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

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ABSTRACT

Background and aim: This research addressed predicting the risk levels of breast cancer recurrence through the Circulating Tumor DNA (ctDNA) diagnostic method. The primary objective of the research was the evaluation of the clinical outcomes of cases suffering from breast cancer who exhibited positive and negative ctDNA.

Material and methods: To achieve the objectives of the study, databases at the international scale, including Web of Science, PubMed, Science Direct, Wiley, Scopus, EBSCO, Web of Knowledge, ISI, Embase, Google Scholar, and Elsevier, were searched according to PRISMA 2020-27-item checklist and respective keywords from 2019 to February 2024. Moreover, the inverse-variance method and the fixed effect model were applied to the research. In addition, we used STATA/MP v17 for statistical analyses of the data (Sig, < 0.05).

Results: Based on the search, 11 articles were chosen, considering the inclusion criteria intended for the research. The odds ratio (OR) of ctDNA measurements with the positive result equaled 47% with a significant p-value compared to the negative ctDNA. Thus, similar overall survival was found in three (3) time points (P = 0.83). Furthermore, the detection rate of the positive versus negative ctDNA was found to be 72% (ES:72% 95% CI; 54%-89%) in the baseline and 44% (ES:44% 95% CI; 12%-100%) during neoadjuvant chemotherapy. Consequently, the negative conversion rate of the positive versus the negative ctDNA in the baseline-during neoadjuvant chemotherapy equaled 52% (ES:0.52 95% CI; -0.30-1.33), but it was 60% during neoadjuvant chemotherapy before the surgical operation (ES:0.60 95% CI; -0.71-1.91). Given testing the group differences, we did not observe any significant differences between the mentioned time points.

Conclusions: The performed meta-analysis revealed the potential of ctDNA to be applied as one of the reference indexes for evaluating the treatment effects during NAT, before and after surgical operation, and at baseline.

1. Introduction

Breast cancer is the most common cancer among women.[1] According to the statistics of the World Health Organization, one out of every 8 to 10 women will get breast cancer.[2] With over 2.3 million new cases and 685,000 deaths in 2020, breast cancer is the most commonly diagnosed cancer worldwide.[3] It is predicted that by 2070, new cases of breast cancer will reach about 4.4 million people.[4] Breast cancer is divided into three categories in terms of clinical characteristics: 1. Lobular Carcinoma in Situ (LCIS), 2. Ductal Carcinoma In Situ, and 3. Invasive breast carcinoma.[5] Breast cancer is a highly heterogeneous disease that is caused by the interaction of genetic and environmental risk factors and leads to the progressive accumulation of genetic and epigenetic changes in breast cancer cells.[6] Although epidemiological evidence emphasizes the existence of special risk factors such as age, obesity, alcohol consumption, and exposure to estrogen during life, the existence of a family history of breast cancer is considered the strongest risk factor for this disease.[7] Almost 20% of all breast cancers are familial types, and in terms of pathogenesis, they have a specific dependence on the special predisposing gene of that disease.[8, 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, various 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 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] Therefore, in the present study, predicting the risk of

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breast cancer recurrence using the ctDNA diagnostic method was investigated. This study aimed to evaluate the clinical outcome of 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 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].

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; 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, 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 and included the following items: author name, study title, year of publication, type of study, number of patients, Treatment protocol, and mean of age.

Article quality assessment

The Newcastle-Ottawa Scale (NOS) is used to evaluate the quality of cohort, observational, and case-control studies.[17] NOS has a maximum of 9 grades, classified into 3 criteria. Any study with scores equal to or higher than 7 is considered high quality, 2 to 6 is average quality, and equal to and less than 1 is 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 ratio, risk ratio, hazard ratio, detection rates, and proportion 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, 388 articles were found, and after reviewing the titles of the articles, 29 duplicate and overlapping articles were removed. Abstract 324 possibly related articles were reviewed, and 286 unrelated articles were identified and eliminated. The full text of the remaining 38 articles was reviewed, and finally, eleven suitable articles were selected to enter the meta-analysis stage (Fig. 1).

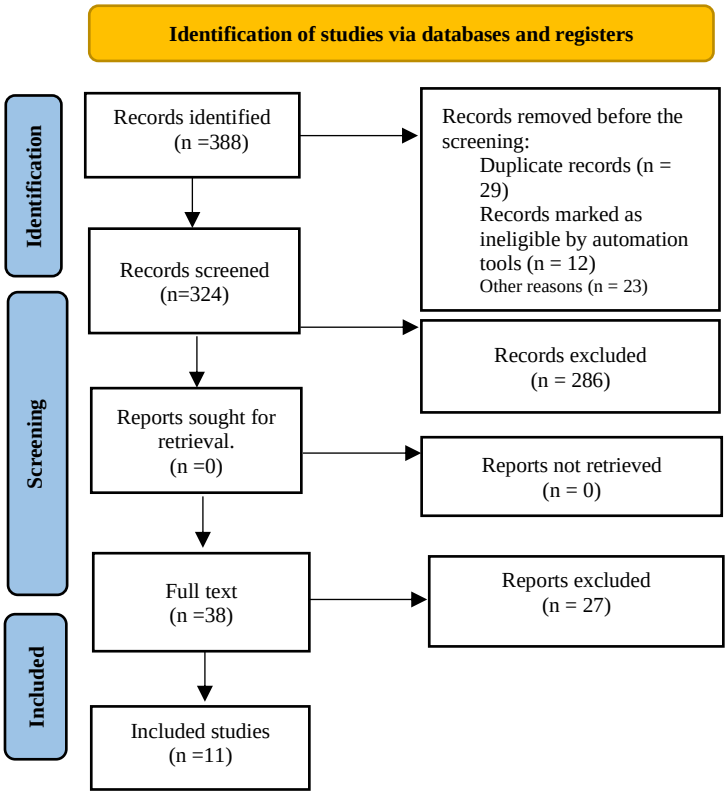

Fig. 1. PRISMA 2020 Checklist.

Study characteristics

Nine hundred seventy-five patients with breast cancer were examined at different time points. The meaning of different time points, baseline, was during chemotherapy, before, and after surgery. ctDNA method differed in each study; only a few studies used similar methods. Other characteristics are reported in Table 1.

Quality assessment

All the selected studies were of medium to high quality based on the quality measurement tools. In the cohort studies, only two scored 6 out of 9, indicating medium quality; the other eight had high quality (Table 2). A case-control study was also investigated, the quality of which was favorable (Table 3)

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

No.	Study, Years	Study design	Sample size	Mean or range of age	ctDNA method	Treatment protocol	Follow-up (years)
1	Magbanua et al., 2023[20]	Cohort study	283	49.2	PCR-NGS	Neoadjuvant treatment; surgery	5
2	Lipsyc-Sharf et al., 2022[21]	Prospective study	83	29-71	NGS/ RaDaR assays	Neoadjuvant treatment; surgery	10.4
3	Zhou et al., 2022[22]	Translational study	142	≤50 >50	NGS	Surgery; Anthracycline/Cyclophosphamide	NR
4	Janni et al., 2022[23]	Case-control	38	NR	WES and RaDaR assays	Surgery	3
5	Lin et al., 2021[24]	Cohort study	95	35-80	NGS	Neoadjuvant treatment; surgery	5.1
6	Chen et al., 2021[25]	Cohort study	80	61.28	NGS	Surgery: Neoadjuvant endocrine therapy with exemestane	2
7	Magbanua et al., 2021[26]	Cohort study	84	NR	PCR-NGS	Surgery; paclitaxel+ anthracycline	4.8
8	Ortolan et al., 2021[27]	Prospective study	31	≤50 >50	ddPCR	Surgery, anthracycline/taxane	3
9	Cavallone et al., 2020[28]	Cohort study	26	48.9	ddPCR	Surgery: Anthracycline/taxane	5.2
10	Rothé et al., 2019[29]	Experimental Design	69	23-80	ddPCR	Surgery; paclitaxel+ Anti-HER2 therapies	6.64
11	Li et al., 2020[32]	Observational, prospective, single-center study	44	26- 68	NGS	Surgery: Doxorubicin epirubicin, cyclophosphamide or docetaxel, or Herceptin	3.8

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	
Magbanua et al., 2023[20]	1	1	1	1	1	1	1	1	8
Lipsyc-Sharf et al., 2022[21]	1	1	1	1	0	1	1	1	7
Zhou et al., 2022[22]	1	1	1	1	0	1	1	1	7
Lin et al., 2021[24]	1	1	1	1	1	1	1	1	8
Chen et al., 2021[25]	1	1	1	1	0	1	1	1	7
Magbanua et al., 2021[26]	1	1	1	1	1	1	1	1	8
Ortolan et al., 2021[27]	1	1	1	1	1	1	1	1	8
Cavallone et al., 2020[28]	0	1	1	1	0	1	1	1	6
Rothé et al., 2019[29]	0	1	1	1	0	1	1	1	6
Li et al., 2020[32]	1	1	1	1	1	1	1	1	8

Table 3. Risk assessment of bias in case-control 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	
Janni et al., 2022[23]	0	1	0	1	0	1	1	1	5

ctDNA measurements

The fixed-effects odds ratio of positive ctDNA showed that OR = 0.47, 95% CI; 0.35-0.59, p-value < 0.001, which means the odds ratio of positive ctDNA measurements was 47% with a significant p-value than negative ctDNA (Fig. 2). The heterogeneity test showed that Q = 34.42, p-value < 0.001, I^2 = 73.85%, which denotes a high heterogeneity among studies with significant p-value.

Subgroup meta-analysis showed that positive ctDNA during neoadjuvant chemotherapy treatment had a significantly lower rate of pCR than negative ctDNA (OR = 0.16, 95% CI; 0.3-0.35, p-value < 0.001). No significant difference was observed in other time intervals (Fig. 2).

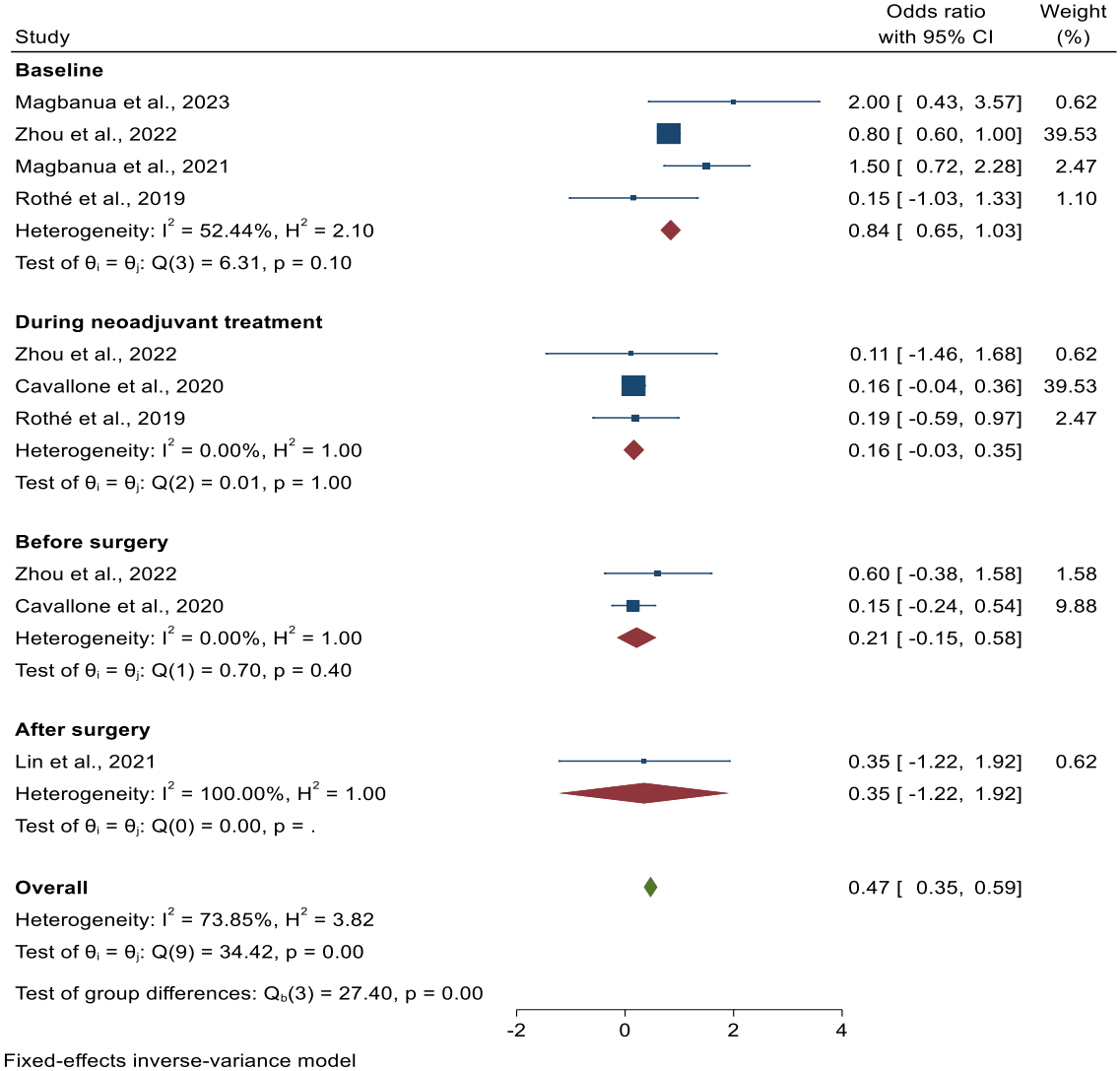

Fig. 2. The forest plot showed ctDNA measurements.

ctDNA measurements and relapse outcome

The fixed-effects relative risk of rate of relapse outcome showed that RR = 25.24, 95% CI; 24.23-26.24, p-value < 0.001, which means relative risk of relapse outcome in positive ctDNA vs negative ctDNA was 25.24% with a significant p-value (Fig. 3). The heterogeneity test showed that Q = 2513.02, p-value < 0.001, I^2 = 99.92%, which denotes a high heterogeneity among studies with significant p-value. Significantly higher rates of relapse were observed after surgery (RR = 32.83, 95% CI; 31.66-34.00, p-value < 0.001) (Fig. 3).

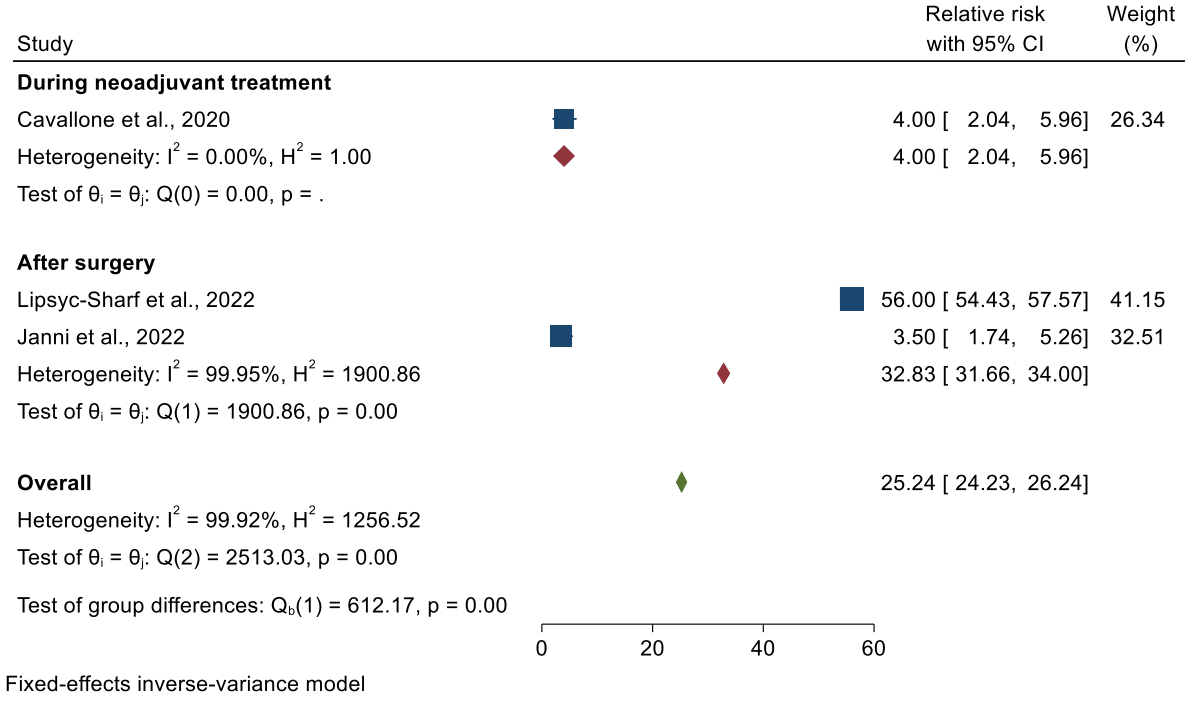

Fig. 3. The forest plot showed an association between positive vs negative ctDNA and relapse outcome.

ctDNA and overall survival

The fixed-effects hazard ratio overall survival showed that HR = 4.38, 95% CI; 3.94-4.81, p-value<0.05, which means overall survival in positive ctDNA vs negative ctDNA was 4.38% with no significant p-value (Fig. 4). The heterogeneity test showed that Q = 163.85, p-value < 0.001, I^2 = 97.56%, which denotes a high heterogeneity among studies with significant p-value. Similar overall survival was observed at three-time points (P=0.83) (Fig. 4).

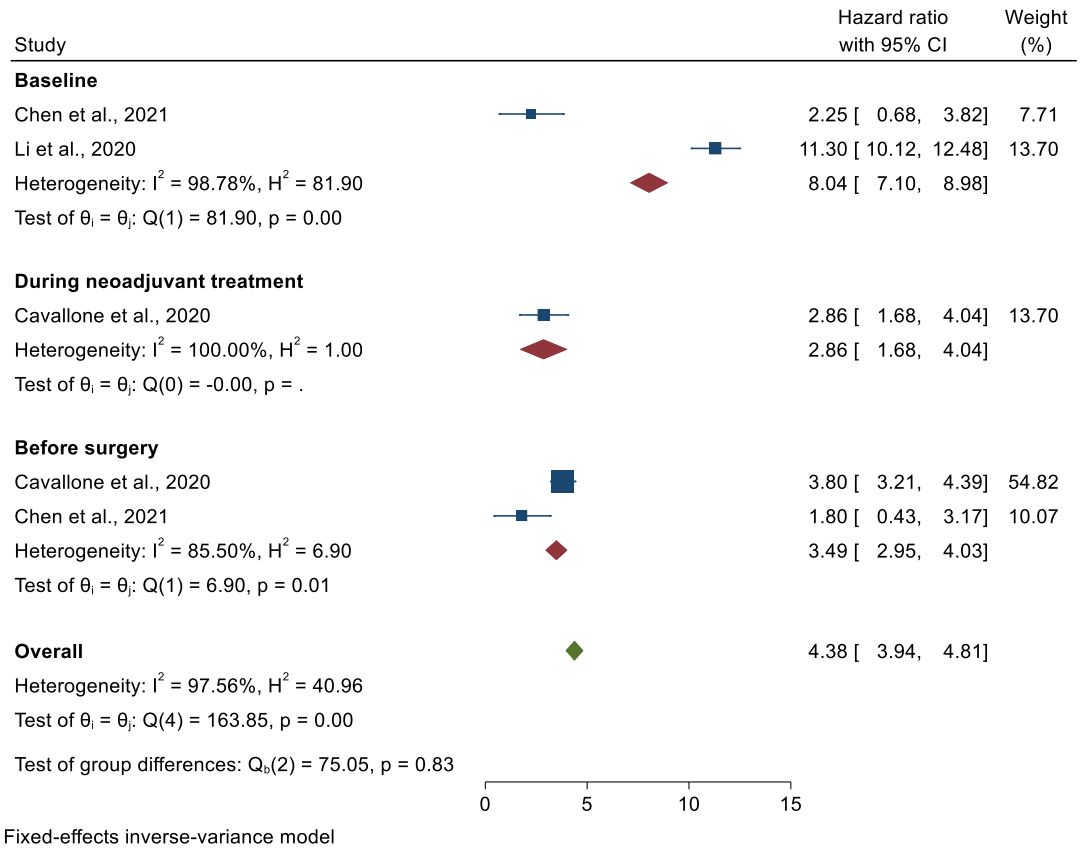

Fig. 4. The forest plot showed an association between positive vs negative ctDNA and overall survival.

ctDNA detection rates

The detection rates of positive vs. negative ctDNA in baseline were 72% (ES:72% 95% CI; 54%-89%); during neoadjuvant chemotherapy 44% (ES:44% 95% CI; 12%-100%); before surgery 11% (ES:11% 95% CI; 7%-30%) and after surgery 33% (ES:33% 95% CI; 1%-50%) (Fig. 5). mtDNA detection rates were significantly higher at baseline than at other time points (P<0.01). The heterogeneity test showed that Q = 23.52, p-value=0.22, and I^2 = 19.21%, which denotes a low heterogeneity among studies.

Negative conversion rate

The Negative conversion rate of positive vs negative ctDNA in baseline-during neoadjuvant chemotherapy was 52% (ES:0.52 95% CI; -0.30-1.33); during neoadjuvant chemotherapy before surgery 60% (ES:0.60 95% CI; -0.71-1.91); baseline-after neoadjuvant chemotherapy 73% (ES:0.73 95% CI; -0.04-1.50); baseline-before surgery 30% (ES:0.30 95% CI; -1.46-2.06), baseline-after surgery 75% (ES:0.75 95% CI; -1.21-2.71). the heterogeneity test showed that Q = 0.82, p-value=1.00, I^2 = 0%, which denotes a low heterogeneity among studies. According to the test of group differences, there was no significant between time points (Fig. 6).

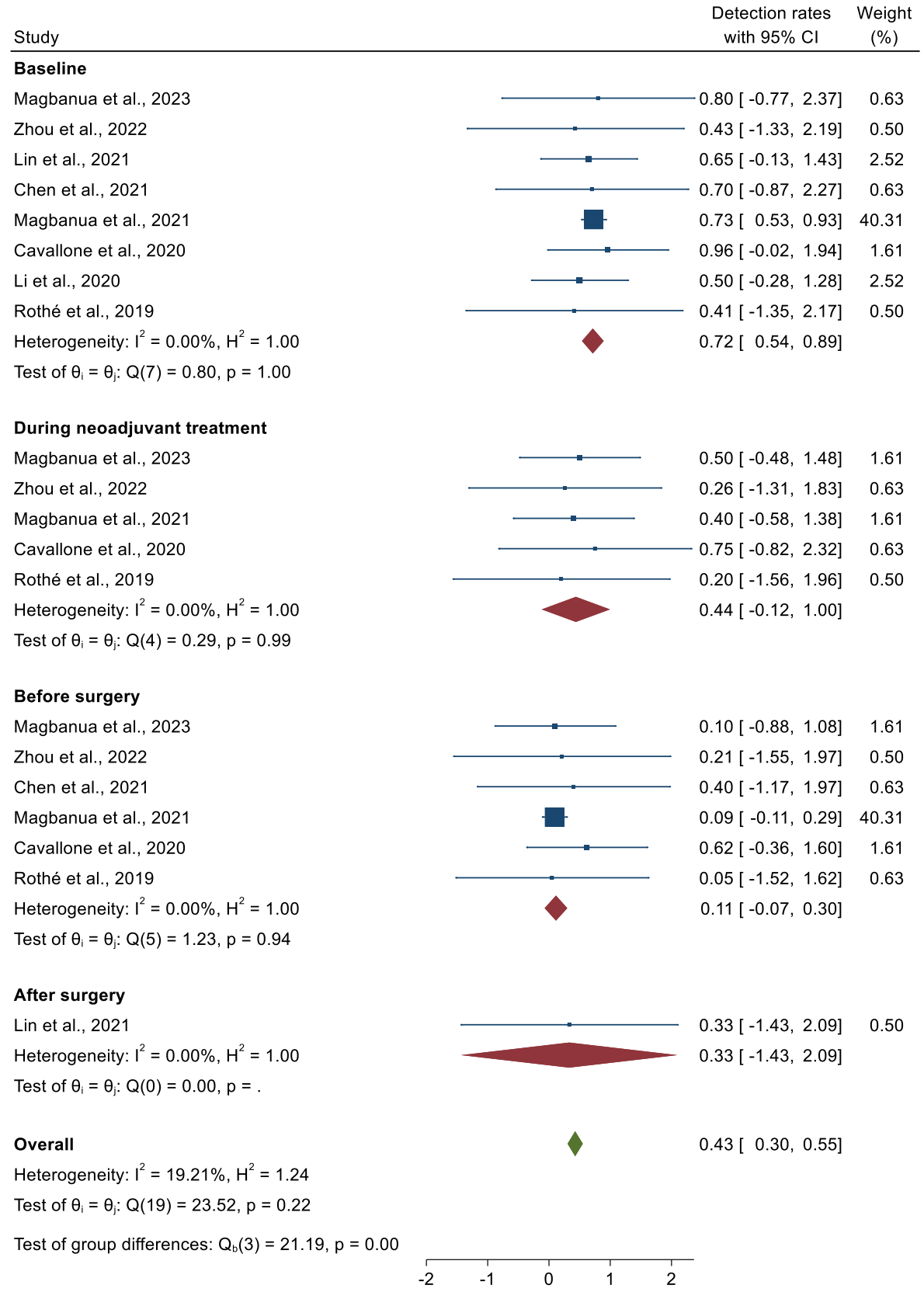

Fig. 5. The forest plot showed tDNA detection rates.

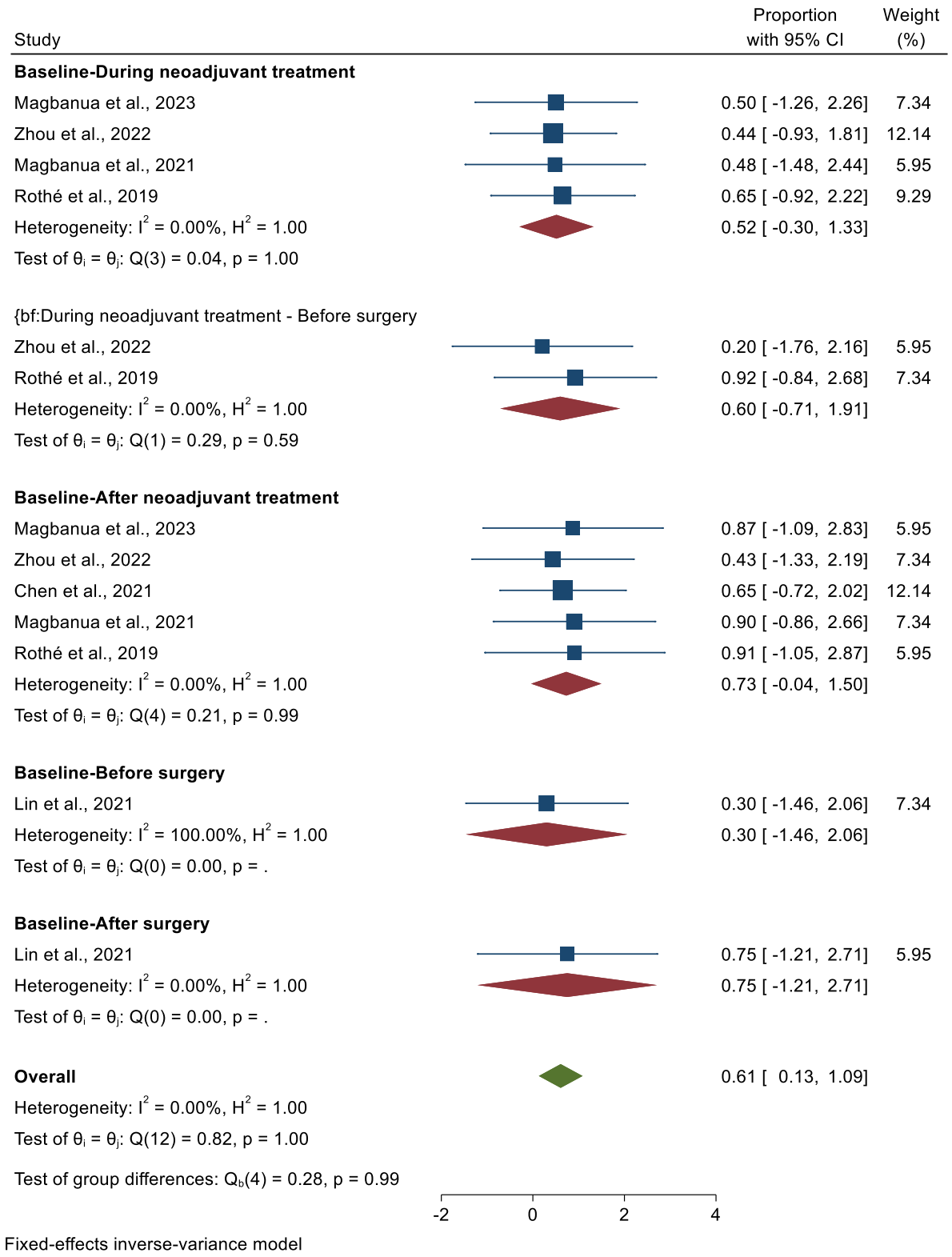

Fig. 6. The forest plot showed a Negative conversion rate.

4. Discussion

Considering that we have seen much progress in the field of breast cancer in recent years, there are many challenges in breast cancer diagnosis. The findings of studies have shown that ctDNA is related to clinical prognosis. Also, ctDNA detection can be more sensitive than imaging.[30, 31] In the present study, for the evaluation of ctDNA by pCR, it was observed that the odds ratio of positive ctDNA measurements was 47%, and a significantly lower rate of pCR was observed during neoadjuvant chemotherapy. Residual cancers that

do not shed detectable levels of ctDNA may be biologically different from those that do and may represent a less aggressive type of cancer with less metastatic potential. These findings can help the patient decide whether additional treatment should be performed after initial neoadjuvant chemotherapy.[20] Then, in the present study, ctDNA measurements and relapse outcomes were investigated, and higher rates of relapse were observed after surgery. Then, by examining overall survival in patients with ctDNA data in different periods, as expected, the weakest survival results were observed in patients who did not clear their ctDNA before surgery. Patients who were ctDNA negative at all time points and did not achieve pCR may have pretreatment and residual tumors that are less aggressive and proliferative and, therefore, less likely to relapse. Therefore, patients with undetectable ctDNA levels may be eligible for de-escalation in both the neoadjuvant and adjuvant arms. Recent studies in early-stage breast cancers have shown that ctDNA before[32, 33] and after neoadjuvant chemotherapy[26, 28, 34, 35] were prognostic of poor survival. Neoadjuvant chemotherapy is considered an essential method in the treatment of breast cancer; after neoadjuvant chemotherapy, a pathological examination can evaluate the results of neoadjuvant chemotherapy.[36] The present study observed that pCR was significantly lower in ctDNA-positive patients during neoadjuvant chemotherapy than in ctDNA-negative patients. Therefore, ctDNA can be used as a method next to clinical diagnostic tools. The heterogeneity between the studies was high in the current study, so the findings should be interpreted with caution. The cause of this heterogeneity can be related to the ctDNA method. Therefore, future studies should use the same ctDNA method. Conducting studies with a larger sample size is also suggested to confirm the evidence and provide stronger results.

5. Conclusion

Based on the present meta-analysis, ctDNA can be used as a reference index to evaluate the therapeutic effect at baseline, during NAT, and before and after surgery. The detection rate of positive vs negative ctDNA in baseline was 72%. Survival rate was correlated with ctDNA positivity.

Conflict of Interest

The authors declared that there is no conflict of interest.

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