Radiomics
Wang J (73)	2015	Japan	Case-control	TN	Support vector machines	Radiomics

BRCA, breast cancer; TNBC, triple negative breast cancer; HER2, HER2-overexpressed subtypes of breast cancer molecules; CNN, convolutional neural network; DNN, deep neural network.

like or TNBC, and HER2 subtypes were 0.76 (95% CI: 0.60–0.96), 0.78 (95% CI: 0.69–0.87) 0.87 (95% CI: 0.83–0.91), and 0.83 (95% CI: 0.81–0.86), respectively.

The c-statistic values of the BRCA molecular subtypes identified by gene-transcriptomic ML were 0.96 (95% CI: 0.93–0.99), 0.93 (95% CI: 0.91–0.95), 0.98 (95% CI: 0.95–1.00), and 0.97 (95% CI: 0.96–0.98), respectively (*Table 3, Figure 3*).

In the testing cohort, statistical analysis was conducted on the data available and the results showed that the predicted c-index values for molecular subtypes of BRCA exceeded 80% for both sets of the ML models.

Sensitivity and specificity

A bivariate mixed-effects model was used for the meta-analysis of TP, FP, FN, and TN, and the sensitivity of the

ML method for each molecular subtype was summarized. The sensitivity and specificity of radiometrics ML for molecular subtype identification of Luminal A were 0.79 (95% CI: 0.72–0.84) and 0.85 (95% CI: 0.73–0.92), for Luminal B were 0.84 (95% CI: 0.69–0.93) and 0.86 (95% CI: 0.64–0.96), for Basal-like or TNBC were 0.82 (95% CI: 0.75–0.87) and 0.86 (95% CI: 0.78–0.91), for HER2 were 0.84 (95% CI: 0.81–0.87) and 0.83 (95% CI: 0.71–0.90), and for Luminal subtypes (Luminal A + Luminal B) were 0.79 (95% CI: 0.72–0.84) and 0.85 (95% CI: 0.73–0.92), respectively.

The sensitivity and specificity of the gene-transcriptomic. ML for the identification of Luminal A were 0.89 (95% CI: 0.87–0.92) and 0.95 (95% CI: 0.89–0.98), for Luminal B were 0.79 (95% CI: 0.64–0.89) and 0.86 (95% CI: 0.91–0.98), for Basal-like or TNBC were 0.97 (95% CI: 0.93–

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Table 2 Basic information of sample number of training set and validation set included in the study

| First author	Publication year	No. of subtype samples in training set	No. of samples in training set	No. of subtype samples in validation set	Sample size for external validation
Ma M (36)	2022	NA	450	71, 64	150
Leithner D (37)	2020	8, 34, 6, 16	64	3, 15, 2, 7	27
Chen L (38)	2019	34, 37, 120, 63	254	NA	NA
Zhao Y (39)	2020	NA	NA	262, 208, 891, 423	1784
Huang CC (40)	2013	57, 35, 23, 12	139	57, 35, 23, 12	139
Yu Z (41)	2020	192, 82, 564, 207, 40	1085	NA	NA
Liu T (42)	2022	127, 56, 326, 151	660	14, 6, 43, 21	84
Adabor ES (43)	2019	187	806	NA	NA
Huang Y (44)	2021	25	137	NA	NA
Lopez-Rincon A (45)	2020	139	183	NA	NA
Wu J (46)	2021	110	1102	NA	NA
Mohaiminul Islam M (47)	2020	116, 87, 464, 268	935	210, 153, 255, 224	842
Wilson TR (48)	2014	14	173	NA	NA
Seo MK (49)	2020	15, 10, 38, 21	84	NA	NA
Couture HD (50)	2018	179	571	NA	288
Fan M (51)	2017	7, 34, 8, 11	60	NA	36
Jiang M (52)	2021	NA	1275	18, 42, 116, 229	405
Moon WK (53)	2015	85	169	NA	NA
Talari ACS (54)	2019	30, 30, 30, 30	120	NA	NA
Nie Z (55)	2021	57	226	NA	NA
Zhou J (56)	2021	63	244	16	62
Fan M (57)	2019	39, 37, 54, 80	210	NA	NA
Wu M (58)	2011	40, 76, 96, 151	363	NA	NA
Zhou J (59)	2021	53	200	23	106
Wu T (60)	2019	23	140	NA	NA
Ma W (61)	2019	40, 141	227	NA	NA
Wang W (62)	2022	42, 27, 11	84	43, 27, 11	84
Wu J (63)	2017	151, 96, 76, 40	363	NA	NA
Wu M (64)	2019	134	134	NA	NA
Xie T (65)	2019	60	177	57	162
Yang X (66)	2020	149, 118	684	NA	122
Zhang X (67)	2021	24, 10	99	19, 10	83
Zhang Y (68)	2021	63	244	16	62
Zhou J (69)	2019	82, 27, 305, 471	461	NA	461
Saha A (70)	2018	48	178	NA	NA
Sutton EJ (71)	2016	110	220	43	80
Wang F (72)	2022	153	220	80	NA
Wang J (73)	2015	11, 4, 42, 27	84	NA	NA
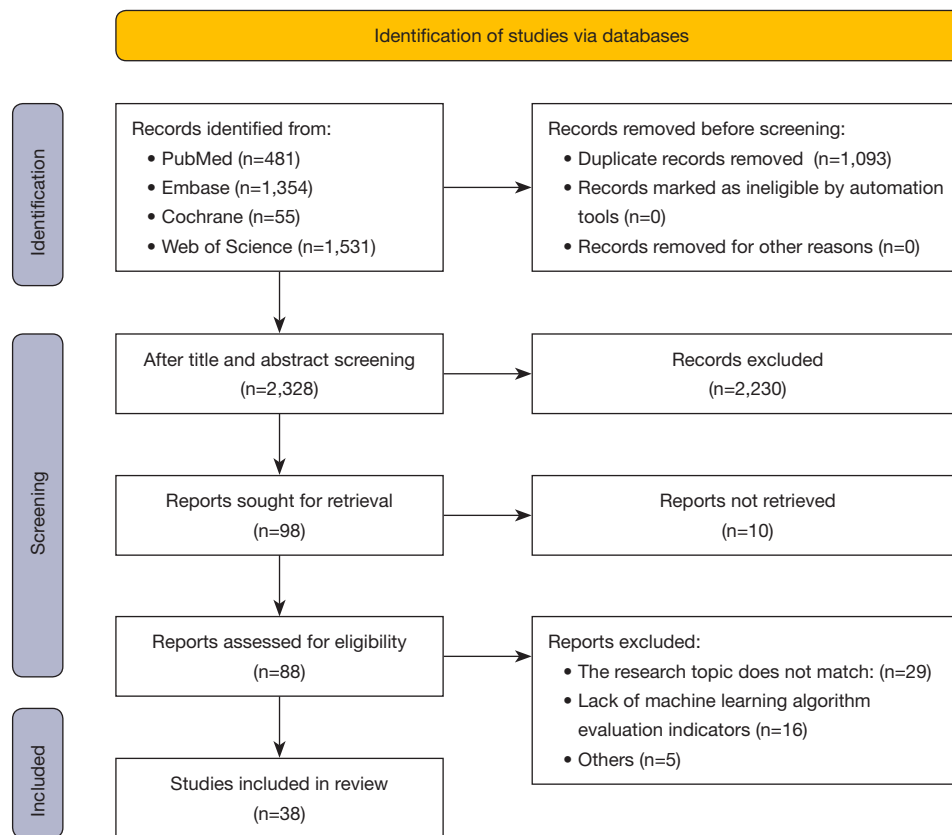
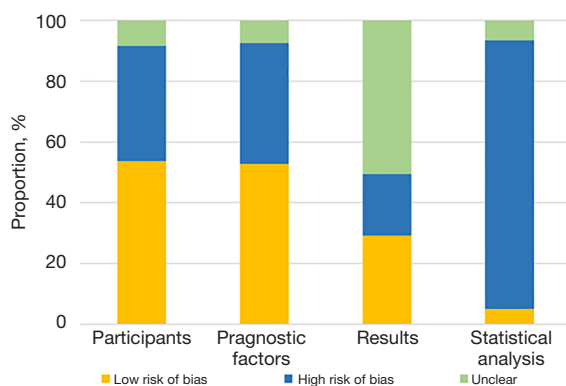**Figure 1** PRISMA flow chart detailing the systematic search process.

Figure 2 Risk bias factors.

0.98) and 0.99 (95% CI: 0.96–1.00), for HER2 were 0.92 (95% CI: 0.85–0.96) and 0.96 (95% CI: 0.94–0.97), and for Luminal subtypes (Luminal A + Luminal B) were 0.86 (95% CI: 0.80–0.90) and 0.96 (95% CI: 0.92–0.97), respectively (*Table 4*, *Figures 4,5*).

Discussion

This systematic review and meta-analysis indicated that ML based on radiomics and genomics can achieve satisfactory performance in predicting BRCA molecular subtypes. The accuracy of gene-transcriptomic ML was superior to that of radiomics ML, but the diagnostic accuracy of identification of BRCA molecular subtypes using radiological data analysis has theoretical support. We also found that ML was more accurate in identifying the Basal-like/TNBC subtype than other BRCA molecular subtypes.

The gene transcriptome data analyzed in the present study clarified the ability of ML to identify the intrinsic biological subtypes of TNBC, HER2+, and luminal BRCA using whole-gene database analysis, with good accuracy. Genetic diagnosis is the gold standard for cancer diagnosis, and whole genomic amplification provides an opportunity to conduct in-depth investigations of the role of epigenetic processes in cancer. Unfortunately, as epigenome map and cancer sample data accumulates,

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Table 3 Meta-analysis results of C-index, sensitivity, and specificity of molecular subtypes in the training set

Modeling variable	Subtype	n	C-statistic	n	Sensitivity	Specificity
Radiomics	Luminal	12	0.77 [0.71, 0.83]	12	0.79 [0.72, 0.84]	0.85 [0.73, 0.92]
	Luminal A	4	0.76 [0.60, 0.96]	5	0.76 [0.68, 0.82]	0.86 [0.62, 0.96]
	Luminal B	4	0.78 [0.69, 0.87]	5	0.84 [0.69, 0.93]	0.86 [0.64, 0.96]
	Mixed	4	0.76 [0.73, 0.80]	2	NA	NA
	Basal-like or TNBC	15	0.87 [0.83, 0.91]	19	0.82 [0.75, 0.87]	0.86 [0.78, 0.91]
	HER2	16	0.83 [0.81, 0.86]	13	0.84 [0.81, 0.87]	0.83 [0.71, 0.90]
Gene	Luminal	10	0.94 [0.92, 0.96]	16	0.86 [0.80, 0.90]	0.96 [0.92, 0.97]
	Luminal A	5	0.96 [0.93, 0.99]	8	0.89 [0.87, 0.92]	0.95 [0.89, 0.98]
	Luminal B	5	0.93 [0.91, 0.95]	8	0.79 [0.64, 0.89]	0.96 [0.91, 0.98]
	Mixed	NA	NA	NA	NA	NA
	Basal-like or TNBC	5	0.98 [0.95, 1.00]	9	0.97 [0.93, 0.98]	0.99 [0.96, 1.00]
	HER2	6	0.97 [0.96, 0.98]	11	0.92 [0.85, 0.96]	0.96 [0.94, 0.97]

TNBC, triple negative breast cancer; HER2, human epidermal growth factor receptor 2; NA, not available.

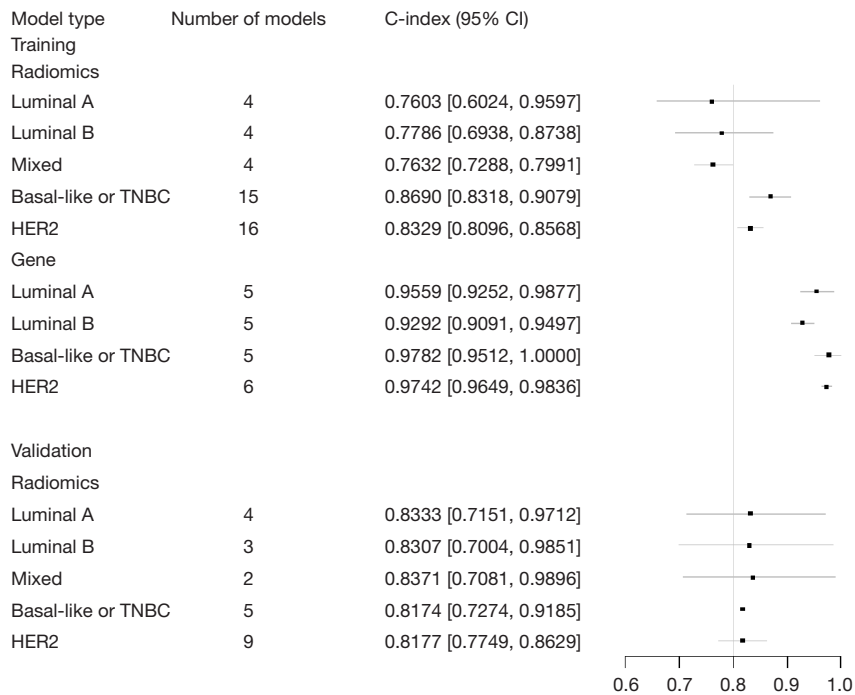| Model type	Number of models	C-index (95% CI)
Training		
Radiomics		
Luminal A	4	0.7603 [0.6024, 0.9597]
Luminal B	4	0.7786 [0.6938, 0.8738]
Mixed	4	0.7632 [0.7288, 0.7991]
Basal-like or TNBC	15	0.8690 [0.8318, 0.9079]
HER2	16	0.8329 [0.8096, 0.8568]
Gene		
Luminal A	5	0.9559 [0.9252, 0.9877]
Luminal B	5	0.9292 [0.9091, 0.9497]
Basal-like or TNBC	5	0.9782 [0.9512, 1.0000]
HER2	6	0.9742 [0.9649, 0.9836]
Validation		
Radiomics		
Luminal A	4	0.8333 [0.7151, 0.9712]
Luminal B	3	0.8307 [0.7004, 0.9851]
Mixed	2	0.8371 [0.7081, 0.9896]
Basal-like or TNBC	5	0.8174 [0.7274, 0.9185]
HER2	9	0.8177 [0.7749, 0.8629]

Figure 3 The C-statistic values of breast cancer molecular subtypes identified by gene-transcriptomic machine learning for Luminal A, Luminal B, Basal-like or TNBC, triple negative breast cancer; HER2, human epidermal growth factor receptor 2.

Table 4 Meta-analysis results of C-index, sensitivity, and specificity of molecular subtypes in the validation set

Modeling variables	Subtype	n	C-statistic	n	Sensitivity	Specificity
Radiomics	Luminal	9	0.84 [0.77, 0.91]	8	0.86 [0.71, 0.94]	0.76 [0.51, 0.91]
	Luminal A	4	0.83 [0.72, 0.97]	3	NA	NA
	Luminal B	3	0.83 [0.70, 0.98]	3	NA	NA
	Mixed	2	0.84 [0.71, 0.99]	2	NA	NA
	Basal-like or TNBC	5	0.82 [0.73, 0.92]	2	NA	NA
	HER2	9	0.82 [0.77, 0.86]	7	0.66 [0.53, 0.77]	0.83 [0.70, 0.91]
Gene	Luminal	NA	NA	8	0.76 [0.70, 0.81]	0.93 [0.91, 0.95]
	Luminal A	NA	NA	4	0.80 [0.76, 0.84]	0.93 [0.91, 0.95]
	Luminal B	NA	NA	4	0.69 [0.61, 0.76]	0.93 [0.89, 0.96]
	Mixed	NA	NA	NA	NA	NA
	Basal-like or TNBC	NA	NA	4	0.94 [0.80, 0.98]	0.99 [0.97, 1]
	HER2	NA	NA	4	0.71 [0.65, 0.76]	0.96 [0.94, 0.97]

TNBC, triple negative breast cancer; HER2, human epidermal growth factor receptor 2; NA, not available.
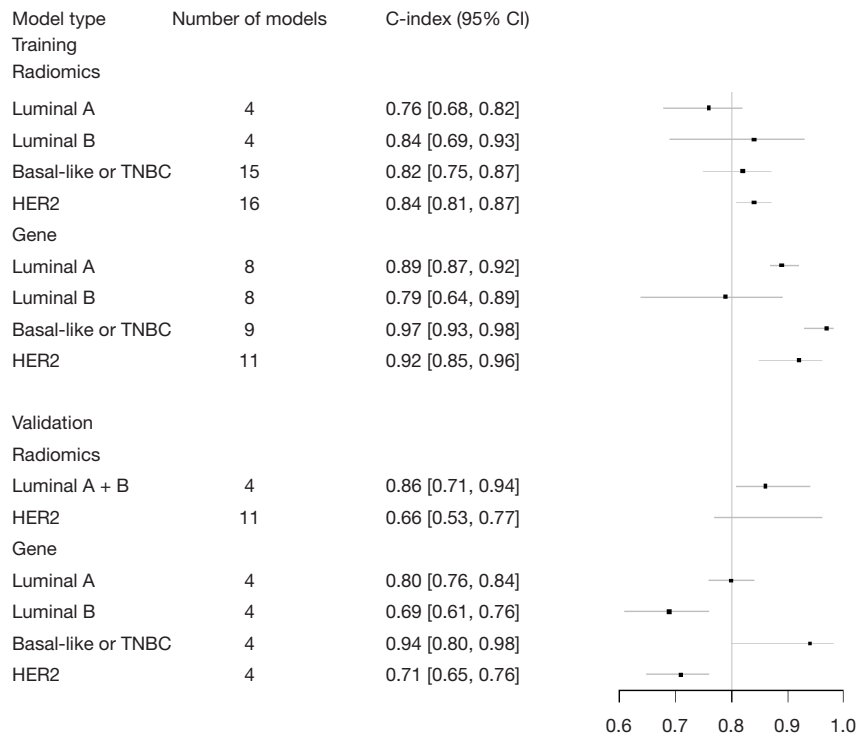
Figure 4 The sensitivity of breast cancer molecular subtypes identified by gene-transcriptomic and radiomics machine learning for Luminal A, Luminal B, Basal-like or TNBC, and HER2 subtypes. TNBC, triple negative breast cancer; HER2, human epidermal growth factor receptor 2.
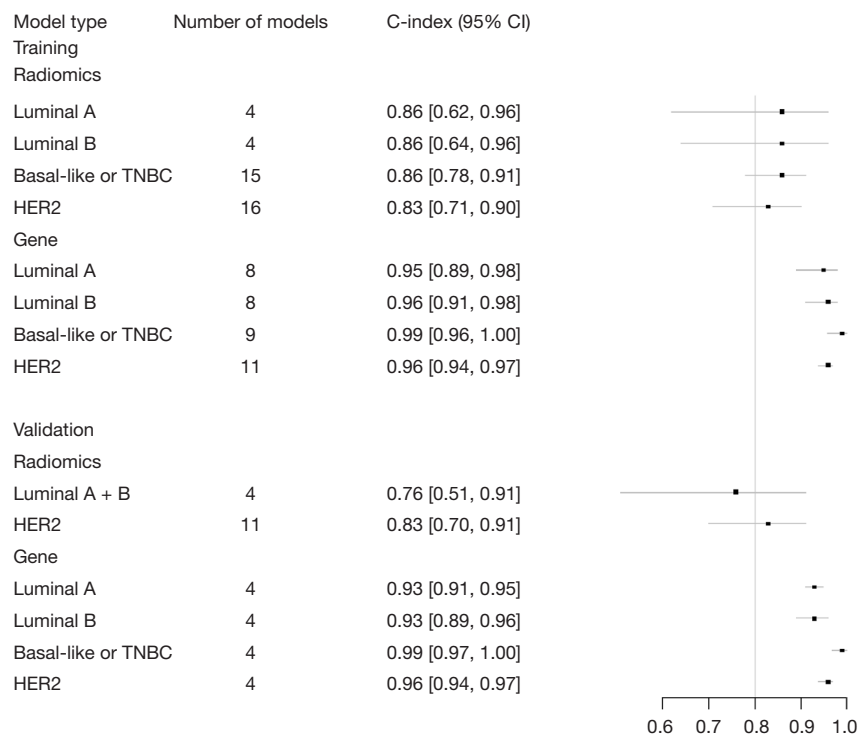
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Model type	Number of models	C-index (95% CI)
Training		
Radiomics		
Luminal A	4	0.86 [0.62, 0.96]
Luminal B	4	0.86 [0.64, 0.96]
Basal-like or TNBC	15	0.86 [0.78, 0.91]
HER2	16	0.83 [0.71, 0.90]
Gene		
Luminal A	8	0.95 [0.89, 0.98]
Luminal B	8	0.96 [0.91, 0.98]
Basal-like or TNBC	9	0.99 [0.96, 1.00]
HER2	11	0.96 [0.94, 0.97]
Validation		
Radiomics		
Luminal A + B	4	0.76 [0.51, 0.91]
HER2	11	0.83 [0.70, 0.91]
Gene		
Luminal A	4	0.93 [0.91, 0.95]
Luminal B	4	0.93 [0.89, 0.96]
Basal-like or TNBC	4	0.99 [0.97, 1.00]
HER2	4	0.96 [0.94, 0.97]

Figure 5 Specificity of breast cancer molecular subtypes identified by gene-transcriptomic and radiomics machine learning for Luminal A, Luminal B, Basal-like or TNBC, and HER2 subtypes. TNBC, triple negative breast cancer; HER2, human epidermal growth factor receptor 2.

the analysis and utilization of such data become difficult. ML greatly improves efficiency due to its flexibility and learning ability to latent structures (74). For example, partial least squares (PLS) regression has been applied to BRCA intrinsic taxonomy and five distinct molecular subtypes were successfully identified (40). Wilson *et al.* used multiple model classifiers to determine estrogen receptor (ER), progesterone receptor (PR), and HER2 phenotypes and introduced a new median complement method, which is beneficial for the development of higher sensitivity and a lower FP rate (48). Additionally, ML helps scientists discover new biomarkers that can aid patient prognosis. As for the heterogeneity of BRCA, a single tumor marker is not sufficient. Many studies have focused on determining cancer prognosis and the subtypes of gene characteristics based on gene expression data, which are easily affected by noise signals, reducing accuracy (75). BRCA diagnosis is not limited to such parameters, with more genetic modification patterns, microRNAs and methylation and genetic variants being identified and potentially available. DNA methylation data are more stable than those of gene expression in

cancer prognosis (76), and microRNA also shows several advantages in cancer prediction, prognosis, and therapeutic targets, and it can be obtained from body fluids thereby being noninvasive (77). Unfortunately, due to the existence of large number of differentially methylated genes and microRNAs, human verification is not yet available, but the present study showed how this can be effectively solved by using ML. For example, ML distinguished studies on Basal-like/TNBC from other molecular subtypes using both microRNA data and gene methylation data analysis with a sensitivity and specificity of 87%, 80%, and 100%, and 99%, respectively (38,45). This suggests a bright future for ML in the identification of BRCA molecular subtypes and also provides theoretical support for microRNA, especially gene methylation, as a predictor of BRCA prognosis.

BRCA screening is typically conducted by a variety of medical diagnostic imaging methods, including US, X-ray radiography, and MRI. However, defects in imaging techniques lead to relatively low average sensitivity and specificity ($\approx70\%$) for clinical diagnosis (78,79). The ability of radiomics to analyze images to obtain various

quantitative features from single or multiple imaging patterns and highlight such characteristics that are not visible to the naked eye greatly enhances the discriminative and predictive potential of medical imaging. Presently, radiomics can not only differentiate between benign and malignant tumors, tumor types and grades, but also support the prediction of response to neoadjuvant chemotherapy and recurrence (80). Our study revealed that the sensitivity and specificity of radiomics-based ML models in predicting BRCA molecular subtypes were as high as 80%, and some even reached 90%. The therapeutic benefit was similar to that of the gene-transcriptomics ML models, which is effectively avoiding the invasive procedure of needle biopsy for traditional diagnosis of the BRCA molecular subtype. ML diagnosis also overcomes the issue of inexperience of radiologists, and takes full advantage of image analysis, such as subtype analysis of H&E-stained histological images of BRCA, distinguishing Basal-like from non-Basal-like BRCA molecular subtypes with 75–80% accuracy, thus reducing the high cost of RNA-based genomic testing (55). In our study, the number of included studies of radiomics was more than that of genomics, indicating that radiomics is an emerging field receiving extensive attention. It can be used to maximize information extraction from almost all of the medical imaging modalities. Twelve such studies involved MRI, which is known to have higher resolution than X-ray or US. MRI has the best specificity and sensitivity of all imaging tools available, and we can take advantage of this technique to develop more accurate ML models. It is worth noting that our study results indicated that the average c-index value of radiomics in the prediction of BRCA molecular subtypes was 0.796, while that for transcriptomics was 0.956, implying that further efforts should be made to improve the accuracy of radiometric prediction models.

TNBC lacks the ER, PR, and HER2. It is characterized by young onset, high invasiveness, high recurrence rate, and poor prognosis (81). Studies have shown that neoadjuvant therapy for TNBC is highly effective and improves the pathological complete remission rate (82). The current study revealed that, regardless of gene-transcriptomic or radiomic analysis, ML was more effective in identifying Basal-like/TNBC BRCA, especially with the application of a radiomics ML model (*Figure 3*). As TNBC and Basal-like BRCA have many similarities in their clinical manifestation, histological morphology, and immunophenotype (83), and because of the limited number of study cases, we regarded Basal-like and TNBC as similar. However, further research has raised the question of whether Basal-like and TNBC

can be compared (84). TNBC can be subdivided into several subtypes, and studies have shown that its spectrum of germline variation differs from other subtypes, and ethnic differences have been discovered (85). Using the promising effect of ML revealed in this research, we can develop more ML models to investigate the difference between Basal-like and TNBC subtypes, and distinguish the different subtypes of TNBC as a breakthrough in the treatment of refractory BRCA and precision treatment, such actively adopting neoadjuvant treatment preoperatively.

Our systematic review and meta-analysis comprehensively and systematically assessed the potential of gene transcriptome and radiomics-based ML models for predicting BRCA molecular subtypes, and demonstrated that the major advantage of ML is the ability to learn and develop algorithms without human intervention. Additionally, this research supported the application of virtual network deep learning and convolutional neural networks (CNN) to diagnose BRCA molecular subtypes using more fundamental artificial intelligence approaches. However, our study also has several limitations. The number of samples was small and there needs to be further continuous mining of relevant research to prove the accuracy of ML predictions. It also lacked external validation and enough testing sets for validation. To further improve the accuracy of ML for identifying molecular subtypes of BRCA, we need to be aware of the following. First, the reduction of data noise before ML application can improve model accuracy. Studies have shown that dimensionality reduction through the number of principal components for cross-validation, and the use of noise reduction techniques can significantly improve model accuracy (31). In the existing research, the application of cross-validation is not yet comprehensive, and noise reduction technology needs to be further improved. Second, the indications used for ML model training should be increased and function models should be continuously fine-tuned. One task of an ML model is to propose some predictors or features, and the other is to determine a function that can be used to associate eigenvalueswith disease prediction (class assignment) (86). Feature selection is the core of ML, and sufficient predictors guarantee improved accuracy of ML models, but this was limited by our lack of exploration of the mechanism of disease occurrence and development. Despite there being many options for functional models, the selection of optimal free parameter values to fit the model is not easy, implying that we need more training examples. This is both an opportunity and a challenge for ML to

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predict the development of molecular subtypes of BRCA. The treatment of BRCA is developing in the direction of precision medicine, and ML models are of great significance for de-escalation therapy of minimally invasive techniques, surgery, and chemotherapy.

Conclusions

Data from this systematic review and meta-analysis support radiomics and gene-transcriptomic ML model analyses, which have ideal predictive accuracy in determining early the BRCA molecular subtypes. However, compared with radiomics, gene transcriptomics yielded better results although radiomics is simpler and more convenient in operation from a clinical point of view. As the paradigm shifts to individualized medicine with minimally invasive techniques, prospective translational oncology research may focus on the development of radiomic techniques.

Footnote

Reporting Checklist: The authors have completed the MOOSE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-5986/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5986/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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