Prognosis assessment of CD44+/CD24− in breast cancer patients: a systematic review and meta-analysis

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Abstract
Purpose This meta-analysis investigated the relationships between the CD44+/CD24− phenotype and tumor size, lymph node metastasis, distant metastasis, disease-free survival (DFS), and overall survival (OS) in 8036 postoperative breast cancer patients enrolled in 23 studies.

Methods A literature search of PubMed, Medline, Cochrane, Embase, and PMC was conducted to identify eligible studies. The combined odds ratios (ORs) and 95% confidence intervals (95% CIs) were analyzed to evaluate the relationships between the CD44+/CD24− phenotype and the pathological and biological characteristics of breast cancer patients, and the combined hazard ratios (HRs) and 95% CIs were calculated to evaluate the relationships between CD44+/CD24− and DFS and OS of breast cancer patients using Stata12.0 software.

Results The CD44+/CD24− phenotype were not related to the tumor size (tumor size > 2.0 vs ≤ 2.0 cm, combined OR = 0.98, 95% CI 0.68–1.34, \( p = 0.792 \)) and did not promote lymph node metastasis (lymph node metastasis vs. no lymph node metastasis, OR = 0.92, 95% CI 0.67–1.27, \( p = 0.626 \)) and distant metastasis (distant metastasis vs no distant metastasis, combined OR = 3.88, 95% CI 0.93–16.24, \( p = 0.064 \)). The CD44+/CD24− phenotype was negatively correlated with postoperative DFS (HR = 1.67, 95% CI 1.35–2.07, \( p < 0.00001 \)) and OS (combined HR = 1.52, 95% CI 1.21–1.91, \( p = 0.0004 \)).

Conclusion These results suggested expression of the CD44+/CD24− phenotype cannot be used as a reliable indicator of the tumor size, lymph node metastasis, and distant metastasis, however, it can be used be a potential therapeutic targets of DFS, OS in breast cancer patients.

Keywords CD44+/CD24− · Breast cancer · Meta-analysis · Prognosis

Introduction
Breast cancer is the most common cancer in women worldwide [1]. According to the statistics of the World Health Organization (WHO), more than 4 million patients are diagnosed with breast cancer every year, and more than 1 million people die of breast cancer every year [2]. According to multiple studies, breast cancer is a group of heterogeneous tumors with different proliferation rates, invasive capabilities, metastatic potential, and therapeutic effects [3]. Although there are many treatments, including surgery, radiotherapy, chemotherapy, endocrine therapy, targeted therapy, cytotoxic drug therapy, hormone therapy, and immunotherapy, a large proportion of breast cancer patients eventually die of breast cancer recurrence and metastasis. Therefore, early detection of sensitive prognostic markers is particularly important for the prognosis of breast cancer patients [4]. There is evidence indicating that, although many malignant tumors are clonal in nature, they contain heterogeneous cell populations with different biological characteristics, and a small portion of these are cancer stem cells (CSCs) [5]. Some experts believe that these self-renewing CSCs are the main reason for the failure of cancer treatment [6]. In 2003, Al-Hajj and colleagues [7] discovered that cells with the CD44+/CD24− phenotype undergo a process similar to normal stem cell self-renewal and differentiation [8]. Hence, the expression of CD44+/CD24− cells has attracted the interest of experts [9]. Hiroko Nogi found that cells with an expression of CD44+/CD24− are associated with lymph
node metastasis [10], and there are reports suggesting that cells with high expression of this phenotype are associated with poor prognosis of breast cancer [11]. Lee [12] et al. demonstrated that expression of CD44+/CD24− phenotype cells is associated with breast cancer tumor progression, and emphasized the importance of CSC-targeted therapy in the treatment of breast cancer. Other reports have put forward different viewpoints from the above [13] so that the role of CD44+/CD24− tumor stem cells in breast cancer remains controversial [14]. The purpose of this study was to establish a meta-analysis model for investigating the relationships between cells with expression of the CD44+/CD24− phenotype and tumor size, lymph node metastasis, distant metastasis, disease-free survival (DFS), and overall survival (OS) in breast cancer patients.

**Study selection**

We searched the following combinations of medical subject words (MeSH) and text words in the PubMed, Medline, Cochrane, Embase, and PMC databases: (“breast cancer” or “breast cancer”) and (“CD44” and “CD24”) and (“prognosis” or “survival” or “outcome”). Then, in order to find other eligible papers avoiding the omissions of electronic retrieval methods, we further searched the references in the identified preliminary research papers and review articles. The date determining the inclusion of literature was December 2019.

**Data extraction and quality evaluation**

Two independent reviewers (Jingjing Gu and Dandan Chen) read the titles and abstracts of all candidate articles. If the nature of some articles could not be determined from the title or abstract, the full text was reviewed. Any differences in the two quality assessments and data collections were discussed with corresponding author until agreement was finally reached. A predefined form was used for data extraction. The extracted data included: the name of the first author, publication time, country, number of patients, patients with an expression of CD44+/CD24− phenotype, the number of tumors > 2.0 cm, lymph node metastases, distant metastases, follow-up time, detection method, HR, and 95% CI corresponding to OS and DFS. For articles that only included the Kaplan–Meier curve without providing HRs and 95% CIs, we used the methods in Tierney [15] and Parmar et al. [16] to estimate HRs. And the prognosis-related survival rate was extracted from the Kaplan–Meier curve by GetData Graph digitizer 2.24 software. Some papers, from which we still could not obtain the above information even after efforts to contact the author of the original material, were marked as “NA” (not available).

To ensure the quality of each document, the Newcastle–Ottawa-Scale (NOS-Scale) [17] bias assessment tool (Table 1) was used to evaluate the quality of the literature, and was independently completed and checked by two researchers (Jingjing Gu and Dandan Chen). Studies with a total score of 6–9 were regarded as high-quality research, and all papers of included in this meta-analysis were rated 6–9. And the following criteria had to be met: (1) all articles included in this study were cohort studies; (2) research subjects were postoperative patients diagnosed with breast cancer by pathology; (3) expression of CD44+/CD24− in breast cancer was detected by immunohistochemistry (IHC); (4) sufficient data were presented in the paper, including the number of patients with tumor size > 2.0 cm, lymph node metastasis, and distant metastasis, in order to estimate the odds ratio (OR), hazard ratio (HR), and 95% confidence interval (95% CI) that corresponded to the overall survival rate (OS) or disease-free survival rate (DFS), or so that we could calculate these measures based on the information in the article; and (5) the study was published in English.

**Exclusion criteria**

The following publications were excluded: (1) summaries, comments, letters to editors, and articles published in one or more unpublished books; (2) articles that detected CD44+/CD24− in the blood; (3) articles that only reported animal experiments.

**Statistical analysis**

ORs and 95% CIs were used to estimate the relationships between tumor stem cells CD44+/CD24− and breast cancer pathological parameters (tumor size, lymph node status, distant metastasis). We evaluated the correlations between cells with expression of the CD44+/CD24− phenotype and patients’ OS and DFS by HRs and 95% CIs. The extracted data were analyzed using Stata12.0 and RevMan 5.3 analysis software (Cochrane Collaboration). In this study, OR > 1 meant that cells with expression of the CD44+/CD24− phenotype were closely related to tumors > 2 cm, lymph node metastasis, and distant metastasis. HR > 1 indicated that cells with expression of the CD44+/CD24− phenotype were negatively correlated with OS and DFS. The Q test was used to evaluate the heterogeneity of the study, and the I² value indicated the degree of heterogeneity. A p value > 0.05 and I² < 50% meant no heterogeneity, and a fixed-effect model was needed; otherwise, we selected a random-effect model [36]. In addition, we evaluated the publication bias of the studies using Begg’s funnel plot, Begg’s test and Egger’s test. If the graph appeared like a symmetrical inverted funnel and the p values of Begg’s test and Egger’s test were
both > 0.05, this indicated that publication bias was not detected. We verified the reliability of the results by sensitivity analysis. All statistical tests in this meta-analysis were two-tailed and \( p \) values < 0.05 were considered statistically significant.

### Results

#### Characteristics of included studies

According to the above search strategy, a total of 332 articles were initially retrieved. By screening the topics, eight repeated articles and 38 reviews were excluded. In total, 197 articles involving non-human experiments were excluded were excluded by reviewing the abstracts, and we excluded 66 articles that detected the expression of CD44+/CD24− in the blood. Finally, we included 23 studies in the meta-analysis, and the flowchart of the search strategy is shown in Fig. 1. The total number of patients included in this meta-analysis was 8036, from 5 studies on tumor size, 16 studies on lymph node status, and 5 studies on distant metastasis. We conducted 11 studies on OS and 9 studies on DFS.

Table 2 summarizes the main characteristics of the data related to the cancer stem cells CD44+/CD24− in this meta-analysis.

#### Correlations between the CD44+/CD24− markers and the pathological and biological characteristics of breast cancer patients

There are 5 studies including 985 breast cancer patients on tumor size, and the correlation between expression of the CD44+/CD24− phenotype and the tumor size in breast cancer patients is shown in Fig. 2, and overall analysis showed that cells with the expression of CD44+/CD24− phenotype were not related to the tumor size (Fig. 2, tumor size > 2.0 cm vs ≤ 2.0 cm, combined OR = 0.98, 95% CI 0.68–1.34, \( p = 0.792 \), fixed-effect model). There are 16 studies including 3129 breast cancer patients on lymph node
metastasis, and the correlation between expression of the CD44+/CD24− phenotype and the lymph node metastasis in breast cancer patients is shown in Fig. 3, and overall analysis showed that cells with the expression of CD44+/CD24− phenotype were not related to the lymph node metastasis in breast cancer patients (Fig. 3, lymph node metastasis vs no lymph node metastasis, combined OR = 0.92, 95% CI 0.67–1.27, p = 0.626, random-effect model). There are 5 studies including 1024 breast cancer patients on distant metastasis, and the correlation between expression of the CD44+/CD24− phenotype and the distant metastasis in breast cancer patients is shown in Fig. 4, and overall analysis showed that cells with the expression of CD44+/CD24− phenotype were not related to the distant metastasis of breast cancer patients (Fig. 4, distant metastasis vs no distant metastasis, combined OR = 3.88, 95% CI 0.93–16.24, p = 0.064, random-effect model).

Effects of the CD44+/CD24− phenotype on postoperative disease-free survival and overall survival

The above method was used to conduct 11 studies including 5700 breast cancer patients on the OS and 9 studies including 1354 breast cancer patients on the DFS of breast cancer patients. The correlations between the expression of the CD44+/CD24− phenotype and DFS and OS of breast cancer patients are shown in Figs. 5 and 6. The results indicated that expression of the cancer stem cell marker CD44+/CD24− and DFS (Fig. 5, HR = 1.67, 95% CI 1.35–2.07, p < 0.00001, fixed-effect model) and OS (Fig. 6, combined HR = 1.52, 95% CI 1.21–1.91, p = 0.0004, fixed-effect model) were negatively correlated, and their differences were statistically significant.

Publication bias

Begg’s funnel plot, Begg’s test and Egger’s test were used to evaluate publication bias. The graphs of Begg’s funnel plot appeared like a symmetrical inverted, and the correlations between expression of the CD44+/CD24− phenotype and a patient’s tumor size (Begg’s test: p = 0.221, Egger’s test: p = 0.204, Fig. 7), lymph node metastasis (Begg’s test: p = 0.137, Egger’s test: p = 0.174, Fig. 8), distant metastasis (Begg’s test: p = 0.462, Egger’s test: p = 0.066, Fig. 9), DFS (Begg’s test: p = 0.602, Egger’s test: p = 0.78, Fig. 10), and OS (Begg’s test: p = 1, Egger’s test: p = 0.665, Fig. 11) showed there was no obvious publication bias.

Sensitivity analysis

The sensitivity analysis results (Figs. 12, 13, 14, 15 and 16) showed that the correlations between the cells that expressed the CD44+/CD24− phenotype and tumor size, lymph node...
Table 2  Main characteristics of the included studies on CD44+/CD24−

| Name                | Year  | Country    | Marker          | Technology | Cohort | CD44+/CD24−(+): tumor size > 2 cm | CD44+/CD24−(+): LN (+) | CD44+/CD24−(+): M (+) | Follow-up time (months) | Cut-off value | OS    | DFS    |
|---------------------|-------|------------|-----------------|------------|--------|------------------------------------|------------------------|-----------------------|------------------------|---------------|-------|-------|
| Honeth [18]         | 2008  | Sweden     | CD44+/CD24−     | IHC        | 240    | 40                                 | 45                      | 23                    | NA                      | NA            | NA    | NA    |
| Giatromanolaki [19] | 2011  | Greece     | CD44+/CD24−     | IHC        | 139    | NA                                 | 7                       | NA                    | 10%                    | NA            | NA    | NA    |
| Nogi [10]           | 2011  | Japan      | CD44+/CD24−     | IHC        | 271    | NA                                 | 21                      | NA                    | 10%                    | NA            | NA    | NA    |
| Reuben [20]         | 2012  | USA        | CD44+/CD24−     | IHC        | 66     | NA                                 | 17                      | NA                    | 3%                     | NA            | NA    | NA    |
| Ahmed [21]          | 2011  | UK         | CD44+/CD24−     | IHC        | 306    | 22                                 | 15                      | 11                    | NA                      | NA            | NA    | NA    |
| Guler [22]          | 2012  | USA        | CD44+/CD24−     | IHC        | 338    | NA                                 | 8                       | 7                     | NA                      | NA            | NA    | NA    |
| Tsang [23]          | 2012  | Hong Kong  | CD44+/CD24−     | IHC        | 340    | NA                                 | 62                      | NA                    | NA                      | NA            | NA    | NA    |
| Giorlando [24]      | 2012  | USA        | CD44+/CD24−     | IHC        | 103    | NA                                 | 31                      | 60                    | NA                      | (1.10-68.99)   | NA    | NA    |
| Adamczyk [25]       | 2014  | Poland     | CD44+/CD24−     | IHC        | 156    | NA                                 | 42                      | NA                    | NA                      | NA            | NA    | NA    |
| Mendonca [26]       | 2014  | Brazil     | CD44+/CD24−     | IHC        | 28     | 12                                 | 7                       | NA                    | NA                      | NA            | NA    | NA    |
| Kapucuoçu [14]      | 2015  | Turkey     | CD44+/CD24−     | IHC        | 57     | NA                                 | 31                      | NA                    | Scores>3                | NA            | NA    | NA    |
| Chen [4]            | 2015  | China      | CD44+/CD24−     | IHC        | 120    | NA                                 | 41                      | 23                    | 160                    | NA            | 2.12 (1.25-3.57)| 2.05 (1.22-3.46) |
| Zhao [27]           | 2016  | China      | CD44+/CD24−     | IHC        | 242    | NA                                 | NA                      | 80                    | NA                      | 1.98 (0.83-4.72)| 1.43 (0.99-2.07) |
| Bane [28]           | 2013  | Canada     | CD44+/CD24−     | IHC        | 262    | 17                                 | 12                      | NA                    | Scores>3                | NA            | NA    | NA    |
| Seo [29]            | 2016  | UK         | CD44+/CD24−     | IHC        | 241    | NA                                 | 39                      | 118.1                 | 10%                     | 2.02 (1.14-3.57)| 2.29 (1.28-4.09) |
| Rabinovich [30]     | 2018  | Italy      | CD44+/CD24−     | IHC        | 140    | NA                                 | 9                       | NA                    | 180                    | 5%            | 1.63 (0.68-3.89)| 2.86 (0.68-14.06) |
| Mylona [31]         | 2008  | Greece     | CD44+/CD24−     | IHC        | 147    | NA                                 | NA                      | 135                   | 10%                     | 0.7 (0.22-2.21)| 0.76 (0.21-2.15) |
| Lin [32]            | 2007  | China      | CD44+/CD24−     | IHC        | 147    | NA                                 | NA                      | 84                    | NA                      | 2.24 (1.35-3.72)| 1.98 (1.16-3.31) |
| Ali [33]            | 2011  | UK         | CD44+/CD24−     | IHC        | 4152   | NA                                 | NA                      | 102                   | NA                      | 0.73 (0.4-1.33)| NA    | NA    |
| Abraham [34]        | 2005  | India      | CD44+/CD24−     | IHC        | 122    | 20                                 | 16                      | 85.4                  | 5%                      | 1.46 (0.67-3.18)| NA    | 1.22 (0.67-2.22) |
| Aulmann [35]        | 2010  | Germany    | CD44+/CD24−     | IHC        | 50     | NA                                 | NA                      | 41                    | 5%                      | 2.61 (0.49-14.07) | NA    | NA    |
| Hashimoto [9]       | 2012  | Japan      | CD44+/CD24−     | IHC        | 77     | NA                                 | NA                      | 108                   | 10%                     | 1.06 (0.26-4.29)| NA    | NA    |
| Lee [12]            | 2011  | Korea      | CD44+/CD24−     | IHC        | 92     | NA                                 | NA                      | 72                    | 5%                      | 1.78 (0.51-6.15)| NA    | NA    |

(CD44+/CD24−(+):LN (+) means the number of lymph node metastases in patients with high expression of CD44+/CD24− phenotype cells, CD44+/CD24−(+):M means the number of distant metastases in patients with high expression of phenotype cells
NA not available)
Fig. 2 Forest plot was assessed for the correlation of CD44+/CD24− with tumor size > 2 cm in breast cancer. Heterogeneity chi-squared = 1.88 ($df = 4$), $p = 0.758$, $I^2$-squared (variation in OR attributable to heterogeneity) = 0.0%, Test of OR = 1: $z = 0.26$, $p = 0.792$.

Fig. 3 Forest plot was assessed for the correlation of CD44+/CD24− with Lymph node metastasis in breast cancer. Heterogeneity chi-squared = 41.05 ($df = 15$) $p = 0.001$, $I^2$-squared (variation in OR attributable to heterogeneity) = 63.5%, estimate of between-study variance Tau-squared = 0.2506, test of OR = 1: $z = 0.49$, $p = 0.626$. 

NOTE: Weights are from random effects analysis.
metastasis, DFS, and OS of breast cancer patients were stable. However, as shown in Fig. 14, the results of the correlation between expression of the CD44+/CD24− phenotype and the distant metastasis of breast cancer patients were not stable.

Discussion

Since Hamburger [37] et al. explicitly proposed the “cancer stem cell (CSC)” hypothesis for the first time in 1977, research on cancer stem cells has attracted much attention from researchers. The hypothesis proposes that tumors originate from a small subset of rare cells that have the ability to self-renew and differentiate into other cancer cells, thereby promoting tumor cell proliferation, tumor generation, and growth [35]. There is increasing evidence to support the CSC hypothesis [38]. Such research is mainly based on xenotransplantation experiments, in which human breast cancer cells are transplanted into immunocompromised mice. The results have shown that only CSCs (usually <1% of malignant tumors) can produce tumors [39], and also that CSCs are the only cells participating in tumor recurrence and metastasis [40]. Some researchers also believe that CSCs promote tumor growth, invasion, and metastasis by stimulating blood vessels to obtain sufficient blood and nutrition [41]. Some experts have suggested that CSCs in human breast cancer are related to recurrence and metastasis in breast cancer patients [42], and that breast cancer stem cells induce local lymph node metastasis in breast cancer patients [43]. Al-Hajj and colleagues proposed for the first time that cells with expression of the CD44+/CD24− phenotype in breast cancer show the characteristics of tumor stem cells [44]. Many subsequent studies have shown that cells with expression of the CD44+/CD24− phenotype have tumorigenic ability and invasive characteristics [45]. Some experts suggested that breast cancer phenotype CD44+/CD24− cells have greater invasive ability in vitro and greater metastatic ability in vivo than other cells [46]. Studies have shown that expression of the CD44+/CD24− phenotype is associated with DFS and OS in breast cancer patients [47]. However, the role of the CSC phenotype CD44+/CD24− in breast cancer remains controversial. The research results of Mylona et al. showed that there was no obvious correlation between cells with expression of the CD44+/CD24− phenotype and DFS and OS of postoperative patients [13]. Here, we investigated the correlations between the CSC CD44+/CD24− phenotype and the pathological and biological characteristics of breast cancer patients, and the effects of this phenotype on the prognosis of breast cancer patients. We
found that cells with the expression of CD44+/CD24− phenotype were not related to the tumor size and did not promote local lymph node metastasis and distant metastasis. Expression of the CD44+/CD24− marker was negatively correlated with postoperative DFS and OS, and their differences were statistically significant.

The CSC CD44+/CD24− phenotype has always been a research hot spot. Many investigators [48, 49] have a strong interest in the mechanism of the CD44+/CD24− phenotype in breast cancer since there has recently been renewed interest in CSCs. Hence, we felt that the CD44+/CD24− phenotype still has a certain value and significance in predicting the prognosis of breast cancer patients. Some meta-analyses have previously studied the correlations between the CD44+/CD24− phenotype of cancer stem cells and the pathological and biological characteristics of breast cancer patients, and there is also a correlation between the CD44+/CD24− phenotype and prognosis of breast cancer patients. Zhou [50] suggested that expression of the CD44+/CD24− phenotype is not correlated with tumor size and lymphatic metastasis in breast cancer patients, but is negatively correlated with the OS of breast cancer patients. And compared to the article of Zhou [50] we included more studies and the difference of study population and treatment regimens may affect the prognosis of patients, which may be the reasons why our two articles draw different conclusions. However, Wang’s study found that expression of the CD44+/CD24− phenotype was not significantly associated with the OS of breast cancer patients [51]. OS was reported in 7 studies with a total of 2673 breast cancer patients in Wang’s study [51], and the number of articles they included was limited, and there was no consistent threshold standard of CD44+/CD24− phenotype in our study when evaluating biomarkers, which may have contributed to the different results of our study. The two meta-analysis results are different, which highlights and emphasizes the necessity of our meta-analysis. Compared with the studies of Zhou and Wang, our meta-analysis proved that expression of the CD44+/CD24− phenotype is not closely related to tumor size, lymph node metastasis, and distant metastasis in breast cancer patients, but negatively correlated with DFS and OS. In support of our results, we included more research samples found through more search channels. Our meta-analysis involved a total of 23 studies, including 8036 breast cancer patients. More importantly, we did not find heterogeneity or publication bias, and the sensitivity analysis also suggested that the results are stable.

Fig. 5 Forest plot was assessed for the correlation of CD44+/CD24− with DFS in breast cancer. Heterogeneity chi-squared = 8.65 (df = 8); p = 0.373; I-squared (variation in ES attributable to heterogeneity) = 7.5%; test of ES = 1: z = 4.77; p < 0.00001
on the correlation between the expression of the CD44+/CD24− phenotype and the tumor size, lymph node metastasis, DFS and OS in breast cancer patients. Therefore, we conclude that breast cancer cells with expression of the CD44+/CD24− phenotype are not related to the pathological and biological characteristics of postoperative patients with breast cancer, and the phenotype can be used as a tumor marker to predict the DFS, OS of breast cancer patients.
Although our research has many advantages, our study still had certain limitations. For example, on the correlation between cells with expression of the CD44+/CD24− phenotype and distant metastasis, although obvious publication bias was not found in the results, the sensitivity analysis indicated that the results were not stable. There might be several causes for this. First, although we have checked English websites such as PubMed, Medline, Cochrane, Embase, and PMC, there were some unpublished or non-English studies that we did not collect. Second, the breast cancer patients included in the study may have been treated with different treatment methods, which would have a certain impact on the outcome of the study. Third, some studies we included only had Kaplan–Meier survival curves, so that there may have been some deviations in extracting survival data from the survival curves. Fourth, in the studies we included, the authors’ follow-up times (from 41 to 180 months) for patients were different, which may have had a certain impact on the survival data of our study. Fifthly, although the cancer stem cell CD44+/CD24− phenotype was extracted by IHC in the studies we included, the cut-off values (from 3 to 10%) were different. All of the above factors may cause deviations in the research results.

In summary, the results of this study indicated that, in breast cancer patients, tumor cells with expression of the CD44+/CD24− phenotype did not promote tumor tissue growth, lymph node metastasis, and distant metastasis. However, they were closely related to DFS and OS. Therefore, we concluded that the cancer stem cell CD44+/CD24− phenotype cannot be used as a reliable indicator of the tumor size, lymph node metastasis, and distant metastasis, however it can be used be a potential therapeutic targets of DFS, OS in breast cancer patients.
Fig. 13  Sensitivity analysis was used to detect the stability of results about the correlation of CD44+/CD24− with lymph node metastasis in breast cancer.

Fig. 14  Sensitivity analysis was used to detect the stability of results about the correlation of CD44+/CD24− with distant metastasis in breast cancer.
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Author contributions

Author ZM (Doctoral candidate) and author GH (Doctor) have given substantial contributions to the conception or the design of the manuscript, author JG and author DC to acquisition, analysis and interpretation of the data, author ZL and YY to further review the data. All authors have participated to drafting the manuscript, author ZM and author GH revised it critically. All authors read and approved the final version of the manuscript. All authors contributed equally to the manuscript and read and approved the final version of the manuscript.

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Data availability I can always upload the data if needed.

Code availability Stata12.0 and Revman5.3.

Declarations

Conflict of interest We do not have a conflict of interest.

Ethical approval Patients and the public were not involved in the design or conduct of the study.

Consent to participate All the authors agreed to participate.

Consent for publication All the authors agreed to the publishing of this article.

References

1. Bray F, Ferlay J, Soerjomataram I et al (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018(68):394–424
2. Siegel RL, Miller KD, Fuchs HE (2021) Cancer statistics, 2021. CA Cancer J Clin 71(1):7–33
3. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D (2011) Global cancer statistics. CA Cancer J Clin 61:69–90
4. Chen Y, Song J, Jiang Y (2015) Predictive value of CD44 and CD24 for prognosis and chemotherapy response in invasive ductal carcinoma. Int J Clin Exp Pathol 8(9):11287–11295
5. Dalera P, Cho RW, Clarke MF (2007) Cancer stem cells: models and concepts. Annu Rev Med 58:267–284
6. Shan J, Shen J, Liu L et al (2012) Nanog regulates self-renewal of cancer stem cell through IGF pathway in human hepatocellular carcinoma. Hepatology 56:1004–1014
7. Donut G, Al-Hajj M, Abdallah WM et al (2003) Stem cells in normal breast development and breast cancer. Cell Prolif 36:59–72
8. Al-Hajj M, Wicha MS, Benito-Hernandez A et al (2003) Prospective identification of tumorigenic breast cancer cells. Proc Natl Acad Sci USA 100:3983–3988
9. Hashimoto K, Shimizu C, Tsuda H (2012) Immunohistochemical detection of breast cancer stem cells in hormone receptor-positive breast cancer and their role in endocrine therapy and clinical outcome. Oncology 82:168–174
10. Nogi H (2011) Impact of CD44+/CD24− cells on non-sentinel axillary lymph node metastases in sentinel node-positive breast cancer. Oncol Rep 25:1109–1115
11. Ricardo S, Vieira AF, Gerhard R, Leitão D, Pinto R, Cameselle-Teijeiro JF, Milanesi F, Schmitt F, Paredes J (2011) Breast cancer stem cell markers CD44 and CD24 and ALDH1; expression distribution within intrinsic molecular subtype. J Clin Pathol 64(11):937–946
12. Lee HE, Kim JH, Kim YJ (2011) An increase in cancer stem cell population after primary systemic therapy is a poor prognostic factor in breast cancer. Br J Cancer 104(11):1730–1738
13. Mylona E, Giannopoulou I, Fasomytakis E, Nomikos A, Magkou C, Bakarakos P, Nakopoulou L (2008) The clinicopathologic and prognostic significance of CD44+/CD24−/low and CD44+ / CD24+ tumor cells in invasive breast carcinomas. Hum Pathol 39(7):1096–1102
14. Kapucuolu N, Bozkurt KK, Bapinar I et al (2015) The clinicopathological and prognostic significance of CD24, CD44, CD133, ALDH1 expressions in invasive ductal carcinoma of the breast CD44/CD24 expression in breast cancer. Res Pract 211:740–747
15. Tierney JF, Stewart LA, Gherisi D, Burdett S, Sydes MR (2007) Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 8:1–16
16. Parmar MK, Torri V, Stewart L (1998) Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 17:2815–2834
17. Stang A (2010) Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 25(9):603–605
18. Honeth G, Bendahl P-O, Ringnér M (2008) The CD44+/CD24− phenotype is enriched in basal-like breast tumors. Breast Cancer Res 10:R53
19. Giatromanolaki A, Sivridis E, Fiska A (2011) The CD44+/CD24− phenotype relates to ‘triple-negative’ state and unfavorable prognosis in breast cancer patients. Med Oncol 28:745–752
20. Reuben JM, Lee B-N, Gao H (2011) Primary breast cancer patients with high risk clinicopathologic features have high percentages of bone marrow epithelial cells with ALDH activity and CD44 + CD24 + cancer stem cell phenotype. Eur J Cancer 47(10):1527–1536
21. Ahmed MAH, Aleskandarany MA, Rakha EA (2012) A CD44+/CD24− phenotype is a poor prognostic marker in early invasive breast cancer. Breast Cancer Res Treat 133:979–995
22. Guler G, Balci S, Costinean S (2012) Stem cell-related markers in primary breast cancers and associated metastatic lesions. Modern Pathol 37:1–7
23. Tsang JYS, Huang Y-H, Luo M-H (2012) Stem cell-related markers in primary breast cancers and their role in response to endocrine therapy and detection of breast cancer stem cells in hormone receptor-positive breast cancer patients. Med Oncol 24:2515–2521
24. Adamczyk Y, Niemiec JA, Ambicka A (2014) CD44/CD24 as potential prognostic markers in node-positive invasive ductal breast cancer patients treated with adjuvant chemotherapy. J Mol Hist 45:35–45
25. de Mendonca D, Silveira Graudenz M, Callegari-Jacques SM (2014) Expression of cancer stem cell markers in basal and penta-negative breast carcinomas—a study of a series of triple-negative tumors. Pathol Res Pract 210:432–439
26. Zhao H, Tang H, Xiao Q (2016) The Hedgehog signaling pathway contributes to malignant relapse following surgical resection and chemotherapy in patients with invasive ductal carcinoma. J Exp Clin Cancer Res 31:59–68

Springer
33. Ali HR, Dawson S-J, Blows FM (2011) Cancer stem cell markers in breast cancer: pathological, clinical and prognostic significance. Breast Cancer Res 13:R118

34. Abraham BK, Fritz P, McClellan M (2005) Prevalence of CD44+/CD24−/low cells in breast cancer may not be associated with clinical outcome but may favor distant metastasis. Clin Cancer Res 11:1154–1159

35. Aulmann S, Waldburger N (2010) Reduction of CD44+/CD24− breast cancer cells by conventional cytotoxic chemotherapy. Human Pathol 41:574–581

36. Qiu H, Fang X, Luo Q, Ouyang G (2015) Cancer stem cells: a potential target for cancer therapy. Cell Mol Life Sci 72:3411–3424

37. Ali HR, Dawson S-J (2011) Cancer stem cell markers in breast cancer: pathological, clinical and prognostic significance. Breast Cancer Res 13:1–15

38. Reya T, Morrison SJ, Clarke MF, Weissman IL (2001) Stem cells, cancer, and cancer stem cells. Nature 414:105–111

39. Hilbe W, Dirnhofer S, Oberwasserlechner F, Schmid T, Gunsilius E, Hilbe G et al. (2004) CD133 positive endothelial progenitor cells contribute to the tumour vasculature in non-small cell lung cancer. J Clin Pathol 57:965–969

40. Wu S, Yu L, Wang D, Zhou L, Cheng Z, Chai D et al. (2012) Aberrant expression of CD133 in non-small cell lung cancer and its relationship to vasculogenic mimicry. BMC Cancer 12:535

41. Ahmed MA, Aleskandarany MA, Rakha EA, Moustafa RZ, Benhasouna A, Nolan C, Green AR, Ilyas M (2011) Ellis IO A CD44(−)/CD24 (+) phenotype is a poor prognostic marker in early invasive breast cancer. Breast Cancer Res Treat 39:1865–1868

42. Jie B, Wei-Bin C, Xiao-Yu Z (2020) HIF-2α regulates CD44 to promote cancer stem cell activation in triple-negative breast cancer via PI3K/AKT/mTOR signaling. World J Stem Cells 12:87–99

43. Zhou L, Jiang Y, Yan T (2010) The prognostic role of cancer stem cells in breast cancer: a meta-analysis of published literatures. Breast Cancer Res Treat 122:795–801

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