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Original Article

Prognostic significance of neuroendocrine differentiation in breast carcinoma: a meta analysis

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Abstract: Neuroendocrine differentiation (NED) has been observed in breast carcinoma (BC). Several studies have explored the prognostic significance of NED in patients with BC but yielded controversial results. In order to comprehensively appraise the prognostic significance of NED in BC, we carried out the present meta-analysis with the risk ratios (RRs) of 5-year and 10-year survival rates and hazard ratios (HRs) of overall survival (OS) and disease-free survival (DFS) as outcomes of interest. Multiple databases including PubMed, FreQuest and Web of science were searched for literature retrieval. The pooled RRs and HRs with corresponding 95% confidence intervals (CIs) were computed to estimate the prognostic significance of NED in BC patients. All the incorporated studies were high quality based on our quality assessment. The pooled RRs suggested that BC patients with NED had a significantly higher risk of death within 5 years and 10 years than those without NED (5-year survival rate: RR=2.338, 95% CI: 1.269-4.309, P=0.006; 10-year survival rate: RR=1.227, 95% CI: 1.010-1.490, P=0.039); the pooled HRs indicated that BC patients with NED had significantly worse OS and DFS than those without NED (OS: HR=1.826, 95% CI: 1.197-2.786, P=0.005; DFS: HR=2.539, 95% CI: 1.915-3.367, P<0.001). No significant publication bias was observed among these analyses. In conclusion, our meta-analysis demonstrates that the NED is significantly associated with unfavorable prognosis, and BC patients with NED are more likely to have poor prognosis.

Keywords: NED, BC, prognosis, meta-analysis

Introduction

Breast carcinoma (BC), the second leading cause of cancer-related death among women, remains the most common malignancy in females [1]. More than 11,000 deaths are ascribed to BC in the UK every year, and over one million women are newly diagnosed with BC each year worldwide [2, 3]. With advances in diagnosis and clinical management, the number of long-term survivors of BC may become larger [4]. It has been documented in a retrospective review that was aimed to investigate the treatment outcomes and prognostic factors of BC patients receiving combined-modality therapy that overall, the prognosis of BC individuals is favorable with the 5-year overall survival (OS) and disease-free survival (DFS) are 77.5% and 73.8%, respectively [5].

Neuroendocrine differentiation (NED), that marks a structural and functional characteristic of certain carcinomas, has been observed in several types of cancers including BC, prostate cancer, sporadic colorectal cancer, lung cancer and so on [6-10]. NEBC, firstly described in 1963 by Feyrter and Hartmann, is a rare neoplasm with its definition and clinical outcome controversial [11, 12]. The reported incidence of NED is highly variable, ranging from <1% to up to 50% of all BC, which depends on the criteria and detection approaches [12, 13]. And the NED can be assessed in BC when the expression of NE markers is over 50% of the neoplastic cells [9].

There have been some publications exploring the prognostic significance of NED in BC, but the results are inconsistent. Sawaki and colleagues conducted a relevant study to evaluate the prognostic importance of NED in patients with BC and found that there seemed to be no relationship between the NED and the clinical outcomes of patients [14]. However, data from another paper, published in 2013, revealed that compared with NED-negative BC patients those with NED had worse OS and DFS [12]. Herein, in order to comprehensively estimate

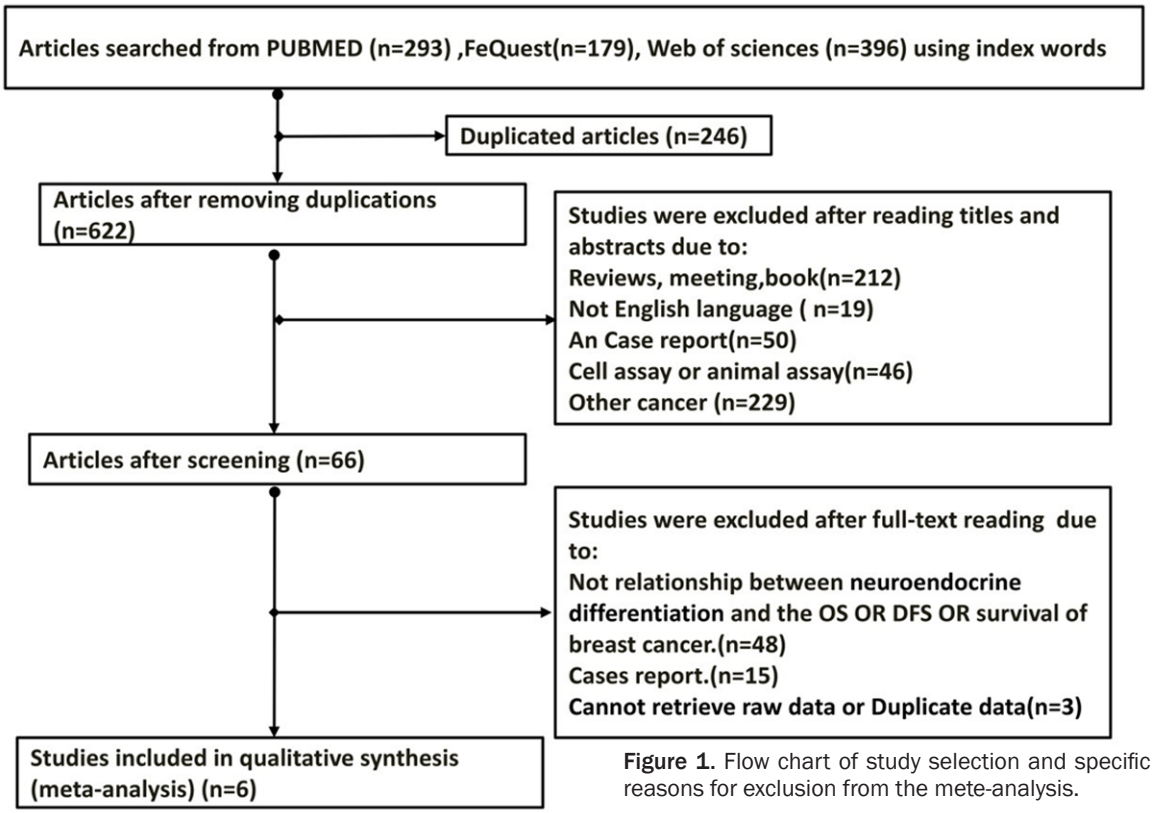

Figure 1. Flow chart of study selection and specific reasons for exclusion from the mete-analysis.

the prognostic significance of NED in BC, we used the risk ratios (RRs) with their corresponding 95% confidence intervals (CIs) of 5-year and 10-year survival rates and hazard ratios (HRs) with the 95% CIs of OS and DFS as outcomes of interest and carried out the present meta-analysis.

Materials and methods

Search strategy

Multiple databases including PubMed, FreQuest and Web of science were searched from inception to June 9, 2016 for literature retrieval. The search terms were set as cancer OR Oncology OR tumor OR malignancy OR neoplasm OR carcinoma AND breast AND (Synaptophysin OR "neuroendocrine differentiation" OR chromogranins). The references cited in the retrieved reviews were screened to find relevant literatures that were missed from the initial search strategy.

Inclusion and exclusion criteria

The eligibility of each retrieved literature was appraised based on the following pre-defined inclusion criteria: (1) studies conducted within a human population rather than animals or cells; (2) studies regarding the prognostic significance of NED in BC; (3) the outcome was the 5-year survival rate, 10-year survival rate or survival curve of BC patients with or without NED; (4) studies published in English. The major exclusion criteria were as follows: (1) duplicated literatures; (2) case report; (3) studies with raw data unavailable; (4) some publication types, such as reviews, letters to editors, news and proceedings.

Data extraction

Two reviewers independently extracted the data from incorporated studies after assessing the suitability of each study based on the above inclusion and exclusion criteria. The following descriptive information was collected: first author, year of publication, location of study, follow-up period, number of BC patients with or without NED, age of patients, diagnosis criteria and detection methods of NED, and 5-year and 10-year survival rates. For OS and DFS, the HRs and their 95% CIs were also collected. If the HR could not be obtained directly, the Engauge Digitizer 4.1 software was adopted for data col-

Table 1. Special characteristics of included studies

First author	Year	Country	Cancer type	Diagnostic criteria	Age (median)	Sample size (NED-negative/ NED-positive	Detection method	Detection criteria	Follow-up time (month)
Krimpen	2004	Netherlands	BC	WHO criteria	59	273/40	IHC	immunohistochemistry using antibodies against chromogranine A (CgA) and synaptophysine (SYN)	1-180
Sawaki	2010	Japan	BC	WHO criteria	52.7	37/13	-	at least one marker including CGA, CD57, and synaptophysin, or at least two markers when one positive marker was NSE	104
Kwon	2014	Korea	BC	WHO criteria	47	1369/59	IHC	at least one focus of cells (≥1% of total tumour cells) showed expression of chromogranin-A and/or synaptophysin during microscopic examination of two consecutive TMA cores.	56 (1-122)
Bogina	2016	Italy	BC	WHO criteria	-	1104/128	IHC	at least 10% of tumour cells showed expression of synaptophysin and/or chromogranin-A.	78 (2-134)
Liu	2015	China	BC	WHO criteria	54.6	975/135	IHC	defined by ≥1% expression of GC and/or SYN or showing morphological NED features	65.6 (1-210)
Zhang	2013	China	BC	WHO criteria	65	475/107	IHC	immunohistochemical staining for NE markers (ie, >50% of the invasive tumor cells expressing synaptophysin (Sy) and/or chromograninA (CgA)	27 (3-134)

BC: breast carcinoma; NED: neuroendocrine differentiation; WHO: World Health Organization; "-": not mentioned; IHC: immunohistochemistry.

Table 2. Quality assessment of the individual study

Study	Selection				Comparability	Outcome			Score
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome not present at start		Assessment of outcome	Follow-up length	Follow-up adequacy	
Krimpen (2004)	*	*	*	*	*	*	*	*	8
Sawaki (2010)	*	*	*	*	*	*	*	*	8
Kwon (2014)	*	*	*	*	*	*	*	*	8
Bogina (2016)	*	*	*	*	*	*	*	*	8
Liu (2015)	*		*		*	*	*	*	6
Zhang (2013)	*		*		*	*	*	*	6

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. Amaximum of two stars can be given for Comparability.

lection from Kaplan-Meier survival curves, and then the SPSS 19.0 software was used for the analysis of Cox regression to generate the HR and its corresponding 95% CI. Corresponding authors of primary studies were contacted to supplement the incomplete information.

Quality assessment

Methodological quality of studies was appraised with the Newcastle-Ottawa Scale (NOS) [15], and a NOS score of 5 or greater was defined as high quality. The study retrieval, data extraction and quality assessment of each included study were conducted independently by two reviewers, and disagreements were ruled out by discussion.

Statistical analysis

In our study, the RRs of 5-year and 10-year survival rates and HRs of OS and DFS were regarded as outcomes of interest, and the RR/HR with a 95% CI was calculated using the STATA

Table 3. Meta-analysis of the prognostic significance of NED in BC patients

Study	RR/HR	Lower Limit	Upper Limit	P (RR/HR)	I^2	P (Heterogeneity)	P (Begg's Test)	P (Egger's test)
5-year survival rate	2.338#	1.269	4.309	0.006#	86.40%	<0.001	1	0.879
10-year survival rate	1.227#	1.01	1.49	0.039#	88.70%	<0.001	1	0.735
OS	1.826*	1.197	2.786	0.005*	78.70%	<0.001	1	0.81
DFS	2.539*	1.915	3.367	<0.001*	<0.01%	0.729	1	0.932

#: RR; *: HR; OS: overall survival; DFS: disease-free survival.

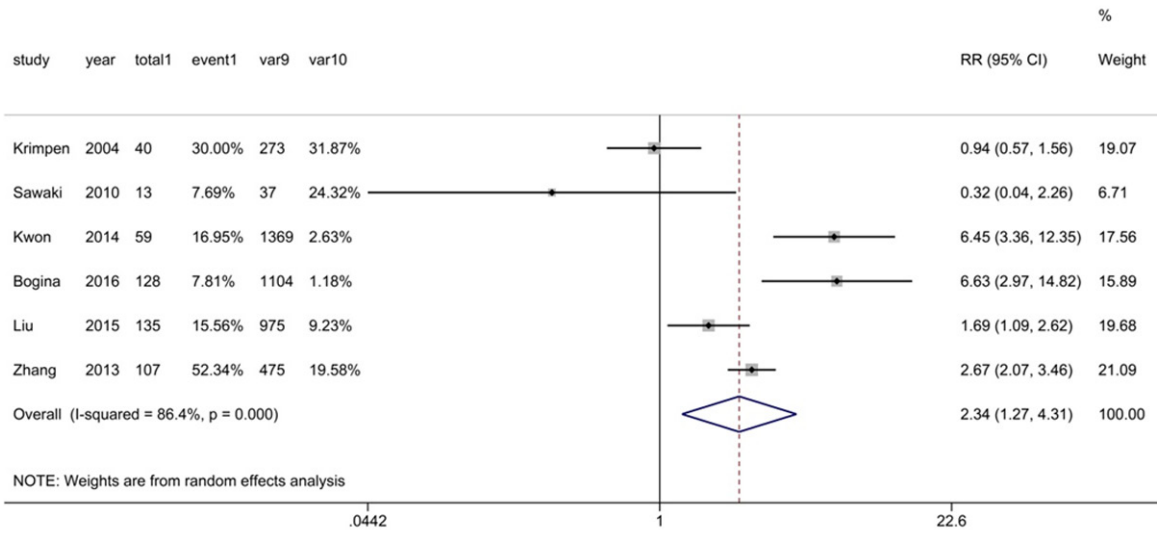

Figure 2. Forest plot of study evaluating the relationship between NED and the 5-year survival rate for BC patients.

12 software (STATA Corp LP, College Station, Texas, United States). Heterogeneity between the incorporated studies was measured by Cochran's Q test and I^2 statistics [16, 17]. A P<0.1 or I^2>50% was considered significant heterogeneity across studies. Otherwise, there was no significant heterogeneity. The random-effects model was applied for the combination of the individual HR or RR estimates in the presence of between-study heterogeneity, while the fixed-effects model was employed when no significant heterogeneity was observed. Possible publication bias was evaluated using the Begg's test and Egger's test. A two-sided P<0.05 was considered to be statistically significant.

The related data in NED-negative BC patients served as reference for the calculation of RR/HR with a 95% CI. ARR/HR>1 indicates that BC patients with NED have poorer survival than those without NED. Sensitivity analysis was carried out by sequentially omitting each study to appraise the impact of the single study on the overall estimation.

Results

Study selection and quality assessment

According to the above search strategy, our primary search of the electronic databases yielded 868 literatures, among which 293 were from PubMed, 179 from FreQuest and 396 from Web of science. After removing duplicated articles, 622 literatures were left for further evaluation. We then excluded 556 literatures after reading titles and abstracts, leaving 66 literatures for full-text reading. Finally, 6 studies [12, 14, 18-21] were included in our meta-analysis, and the detailed process of literature inclusion and exclusion was illustrated in **Figure 1**. The characteristics of each incorporated study were displayed in **Table 1**. The NOS score of each included study was greater than 5 (**Table 2**), revealing that all the eligible studies were high quality in our analysis.

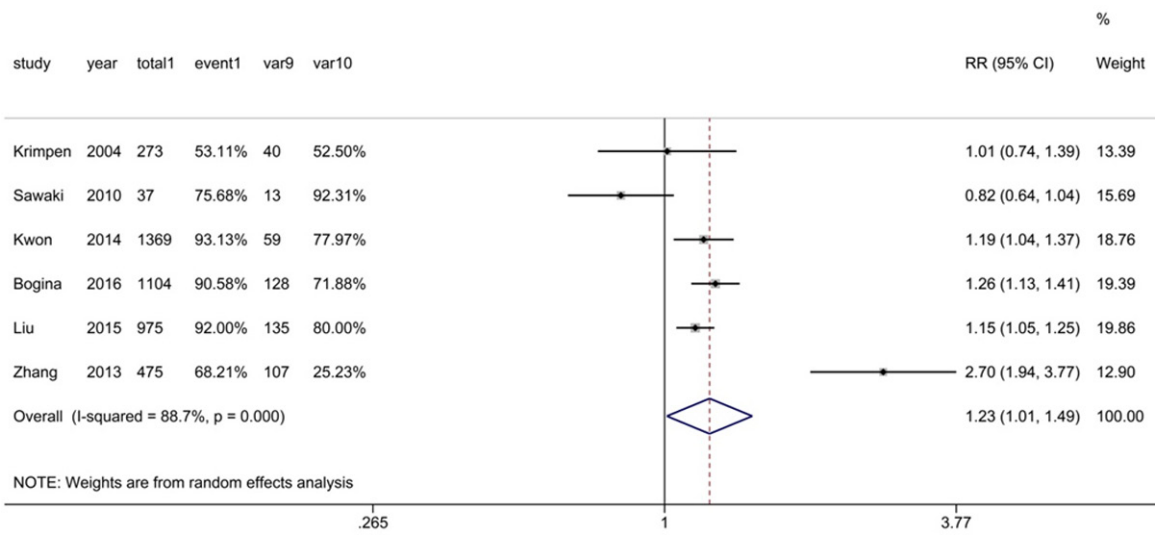

Figure 3. Forest plots of study assessing the relationship between NED and the 10-year survival rate for BC patients.

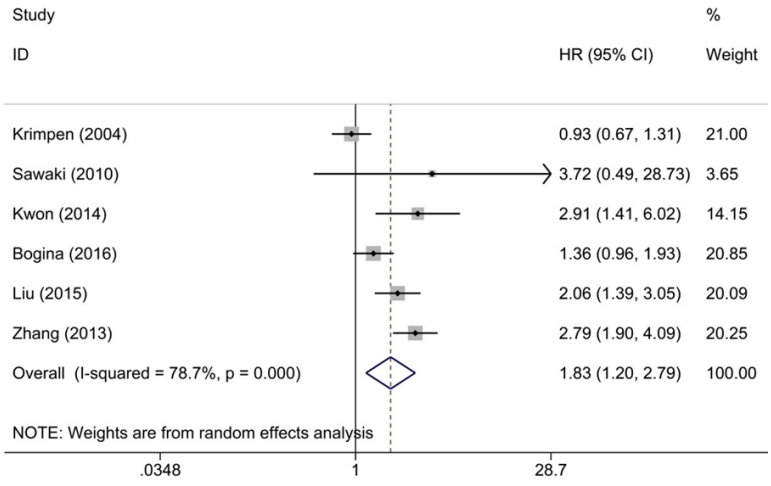

Figure 4. Forest plots of study evaluating the relationship between NED and the OS for BC patients.

The relationship between NED and the 5-year or 10-year survival rate for BC patients

6 studies were meta-analyzed for both the 5-year and 10-year survival rates, respectively. The results were represented in **Table 3**. Large heterogeneity was detected (5-year survival rate: I^2=86.40%; 10-year survival rate: I^2= 88.70%), so the random-effects model was selected to generate the RR with the corresponding 95% CI. The values of RRs were 2.338 (95% CI: 1.269-4.309, P=0.006, **Figure 2**) and 1.227 (95% CI: 1.010-1.490, P=0.039, **Figure 3**) for the 5-year and 10-year survival rates, respectively, which manifested that the NED was remarkably associated with the 5-year and 10-year survival rates for BC patients, and NED-positive BC patients had a significantly higher risk of death within 5 and 10 years, when compared with NED-negative BC individuals.

The relationship between NED and the OS for BC patients

There were 6 eligible studies to evaluate the relationship between NED and the OS for patients with BC, and the results were displayed in **Table 3**. Considering the presence of heterogeneity (I^2=78.70%), the random-effects model was used to calculate the pooled HR with its corresponding 95% CI for OS. The value of HR was 1.826 with its 95% CI ranged from 1.197 to 2.786 (**Figure 4**), and the value of *P* was 0.005, which suggested that remarkable association was detected between the NED and the OS of BC patients, and BC patients with NED had significantly worse OS than those without NED.

The relationship between NED and the DFS for BC patients

4 eligible studies were included to assess the relationship between NED and DFS for BC

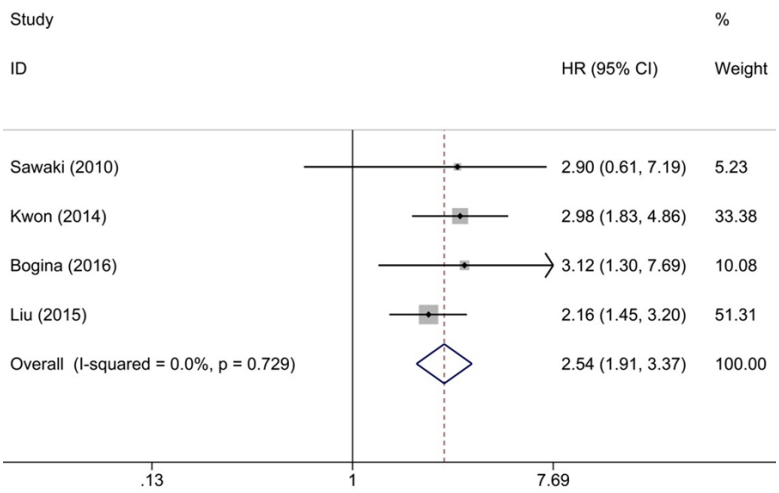

Figure 5. Forest plot of study estimating the relationship between NED and the DFS for BC patients.

patients, and the results were exhibited in **Table 3**. The fixed-effects model was chosen for the calculation of HR and its corresponding 95% CI for DFS due to the absence of heterogeneity (I^2<0.01%). The value of pooled HR was higher than 1 (HR=2.539, 95% CI: 1.915-3.367, **Figure 5**), and the value of *P* was less than 0.05 (P<0.001), signifying that the NED was significantly associated with the DFS for BC patients, and the NED-positive BC patients had more unfavorable DFS compared with NED-negative BC individuals.

Publication bias

Publication bias of the included studies was appraised by funnel plots and Egger's test, and the results were represented in **Table 3** and **Figure 6A-D**. All the four funnel plots were nearly symmetric, demonstrating that there was no evidence of publication bias among these analyses. The values of *P* in the Egger's test and Begg's test for each comparison were higher than 0.1, which further implied that no significant publication bias was observed among these analyses.

Sensitivity analysis

Moreover, sensitivity analysis, that was used to measure the impact of an individual study on the pooled RRs for the 5-year and 10-year survival rates, was assessed by omission of one study at a time. The results (Supplementary Figure 1A and 1B) revealed that none of the included studies dominantly affected the pooled RR and its corresponding 95% CI for the 10-year survival rate, while the study from Zhang et al. could remarkably influence the pooled RR and its corresponding 95% CI for the 5-year survival rate. Thus, another RCT with a large sample size should be implemented for a more reliable and precise estimation of the relationship between the NED and the 5-year survival rate for BC patients.

Discussion

Currently, there is debate regarding the prognostic significance of NED in BC patients, so our meta-analysis incorporated 6 eligible studies was conducted with the RRs of 5-year and 10-year survival rates and HRs of OS and DFS as outcomes of interest. Our results showed that for the 5-year and 10-year survival rates, BC patients with NED were more likely to have a higher risk of death within 5 years and 10 years than those without NED; for the OS and DFS, compared with those without NED, BC patients with NED were more likely to have worse OS and DFS. Our meta-analysis suggested that NED was an indicator of poor prognosis for BC patients.

Although BC is a worldwide health concern among women, accounting for over 410,000 deaths annually, the early stage at diagnosis and proper treatment have rendered it a chronic disease in many countries possessing modern health care systems [2, 4]. It is recorded that about 41% of cancer survivors are patients with a history BC, and women with BC become the largest group of female cancer survivors [22]. Several indicators have been recorded to be correlated with the prognosis of BC. The immunohistochemical method was selected to establish the effect of the Hsc70-interacting protein (CHIP) expression on the prognosis of BC, and the results signified that the overexpression of CHIP predicted a good prognosis for BC patients in postmenopausal phase [23]. Feng and colleagues observed the expression of elongation of long chain fatty acids family

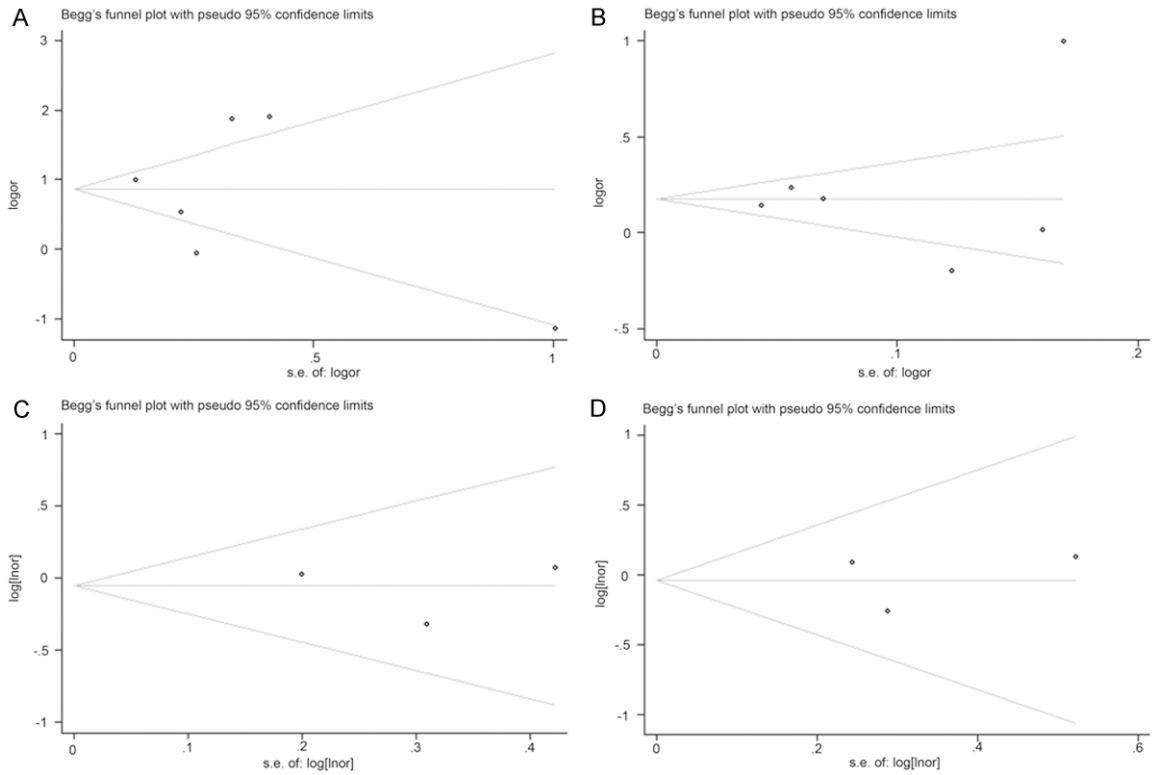

Figure 6. Funnel plots of studies appraising the relationship between NED and the 5-year survival rate (A), the 10-year survival rate (B), the OS (C) and the DFS (D) for BC patients.

member 6 (Elovl6) in tissues of BC patients who had experienced curative mastectomy and detected that positive Elovl6 expression was a poor prognostic predictor for BC patients [24]. In the present study, we conducted a meta-analysis and found that the NED was a poor prognostic indicator for BC patients. The fork head-box A1 (FOXA1), sperm-associated antigen 5 (SPAG5), kruppel-like factor 4 (KLF4) and perilipin-1 (PLIN1) have also been reported as prognostic biomarkers for BC [25-28].

NED, usually determined by immunoreactivity for NE markers, is a phenomenon that can be encountered in certain human tumors including BC [8, 29]. Carcinomas with NED frequently represent a prominent NE cell population on histopathologic examination [6]. Currently, the immunostaining, in which Chromogranin A, Chromogranin B and Synaptophysin are the widely recognized NE markers, is introduced to confirm the detection of NED in BC, considering the fact that it is inadequate to distinguish NEBC from other subtypes of BC just based on clinical features and morphology [9, 30]. A related study, published in 2015, implied that NED-positive BC patients had worse clinical outcomes than NED-negative BC patients [20], which was consistent with the results of current meta-analysis.

Results of our meta-analysis revealed that the NED was associated with the 5-year survival rate, 10-year survival rate, OS and DFS of BC patients, and the NED predicted a worse prognosis for BC patients. A previous meta-analysis, estimating the prognostic significance of NED in colorectal adenocarcinoma, observed that patients with NED had a lower 5-year survival rate [31]. Komiya et al. adopted the immunohistological staining to investigate the prognostic significance of NED in castration-resistant prostate cancer patients, and detected that the NED was correlated with a worse prognosis [32].

Obvious heterogeneity was detected in the analysis of the 5-year survival rate, 10-year survival rate and OS, while there was in the absence of heterogeneity in the analysis of DFS. And the subgroup analysis or meta-regression analysis should be conducted to find the

source of heterogeneity. However, we failed to carry out the subgroup analysis or meta-regression analysis due to the lack of related data. Considering the characteristics of the included studies we speculated that the follow-up time in each study was not exactly the same, which might be responsible for the large heterogeneity in the analysis of the 5-year survival rate, 10-year survival rate and OS.

Certainly, there existed limitations in the present study. First, among all the 6 included studies, only two of them [18, 19] were conducted on the European population, others [12, 14, 20, 21] on the Asian population. And the subgroup analysis stratified by ethnicity should be carried out in the future, as more relevant studies become available. Second, although all the included studies were high quality, the sample size of one study [14] was relatively small, which may have weakened the statistical power. Additionally, only studies published in English were incorporated in our meta-analysis and may have caused bias for our estimation.

In conclusion, to our knowledge, the current study is the first meta-analysis appraising the prognostic significance of NED in BC patients. And our results suggest that the NED is associated with the prognosis of BC patients, and the NED-positive BC patients are more likely to have unfavorable 5-year and 10-year survival rates, OS and DFS. And NED is a poor prognostic indicator for BC patients.

Disclosure of conflict of interest

None.

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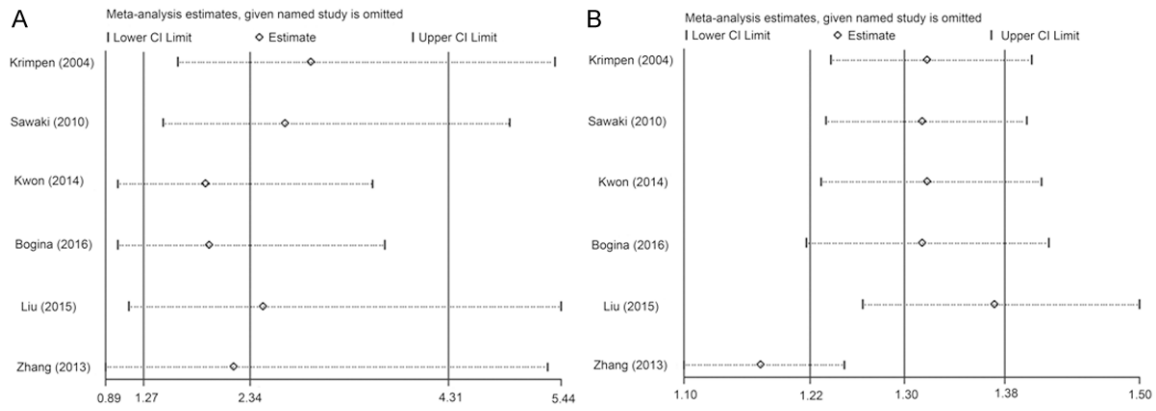

Supplementary Figure 1. Sensitivity analysis of the 5-year survival rate (A) and 10-year survival rate (B).