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Evaluation of the Clinical Outcome of Metastatic Breast Cancer Patients with Negative and Positive Circulating Tumor DNA: A Systematic Review and Meta-analysis

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ABSTRACT

Background and aim: The present study was conducted with the aim of evaluating the clinical outcome of metastatic breast cancer patients with negative and positive circulating tumor DNA.

Material and methods: Searching international databases PubMed, Web of Science, Scopus, Science Direct, Web of Knowledge, EBSCO, Wiley, ISI, Elsevier, Embase databases, and Google Scholar search engine based on PRISMA 2020-27-item checklist and keywords Related to the objectives of the study, it was carried out from 2019 to February 2024. a model with fixed effect and inverse–variance method was used. All statistical analyses are done using STATA/MP software. v17 was done considering the significance of less than 0.05.

Results: Six studies were selected according to the inclusion criteria. Compared with patients with negative ctDNA, those with positive ctDNA had a higher risk for progression-free survival and overall survival (HR 2.02, 95% CI 0.71-3.33; P-value < 0.001) and (HR 2.78, 95% CI 1.47-4.10; P-value < 0.001), respectively.

Conclusions: In metastatic breast cancer patients, it was individually and jointly associated with progression-free survival and overall survival-positive circulating tumor DNA.

1. Introduction

Today, the prevalence of breast cancer is increasing, and it is the most common type of cancer among women.[1] In recent years, the prevalence of the disease has been growing, and the data shows that the survival rate of patients up to five years and ten years after diagnosis was 88 and 81%, respectively.[2] It is predicted that by 2070, new cases of breast cancer will reach about 4.4 million people.[3] Breast cancer metastasis is the cause of most of the deaths caused by breast cancer.[4] Diagnosing breast cancer metastasis in the early stages will help to determine the best way to control and prevent the progression of breast cancer or to control the disease and improve the patient's quality of life.[5] Currently, diagnosis of breast cancer metastasis is based on clinical signs of spread to other organs, biopsy of affected organs, radiological evaluations, imaging methods, and tumor serum markers.[6] Knowing the pre-diagnosis methods of cancer can be very important.[7]

Breast cancer metastasis, in other words, the spread of the tumor around the chest and lymph nodes, is an important complication of this disease, which leads to treatment failure and reduced patient survival.[8] Predicting the probability of metastasis is very important in understanding the disease and its treatment.[9] In the direction of screening, diagnosis, and treatment of breast cancer, many advances have been made so far. However, current diagnostic methods are invasive, and their use to predict the prognosis of breast cancer has limitations. Studies have shown that the use of biomarkers can also help in diagnosis. However, degrees of limitations have been reported for these methods.[10] Studies have shown that circulating tumor DNA (ctDNA) can analyze individual genetic changes by fully identifying target genes. The detection of ctDNA in hematological cancers has been widely investigated and has been proven; however, its detection in solid tumors is controversial and challenging.[11] The findings of studies have shown that ctDNA can be effective in the prognosis of solid tumors (lung cancer, breast cancer, pancreatic cancer).[12-15] However, even though ctDNA can predict patient survival, this field has many challenges. Therefore, the present study was conducted to evaluate the clinical outcome of metastatic breast cancer patients with negative and positive circulating tumor DNA.

2. Material and methods

Search strategy and Information sources

Searching international databases PubMed, Web of Science, Scopus, Science Direct, Web of Knowledge, EBSCO, Wiley, ISI, Elsevier, Embase databases, and Google Scholar search engine based on PRISMA 2020-27-item checklist[16] and keywords Related to the objectives of the study, it was carried out from 2019 to February 2024. The keywords were standardized in MeSH and used for searching. In addition, the reference list of the selected articles was screened to find relevant studies. The search strategy was (((((((("Breast Neoplasms"[Mesh]) OR ("Breast

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Neoplasms/diagnosis"[Mesh] OR "Breast Neoplasms/genetics"[Mesh] OR "Breast Neoplasms/prevention and control"[Mesh] OR "Breast Neoplasms/therapy"[Mesh])) AND ("Prognosis"[Mesh] OR "Survival Analysis"[Mesh])) OR ("Survival"[Mesh] OR "Mortality"[Mesh])) OR "Treatment Outcome"[Mesh]) AND "Circulating Tumor DNA"[Mesh]) OR "DNA, Neoplasm"[Mesh]) AND) AND "Neoplasm Metastasis"[Mesh]) OR "Neoplasm Metastasis/diagnosis"[Mesh].

At first, a list of titles and abstracts of all articles searched in the databases under review was prepared. This work was done independently by two researchers. The articles with duplicate titles were removed. Next, the abstracts of the articles were checked to find suitable studies, and all the searched studies were saved in EndNote. The software performed X8 software and the rest of the steps.

Study selection criteria

The inclusion criteria for the studies were randomized control trial studies, cohort studies, observational studies, cross-sectional studies, metastatic breast cancer patients, measurement of ctDNA, report of clinical outcome, and Publication in English. The exclusion criteria were chosen: irrelevant in terms of study design and research topic, studies that did not contain enough information, low-quality studies, studies with incomplete data, case series studies, Review studies, case reports, letters to the editor, and conferences.

Selection and data collection process

Two researchers independently extracted data from the articles using a standard data collection form prepared in advance to reduce reporting bias and errors in data collection. The study team first designed this form, which included the following items: author name, study title, year of publication, type of study, number of patients, Treatment protocol, and mean age.

Article quality assessment

The Newcastle-Ottawa Scale (NOS) evaluates the quality of cohort, observational, and case-control studies.[17] The NOS has a maximum of 9 grades, which are classified into 3 criteria. Any study with scores equal to or higher than 7 is considered high quality, with 2 to 6 being average quality and equal to and less than 1 being poor quality.

The Cochrane risk-of-bias tool for randomized trials (RoB 2) is recommended for assessing the risk of bias in randomized trials.[18] Bias is assessed as a judgment (high, low, or unclear) for individual elements from five domains (selection, performance, attrition, reporting, and others).

Meta-analysis

The odds and hazard ratios with a 95% confidence interval (CI) were used. The I^2 statistic, used to measure inconsistency, was used to analyze the degree of variation across studies (heterogeneity). Low levels of heterogeneity were defined as I^2=25–49%, moderate levels as I^2=50–74%, and high levels as I^2=75–100%.[19] A model with fixed effect and Inverse–variance was used. All statistical analyses are done using STATA/MP software. v17 was done considering the significance of less than 0.05.

3. Results

Study selection

In the first stage of the search, 375 articles were found, and after reviewing the titles of the articles, 49 duplicate and overlapping articles were removed. Abstract: 291 possible related articles were reviewed, and 263 unrelated articles were identified and eliminated. The full text of the remaining 28 articles was reviewed, and finally, six suitable articles were selected to enter the meta-analysis stage (Fig. 1).

Study characteristics

Five hundred seventy-five metastatic breast cancer patients were examined. ctDNA method and other characteristics are reported in Table 1.

Quality assessment

Based on the quality measurement tools, all the selected studies were of high quality, with 8/9 scores. (Table 2)

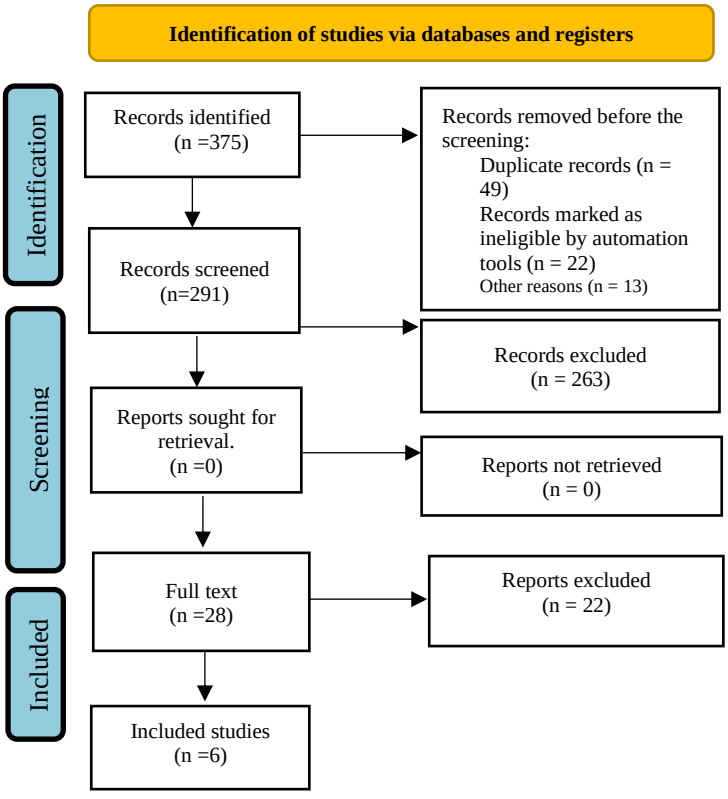

Fig. 1. PRISMA 2020 Checklist.

Table 1. The characteristics of the selected articles according to the purpose of the study.

No.	Study, Years	Study design	Number of metastatic breast cancer patients	Mean age (years)	Number of blood samples	ctDNA method	Outcome
1	Park et al., 2024[20]	Prospective study	98	45	98	dPCR	Patient progression-free survival
2	Keup et al., 2020[21]	Cohort study	18	>50	37	NGS	Patient progression-free survival
3	Clatot et al., 2020[22]	Prospective study	103	66	596	dPCR	Patient progression-free survival, overall survival
4	Li et al., 2020[23]	Pilot Study	45	48	45	NGS	Overall survival
5	Ye et al., 2019[24]	Cohort study	117	54.5	227	dPCR	Patient progression-free survival, overall survival
6	Fernandez-Garcia et al., 2019[25]	Cohort study	194	59.50	194	dPCR	Patient progression-free survival, overall survival

Table 2. Risk assessment of bias in cohort studies.

Study, years	Selection			Comparability		Outcome			Score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at the start of the study	Comparability of cohorts based on the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow-up of cohorts	
Park et al., 2024[20]	1	1	1	1	1	1	1	1	8
Keup et al., 2020[21]	1	1	1	1	1	1	1	1	8
Clatot et al., 2020[22]	1	1	1	1	1	1	1	1	8
Li et al., 2020[23]	1	1	1	1	1	1	1	1	8
Ye et al., 2019[24]	1	1	1	1	1	1	1	1	8
Fernandez-Garcia et al., 2019[25]	1	1	1	1	1	1	1	1	8

Compared with patients with negative ctDNA, those with positive ctDNA had a higher risk for progression-free survival (HR 2.02, 95% CI 0.71-3.33; P-value < 0.001) (Fig. 2). The heterogeneity test showed that Q = 3.61, p-value=0.46, I^2 = 0%, which denotes a low heterogeneity among studies.

Compared with patients with negative ctDNA, those with positive ctDNA had a higher risk for death (HR 2.78, 95% CI 1.47-4.10; P-value < 0.001) (Fig. 3). The heterogeneity test showed that Q = 1.57, p-value=0.67, I^2 = 0%, which denotes a low heterogeneity among studies.

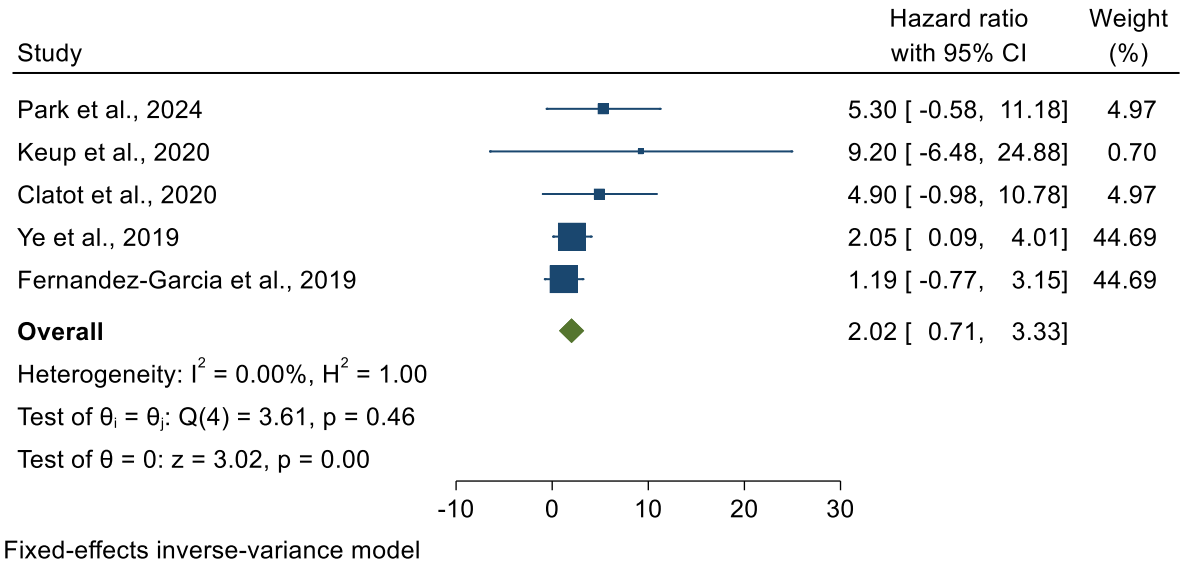

Fig. 2. The forest plot showed a cfDNA level with patient progression-free survival.

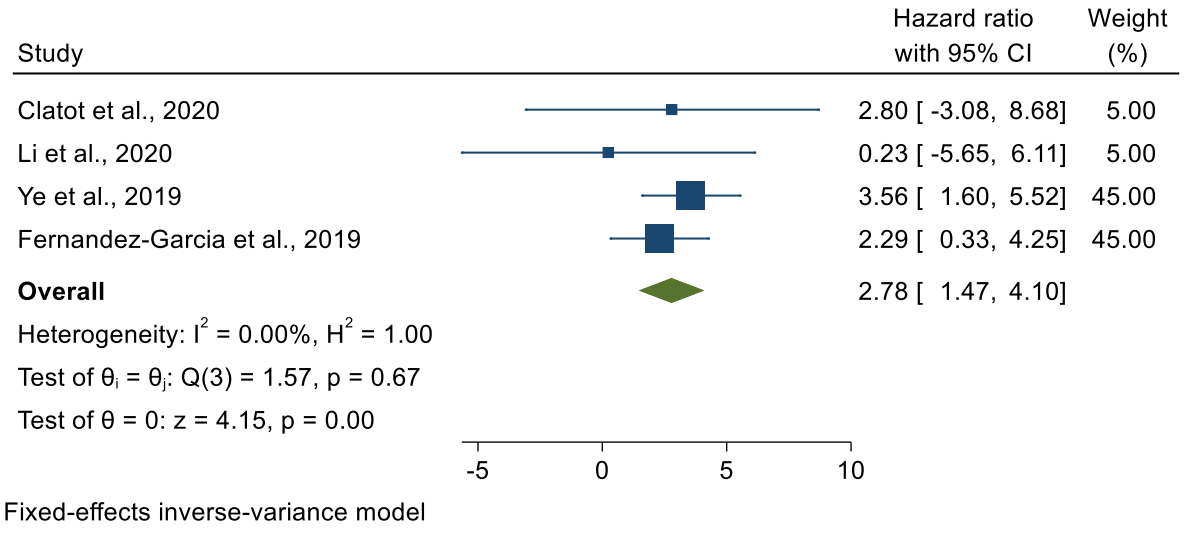

Fig. 3. The forest plot showed cfDNA level with patient overall survival.

4. Discussion

It forms an important part of free nucleic acids in plasma. Quantitative and qualitative changes of this marker are used to identify and track all types of cancers, prenatal diagnoses, cardiovascular diseases, and organ transplants. The origin of cfDNA in healthy people's plasma is mainly from cell apoptosis. However, studies have shown that living cells may also actively release DNA fragments into the plasma.[26] ctDNA subset of cfDNA secreted from cancer cells and tumors into the bloodstream. Most of the DNA is inside the cell nucleus. As the tumor grows, the cells die and are replaced by new cells. Are replaced. Dead cells break down, and their contents, including DNA, are released into the bloodstream. Circulating tumor DNA is single- or double-stranded DNA released into the blood by tumor cells and contains the original tumor mutations.[27] In recent years, liquid biopsy based on ctDNA analysis has greatly contributed to molecular diagnosis and monitoring of cancer. Studies show that genetic mutation screening using ctDNA is highly sensitive and specific, suggesting that ctDNA analysis may significantly improve current tumor detection systems and even facilitate early-stage diagnosis. In addition, ctDNA analysis can accurately determine tumor progression and prognosis and aid in targeted therapy.[28]

Circulating cfDNA has been recognized for its clinical significance in various malignancies, including breast cancer. In cancer patients, the production of larger cfDNA fragments due to processes such as necrosis results in elevated cfDNA levels compared to those in healthy individuals.[29] Studies have shown that ccfDNA is directly related to the clinical outcomes of cancer patients.[30] According to our knowledge, this is the first meta-analysis that investigated the clinical outcome of metastatic breast cancer patients with negative and positive circulating tumor DNA. In this study, we have tried to provide new evidence that ccfDNA can have prognostic value in metastatic breast cancer patients. A systematic study and meta-analysis showed that there is a statistically significant relationship between increased ccfDNA and worse survival in solid tumors.[31] Based on the present study's findings, ccfDNA levels are related to clinical outcomes in metastatic breast

cancer patients. Consistent with the results of the present study, Shaw et al., 2017 reported that (OS: HR 2.2, P =0.03).[32]

5. Conclusion

Positive circulating tumor DNA was individually and jointly associated with progression-free survival and overall survival in metastatic breast cancer patients. In patients with metastatic breast cancer, ctDNA is reflective of overall survival. Importantly, ctDNA levels are the best predictor of disease response and progression-free survival; however, analysis of ctDNA as a paired test provides additional prognostic information and allows further stratification of patients.

Conflict of Interest

The authors declared that there is no conflict of interest.

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