The circulating level of Non-coding RNA for breast cancer diagnosis

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Abstract

Background: The expression of non-coding RNAs were closely related to breast cancer progression. However, there were no systemic analysis of non-coding RNAs in breast cancer diagnosis of the blood circulatory system. Herein, we aimed to collect all the evidence to test the potential role of non-coding RNAs as novel biomarkers in human breast cancers.

Methods: A comprehensive search strategy was used to search relevant literatures in the Web of Science, PubMed, and Embase databases from January 2012 to November 2019. The correlation of non-coding RNAs expression in serum, plasma or blood circulatory system and the diagnostic accuracy of BC markers were analyzed. The methodological quality of each study was assessed using the QUADAS-2. Statistical analysis was used the STATA (version 12.0), Meta-Disc (version 1.4) and Review Manager (version 5.3) software.

Results: The present meta-analysis of the non-coding RNAs expression data of BC patients and healthy specimens' bloodfrom 2392 patients in 24 publications (32 studies). The pooled sensitivity, specificity, and AUC values were 0.82, 0.83, and 0.89, respectively. Subgroup analyses showed that the expression of non-coding RNA (miRNA, circRNA, andlncRNA) in the blood circulatory system (including blood, plasma, and serum) of BC was more prone to be detected in TNM stage and subtype of BC group, with a high value of the sensitivity and AUC.

Conclusions: The blood circulatory system (including blood, plasma, and serum) of miRNAs, circRNAs, and lncRNAs detection may be effective for diagnosing breast cancer, particularly in TNM stage, subtype of BC (ER/PgR, PR or HER2/c-erbB-2) group of breast cancer. Further studies are needed to identify the value of these non-coding RNAs as novel markers in clinical.

Background

Breast cancer is the most common cancer and is the second leading cause of cancer death among women worldwide, and the breast cancer incidence rate increased every year, but the death rate continues to decline [1, 2], Increased survival is due to the dramatic shift in the screening methods, early diagnosis, and breakthroughs in treatments. Currently, clinical practice typically uses a classification of five subtypes breast cancer on the basis of histological and molecular characteristics, including ER, PR, HER2 and Ki67 [3]. Molecular biomarkers play an increasing important role in cancer diagnosis and management. The discovery and use of specific prognostic and predictive biomarkers have enabled the application of targeted precision therapies to specific molecular subgroups of patients likely to gain benefit. Additionally, the use of biomarkers can allow for the identification of patients with a favorable prognosis who can safely be spared from unnecessary overtreatment. In advancement towards precision medicine, the field of cancer biomarker discovery has rapidly expanded over the last few decades.

Currently, there are few serum markers used in breast cancer clinical diagnosis. Some studies have identified as possible breast cancer markers the proteins CA 15-3 and CA 27-29, carcinoembryonic

antigen (CEA), which implicated in cell adhesion, immunity, and metastasis [4]. These kinds of carcinoma antigens are not useful in the early detection of breast cancer. With advances in high-throughput technology, some non-coding RNAs can be detected and differentially expressed in the blood circulatory system of breast cancer patients.

The emergence of non-coding RNAs as crucial regulators of gene expression has been associated with various cancers[5]. The non-coding RNA (ncRNA) is a function of RNA molecular that is transcribed from DNA but no or limited protein-coding potential. The large family of ncRNAs comprises diverse regulatory RNAs, including microRNA (miRNA) spanning 19 to 25 nucleotides in length, long non-coding RNAs (lncRNAs) with over 200 nucleotides base long, and recently discovered circular RNAs (circRNAs) formed by back-splicing and more stable than other ncRNAs [6]. Currently, about 30424 mature microRNAs have been reported and more than 2500 mature miRNAs have been discovered in mammalian systems [7]. Many studies observed elevated levels of miRNAs in the circulation from breast cancer patients, such as miR-21 [8], miR-20b-5p [9], miR-34a [10-12], miR-133a [13, 14], miR-145 [15], miR-181a [16], miR-424 [17], miR-801 [18, 19], and so on [20-26]. According to the GEN-CODE analysis 27817 transcripts originating from 15931 genes can be identified as lncRNAs [27]. Tumor suppressor lncRNA usually deregulated in the development of diseases. lncRNA such as H19, HOTAIR, and XIST were abnormal expressed in breast cancer patients serum compared with control [28-30]. CircRNAs exist in exosomes and plasma and 343 differentially circRNAs expressed in the plasma[31]. Their expression profiles are specific in different stages of cancer [32]. A vast number of circRNAs have been discovered in different types of cancer and activated in either inhibiting tumor progression or promoting tumorigenesis [33, 34]. Therefore, these three kinds of ncRNA signatures from cancer and metastases have been used to classify different types of cancer, representing potential biomarkers for diagnosis, prognosis, and therapy.

This meta-analysis to summarize the overall accuracy of miRNAs, lncRNAs, and circRNAs in circulatory system of breast cancer patients. This study evaluated the sensitivity and specificity of ncRNAs and the efficacy of ncRNAs as biomarkers for the diagnosis of breast cancer.

Methods

This manuscript adheres to PRISMA guidelines (Supplement Table 1)

2.1 Search strategy

Sources of studies included the databases of the Web of Science, PubMed, and Embase for the studies of diagnostic value of blood non-coding RNAs including miRNAs, circRNAs, and LncRNAs in breast cancer, which published in English language up to November 20, 2019. We searched key words as “breast cancer” or “mammary cancer” or “breast tumor” or “mammary tumor” or “breast carcinoma” or “mammary carcinoma” or “breast neoplasms” or “mammary neoplasms” and (“blood” or “serum” or “plasma” or “circulating”) and “RNA” and “area under the Curve of *ROC* (AUC)”. Two independently researchers (JZ and ZJ) identified inclusion articles from the titles, abstracts, and full texts. Other two investigators (MW and YG) extracted the data. Any disagreement to be resolved by the arbitrator (HW).

2.2 Inclusion and exclusion criteria

The following criteria were used for the articles in this meta-analysis (Figure 1).

These studies met the following inclusion criteria:

1. The expression of miRNAs, circRNAs, or lncRNAs in breast cancers were detected.
2. Sample size, SEN, SPE, PLR, NLR, and AUC data were available.
3. Case-control were available in the studies.
4. Studies on miRNAs, circRNAs, or lncRNAs from the blood, serum, plasma, or circulating of breast cancer patients.
5. Research articles and conference abstracts were included.

Consequently, studies were excluded ground on the following criteria:

1. Studies in humans.
2. Not English writing studies.
3. Lack of SEN and SPE data studies
4. Lack of control groups studies.
5. Studies of RNA-seq databases.
6. Reviews, case reports, letter or meta articles.

2.3 Data extraction

We extracted the data from included studies.

1. In these studies, data to be extracted includes first author, publication year, blood specimen type, name of ncRNAs and patient origin.
2. We focused on the level of sensitivity, specificity and AUC, and the expression of miRNAs, circRNAs, or lncRNAs, and collected information about the sample size, cut-off value, reference gene and so on.
3. The clinicopathological characterizes data of the patients were assembled including gender, age, tumor size, tumor number, ER, PR, HER2, TNM stage, lymphatic metastases, and Ki67 in breast cancer patients.

2.4 Statistical analysis

Data analysis and statistical software STATA (version 12.0), Meta-Disc1.4 and Review Manager (version 5.3) was used to analyze the diagnostic value. The pooled SEN, SPE, PLR, NLR, DOR, and AUC of miRNAs, circRNAs, and lncRNAs, were calculated the diagnostic value for cancers from each study. The statistical heterogeneity was analyzed by Q test, I square (I2) and Tau square (T2). A two-sided $p<0.05$ was considered statistically significant. A random effect model (DerSimonian-Laird) was used for higher

heterogeneity (I2>50%), when I2<50% using the fixed effect model (Mantel-Haenszel). Meta-regression was performed to analyses the potential sources of heterogeneity. If tau-square less than 0.04 was defined as mild, 0.04 to 0.14 was moderate, and it greater than 0.40 was severe[35]. The Deek's funnel plot asymmetry was used to test publication bias.

Results

3.1 Search and description of studies

The flow diagram for literature research processes was shown in Figure 1. All the diagnostic values of non-coding RNAs in BC patients were collected and evaluated. 2392 BC blood specimens and 1738 healthy specimens' blood individuals from 32 studies (24 articles) published from January 2012 to November 2019 were contained in this meta-analysis (Table 1 and Supplement Table 2).

Among the 32 studies, 28 studies explore the association with 50 miRNA expression, 1 study investigated 1 circRNA, and the other 3 studies focused on 3 lncRNA. In terms of samples, blood specimens from whole blood, plasma, and serum and the sample size from 10 to 177. All studies used quantitative real time polymerase chain reaction (qPCR), excepted one study used absolute RT-qPCR. Histopathological grading information was provided in all studies. Seventeen studies were shown 29 miRNA up-regulated in breast cancers, and six studies were reported 7 miRNA down-regulated expression, and four studies were shown 1 lncRNA down-regulated, 2 lncRNA up-regulated, and 1 circRNA up-regulated in breast cancer (Table 2). The endogenous reference, quantitative method and cut-off value are not uniform in all studies. Three studies did not mention 14 miRNA expression changes.

The difference expression between ncRNAs and clinic-pathological factors were shown in Table 3, including tumor size, TNM stage, lymphatic metastasis, tumor invasion, ER/PgR, PR, HER2/c-erbB-2, and Ki67.

In addition, all the studies independently scored the included studies based on Quality assessment of diagnostic accuracy studies-2 (QUADAS-2) score system (Review Manager), including patient selection, index tests, reference standard, and flow and timing [36]. Each domain is assessed in terms of the risk of bias, which should answer as “yes”, “no”, or “unclear”, and phrase such that “yes” indicates low risk of bias. And the first 3 domains are also assessed in terms of concerns about applicability, which should rate as “low”, “high”, or “unclear”, and the “unclear” category should be used only when insufficient data are reported.

Detailed results of the QUADAS-2 assessment are provided in supplement Figure 1. All studies showed risk of bias, because thresholds for index test positivity had been predefined, and all the patients had the same reference standard. Thirty-two documents included in the gold standard, but did not mention whether or not to use the blind method. All of them had relatively high quality in supplement Figure 1, indicating the relatively the reliable foundation of our analysis.

3.2 Meta-analysis

Thirty-two studies involving 3 types of RNA with 2392 BC patients investigated the diagnostic value of non-coding RNAs as the biomarkers of cancer, and a meta-analysis of the SEN, SPE, PLR, NLR, DOR, and AUC for non-coding RNAs were plotted in the breast cancer diagnosis. The random effect model was chosen to analyze the inconsistency (I^2=100 > 50). The pooled SEN was 0.82(95%CI:0.76-0.86) (Figure 2A), SPE was 0.83(95%CI:0.75-0.88) (Figure 2B), PLR was 4.67(95% CI:3.19-6.84) (Figure 2C), NLR was 0.22(95%CI:0.17-0.29) (Figure 2D), DOR was 20.91(95%CI:12.01-36.40) (Figure 2E) and AUC values was 0.89 (95%CI:0.86-0.91) (Figure 2F). Then, the funnel plots implied that publication bias has no effect on the result (p=0.45) (Figure 2G). These results indicated a relatively moderate diagnostic accuracy of non-coding RNA in detection of cancer patients' blood.

3.3 Meta-regression analyses

Using meta-regression to find the potential sources of heterogeneity, including TNM stage, lymphatic metastasis (tumor invasion), ER/PgR, PR and HER2/c-erbB-2. Meta-regression analysis was shown in Table 4, the result suggested that TNM stage, was the major cause of heterogeneity. There are only 15 studies reported association expression of non-coding RNA with clinicopathological features. The significant association for TNM stage, (p=0.0321) but not ER/PgR (p=0.3257), PR (p=0.2519), HER2/c-erbB-2 (p=0.5598) and lymphatic metastasis (tumor invasion) (p=0.1401) were shown. And p-value of TNM stage was less than 0.05, that means the TNM stage is the reason for the formation of heterogeneity.

We also show the construction of a bivariate boxplot which is useful tool for the detection of heterogeneity for each study (Figure 2H). There are 4 studies not located in the boxplot, including four studies (Eichelser C2, miR-93; Mishra S2, miR495; Zaleski M, miR34a; Swellam M2, miR222). But 3 of 4 studies (Eichelser C2, miR-93; Mishra S2, miR495; Zaleski M, miR34a) did not associate with TNM stage. That means TNM stage is the major causes of heterogeneity. We further excluded these 4 studies, found by influence analysis and detection in supplement Figure 2. After exclusion, the level of SEN decreased from 0.82 to 0.79, the NLR increased from 0.22 to 0.25, the DOR decreased from 21 to 19, and AUC increased from 0.89 to 0.87, and SPE and PLR not changed, showing minimal change with our overall analysis. The results confirmed that these 4 studies were not the cause for heterogeneity.

Furthermore, we used meta-regression (Meta-Disc) to analysis the source of samples which divided into blood (8 studies), plasma (13 studies), and serum (11 studies) three subgroups. The p-value of these three groups (p=0.4670 in blood group; p=0.5495 in plasma group; p=0.3517 in serum group) were more than 0.05, that means the sample source was not the main reason for the formation of heterogeneity (supplement table 3-5). We also test meta-analysis of the SEN, SPE, and AUC for these three groups (blood, plasma, and serum), the pooled SEN values were 0.84, 0.82, and 0.79, the pooled SPE values were 0.84, 0.84, and 0.80, and AUC values were 0.91, 0.90, and 0.85, respectively (supplement Figure 3). These

results shown a little change, and confirmed that the samples source was not the reason for heterogeneity.

Therefore, we performed subgroup analysis for the expression of non-coding RNAs in different clinicopathological features. Eight studies showed significant differences among TNM stage. We conducted subgroup analysis on these studies. In addition, there was no significant effect in subtype of BC and lymphatic metastasis meta-regression, 5-6 studies showed significant difference in non-coding RNA expression in breast tumors and healthy people, and we also conducted subgroup analysis on these studies.

3.4 Subgroup analysis

3.4.1 TNM

Among all the studies, 8 studies show significant differences, and other 10 studies show no significant differences, the rest of 14 studies have no data. These eight studies including 814 patients evaluated the expression of non-coding RNAs as diagnostic biomarkers for BC. The meta-analysis of the SEN, SPE, PLR, NLR, DOR, and AUC for non-coding RNA association with TNM stage. The random effect model was used to analyze (I^2>50%). The pooled SEN (Figure 3A), SPE (Figure 3B), PLR (Figure 3C), NLR (Figure 3D), DOR (Figure 3E), and AUC values (Figure 3F) were 0.87 (95%CI: 0.78–0.93), 0.84 (95%CI: 0.72–0.91), 5.5 (95%CI: 3.0–10.1), 0.15 (95%CI: 0.08–0.27), 37.00 (95%CI: 13–101), and 0.92 (95%CI:0.90–0.94), respectively. The funnel plot suggested that publication bias had no significant effect on diagnostic assessment (p=0.29) (Figure 3G).

3.4.2 Metastasis or invasion

Seven studies involving of 520 patients investigated the diagnostic values of non-coding RNAs as the biomarker association with metastasis or invasion, and the meta-analysis of the SEN, SPE, DOR, and AUC were plotted, using random effect model (I^2>50%). The pooled SEN (Figure 4A), SPE (Figure 4B), PLR (Figure 4C), NLR (Figure 4D), DOR (Figure 4E), and AUC values (Figure 4F) were 0.78 (95%CI: 0.68–0.86), 0.85 (95%CI:0.77–0.91), 5.3(95%CI:3.5–8.0), 0.25 (95%CI: 0.17–0.38), 21 (95%CI: 12–37), and 0.89 (95%CI:0.86–0.92), respectively. In addition, the funnel plot suggested that the publication bias had no significant impact on assessment (p=0.07) (Figure 4G).

3.4.3 Subtypes of BC

Six studies including 581 patients evaluated the diagnostic value of non-coding RNA as a biomarker association with subtype of BC, including ER/PgR, PR. HER2/c-erbB-2. Using random effect models, the pooled SEN (Figure 5A), SPE (Figure 5B), PLR (Figure 5C), NLR (Figure 5D), DOR (Figure 5E), and AUC values (Figure 5F) were 0.89 (95%CI: 0.72–0.96), 0.91 (95%CI: 0.77–0.97), 10.1 (95%CI: 3.5–29.2), 0.13 (95%CI: 0.05–0.34), 80 (95%CI: 15–434), and 0.96 (95%CI: 0.94-0.97), respectively. The funnel plots

indicated that the publication bias probably might have no effect on evaluation (p=0.82) (Figure 5G). Among these three subgroups, subtype of BC group shows high level of SEN, SPE and AUC value.

Discussion

There was no meta-analysis on the expression of non-coding RNAs in blood system of breast tumor patients by now. In this study, we collected studies on the expression of non-coding RNAs in blood system of breast tumor patients from published studies, including 29 miRNAs[8-15, 17-20, 22, 23, 25, 26, 29], 2 lncRNAs [28, 30] and 1 circRNA [34] up-regulated, 7 miRNAs [15, 16, 21, 24] and 1 lncRNA[29] down-regulated. In this meta-analysis study, the diagnostic value of non-coding RNAs was evaluated as biomarkers for breast cancer in blood, serum and plasma. As for the overall non-coding RNAs expressions, the pooled SEN, SPE, PLR, NLR, DOR, and AUC values were 0.82(95%CI:0.76-0.86), 0.83(95%CI:0.75-0.88), 4.67(95% CI:3.19-6.84), 0.22(95%CI:0.17-0.29), 20.91(95%CI:12.01-36.40), and 0.89 (95%CI:0.86-0.91), respectively. Among all non-coding RNAs were investigated in this study, miRNA-34a showed effective diagnostic accuracy (AUC: 0.995; SEN: 0.974; SPE: 1) in plasma of BC patient.

The above results showed that non-coding RNAs indicated diagnostic biomarkers for breast cancer. However, it should be noted that there was substantial heterogeneity in the pooled estimates. We performed the meta-regression based on the variables including clinicopathological features, heterogeneity boxplot, and source of samples. The value of SEN, SPE, PLR, NLR, DOR, and AUC were list in Table 5. When we excluded 4 studies out of heterogeneity boxplot, the value of SEN, SPE, and AUC changed limited. Based on source of samples, we divided all studies into 3 subgroups such as blood, plasma, and serum. The value of SEN, SPE, and AUC were no significant difference among these 3 subgroups. In the clinicopathological features group, including lymphatic metastasis (tumor invasion), and subtype of BC (ER/PgR, PR or HER2/c-erbB-2) subgroups, the p value of them were higher than 0.1. Only in the TNM stage subgroup, p value was less than 0.05, that means the heterogeneity may come from the TNM stage. But using the Tau-square statistic (STATA), which heterogeneity explained by TNM stage, lymphatic metastasis (tumor invasion), subtype of BC (ER/PgR, PR or HER2/c-erbB-2) subgroups. The results showed that TNM stage group and lymphatic metastasis (tumor invasion) group tau-square were 0.0260 and 0.0054, less than 0.04, suggesting mild heterogeneity (supplement table 6). However, the subtype of BC subgroup shown the highest value of SEN, SPE, and AUC, then TNM stage subgroup shown the second higher value of SEN, SPE, and AUC. It is possible that the non-coding RNAs might be suitable for use as diagnostic biomarkers for TNM stage and subtype of BC, but more clinical dates should be needed to prove this.

The samples in all the studies were taken from three sources: blood, plasma, and serum. Whole blood contains the plasma, white blood cells, and red blood cells. Plasma is the liquid, cell-free part of blood, that has been treated with anti-coagulants. Serum is the liquid part of blood after coagulation, devoid of clotting factors as fibrinogen. Therefore, the non-coding RNA extracted from the whole blood included extracellular and intracellular RNA. Additionally, miRNAs and circRNAs are abundant in the circulating [37]. Therefore, the amount of non-coding RNA extracted from different components is not the same.

Serum for non-coding RNAs screening is suitable for breast cancer detection [38]. Only one study compared the level of miRNA-155, CA 15-3, CEA, and TPS in serum from breast cancer patient, when before surgery, after surgery, and after chemotherapy [25].The level of miR-155 increased after surgery, and decreased to the preoperative level after chemotherapy, other molecular markers shown no change trend. It's implied that we can use the serum level of miRNA as an indicator for chemotherapy treatment response. Especially in the post-operative treatment of patients, circulating miRNA might evaluate the therapeutic and toxicity effect in breast cancer patients [39]. Endocrine therapy is the most effective treatment for ER+ breast cancer, but its effectiveness is limited by high rates of hormone resistance during treatment [40]. For past several years, non-coding RNAs have also gained attention as the putative regulators and determinants of tamoxifen resistance. A number of reports have documented evidence from in vitro and/or in vivo studies, as well as from evaluation of clinical samples, to showcase the power of non-coding RNAs as mediators of tamoxifen resistance and the predictors of disease relapse [41]. A major limitation to using circulating miRNAs as biomarkers is their low abundance [42].

A meta-analysis is a statistical method for combining the results of different studies on the same topic and it may resolve conflicts among studies [43]. In this meta-analysis the patients in the individual studies can be substantially different with respect to diagnostic criteria, geographic region, and the time when the trial was conducted, among other factors [44]. And some including studies usually exclude unevaluable patients, therefore the published results tend to overestimate real treatment benefits[45]. The Heterogeneity variation among studies is due to dissimilarity in the results of individual studies. In some cases, the dissimilarities in results was due to the differences of within-study in the cut-off value, or any other reasons. Using meta-regression, the result suggested that TNM stage, was the major cause of heterogeneity. The patients of disease severity were not completely.

Breast cancer is a leading cause of death worldwide, and the main reason is lack of effective biomarker in early detection. The high prevalence of breast cancer motivates the development of better screening and diagnostic technologies. Serum and plasma are the most commonly sample for circulating miRNA and other non-coding RNA detection by qRT-PCR. Because of tissues not suitable for mass IHC screening. Serum markers were less well established in breast cancer, the most widely used serum markers in breast cancer are CA15-3 and carcinoembryonic antigen (CEA). Other markers include BR27.29 (also known as CA27.29), tissue polypeptide antigen (TPA), and tissue polypeptide specific antigen (TPS) also used detection. But these markers sensitivity and specificity are low[46]. It's a challenge to establish an accurate and reliable panel of circulating miRNAs, circRNAs, and lncRNAs for breast cancer diagnosis, prognosis and prediction of treatment response. In Despite some advances, there is still an important clinical need for the development and validation of novel biomarkers with greater sensitivity, specificity, and clinical utility.

Conclusion

The circulating level of miRNAs, circRNAs, and lncRNAs for breast cancer diagnosis may be effective. But more clinical dates should be need to prove this.

Abbreviations

miRNA, microRNA; lncRNA, long non-coding RNA; circRNA, circular RNA; SEN, sensitivity; SPE, specificity; PLR, positive likelihood ratios; NLR, negative likelihood ratios; CIs, confidential intervals; OR, odds ratio; DOR, diagnostic OR; SROC, summary receiver operator characteristics; AUC, area under the Curve of *ROC*; BC, breast cancer; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing Interests

The authors have declared that no competing interests exist.

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Authors' Contributions

HW conceived and designed the experiments; MW performed the experiments; MW, YG and ZJ analyzed the data; MW, YG and JZ contributed analysis tools; HW and MW wrote the manuscript. All authors have read and approved the manuscript.

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Not Applicable

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Tables

[Please see the supplementary files section to view the tables.]

Figures

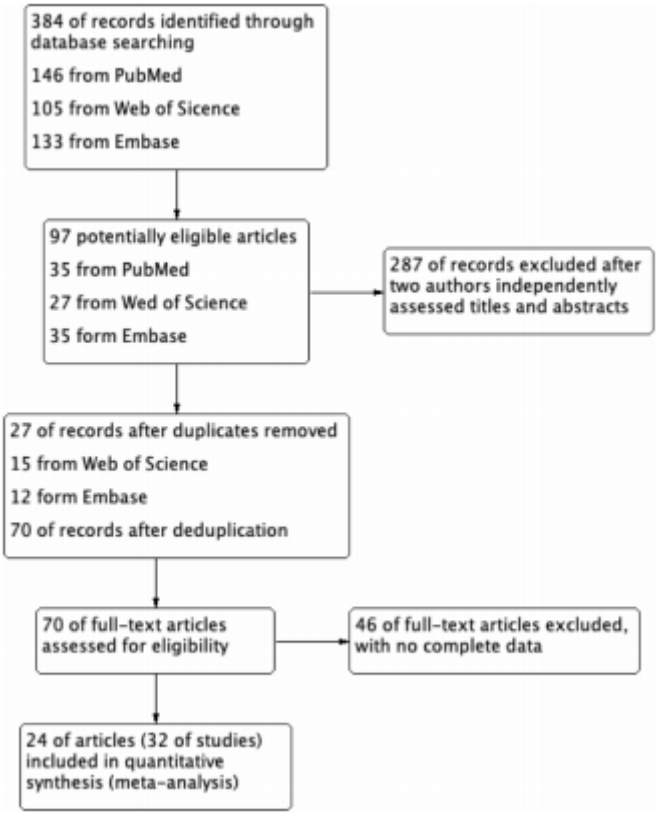

Figure 1

Flowchart of inclusion studies.

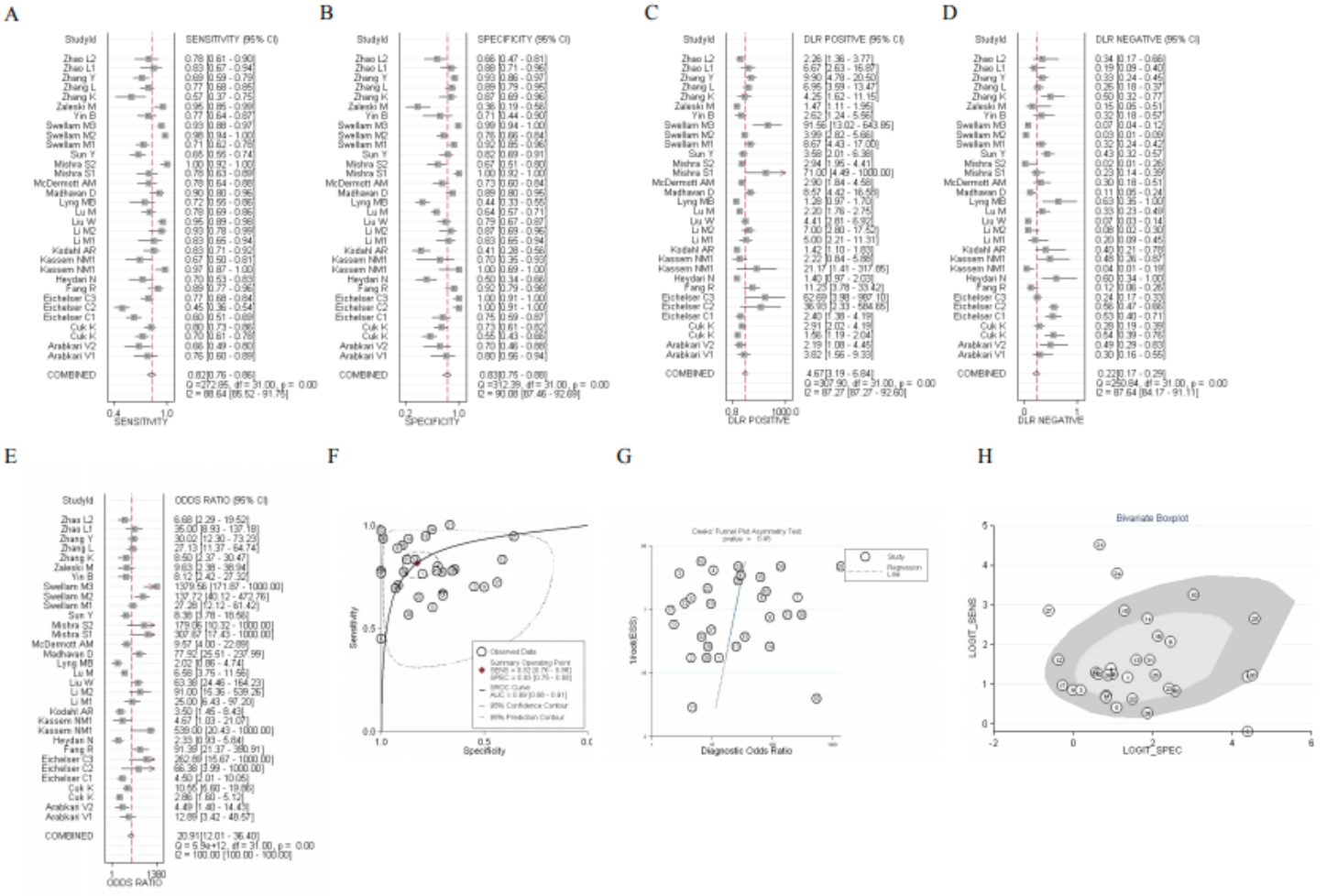

Figure 2

The results of meta-analysis in all studies for BC diagnosis. The forest plots of (A) SEN, (B) SPE, (C) PLR, (D) NLR, (E)DOR, and (F) AUC. (G) Funnel plot to evaluate publication bias. (H)Bivariate boxplot to detected the heterogeneity.

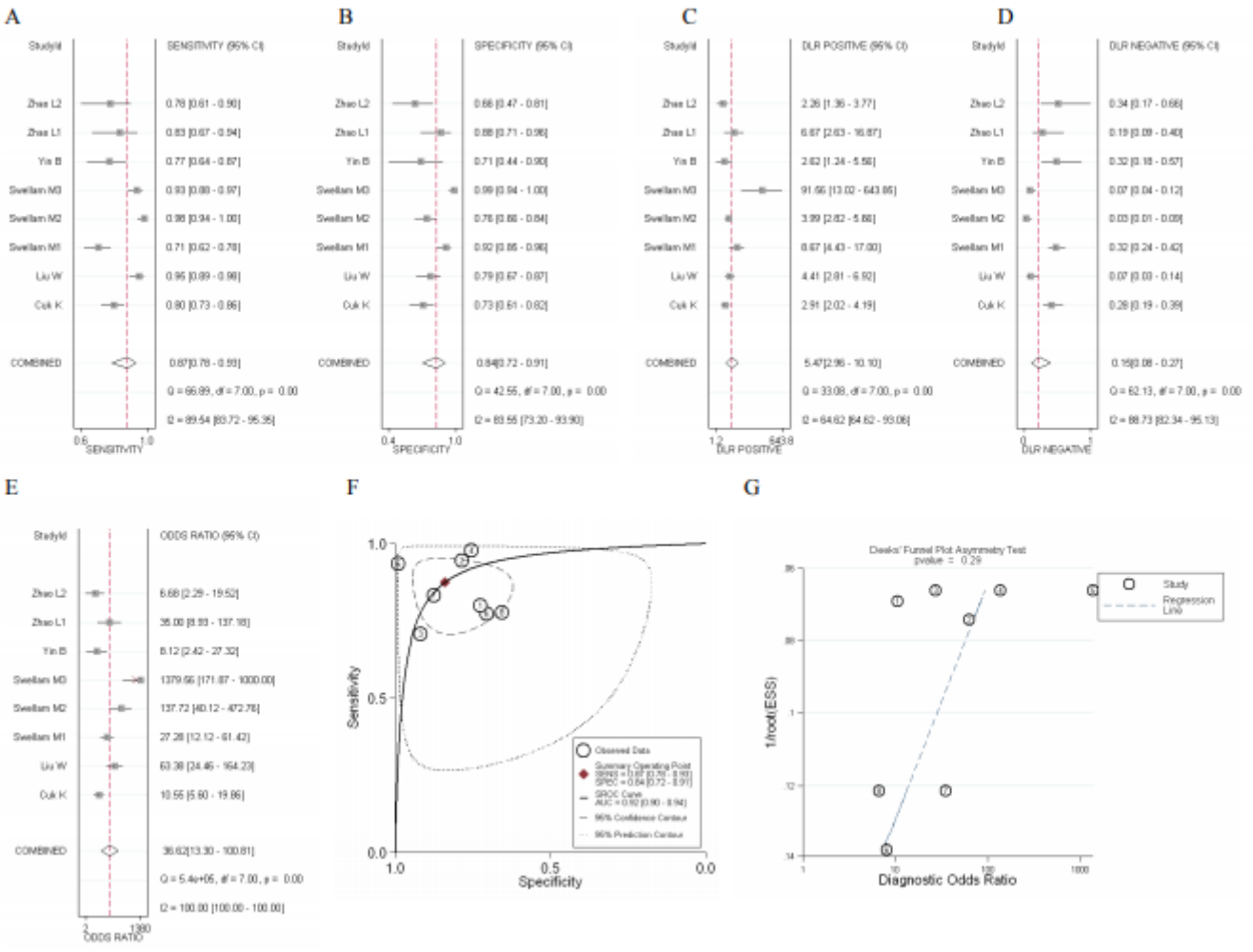

Figure 3

The results of meta-analysis in subgroup of the studies for non-coding RNA association with TNM stage. The forest plots of (A) SEN, (B) SPE, (C) PLR, (D) NLR, (E)DOR, and (F) AUC. (G) Funnel plot to evaluate publication bias.

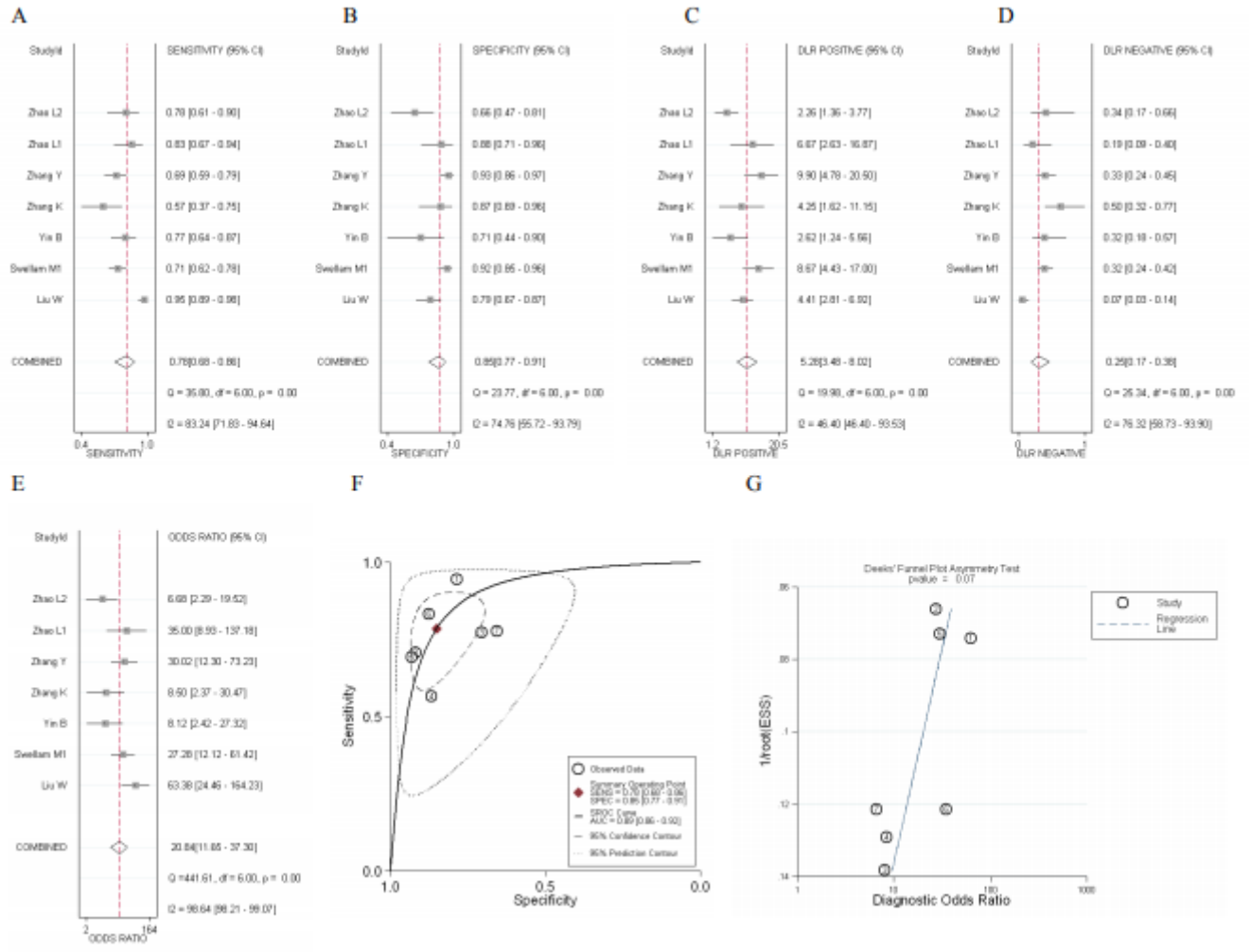

Figure 4

The results of meta-analysis in subgroup of the studies for non-coding RNA association with invasion. The forest plots of (A) SEN, (B) SPE, (C) PLR, (D) NLR, (E)DOR, and (F) AUC. (G) Funnel plot to evaluate publication bias.

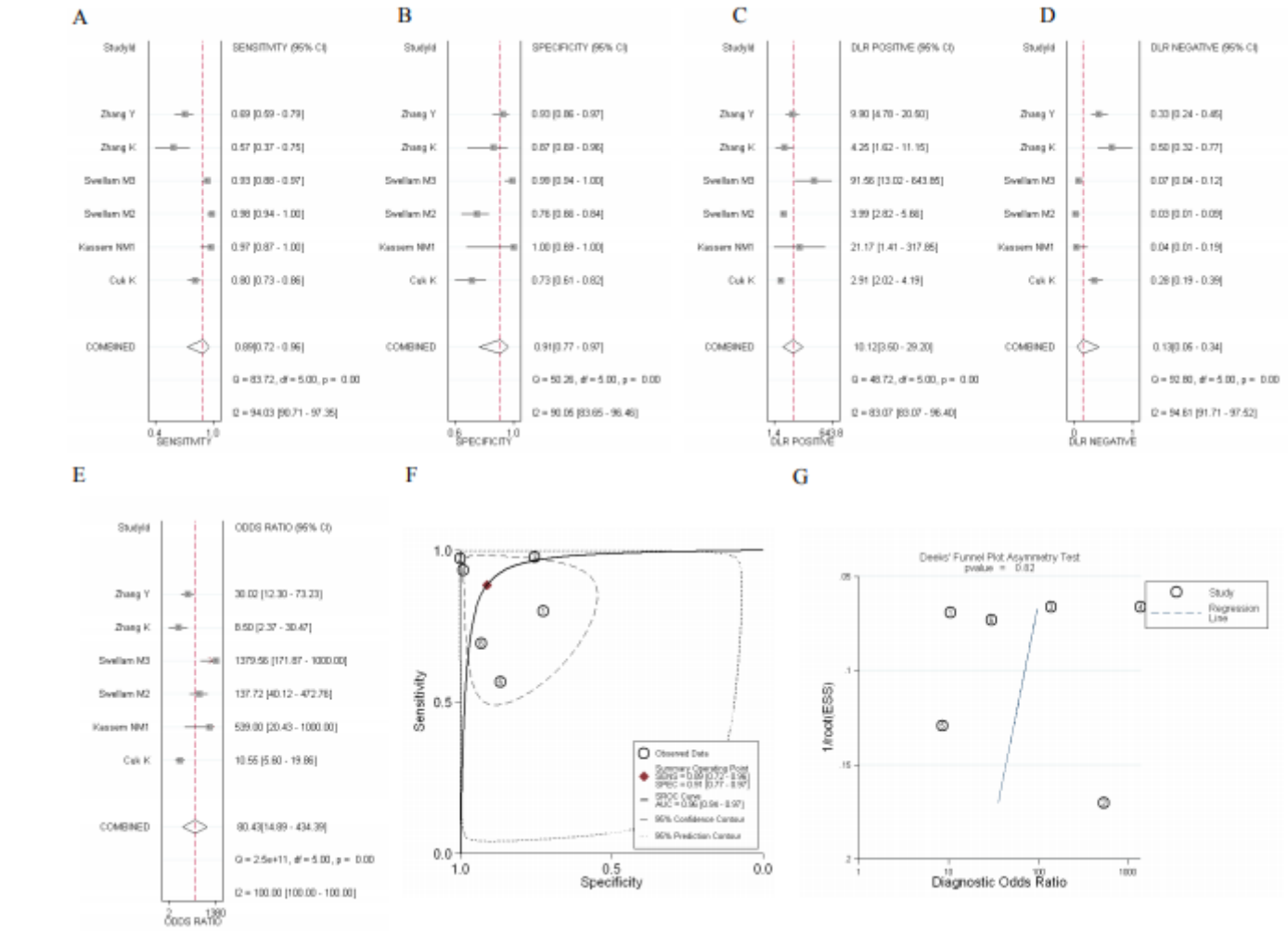

Figure 5

The results of meta-analysis in subgroup of the studies for non-coding RNA association with subtype of BC. The forest plots of (A) SEN, (B) SPE, (C) PLR, (D) NLR, (E)DOR, and (F) AUC. (G) Funnel plot to evaluate publication bias.

Supplementary Files

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