Research Article

microRNA-155 as a potential biomarker in early detection of breast cancer: A meta-analysis

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Abstract

Breast cancer is one of the leading malignancies in women worldwide. Early detection of breast cancer could be the best strategy to hold on to cancer and save lives. Circulatory microRNAs are the most dominant method for diagnosis and monitoring cancers. Here in this study, we aimed to see the potential of miR-155 as a diagnostic biomarker for breast cancer early detection. Eligible studies were analyzed for diagnostic test accuracy using online databases, a univariate model was pooled for sensitivity and specificity, while a bivariate meta-analysis model was employed to plot the Summary Receiver Operator Characteristic (SROC) using R-Studio. A total of 10 selected studies referring to miR-155upregulation were put on the diagnostic test. The results showed the sensitivity and specificity of 0.98 [95% Cl 0.88; 0.99], 0.94 [95% Cl 0.74; 0.98], DOR of 237.635 [95% Cl 22.835; 2473.001] and Area Under the Curve (AUC) of SROC was 0.964 [95% Cl]. Thus, our results have shown that miR-155 could be used as a potential biomarker for the early detection of breast cancer.

Keywords: Breast cancer; Microrna-155; Specificity; Sensitivity; Diagnostic test; Biomarker.

Introduction

Breast cancer is one of the most common cancers among the women globally and it takes 10.4% of all types of cancers making it the second most common type of non-skin cancer [1]. In 2020 about 2-3 million women were diagnosed and 685,000 fatalities were recorded with breast cancer worldwide [2]. Among Asian countries, Pakistan has the highest incidence of breast cancer with an estimation of one out of every nine women developing breast cancer at some point in their lives. According to research published in 2018 by the International Agency for Research on Cancer, around 34,000 new cases of breast cancer were diagnosed in Pakistani women [3].

Recent studies have suggested that early detection of breast cancer could reduce the death rate of the female with breast cancer [4]. Studies have suggested that there are many methods for the early detection of breast cancer, including biopsy, MRI, mammography, and breast MI [5]. However, serum miRNAs are one of the emerging techniques for the early detection of breast cancer [6].

miRNAs are small non-coding RNAs of 19–25 nucleotides that were revealed to control the expression of a wide range of genes and related pathways [7]. The genes of miRNAs account for 1–2% of all known eukaryotic genes; it involves various pathways including apoptosis, cell differentiation, migration, and development [8,9]. According to miRbase, over 2500+ miRNAs are present in the human genome and 60% of mRNA is targeted by these miRNAs [10]. However, amongst these miRNA's, miR-155 is associated with breast cancer.

The miR-155 is generated from an exon of non-coding RNA transcribed by the B-cell integration cluster located on chromosome 21, which is emphasized and investigated extensively [11]. It is a melanoma miRNA that plays a role in a variety of regulated processes, including immuno regulation and cell division [12]. The abnormal expression of miR-155 has been linked to a variety of cancer including lung cancer, breast cancer, and other carcinomas [13]. MiR-155 is elevated in women with breast cancer in several investigations and has been proposed as possible cancer detection diagnostic [14-23].

Here we conducted a meta-analysis on miR-155 to evaluate the Diagnostic Test Accuracy (DTA) in the early detection of breast cancer patients.

Materials and methods

Search strategy

We conducted a thorough search strategy in various databases including Pub Med, Science Direct, Google Scholar, and the Cochrane Library to find the study that aimed at the association between the expression of miRNA-155 and breast cancer in the early detection of breast cancer from 2015 to 2022. The keywords used throughout the literature retrieval were "microRNA-155" or "miR-155" or "miRNA-155" and "breast cancer" or "breast tumor" or "breast carcinoma" or "breast neoplasm" or "early diagnosis" and "serum" or "sera" or "blood" or "plasma". To obtain additional relevant articles, we reviewed conference summaries and reference lists of articles identified in the initial search and even approached authors via email to get additional information if necessary.

Eligibility criteria

All eligible studies retrieved by our search strategy were thoroughly reviewed. Any conflicts in disputed studies were sorted by the detailed discussion that results in consensus. Studies were considered eligible if they meet the following inclusion criteria (1) the diagnosis of breast cancer was made based on the histopathological confirmation, which is widely regarded as the gold standard for a breast cancer diagnosis; (2) studies detecting miR-155 concentration must be in peripheral blood; (3) peripheral blood must have been collected for miR-155 analysis before any treatment; (4) studies presenting sufficient data to allow construction of two-by-two tables, and (5) patients with the benign disease or healthy people served as the control group. Additionally, study exclusion criteria were: (1) duplicate publications; (2) unqualified data; and (3) studies with fewer than 20 patients; All of the literature in line with the above criteria is considered to be qualified studies.

Data extraction

The data were extracted from all eligible studies. The following information was recorded about each study (First Author, Year of publication, Patients and control, expression of miR-155), and data for the 2 x 2 table (sensitivity, specificity, and cutoff) (Table 1).

Statistical analysis

Statistical analysis was conducted using R-Studio, following the recommended meta-analysis methods for diagnostic accuracy [24]. The 2 x 2 contingency tables were constructed using

Table 1: Studies indicating uniformity in evaluation of miR-155 in Breast Cancer.

Studies	Year	Patients/ Control	Sample	Methods	Expression	Ref
Maha M.Itani	2021	41/32	blood	RT-qPCR	UP	[14]
Fatemeh Hosseini Mojahed et al.	2020	36/36	serum	RT-qPCR	UP	[15]
Farzaneh Raeisi et al.	2020	30/15	serum	qRT-PCR	UP	[16]
Elaheh Soleimanpour et al.	2019	30/25	Plasma	RT-PCR	UP	[17]
Menha Swellam et al.	2019	143/39	serum	RT-qPCR	UP	[18]
Sheng-kai Huang et al.	2018	158/107	Blood	RT-qPCR	UP	[19]
Ji-Guang Han et al.	2017	99/21	serum	RT-PCR	UP	[20]
Reham A. A. Elshimy et al.	2017	60/20	serum	qRT-PCR	UP	[21]
Bentolhoda Shooshtarian et al.	2017	90/70	blood	RT-PCR	UP	[22]
Thalia Erbes et al.	2015	24/24	serum	RT-PCR	UP	[23]

the sensitivity and specificity of each study. A recommended standard univariate meta-analysis model was utilized to summarize the sensitivity, specificity, Diagnostic Odds Ratio (DOR), and finally to generate the bivariate Summary Receiver Operator Characteristic (SROC) curve with their 95% Confidence Level (Cls). The pooled sensitivity, specificity, and other related indexes across the studies were calculated using a random-effect model. The heterogeneity was analyzed using i2 and t2 in studies. A value above 50% is considered a significant heterogeneity [25].

Results

A total of 17 studies were identified in the selected period (2015–2022) using various databases. However, based on our inclusion and exclusion criteria 10 studies were analyzed for the final meta-analysis.

Study characteristics and quality assessments

The selected 10 studies consisting of 711 breast cancer patients and 389 healthy controls. All the selected studies had adopted reverse transcription-quantitative PCR (RT-qPCR) for the detection of miRNAs in the patient serum. The Sensitivity, specificity, Diagnostic Odd Ratio (DOR), and SROC were evaluated among the given studies.

Sensitivity and specificity

Forest plots were plotted as shown in Figures 1 and 2. The total sensitivity of included studies was 0.98 [95% Cl 0.88; 0.99] and the total specificity was 0.94 [95% Cl 0.74; 0.98], indicating a potential diagnostic ability. The common effect size was shared among studies and significant heterogeneity was observed for

sensitivity and specificity (I2 = 79% and 73%, respectively).

The first Author and year of publication of each study is mentioned. The sensitivity is given with 95% Confident interval (CIs).
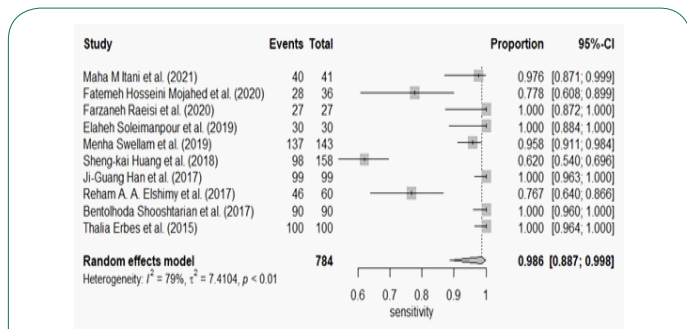

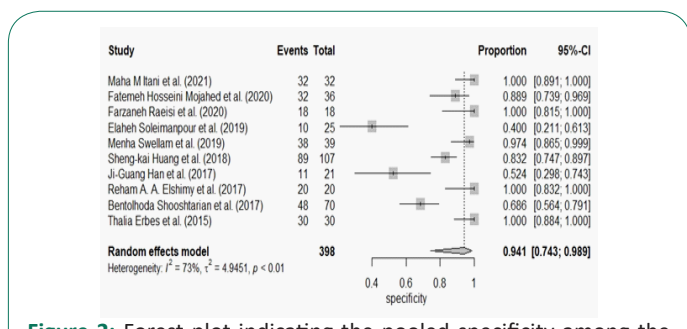**Figure 1:** Forest plot indicating the pooled sensitivity among the studies.

Figure 2: Forest plot indicating the pooled specificity among the studies.

SROC and DOR

The area under the SROC (AUC) curve was used to represent the performance of diagnostic tests. The results are shown in Figures 3 and 4.The pooled Area Under the Curve (AUC) of SROC was 0.964 [95% CI], indicating that miR-155 had excellent test performance. The DOR is 237.635 [95% CI 22.835; 2473.001].
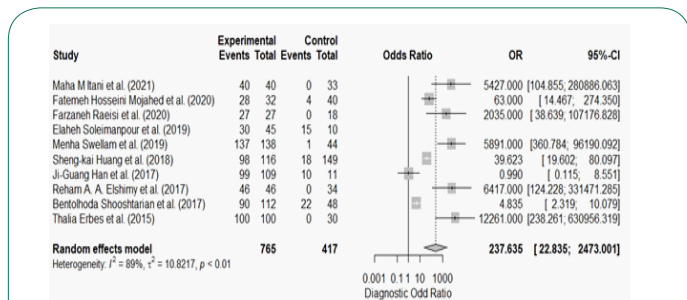

Figure 3: Forest plot indicating the Diagnostic Odd Ratio (DOR) among the studies.
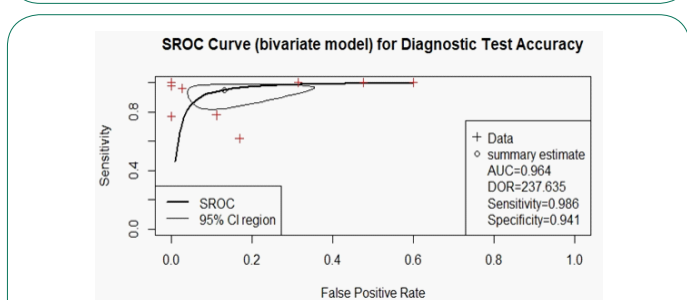

Figure 4: Summary Receiver Operator Characteristic (SROC) Curve for miR-155 analysis. The SROC curve showing AUC of 0.964 indicating miR-155 a potential biomarker.

Threshold effect

The threshold effect is influenced by changes in sensitivity and specificity. Therefore, we used Spearman Correlation Coefficients for evaluating the threshold effect [26]. The Spearman correlation coefficient of sensitivity and specificity in this meta-analysis was -0.212 with a p-value of 0.553, indicating that there is no heterogeneity from the threshold effect. The inconsistency in this meta-analysis may be due to the number of patients, the proportion of participants (stage I, II %), and the endogenous control.

Discussion

Sensitive and specific biomarkers are essential for early cancer diagnosis and disease monitoring. Carcinoembryonic Antigen (CEA) and/or Cancer Antigen 15-23 (CA15-3) are used as serum biomarkers for breast cancer. Unfortunately, these markers have low sensitivity and specificity for breast cancer screening. In recent years, aberrant expression of miRNAs has been widely reported in various carcinomas [14-23]. Half of all known miRNAs have been found in cancer-associated genomic regions or fragile locations, implying that they may have a role in the start and progression of human cancers [27]. Studies have been showing that miRNAs derived from epithelial tumors are rapidly released into the bloodstream [28]. miRNAs are thus potential early diagnostic biomarkers to detect breast cancer and monitor the treatment response of breast cancer patients. Among all uncovered miRNAs, miR-155 is no doubt one of the most attractive ones, which is reported to have potential diagnostic and prognostic value for cancers [14-23]. As the diagnostic role of miR-155 has not yet been well elucidated and has controversial results, however, we performed a comprehensive meta-analysis and estimated the pooled accuracy of miR-155 for cancer detection.

In our meta-analysis the data has shown a promising result, the pooled sensitivity and specificity are 0.98 [95% CI 0.88; 0.99] and 0.94 [95% CI 0.74; 0.98], respectively, indicating a potential biomarker for breast cancer. The Diagnostic Odds Ratio (DOR) defined as the ratio of the odds of a true-positive to the odds of a false-positive, is a single indicator of diagnostic test accuracy that combines the sensitivity and specificity data into a single indicator [29]. The value of DOR ranges from 0 to infinity with higher values indicating better discriminatory test performance. The DOR value was 237.635 [95% CI 22.835; 2473.001] indicates that the circulating miR-155 could be a useful biomarker for breast cancer patients' diagnosis. SROC is usually used to summarize overall test performance, and AUC is calculated to evaluate the accuracy of the selected indicator. To demonstrate excellent accuracy, the valve of AUC should be more than 0.97. An AUC of 0.93 to 0.96 is considered to be very good and 0.75 to 0.92 is good. However, a value of less than 0.75 can be still reasonable, while the test will have an obvious deficiency in its diagnostic accuracy, approaching a random test [30,31]. In this meta-analysis, we show that circulating miR-155 demonstrates good accuracy in the diagnosis of breast cancer, with an AUC of 0.964 [95% CI]. Overall, circulating miR-155 has good sensitivity and specificity in the diagnosis of breast cancer.

Heterogeneity should be analyzed when interpreting the results for meta-analysis. One of the primary causes of heterogeneity in test accuracy studies is the threshold effect, which arises when differences in sensitivities and specificities occur due to different cut-offs or thresholds used in different studies to define a positive or negative test result. For different cut-off

values that were used among the three studies, we used the Spearman correlation coefficient to analyze the threshold. The Spearman correlation coefficient of sensitivity and specificity was -0.212 (p = 0.553), indicating that there is no heterogeneity in the threshold. Although, different methods are used for detecting circulating miR-155. Therefore, different laboratories take different measures to quantify the circulating miR-155, which may contribute to sources of heterogeneity. In addition, the number of patients and the representation of the participants (stage I, II %) in different studies may also involve forming heterogeneity.

However, due to the diversification in the expression of miR-NAs in cancer detection, combination therapy including different miRNAs profiles and circulatory protein may be a novel approach to achieve better results. Different studies have been reported on different miRNAs profiles which have shown more effective results rather than using a particular miRNA.

Competing interest: The author/s declare no competing interest.

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