

Aldehyde dehydrogenase 1 as a predictor of the neoadjuvant chemotherapy response in breast cancer

A meta-analysis

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Abstract

Background: Many reports suggest that aldehyde dehydrogenase 1 (ALDH1) expression is associated with poorer neoadjuvant chemotherapy (NAC) response in patients with breast cancer; however, the prognostic value of this enzyme in cancer has yet to be confirmed. Therefore, we conducted a meta-analysis of related studies to investigate the relationship between ALDH1 expression and the NAC response in breast cancer patients.

Methods: PubMed, Web of Science, ScienceDirect, Cochrane Library, and EMBASE were searched for potentially eligible literature. The study characteristics and relevant data were extracted. Odds ratios (ORs) with 95% confidence intervals (CIs) were pooled to estimate the prognostic role of ALDH1 in the NAC response in patients with breast cancer. The robustness of our results was confirmed by sensitivity and publication bias analyses.

Results: Pooled meta-analysis of 10 eligible studies including 1081 patients indicated an association between high ALDH1 expression and poor NAC responses (pooled OR = 0.44, 95% CI: 0.25–0.77, $P = .004$) with low significant heterogeneity ($I^2 = 55.1\%$, $P = .018$). During subgroup analyses, we found that the recipient sample size presents a potential source of heterogeneity. Begg funnel plot and Egger test showed no possible publication bias. Sensitivity analysis suggested that the pooled OR was robust.

Conclusion: Our results suggested that higher ALDH1 expression is associated with poorer NAC responses in patients with breast cancer. However, given the limited number of studies analyzed in this work, more studies are necessary to verify our results.

Abbreviations: ALDH1 = aldehyde dehydrogenase 1, CI = confidence interval, NAC = neoadjuvant chemotherapy, OR = odds ratio, OS = overall survival.

Keywords: aldehyde dehydrogenase 1, breast cancer, neoadjuvant chemotherapy, prognosis

1. Introduction

Breast cancer, the most common malignancy in women worldwide, is responsible for nearly one-fifth of deaths in women aged 40 to 50 years.^[1] Despite advances in the current understanding on breast cancer carcinogenesis and therapeutic agents, the disease remains a very lethal malignancy.^[2,3]

Neoadjuvant chemotherapy (NAC) is frequently adopted to reduce the size and extent of locally advanced tumors; it aims to render locally advanced cancers operable and facilitate breast-conserving surgery.^[4] However, neoadjuvant therapy is a double-

edged sword for advanced cancer patients who are not suitable for this treatment.^[5] Thus, early prediction of the success of neoadjuvant therapy is critical for determining whether a current treatment should be continued, stopped, or changed to a more aggressive regimen. Recent evidence suggests that biological markers may be useful for identifying those patients who would benefit best from NAC.^[6]

In previous decades, tumors were believed to be maintained by cancer stem cells (CSCs), which are responsible for cancer metastasis and recurrence.^[7] Therefore, CSC markers are used to identify CSCs and study their effect on the occurrence and development of tumors. Whereas aldehyde dehydrogenase 1 (ALDH1) was recently identified to be a CSC marker associated with tumorigenesis in breast cancer,^[8–17] the clinical data available are insufficient to enable identification of its prognostic significance in patients with the disease. Therefore, we performed a meta-analysis to evaluate the value of ALDH1 as a prognostic marker in breast cancer patients.

2. Method

A systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.^[18] This protocol has been registered in the PROSPERO network (registration number: CRD42018096424). An ethical review was not necessary due to the nature of this study.

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2.1. Literature search

Eligible articles for this comprehensive meta-analysis were identified using the electronic databases of PubMed, Web of Science, ScienceDirect, Embase, and Cochrane Library up to May 2018. Search terms, including “breast cancer,” “neoadjuvant chemotherapy or aldehyde dehydrogenase 1,” and “prognosis,” were searched in the title, abstract, or keywords of published articles. The references of the eligible publications were extensively reviewed to identify additional articles for inclusion in this work.

The inclusion criteria were as follows: the included patients were diagnosed with breast cancer, the full-text publication evaluated the association between ALDH1 expression and the NAC response, and the study included enough data to obtain odds ratios (ORs) and 95% confidence intervals (CIs) for the NAC response. When 2 publications reported data from overlapping samples, the study containing the larger dataset was included. Reviews, case reports, cell experiments, inefficient data, and meta-analyses were excluded from this analysis. For studies without enough data to obtain ORs, the corresponding authors were contacted by email.

2.2. Data extraction and quality assessment

All data were extracted independently by 2 reviewers (LJ and ZB) according to the inclusion criteria. In case of disagreement, a third author (LYH) was consulted, and this author provided a final decision on the discrepancy. The following information was extracted from each study: first author, publication year, ethnicity, and number of patients. ORs and 95% CIs obtained directly from published articles were integrated into the meta-analysis according to the study conducted.

The risk of bias was independently evaluated by 2 reviewers (YYF and JJ) for each study as low, moderate, or high using

criteria adapted from Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2).^[19]

2.3. Statistical analysis

All analyses were conducted using STATA/MP 14.2 (StataCorp, College Station, TX). We quantified the pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic ORs with 95% CIs to evaluate the predictive value of ALDH1 in the NAC response. A summary receiver operating characteristic (SROC) curve was generated to explain the interaction between sensitivity and specificity. Areas under the curve (AUC) were calculated to assess the diagnostic ability of a test. When no heterogeneity was observed ($P > .1$; $I^2 < 50\%$), fixed-effects model analysis was performed; otherwise, the random-effects model was used. Low heterogeneity among studies was defined as $I^2 < 25\%$, moderate heterogeneity was defined as $I^2 = 25\%$ to 50% , and high heterogeneity was defined as $I^2 > 50\%$. One-way sensitivity analysis was conducted to assess the stability of the results by deleting 1 study at a time to reflect the influence of the individual dataset to the pooled OR. Begg funnel plots and Egger linear regression were used to test for publication bias. All statistical tests were two-sided, and $P < .05$ was considered to indicate statistical significance.

3. Results

3.1. Literature search

The literature search process was summarized in a flow diagram according to PRISMA and is illustrated in Figure 1. After duplicate publications were removed and the remaining abstracts and full texts were meticulously reviewed, 10 publications were finally determined to be eligible for the present pooled analysis.

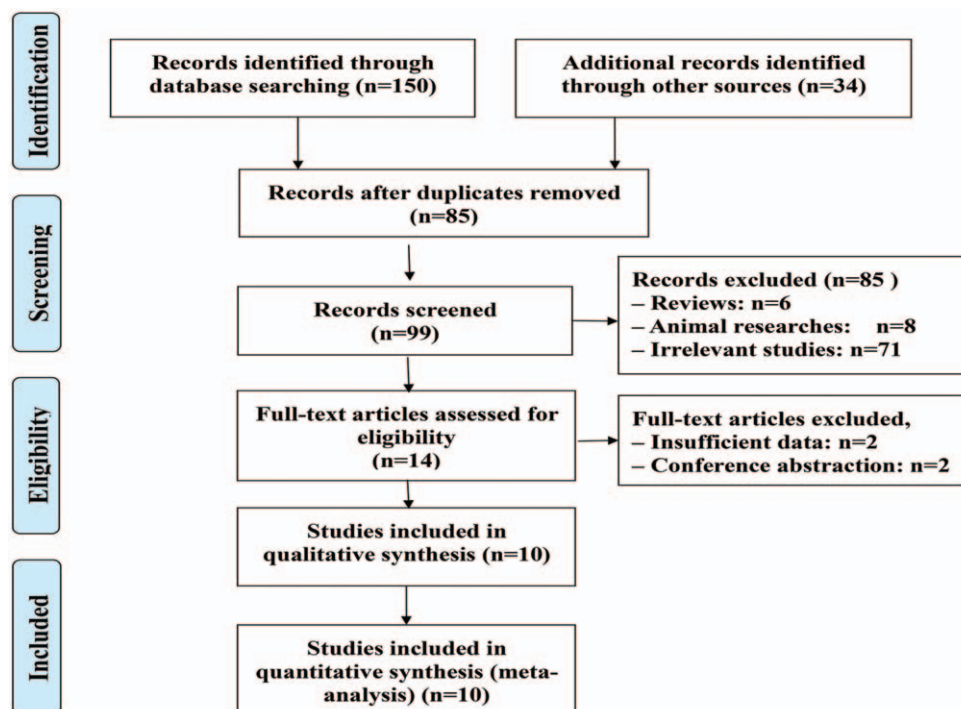


Figure 1. Flow diagram of the inclusion and exclusion of studies.

Table 1**Characteristics of the included studies.**

Study	Study Region	Clinical stage	No. of patients	Definition of ALDH1 (+)	ALDH1 status (No. of patients)		Method	Study period
					Positive	Negative		
Alamgeer et al (2014)	Australia	I–III C	119	Positive-stained tumor cells $\geq 5\%$	56	63	IHC	2004–2011
Aomatsu et al (2012)	Japan	IIA–IIIA	102	Positive-stained tumor cells $\geq 10\%$	16	86	IHC	2004–2009
Chatterjee et al (2015)	India	II B–III C	66	Positive-stained tumor cells $\geq 5\%$	29	37	IHC	2013
Gong et al (2010)	China	II–III	192	Positive-stained tumor cells $\geq 20\%$	38	154	IHC	2003–2008
Kida et al (2016)	Japan	I–III	234	Positive-stained tumor cells $\geq 1\%$	88	146	IHC	2004–2013
Lee et al (2018)	Korea	II–III	40	Positive-stained tumor cells $\geq 10\%$	23	17	IHC	2006–2015
Reuben et al (2011)	USA	I–III	30	Positive-stained epithelial cells $\geq 39\%$	27	3	TMA	2006–2008
Sakakibara et al (2011)	Japan	I–III	115	Positive-stained tumor cells $\geq 5\%$	35	80	IHC	2002–2008
Tanei et al (2009)	Japan	I–III	108	Positive-stained tumor cells $\geq 5\%$	21	87	IHC	2003–2007
Tiezzi et al (2013)	Brazil	II–III	75	NA	25	50	IHC	2005–2011

ALDH1 = aldehyde dehydrogenase 1, IHC = immunohistochemistry, NA = not available, No. = number, TMA = tissue microassay.

Inclusion of the publications in this analysis was based on the selection criteria described above.

3.2. Characteristics of the included studies

Table 1 summarizes the detailed information on the included studies. A total of 1081 breast cancer patients from 7 countries (Australia, China, Korea, Japan, India, Brazil, and the USA) were enrolled in our meta-analysis. All of the studies were published between 2009 and 2018, and the sample size ranged from 30 to 243.

3.3. Quality assessment

Each of the 10 eligible studies included in our meta-analysis was assessed for quality according to QUADAS-2. All of the articles were suggested to have moderate-to-high quality and, thus, considered appropriate for meta-analysis (Fig. S1, <http://links.lww.com/MD/C425>)

3.4. Correlation of ALDH1 expression with clinicopathological characteristics and overall survival

The main clinicopathological parameters obtained from the included studies are shown in Table 2. The overall analysis showed that ALDH1 expression was significantly correlated with lymphatic invasion (OR = 1.791, 95% CI: 1.351–2.374, $P < .001$), tumor size (OR = 2.532, 95% CI: 1.151–5.570, $P = .021$), estrogen receptor status (OR = 0.536, 95% CI: 0.404–0.710, $P < .001$), and progesterone receptor status (OR = 0.634, 95% CI: 0.480–0.837, $P = .001$). However, no evidence showed that ALDH1 expression was correlated with TNM stage

(OR = 2.362, 95% CI: 0.871–6.411, $P = .092$), HER-2 status (OR = 0.976, 95% CI: 0.403–2.366, $P = .498$), and age (OR = 0.955, 95% CI: 0.545–1.672, $P = .872$).

In addition, on the basis of the data indirectly obtained from the available studies,^[8,11,12] overall survival (OS) was analyzed by the Kaplan–Meier method and compared using the log-rank test. The result indicated that ALDH1 expression was associated with poor OS (log-rank test, $P = .033$, Fig. S2, <http://links.lww.com/MD/C425>).

3.5. Pre-operative ALDH1 expression and the NAC response

Heterogeneity was significant across studies ($I^2 = 55.1\%$, $P = .018$), and pooled results determined from the random-effects model demonstrated that ALDH1 expression was associated with the NAC response (OR = 0.44, 95% CI: 0.25–0.77, $P = .004$; Fig. 2). This result suggests that patients with high ALDH1 expression also exhibit poorer NAC responses. The pooled sensitivity, specificity, PLR, and NLR were 0.27 (95% CI: 0.12–0.48), 0.56 (95% CI: 0.44–0.68), 0.6 (95% CI: 0.4–1.0), and 1.30 (95% CI: 1.10–1.54), respectively. An AUC value of 0.44 (95% CI: 0.40–0.48) indicated effective ability for prognostic detection.

3.6. Heterogeneity, sensitivity analysis, and publication bias assessment

To address the heterogeneity among analyzed studies, we performed meta-regression analyses by sample size (< 100 or ≥ 100), ethnicity (Asian or Non-Asian), and publication year (before 2015 or after 2005). The results confirmed that the

Table 2**Overall analysis of ALDH1 expression association with clinical features.**

	Number of studies	Number of patients	OR (95% CI)	P-value	I^2 (P-value)
Lymph node status	8	1398	1.791 (1.351–2.374)	<.001	.5% (.425)
Tumor size	5	1102	2.532 (1.151–5.570)	.021	76.5% (.002)
TNM stage (I–IV III–IV)	6	631	2.362 (0.871–6.411)	.092	82.9% (.001)
Estrogen receptor status (–/+)	6	1184	0.536 (0.404–0.710)	<.001	37.0% (.160)
Progesterone receptor status (–/+)	6	1333	0.634 (0.480–0.837)	.001	.0% (.457)
HER-2 status (–/+)	6	1174	0.976 (0.403–2.366)	.498	78.8% (<.001)
Age	6	1221	0.955 (0.545–1.672)	.872	57.4% (.039)

ALDH1 = aldehyde dehydrogenase 1, CI = confidence intervals, HER-2 = human epidermal growth factor 2 receptors, OR = odd ratio.

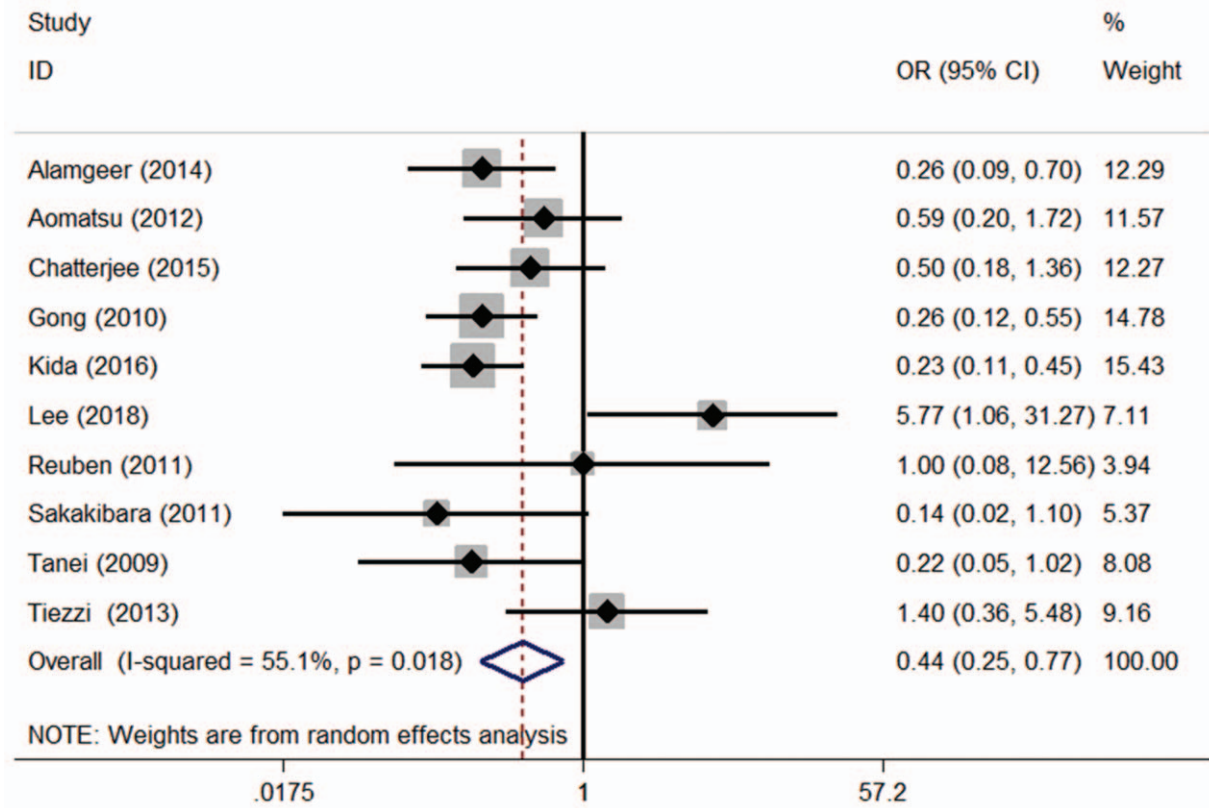


Figure 2. Forest plot of the association of ALDH1 expression with the neoadjuvant chemotherapy response. ALDH1 = aldehyde dehydrogenase 1.

Table 3

Meta-regression analysis of potential sources of heterogeneity.

Heterogeneity factors	Coefficient	SE	Z	P-value	95% CI (lower limit, upper limit)
Sample size	1.585	0.604	2.63	.039	0.108, 3.062
Publication year	0.138	0.672	0.20	.845	-1.507, 1.782
Ethnicity	-0.281	0.617	-0.46	.664	-1.791, 1.228

CI = confidence intervals, SE = standard error.

number of patients per study may be a major source of heterogeneity (Table 3). Subgroup analyses were performed, and the main results are presented in Table 4.

No evidence of publication bias was observed based on visual inspection of the funnel plots (Fig. 3) or Begg’s ($P = .07$) or Egger’s

tests ($P = .140$). Given that heterogeneity was observed in the meta-analysis, sensitivity analysis was performed for the studies included in this work. Figure 4 shows that the results of most of the included studies are close to the central line without obvious deviation.

Table 4

Subgroup analysis.

	Number of studies	OR (95% CI)	P	I ² (P value)
Sample size				
<100	4	1.28 (0.43–3.85)	.665	51.9% (.101)
≥100	6	0.27 (0.18–0.40)	<.001	0% (.738)
Publication year				
before 2015	7	0.37 (0.22–0.63)	<.001	21.1% (.269)
after 2015	3	0.72 (0.16–3.31)	.674	83.9% (.002)
Ethnicity				
Asia	7	0.41 (0.21–0.79)	.008	60.6% (.019)
Non-Asia	3	0.61 (0.18–2.09)	.429	51.8% (.126)

CI = confidence intervals, OR = odd ratio.

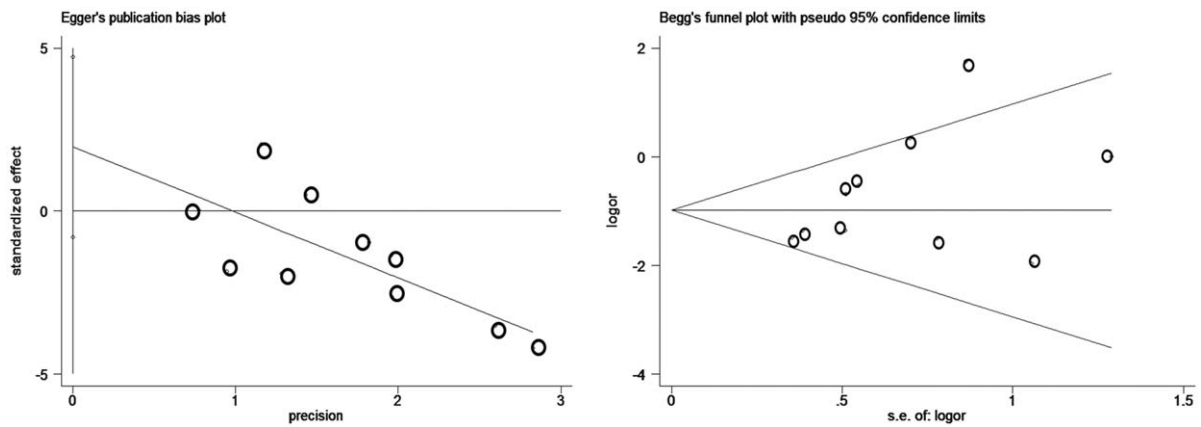


Figure 3. Funnel plots for publication bias.

4. Discussion

To the best of our knowledge, the present study is the first meta-analysis to evaluate the pathological and prognostic association of ALDH1 expression with the NAC response in breast cancer. The outcomes of 1,081 patients with breast cancer from 10 relevant articles associated with ALDH1, prognosis, and pathology were summarized, and the results demonstrated a clear correlation between high expression levels of ALDH1 and poor pathological responses to NAC.

ALDH1 can inactivate integral agents of NAC; therefore, breast cancer patients with high ALDH1 expression may have a low survival rate [20] and increased risk of recurrence.[10] Two other studies on all types of breast cancer also reported that the ALDH1 protein is a potential predictive marker of early local tumor recurrence and distant metastasis.[21,22]

Given the significant heterogeneity observed across the analyzed studies, we performed subgroup and meta-regression

analyses to explore the sources of heterogeneity. The results of subgroup analysis suggested that sample size (fewer than 150 or more than 150) altered the significance of the prognostic role of ALDH1 in the NAC response (OR=1.28, 95% CI: 0.43–3.85 versus OR=0.27, 95% CI: 0.18–0.40), similar to the meta-regression results ($P=.039$). This finding indicates that differences in sample size may bring about heterogeneity.

The present study presents certain limitations. First, considerable heterogeneity among analyzed studies was found. However, we applied a relatively conservative random-effects model to address this issue; the prognostic value of ALDH1 in breast cancer may be underestimated by heterogeneity. Second, some of the included studies were retrospective cohort studies and likely to be affected by some biases, such as selection bias. Other prospective cohort studies are needed to provide a more appropriate evaluation of the role of ALDH1 in the NAC response. Third, the cut-off value of ALDH1 expression varied

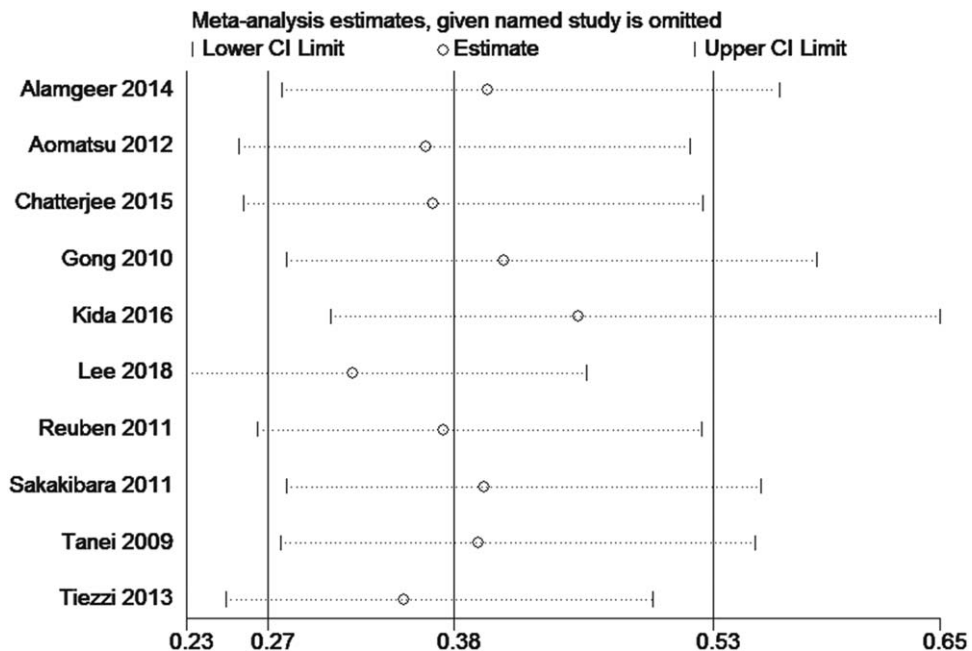


Figure 4. Sensitivity analysis of the relationships between ALDH1 expression and the neoadjuvant chemotherapy response. ALDH1 = aldehyde dehydrogenase 1.

across different studies, and a consensus value was rather difficult to reach. Fourth, among the selected studies, the patients' populations, methodologies for detecting ALDH1 expression level, and NAC regimens varied widely, which may have influenced the pooled analysis. Finally, the small number of samples might have weakened our conclusion. Thus, to obtain a more reliable conclusion, larger and more standardized studies are required in the future.

In conclusion, this meta-analysis demonstrated that high levels of ALDH1 expression are associated with poorer NAC responses in breast cancer patients, which suggests that ALDH1 is a valuable prognostic marker. Thus, clinicians should formulate NAC treatment regimens for breast cancer patients based on pre-treatment ALDH1 levels.

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