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Non-sentinel lymph node metastases risk factors in patients with breast cancer with one or two sentinel lymph node macro-metastases

Liu-yan Xu [a,1], Jing Zhao [a,1], Xuan Wang [a], Xin-yan Jin [b], Bei-bei Wang [c], Ying-yi Fan [a], Xiao-hua Pei [d,*]

[a] The Third affiliated hospital of Beijing University of Chinese Medicine, Beijing 100029, China
[b] Center for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing 100029, China
[c] The First Affiliated Hospital of Henan University of Chinese Medicine, Zhengzhou 450000, China
[d] The Xiamen Hospital of Beijing University of Chinese Medicine, Xiamen 361001, China

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ABSTRACT

Approximately 59 % of patients with breast cancer with one or two sentinel lymph nodes (1–2 SLN) macrometastases do not benefit from axillary lymph node dissection (ALND), which may also incur morbidities. It is necessary to evaluate the association between various clinicopathological characteristics and non-sentinel lymph node metastases (non-SLNM) in patients with breast cancer with 1–2 SLN macrometastases, and determine whether they 1–2 should avoid ALND. Eight electronic literature databases (PubMed, Embase, Web of Science, Cochrane Library, China National Knowledge Infrastructure, Chinese Scientific Journal, Wanfang, and Chinese Biomedical Literature) were searched from their inception to June 30, 2023, and two reviewers independently extracted the data and assessed the risk of bias. Association strength was summarized using odds ratios (OR) and 95 % confidence intervals (CI). Heterogeneity was accounted for using a subgroup analysis. Publication bias was evaluated using funnel plots and Egger's test. There were 25 studies with 8021 participants, and 27 potential risk factors were evaluated. The risk factors for non-SLNM in patients with 1–2 SLN macrometastatic breast cancer include the following: factors of primary tumor: multifocality (OR (95 % CI (2.63 (1.96, 3.54))), tumor size ≥ T2 (2.64 (2.22, 3.14)), tumor localization (upper outer quad) (2.06 (1.23, 3.43)), histopathological grade (G3) (2.45 (1.70, 3.52)), vascular invasion (VI) (2.60 (1.35, 4.98)), lymphovascular invasion (LVI) (2.87 (1.80, 4.56)), perineural invasion (PNI) (3.16 (1.18,8.43)). Factors of lymph nodes: method of SLNs detected (blue dye) (3.85 (1.54, 9.60)), SLN metastasis ratio ≥0.5 (2.79 (2.24, 3.48)), two positive SLNs (3.55, (2.08, 6.07)), zero negative SLN (3.72 (CI 2.50, 4.29)), extranodal extension (ENE) (4.69 (2.16, 10.18)). Molecular typing: Her-2 positive (2.08 (1.26, 3.43)), Her-2 over-expressing subtype (1.83 (1.22, 2.73)). Factors of examination/inspection: axillary lymph nodes (ALNs) positive on imaging (3.18 (1.68, 6.00)), cancer antigen 15-3 (CA15-3) (4.01 (2.33,6.89)), carcinoembryonic antigen (CEA) (2.13 (1.32–3.43)). This review identified the risk factors for non-SLNM in patients with 1–2 SLN macrometastatic breast cancer. However, additional studies are needed to confirm the above findings owing to the limited number and types of studies included.

* Corresponding author.
E-mail addresses: pxh_127@163.com, 13911683278@163.com (X.-h. Pei).
[1] The two authors contributed equally to this work.

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1. Introduction

Breast cancer is the most commonly diagnosed cancer, the leading cause of death in women, and has the highest incidence of malignant tumors [1]. Axillary lymph nodes (ALNs) status is one of the most crucial prognostic indicators of invasive breast cancer. Sentinel lymph node biopsy (SLNB) is an accepted method for identifying the pathologic axillary status in early cancer cases with clinically negative axillae, allowing for the accurate and reliable staging of axillary nodal status [2]. Axillary lymph node dissection (ALND) is an essential procedure for managing breast cancer at the regional level, for nodal staging and disease control. ALND can be safely omitted when sentinel lymph nodes (SLN) are histologically negative, therefore, overall survival (OS) or local disease control are not compromised [3]. However, ALND remains the standard of care for patients with positive SLNs owing to its prognostic and therapeutic implications [4]. Recent extensive prospective clinical studies (ACOSOG Z0011, AMAROS, IBCSG 23-01) suggest that ALND is not recommended for patients on early breast cancer stages (T1–2N0) with 1–2 metastatic SLN (mSLN) [5–7]. However, these results should be interpreted with caution because the above studies included relatively few mastectomy patients; for example, ACOSOG Z0011 did not include patients who had a mastectomy, and AMAROS included approximately 17 % of patients who had a mastectomy (approximately 29 % had micrometastases), IBCSG 23-01 included only 9 % of the patients (all micrometastases). The studies did not indicate the effect of omitting ALND on the survival and prognosis of patients with cT1–2 stage cancer. ALND remains the first recommended treatment strategy for patients with stage cT1–2, 1–2 SLN macrometastases or micrometastases breast cancer who undergo mastectomy but do not receive postoperative axillary radiotherapy, according to the recommendations of the 4th edition of the National Comprehensive Cancer Network (NCCN) Breast Cancer Treatment Guidelines published in 2022 and the 2021 edition of the Breast Cancer Treatment Guidelines and Specifications published by the Breast Cancer Professional Committee of the Chinese Anti-Cancer Association. However, ALND is associated with a high incidence of postoperative complications, including lymphedema, sensory impairment, shoulder joint motion limitation, and medically induced nerve damage, all of which affects quality of life [8,9]. Subgroup analysis of the AMAROS study revealed that approximately 41 % of patients had additional metastases in non-sentinel lymph nodes (non-SLNs) with SLN macrometastases. Therefore, the remaining 59 % of patients with disease-free non-SLN will not undergo ALND, thus avoiding morbidities associated with the procedure [10].

Most patients in the ACOSOG Z0011, AMAROS, and IBCSG 23-01 studies received breast-conserving surgery and the axillary management decision of mastectomy was different from that of breast-conserving surgery. It is necessary to be cautious when exempting ALND for breast cancer patients who underwent mastectomy and with 1–2 mSLN. This systematic review and meta-analysis aimed to determine the predictors of non-sentinel lymph node metastases (non-SLNM) by evaluating the clinicopathological characteristics of patients with 1–2 mSLN. The purpose was to avoid the occurrence of overtreatment or undertreatment of the axilla and to better define the individual therapeutic approach, considering the SLN status and other clinicopathological factors.

2. Materials and methods

Guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) were followed in the present review [11], which was registered at PROSPERO before the initial screening (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=351816; ID: CRD42022351816).

2.1. Eligibility criteria

(I) Study type: Observational studies assessing independent risk factors for axillary lymph node metastasis (ALNM) in patients with breast cancer with one or two positive SLN; articles must include original data and be published in English or Chinese. (II) Women of any age or race with histologically confirmed breast cancer, radiological and physical examinations confirming clinically negative ALNs, or examinations confirming positive ALNs, but negative pathological results of puncture biopsy; successful SLND and ALND; histologically confirmed 1–2 SLNs with macrometastases (metastases >2 mm); first-time breast cancer diagnosis; and no neoadjuvant systemic therapy, regardless of age or race. (III) Exposure: exposure to non-SLN metastasis. Breast cancer with 1–2 SLN-positive and non-SLN metastases were categorized as exposed, while those with 1–2 SLN-positive and non-SLN-negative metastases were categorized as non-exposed.

2.2. Exclusion criteria

The following studies were omitted: male sex, in situ carcinomas, neoadjuvant chemoradiation, >2 positive SLNs, micrometastasis or isolated tumor cells in SLNs, presence of ALNM or distant metastasis demonstrated clinically, presence of other malignant diseases, and pregnancy.

2.3. Data sources and searches

The review was conducted by searching PubMed, Embase Database, Web of Science, Cochrane Library databases, China National Knowledge Infrastructure (CNKI), Chinese Scientific Journal Database (VIP), Wanfang Database, and Chinese Biomedical Literature Database (Sino-Med) from inception to June 30, 2023. Additionally, the bibliographies of the identified relevant articles and reviews were manually screened for eligible studies.

The keywords used were as follows: breast cancer, breast tumor, mammary cancer, breast malignant, mammary carcinoma, sentinel lymph nodes, sentinel nodes, risk factors, factors, social risk factors, influencing factors, and dangerous factors. Appendix A describes the PubMed search strategy.

2.4. Study selection

Using a reference management system (Note Express v3.5.0.9054, http://www.inoteexpress.com/aegean/index.php/home/ne/index.html, accessed September 16, 2021), all potentially eligible studies were uploaded, and duplicates were removed. Two authors (XLY and ZJ) independently selected studies based on the inclusion and exclusion criteria. Any disagreements regarding study selection were resolved by consensus and, if necessary, by a third author (JXY).

2.5. Data collection process

Two reviewers (XLY and ZJ) independently extracted the following data: title, first author, study design, publication year, publication journal, start and completion dates, study institution, geographical information (country), and study characteristics (sample size, risk factors, number of events and nonevents in the case and control groups, relative ORs, and 95 % Cis). The data were entered into a Microsoft Excel spreadsheet (https://www.microsoft.com/, accessed November 9, 2021).

2.6. Methodological quality and risk of bias assessment

The risk of bias in the included studies was assessed using a modified version of the Newcastle-Ottawa Scale (NOS) for observational studies [12]. This eight-question star rating system assigns a maximum of nine stars across three domains: selection (four stars), comparability (two stars), and measurement of exposure (a risk factor) in case-control studies, or outcomes (dental caries) in cohort studies (three stars). Studies with fewer than five stars were deemed to have a high risk of bias, whereas those with a total score greater than seven were deemed to be of high quality. Two reviewers (XLY and WX) independently extracted the data and assessed the risk of bias, and a third reviewer (ZJ) resolved any discrepancies.

2.7. Statistical analysis

For each factor, the odds ratio (OR) and 95 % confidence intervals (CI) were computed using a comprehensive meta-analysis software (Stata 16.1, https://www.stata.com/, accessed October 9, 2022) with an alpha set to 0.05. Cochran's Q test was used to assess heterogeneity, deriving the magnitude from I^2. When $I^2 > 50$ % and the Q chi-squared test result was <0.1, statistical

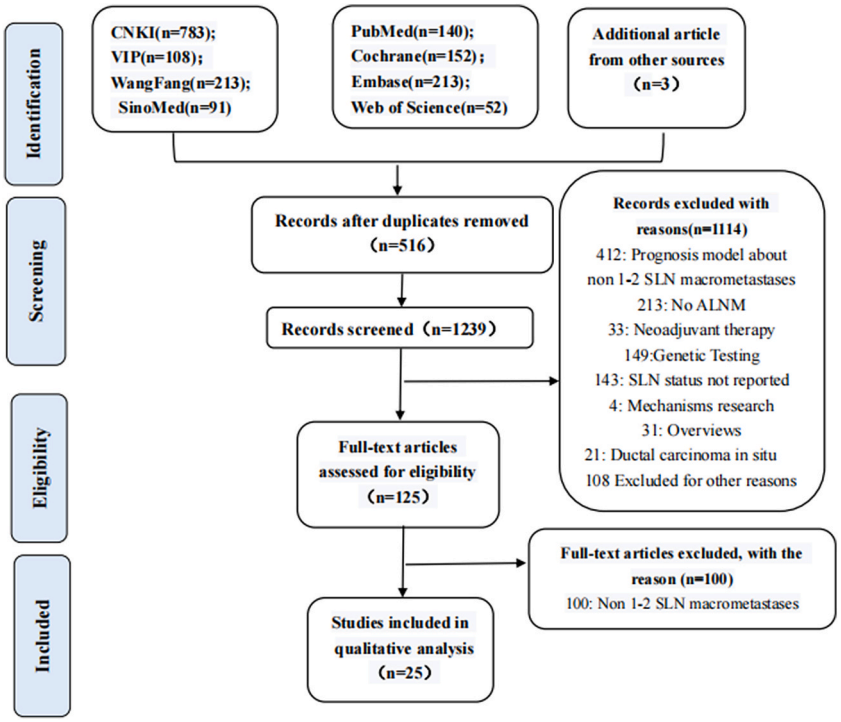

Fig. 1. Flow diagram of the study selection.3.2 Study characteristics.

heterogeneity was assumed, and a random-effects model was applied. Otherwise, there was no statistically significant heterogeneity between the trials, and a fixed-effects model was used [13]. A subgroup analysis was applied to factors with apparent heterogeneity. Heterogeneity was addressed using subgroup analyses performed as a meta-analysis based on the number of exposed and unexposed individuals in the case and control groups. If at least ten studies were available, we examined potential small-study effects, such as publication bias, using the funnel plot and Egger's test, where $P < 0.05$ indicates publication bias [14].

Table 1
Characteristics of the included studies.

Study ID	study duration	Areas	Sample source	Study Design	IRB approval	Sample size (T/C)	Factors
Huang Z2023 [15]	2017.1–2022.2	China	Hospital	Case–control studies	Yes	96/177	tumor size; SLN metastasis ratio; tumor localization;
Zeng H 2022 [16]	2016.12–2021.12	China	Hospital	Case–control studies	NR	55/130	tumor size; VI; SLN metastasis ratio;
Wu F 2022 [17]	2015.1–2020.9	China	Hospital	Case–control studies	Yes	54/783	VI; SLN metastasis ratio;
Xie YJ2022 [18]	2018.3–2022.3	China	Hospital	Case–control studies	Yes	59/99	tumor size; VI; SLN metastasis ratio;
LiuL 2022 [19]	2013.1–2020.12	China	Hospital	Case-control studies	NR	104/361	ER; PR; Her-2 positive; Ki-67; tumor localization; distance from nipple; no. of SLNs detected; tumor size; ILC;
ZhangL 2021 [20]	2009.6–2018.6	China	Hospital	Case-control studies	Yes	101/173	no. of positive SLN; method of slns detected; histopathological grade; molecular subtype;
YuY I 2021 [21]	2016.4–2020.7	China	Hospital	Case–control studies	Yes	182/436	tumor localization; histopathological grade; LVI; no. of negative SLN; no. of positive SLN;
YuY II 2021 [21]	2016.10–2019.11	China	Hospital	Case–control studies	Yes	163/369	tumor localization; histopathological grade; LVI; no. of negative SLN; no. of positive SLN; CA15-3; CEA;
MengL 2020 [22]	2016–2018	China	Hospital	Case-control studies	Yes	149/234	ALNs status on imaging; No. of negative SLN; SLN metastasis ratio; VI; Her-2 positive; Ki-67; molecular subtype;
HeZ 2020 [23]	2000.8–2018.11	China	Hospital	Case-control studies	NR	235/331	no. of negative SLN; SLN metastasis ratio; LVI;
Azmi L 2019 [24]	2010.3–2018.12	Turkey	Hospital	Case-control studies	NR	38/72	Her-2 positive; PNI; size of SLN metastasis; ENE;
Amina M2019 [25]	2010.4–2017.10	China	Hospital	Case-control studies	NR	86/208	VI; SLN metastasis ratio;
MoWJ 2019 [26]	2016.1–2017.12	China	Hospital	Case-control studies	NR	64/166	tumor size; tumor localization; SLN metastasis ratio;
WangXY 2019 [27]	2012.1–2016.12	China	Hospital	Case-control studies	Yes	90/306	tumor size; histopathological grade; no. of negative SLN; ALNs status on imaging;
GaoSY 2018 [28]	2009.6–2017.12	China	Hospital	Case-control studies	NR	41/52	ER; no. of positive SLN;
DongLF 2018 [29]	2013.1–2015.10	China	Hospital	Case-control studies	Yes	87/128	tumor size; no. of negative SLN; LVI; Her-2 positive;
Bahadır 2018 [30]	2010.10–2014.10	Turkey	Hospital	Case-control studies	NR	32/69	LVI; Her-2 positive; Ki-67; ENE;
ZhengJW 2018 [31]	2009.3–2017.3	China	Hospital	Case-control studies	Yes	42/77	LVI; tumor size; Her-2 positive; histopathological grade;
CaoTF 2017 [32]	2012.1–2015.12	China	Hospital	Case-control studies	NR	54/64	tumor size; VI; SLN metastasis ratio;
LiangYS 2017 [33]	2014.01–2016.12	China	Hospital	Case-control studies	NR	29/65	ER; PR; histopathological grade; VI; no. of positive SLN; tumor size; molecular subtype;
HuangJH 2017 [34]	2011.1–2017.6	China	Hospital	Case-control studies	NR	64/199	tumor size; multifocality; histopathological grade; VI; SLN metastasis ratio; ALNs status on imaging; molecular subtype;
WangWY 2016 [35]	2013.1–2014.12	China	Hospital	Case-control studies	NR	8/80	histopathological grade;
Bekir 2016 [36]	2003–2016	Turkey	Hospital	Case-control studies	NR	70/137	tumor size; LVI; Size of SLN metastasis; no. of negative SLN;
ChenJY 2015 [37]	2005.3–2011.6	China	Hospital	Case-control studies	Yes	961	size of SLN metastasis; LVI; no. of negative SLN; no. of positive SLN;
Chie 2015 [38]	2010.1–2014.12	Japan	Hospital	Case–control studies	Yes	17/27	LVI; tumor size;
G.Canavese2014 [39]	2004.1–2010.12	Italy	Hospital	Case–control studies	Yes	141/256	tumor size; Her-2 positive; Ki-67; no. of positive SLN; histopathological grade;

Note: IRB, Institutional Review Board; VI, vascular invasion; LVI, lymphovascular invasion; PNI, perineural invasion; ENE, extranodal extension; ER (+), estrogen receptor-positive; PR(+), progesterone receptor-positive; Her-2, human epidermal growth factor receptor 2; ILC, invasive lobular carcinoma.

Table 2
Quality assessment of the included studies.

Study	Selection				Comparab -ility	Exposure			Scores
	Adequate definition of cases	Represe-ntativene-ss of the cases	Selecti-on of controls	Definiti-on of controls	Control for important factor	Ascertain-ment of exposure	Same met-hod of ascertain-ent for cases and controls	Non-respo-nse rate	
Huang Z2023	★	★	★	★	★	★	★	★	8
Zeng H 2022	★	★	★	★	★	★	★	★	8
Wu F 2022	★		★	★	★	★	★	★	7
Xie YJ2022	★	★	★	★	★	★	★	★	8
LiuL 2022	★	★	★	★	★	★	★	★	8
ZhangL 2021	★		★	★	★	★	★	★	7
YuY 2021	★		★	★	★	★	★	★	7
HeZ 2020	★		★	★	★	★	★		6
MengL 2020	★	★	★	★	★	★	★	★	8
Azmi L 2019	★	★	★	★	★	★	★	★	8
WangXY 2019	★		★	★	★	★	★		6
AMN 2019	★	★	★	★	★	★	★	★	8
MoWJ 2019	★		★	★	★	★	★	★	7
Zheng JW 2018	★	★	★	★	★	★	★	★	8
Bahadır 2018	★	★	★	★	★	★	★	★	8
DongLF 2018	★	★	★	★	★	★	★	★	8
GaoSY 2018	★	★	★	★	★	★	★	★	8
CaoTF 2017	★		★	★	★	★	★	★	7
LiangYS 2017	★		★	★	★	★	★	★	7
Huang JH 2017	★	★	★	★	★	★	★	★	8
WangWY 2016	★	★	★	★	★	★	★	★	8
Kekir B 2016	★	★	★	★	★	★	★	★	8
ChenJY 2015	★	★	★	★	★	★	★		7
Chie T 2015	★		★	★	★	★	★	★	7
G. Canavese2014	★		★	★	★	★	★		6

3. Results

3.1. Identification of studies

Initially, 1752 relevant articles were identified from eight databases. By examining the references of the pertinent articles, three additional articles were identified. Duplicate studies accounted for 516 of these exclusions, whereas screening titles and abstracts resulted in another 1114 exclusions. The full texts of 125 articles were evaluated and 25 studies met the inclusion criteria [15–39]. Fig. 1 depicts the search and selection procedures.

3.2. Study characteristics

In total, 25 studies involving 8021 participants were included (one study did not report the number of cases in the observation and control groups). All studies were case-control studies (case groups were patients with breast cancer with 1–2 SLN-positive and non-SLN metastases, control groups were patients with 1–2 SLN-positive and non-SLN-negative metastases) conducted in hospitals using record linkages or medical records to objectively determine the presence of breast cancer. Thirteen of the included studies were published in Chinese and 12 were published in English. China (n = 20), Turkey (n = 3), Italy (n = 1), and Japan (n = 1) were among the 25 included studies, with varying geographical locations and ethnic backgrounds. In addition, one study included two subgroup cohorts [21]. Table 1 presents the characteristics of the included studies.

Table 3
Overview of the meta-analysis of the risk factors.

Categorize by	Factors	Studies	Heterogeneity test			Pooled OR (95 % CI)	P-value
			Q chi-squared value	I^2 value (%)	P-value heterogeneity		
factors of primary tumor	multifocality	2 [21,34]	2.20	9.2	0.33	2.63 (1.96, 3.54)	0.00
	tumor size	[14,15,16,18,19,26,27, 29,31–34,36,38,39]	115.02	88.7	0.00	1.45 (1.30, 1.63)	0.00
	tumor localization	3 [15,19,26]	4.78	58.2 %	0.091	2.06 (1.23, 3.43)	0.00
	histopathological grade	7 [20,21,27,33–35,39]	3.67	0	0.82	1.95 (1.61, 2.37)	0.00
	VI	8 [16–18,22,25,32–34]	35.7	80.4	0.00	2.47 (1.30, 4.67)	0.01
	LVI	8 [21,23,29–31,36–38]	25.25	68.3	0.00	3.15 (2.14, 4.62)	0.00
molecular typing	ER	3 [19,28,33]	0.45	0	0.80	0.5 (0.23, 1.09)	0.08
	PR	2 [19,33]	0.12	0	0.73	1.86 (0.65, 5.32)	0.25
	Her-2 positive	7 [19,22,24,29–31,39]	25.06	76.1	0.00	2.13 (1.12, 4.05)	0.02
	Ki-67 status	3 [19,22,30]	9.50	78.9	0.01	1.16 (0.48, 2.81)	0.74
	Luminal B-like	3 [20,22,34]	2.95	32.2	0.23	0.90 (0.45, 1.77)	0.70
	Her-2 over-expressing subtype	3 [20,22,34]	5.64	64.5	0.06	1.77 (0.5, 6.26)	0.38
	TNBC	2 [20,34]	4.28	76.6	0.04	0.95 (0.16, 5.81)	0.96
factors of examination/ inspection	ALNs status on imaging	3 [22,27,34]	11.38	82.4	0.00	3.64 (1.52, 8.72)	0.00
factors of lymph nodes	no. of negative SLNs≥1	6 [21,22,27,29,36,37]	65.30	90.8	0.00	1.35 (0.63, 2.93)	0.44
	no. of positive SLNs	7 [20,21,23,28,33,37,39]	19.96	64.9	0.01	2.98 (2.08, 4.26)	0.00
	size of SLN metastasis	3 [24,36,37]	17.04	88.3	0.00	1.99 (0.82, 4.86)	0.13
	SLN metastasis ratio	10 [15–18,22,23,25,26, 32,34]	96.44	90.7	0.00	2.31 (1.38, 3.85)	0.00
	ENE	2 [24,30]	0.13	0	0.72	4.69 (2.16, 10.18)	0.00

3.3. Methodological quality

Overall, the quality of the included studies was acceptable. Fourteen of the included studies met the NOS criteria for high-quality research. Table 2 provides detailed information on quality assessment.

3.4. Meta-analysis results

3.4.1. Meta-analysis of the primary outcome

There was no significant heterogeneity among the following risk factors: multifocality, histopathological grade, extranodal extension (ENE), estrogen receptor (ER), progesterone receptor (PR), and luminal B-like. Data were pooled using a fixed-effects model. Among the following risk factors, heterogeneity was evident: tumor size, tumor localization, vascular invasion (VI), lymphovascular invasion (LVI), Her-2 positive, Ki-67 status, Her-2 over-expressing subtype, triple-negative breast cancer (TNBC), ALNs status on imaging, SLN metastasis ratio, no. of negative SLNs ≥1, no. of positive SLNs and the size of the SLN metastasis. The data were pooled using a random-effects model.

Table 3 summarizes the findings of the meta-analysis. Three studies examined tumor localization (upper outer quadrant) as a factor [15,19,26]; however, one study [26] reported an error in the 95 % CI [1.506, 0.121], and another study [15] did not report OR values or 95 % CI. Therefore, the number of exposed and unexposed patients in the case and control groups of the three studies were merged. The individual results from the included studies are presented in Table 4. Multifocality, tumor size, tumor localization, histopathological grade, VI, LVI, ENE, PNI, Her-2 positivity, SLN metastasis ratio, no. of positive SLNs, detection of SLNs (blue dye), ALNs status on imaging, and cancer antigen 15-3 (CA15-3) and carcinoembryonic antigen (CEA) levels were identified as significant risk factors for non-SLNM in patients with breast cancer and 1–2 SLN macrometastases. No. for SLNs detected >5 was a protective factor. Appendix B presents the forest plots of meta-analysis of the primary outcome.

3.4.2. Subgroup analyses

Subgroup analyses of factors with high heterogeneity (Table 3) were performed to explore the heterogeneity and non-SLNM risks in patients with breast cancer patients with 1–2 SLN macrometastases. Three studies [24,36,37] that reported the size of SLN metastases were ineligible for meta-analysis because two studies [24,37] failed to report the numbers of exposed and unexposed patients in the case and control groups, respectively. Ten studies [15–18,22,23,25,26,32,34] assessed the SLN metastasis ratio; however, three studies [25,26,32] differed in different layers, and two studies [15,18]failed to report the number of exposed and unexposed patients in the case and control groups; therefore, they could not be included in the analysis.

Table 5 summarizes the results of the subgroup analyses, which revealed that tumor size ≥ T2, tumor localization (upper outer quadrant), histopathological grade (G3), VI (positive), LVI (positive), two positive SLNs, zero negative SLN, SLN metastasis ratio ≥0.5, ALNs positive on imaging, Her-2 over-expressing subtype and Her-2 positive were the significant risk factors for non-SLNM in breast cancer patients with 1–2 SLN macrometastases. Tumor size (T1), tumor in other quadrants, histopathological grade (G1), VI (negative), LVI (negative), one positive SLN, no. of negative SLNs ≥1, SLN metastasis ratio <0.5, ALNs negative on imaging, and Her-2 negative were the protective factors.

3.5. Publication bias

The funnel plot and Egger's test were based on twelve studies that reported tumor size risk factors (T1 or ≥ T2) and the number of exposed and unexposed patients in the case and control groups. Funnel plots of the tumor size (T1 or ≥ T2) do not indicate significant asymmetry (Figs. 2 and 3). Egger's publication bias test for tumor size (T1) (Std. Err. = 1.129, t = −1.60, P = 0.14) and tumor size (≥T2) (Std. Err. = 1.131, t = 1.58, P = 0.146) revealed that the included studies did not have statistically significant publication bias (P > 0.05).

4. Discussion

Axillary lymph nodes status is an important factor related to breast cancer staging and is one of the main determinants of treatment decisions. Currently, there has been no prospective investigation into the potential relationship between the clinicopathological

Table 4
Overview of risk factors that cannot be meta-analyzed.

Factors	Study	Sample size	Pooled OR (95 % CI)
PNI	1 [24]	110	3.16 (1.18, 8.43)
age > 50	1 [34]	263	1.26 (0.69, 2.32)
the Distance from nipple > 3 cm	1 [19]	465	1.44 (0.89, 2.31)
ILC	1 [19]	465	0.37 (0.08, 1.71)
no. of SLNs detected > 5	1 [19]	465	0.49 (0.27, 0.91)
the method of SLNs detected (blue dye)	1 [20]	274	3.85 (1.54, 9.60)
CA15-3 positive	1 [21]	532	4.01 (2.33, 6.89)
CEA positive	1 [21]	532	2.13 (1.32, 3.43)

Table 5
Subgroup analysis of the risk factors.

Categorize by	Factors		Studies	Effect model	Heterogeneity test			Pooled OR (95 % CI)	P-value
					Q chi-squared value	I^2 value (%)	P-value heterogeneity		
factors of primary breast tumor	tumor size	T1	12	Fixed	15.37	28.4	0.17	0.38 (0.32, 0.45)	0.00
		≥T2	12	Fixed	15.32	28.2	0.17	2.64 (2.22, 3.14)	0.00
	tumor localization	upper outer quadrant	3	Random	4.78	58.2	0.09	2.06 (1.23, 3.43)	0.01
		other quadrants	3	Random	4.78	58.2	0.09	0.49 (0.29, 0.81)	0.01
	histopathological grade	G1	7	Fixed	8.60	18.6	0.28	0.31 (0.21, 0.45)	0.00
		G2	5	Fixed	7.83	48.9	0.10	0.83 (0.63, 1.08)	0.16
		G3	7	Random	15.81	55.7	0.03	2.45 (1.70, 3.52)	0.00
	VI	negative	8	Random	42.88	83.7	0.00	0.38 (0.20, 0.74)	0.00
		positive	8	Random	42.88	83.7	0.00	2.60 (1.35, 4.98)	0.00
	LVI	negative	8	Random	31.40	77.7	0.00	0.35 (0.22, 0.56)	0.00
		positive	8	Random	31.40	77.7	0.00	2.87 (1.80, 4.56)	0.00
factors of lymph node	no. of positive SLNs	1	6	Random	42.48	85.9	0.00	0.28 (0.16, 0.48)	0.00
		2	6	Random	42.48	85.9	0.00	3.55 (2.08, 6.07)	0.00
	no. of negative SLNs	0	5	Fixed	1.39	0	0.85	3.72 (2.50, 4.29)	0.00
		≥1	5	Fixed	3.54	0	0.62	0.25 (0.20, 0.32)	0.00
	SLN metastasis ratio	< 0.5	5	Fixed	4.19	4.6	0.38	0.36 (0.29, 0.45)	0.00
		≥0.5	5	Fixed	4.19	4.6	0.38	2.79 (2.24, 3.48)	0.00
factors of examination/ inspection	ALNs states on imaging	negative	3	Random	7.70	74	0.02	0.32 (0.17, 0.60)	0.00
		positive	3	Random	7.70	74	0.02	3.18 (1.68, 6.00)	0.00
factors of molecular typing	molecular subtype	Luminal A-like	3	Fixed	1.94	0	0.38	0.86 (0.58, 1.28)	0.50
		Luminal B-like	4	Fixed	5.59	46.3	0.13	1.02 (0.78, 1.34)	0.95
		TNBC	4	Fixed	4.94	39.3	0.18	0.83 (0.53, 1.30)	0.67
		Her-2 over-expressing subtype	3	Fixed	0.01	0	0.99	1.83 (1.22, 2.73)	0.00
	Her-2 status	negative	7	Random	22.71	73.6	0.00	0.48 (0.29, 0.79)	0.00
		positive	7	Random	22.71	73.6	0.00	2.08 (1.26, 3.43)	0.00

Note: G1: histopathological grade 1, G2: histopathological grade 2, G3: histopathological grade 3.

characteristics of patients with 1–2 SLN macrometastatic breast cancers and those with non-SLNM. This study is the first systematic review and meta-analysis to examine the potential non-SLNM clinicopathological characteristics in breast cancer patients with 1–2 SLN macrometastases.

4.1. Factors of primary tumor

Tumor size, multifocality, tumor localization, histopathological grade and VI/LVI have been confirmed to be the main factors affecting the prognosis of axillary lymph nodes [40,41]. The findings of this study indicate that tumor size, T2, tumor localization (upper outer quadrant), multifocality, and G3, VI (positive), and LVI (positive) are risk factors for non-SLNM in patients with breast cancer with 1–2 positive SLN. These findings contribute to decision-making by breast surgeons regarding lymph node management.

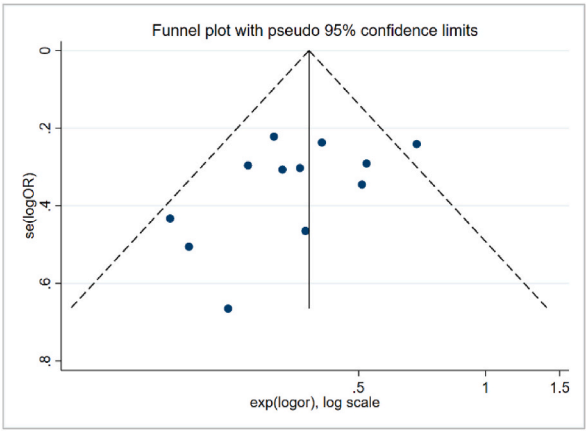

Fig. 2. Funnel plot of risk of bias (Tumor Size: T1).

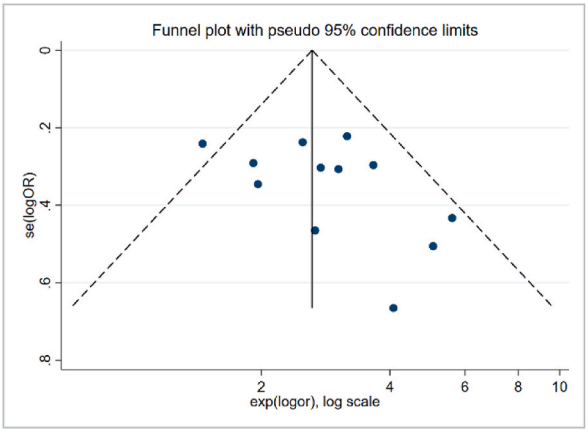

Fig. 3. Funnel plot of risk of bias (Tumor Size: ≥ T2).

Before surgery, breast surgeons can predict the status of axillary lymph nodes based on the pathological results of tumor puncture and the diameter and location of the primary tumor. If the tumor is located in the outer upper quadrant, with a diameter of ≥2 cm, and multiple lesions, the pathological results of puncture suggest that the histological classification is 3, and/or lymphatic vessel or vascular invasion, the risk of non-SLNM is high. Doctors should inform patients undergoing mastectomy of the potential risks or complications of ALND during preoperative conversations and make appropriate preoperative preparations.

Only one study reported PNI in the included studies, therefore predictive value for non-SLNM in 1–2 positive SLN patients with breast cancer still needs further clarification. Duraker et al. [42] discovered that the risk of LVI and ALNM significantly increased in PNI-positive patients. However, Karak et al. [43] concluded that there was no statistically significant difference in disease-free survival between PNI-positive and PNI-negative patients. However, this did not adequately explain the impact of PNI on the prognosis of ALNs. As an indicator of tumor aggressiveness, the PNI is regarded as the fourth metastatic mode of malignant tumors, in addition to implantation, lymphatic metastasis, and hematogenous metastasis, and plays a crucial role in determining the prognosis of tumors. Furthermore, PNI may be the only mode of metastasis for some tumors if there is no lymph node or blood invasion [44]. Therefore, the impact of PNI on non-SLNM should be considered, and the PNI status should be included in the pathological report. Additionally, the possibility of non-SLNM should be communicated to patients with breast cancer with a positive PNI, but no additional ALND.

4.2. Factors of lymph nodes

Studies have reported that the higher the number of SLN metastases, the higher is the risk of non-SLNM [41,45]. Non-SLNM was also related to the ratio of the number of positive SLN to the number of SLN detected, and the metastasis rate increased with an increase in this ratio [46,47]. The results of our study showed that two positive SLNs, and the SLN metastasis ratio ≥0.5 were the risk factors for non-SLNM in patients with 1–2 SLN positive breast cancer. The protective factors include number of SLNs detected >5, 1 positive SLN, ≥1 negative SLN, and SLN metastasis ratio <0.5. According to the 8th edition of the American Joint Commission on Cancer breast cancer staging manual, less than six lymph nodes detected by SLNB in breast cancer are considered SLNs [48]. For patients undergoing

mastectomy, if the frozen section examination indicated two positive SLNs and the ratio of the number of positive SLNs to the number of SLNs detected ≥0.5, that is, when the ratio is 2/2, 2/3, 2/4, it can be considered that non-SLN has a high risk of metastasis, and further ALND is recommended. If only one positive SLN is detected during surgery, and the ratio of the number of positive SLN to the number of SLN detected is < 0.5, that is, the ratio is 1/3, 1/4, or 1/5, the risk of non-SLNM is relatively low, and remitting from ALND can be considered based on other clinical factors of the patients who underwent mastectomy. Notably, in the included studies, one of the research results showed that no. of SLN detected >5 was a protective factor against non-SLNM in patients with 1–2 positive breast cancers. If five SLNs are detected and two positive SLNs are examined, there is a risk of non-SLNM. According to the results of our study, two positive SLNs and the SLN metastasis ratio ≥0.5 are risk factors. Therefore, the number of positive SLNs to the number of SLNs detected was 2:5, indicating that the SLN metastasis ratio is 0.4 < 0.5. It can be considered that when five SLNs are detected and two positive SLNs are examined, there is a low risk of non-SLNM, and exemption from ALDN can be considered. Therefore, based on these results, it can be concluded that there is a higher risk of non-SLNM when the number of SLNs detected is ≤ 4 and two of them were positive. If the number of SLN detected is ≥ 5 and two of them were positive, there is a lower risk of non-SLNM. When one positive SLN is detected, the higher the number of SLN detected, the lower the risk of non-SLNM, and exemption from ALDN can be considered.

Only two studies reported ENE, cancer cells passing through the capsule of the lymph nodes into the perinodal tissue. It is considered a poor prognostic indicator and is related to other risk factors, such as tumor size, LVI, and tumor burden of non-SLNs [49]. In the ACOSOG Z0011 and AMAROS, SLN with gross node extension is an indication for ALND. Although patients with gross ENE were excluded from the ACOSOG Z0011 and AMAROS trials, the management of microscopic ENE was not explicitly described. Barrio et al. [50] further found that among patients who met the conditions of Z0011, even if no conventional lymph node radiotherapy was performed, the lymph node recurrence rate of patients with microscopic extranodal extension after SLNB treatment was low. Based on these results, we believe that the presence of metastatic ENE should not be considered a routine indication for ALND, and the treatment of the armpit should be determined based on comprehensive pathological characteristics, such as tumor size, histopathological grade, lymph node status, and molecular subtype.

Only one study included in these analyses examined the association between SLNB with blue dye alone and non-SLNM. SLNB with methylene blue alone was considered a risk factor for non-SLNM in patients with breast cancer with 1–2 SLN macrometastases. According to previous studies, using blue dye alone is associated with the highest rate of false-negative results [51] and an increased risk of non-SLNM [5,52]. Other studies found no statistical difference in the SLN detection rate and false-negative rate between blue dye and radioactive tracers along with blue dye. However, they discovered that the false-negative rate of SLNB in patients with breast cancer aged ≥50 years was significantly higher than that in patients aged <50 years. In contrast, the detection rate of SLN in the ≥50 years group was significantly lower than in the <50 years group [53]. The same conclusion was reached in a study by McMasters et al. [54], who suggested that the reason may be that in middle-aged and older women, breast tissue and lymph nodes are partially replaced by adipose tissue, the density of lymphatic vessels is reduced, and the phagocytosis of reticuloendothelial tissue in the lymph nodes is weakened by the mechanical barrier, reducing the ability of lymph nodes to retain the blue dye and preventing the smooth drainage of the blue dye from the focal site to the SLNs. Therefore, it is suggested that breast surgeons master the applicable indications and technical operations for SLNB. In addition, because the ability of lymph nodes to retain blue dye may be relatively weak in those aged ≥50 years, the search time for lymph nodes should be accelerated to avoid the blue dye draining out of lymph nodes too quickly, which makes SLN challenging to detect, or the combined method of a radioactive tracer and blue dye should be used to improve the accuracy of localization and mitigate the rate of missed SLN and the risk of non-SLNM by the determination of instruments and equipment [55].

4.3. Factors of molecular typing

The findings of this study indicate that Her-2 positive and Her-2 over-expressing subtype are risk factors for non-SLNM in breast cancer patients with 1–2 SLN macrometastases. Crabb et al. also found that the clinical pathological data of 4444 patients with breast cancer [56]; compared with Luminal A-like, Luminal B-like (OR = 1.04, 95 % CI:0.741–1.44) and Her-2 over-expressing subtype (OR = 1.19, 95 % CI:0.872–1.63) patients with breast cancer had an increased risk of ALN metastasis, while triple-negative breast cancer with poor prognosis (OR = 0.607, 95 % CI:0.453–0.812) had no increased risk of ALNs metastasis, Yang et al. also reached the same conclusion [57]. Our results did not indicate the impact of TNBC (OR = 0.83, 95 % CI:0.53–1.30) and Luminal B-like (OR = 1.02, 95 % CI:0.78–1.34) breast cancer on the risk of non-SLNM. However, some studies believe that although the prognosis of TNBC is poor, the probability of non-SLNM is low [58,59], and its aggressiveness may be mainly manifested by the fact that the disease is prone to distant metastasis at an early stage [56,60,61]. In particular, the risk of visceral metastasis is greater [60], which may be related to its hematogenous rather than lymphatic spread, therefore, visceral metastasis rather than ALNs metastasis is more likely to occur. Combined with our results, we can infer that lymph node metastasis may be a predictor of the clinical behavior of Her-2 positive breast cancer, but its predictive value for TNBC needs to be further clarified in clinical research. Currently, there are two prospective single-arm trials, EUBREAST-01 [62] and ASICS [63], to study whether cN0 patients with breast cancer with Her-2 positive or triple negativity can undergo SLNB without affecting tumor safety after early systemic treatment. The results of these studies are expected to lead to further breakthroughs in axillary treatment decisions for cN0 patients with Her-2 positive or triple breast cancer. Based on the above factors, Her-2 positive patients with breast cancer with 1–2 positive SLNs still need to be carefully assessed for their risk of non-SLNM.

The results of this study suggest that Her-2 negative is a protective factor for non-SLNM in breast cancer with 1–2 positive SLN, but no beneficial effect for Luminal A-like and Luminal B-like subtypes on non-SLNM in 1–2 positive SLN breast cancer was found. The results of Rx PONDER study published for the first time suggest that postmenopausal patients with hormone receptor (HR) positive/Her-2 negative and 1–3 ALN positive patients can safely avoid chemotherapy if they receive 21 Genetic test (Oncotype DX) and a risk score≤ 25 [64]. This result emphasizes the importance of lymph node status, and the selection of axillary surgical treatment strategies.

How to judge the risk of non-SLNM in HR positive/Her-2 negative breast cancer patients with 1–2 positive SLN? Is necessary to determine the total lymph node burden by ALND and provide a reference for systematic treatment? Research results have shown that [3,65–67], the proportion of 1–2 positive SLN patients with total over three ALNs metastasis after receiving ALND is 5.7–18.9 %, indicating that more than 80 % of these patients have a lower risk of non-SLNM because the number of metastatic ALNs is ≤ 3. In the RxPONDER study, the axillary management of patients with 1–2 positive SLN was determined by a physician, and ALND was not required. The results showed that there was no statistically significant difference in the 5-year recurrence-free survival rate between the groups undergoing different axillary surgeries in the premenopausal and postmenopausal subgroups ($P = 0.69$ vs $P = 0.26$). However, with the extension of follow-up time in the RxPONDER study, there may still be no statistically significant differences in disease-free survival between different axillary surgical treatment groups. These data suggest that the disease-free survival and risk of recurrence and metastasis in 1–2 positive SLN patients may not be related to their axillary management methods, but rather to their risk score and whether they have received chemotherapy. Axillary intervention may be possible with the downward trend in axillary surgery, even in specific subgroups [68]. Therefore, we believe that for HR positive/Her-2 negative breast cancer with 1–2 positive SLN, it is recommended to exempt ALND, and use the 70 genetic test (Mamma Print) and 21 genetic test (Oncotype DX) to assess the recurrence risk to guide the decisions of systemic treatment.

4.4. Factors of examination/inspection

Preoperative adjuvant examinations and tests can help predict non-SLN prognosis in patients with breast cancer. Positive imaging and circulating tumor markers, CEA, and (CA15-3) were identified as risk factors for non-SLNM in patients with breast cancer patients with 1–2 SLN metastases. The high accuracy of imaging in assessing SLN statusnecessitates imaging assessment of the ALNs status prior to surgery [69,70]. Patients with preoperative ultrasonographic findings suggestive of abnormal ALNs and negative lymph node puncture results should undergo SLNB. Additionally, the risk of metastatic ALNs should be comprehensively assessed using other clinical indicators. CEA and CA15-3 have been confirmed as breast cancer diagnostic and prognostic factors [71,72]. CEA and CA15-3 levels in serum or ALNs fine-needle aspiration before surgery are proportional to the risk of ALNs metastasis [73,74]. The mechanism underlying the association between CEA, CA15-3, and ALNM is currently unknown. Some studies have suggested that CEA and CA15-3 function as metastasis-promoting adhesion molecules and mucin-1 (MUC-1), respectively, thereby promoting lymph node metastasis in breast cancer cells [75–77]. Consequently, clinicians must consider abnormally elevated preoperative CEA and CA15-3 levels when identifying high-risk groups and determining the ALNs status. However, only one study included in the analyses examined the association between CEA, CA15-3, and non-SLNM; therefore, the predictive value of abnormally elevated serum CEA and CA15-3 levels before surgery for non-SLNM in patients with 1–2 SLN metastases requires further research.

This review has three significant limitations. The first limitation was the absence of methods to adjust for confounding factors in the 25 studies included in this review. Although a multiple logistic regression analysis was used to adjust for confounding factors, this could have been more frequently reported or described. Second, all included studies were case-control studies, the sample size of a single risk factor was small, and the heterogeneity of studies included in a single risk factor was high; the heterogeneity was not reduced significantly by subgroup analysis. Finally, the conclusions of the meta-analysis may have been influenced by factors, such as research design, bias in study selection, and the possibility of insufficient retrieval of relevant studies. In addition, a substantial proportion of these studies were conducted in Asia, which may limit their applicability to patients with breast cancer in other countries or racial groups.

Currently, relevant breast cancer guidelines do not specify whether breast cancer with 1–2 SLN macrometastases undergoing mastectomy or breast-conserving surgery without radiotherapy can be excluded from ALND, and there have been no prospective cohort studies. There is no consensus regarding the risk factors for non-SLNN in breast cancer with 1–2 positive SLN. Currently, the relevant studies are retrospective, single-center, small-sample studies, and their findings lack high-level evidence. This is the first meta-analysis to summarize non-SLNM risk factors in patients with 1–2 SLN macrometastatic breast cancer. This study is the first to conduct a meta-analysis of the relevant literature to summarize the risk factors for non- SLNM. Based on these findings, in early stage breast cancer patients with 1–2 positive SLN, especially those with a low metastasis risk of non-SLNs, it is reasonable to consider exempting the implementation of unnecessary ALND to avoid unnecessary axillary injury, reduce complications related to ALND, and improve the patient's quality of life.

Relevant large-scale clinical research findings also suggest that we should pay attention to the joint application of multi Genetic testing technology and Z0011/AMAROS standard, make full use of the benefits of systemic therapy and radiotherapy, reasonably narrow the scope of surgery so as to reduce complications, expand the "net benefits" of efficacy and improve the quality of life. This study is helpful for surgeons in predicting tumor behavior, provides a basis for standardized and individualized precision treatment of breast cancer, highlights the risk factors that remain controversial, and provides ideas for future research directions.

The significant risk factors for non-SLNM in patients with breast cancer with 1–2 SLN macrometastases identified in this study included the following: factors of primary tumor: multifocality, tumor size $\geq$ T2, tumor localization (upper outer quadrant), histopathological grade (G3), VI, LVI, PNI. Factors of lymph nodes: method of SLNs detected (blue dye), SLN metastasis ratio $\geq$0.5, two positive SLNs, ENE. Factors of molecular typing: Her-2 positive. Examination/inspection factors: ALNs positivity on imaging, CA15-3 positivity, and CEA positivity. The independent risk factors found in this study: multifocality, method of SLNs detected (blue dye), ENE, CA15-3 positive, and CEA positive on the risk of recurrence and metastasis of breast cancer or axillary lymph node metastasis have not been described in various breast cancer guidelines. The above factors cannot be ignored in clinical prediction of non-SLN status for patients with 1–2 positive SLN. Patients with 1–2 positive SLN and above independent risk factors should be informed of the risk of non-SLNM. These findings have implications for the prognosis and treatment of non-SLN in patients with metastatic breast cancer and

1–2 SLN. It is necessary to confirm this relationship further using larger sample sizes, multicenter studies, and prospective studies.

Data availability statement

Data included in article/supp. material/referenced in article.

Additional information

No additional information is available for this paper.

Ethics approval and consent to participate

Not applicable.

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CRediT authorship contribution statement

Liu-yan Xu: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. **Jing Zhao:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. **Xuan Wang:** Investigation, Methodology, Writing – review & editing. **Xin-yan Jin:** Software, Writing – review & editing, Formal analysis. **Bei-bei Wang:** Writing – review & editing, Formal analysis. **Ying-yi Fan:** Writing – review & editing, Formal analysis. **Xiao-hua Pei:** Conceptualization, Formal analysis, Funding acquisition, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e21254.

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