Systematic Review and Meta-Analysis

Medicine

OPEN

Prognosis and clinicopathological characteristics of metaplastic breast cancer

A meta-analysis

Xiaolu Yang, Medical postgraduate student[a], Tiantian Tang, MD[a], Tao Zhou, MD[a,*]

Abstract

Background: To compare the clinicopathological characteristics and prognosis of metaplastic breast cancer (MBC) and triple-negative breast cancer (TNBC).

Methods: A meta-analysis was performed on relevant cohort or case-control studies retrieved by a literature search of the PubMed, EMBASE, Ovid, and Web of Science databases. Hazard ratio (HR) was used to evaluate disease-free survival (DFS) and overall survival (OS), and the odds ratio (OR) and corresponding 95% confidence interval (CI) was used to evaluate clinicopathological characteristics, including age, tumor diameter, lymph node metastasis status, distant metastasis status, TNM staging, and histological grade.

Results: Nine studies were included in the meta-analysis. Compared with TNBC patients, the HRs for 5-year DFS and 5-year OS of those with MBC were 1.64 (95% confidence interval [CI] 1.36 – 1.98; $P < .001$) and 1.52 (95% CI 1.27 – 1.81; $P < .001$), respectively. The OR for age ≥ 50 years, tumor diameter ≤ 5 cm, lymph node-negative, distant metastasis, TNM stage III and IV, and histological grade 3 was 1.63 (95% CI 1.45–1.84), 0.29 (95% CI 0.14–0.58), 1.46 (95% CI 1.13–1.88), 1.59 (95% CI 0.89–2.81), 1.49 (95% CI 0.80–2.77), and 2.25 (95% CI 0.85–5.97), respectively.

Conclusion: Patients with MBC had worse prognosis than those with TNBC. Furthermore, regarding clinicopathological characteristics, patients with MBC mostly presented at ≥ 50 years of age, with tumor diameter > 5 cm, and negative lymph nodes at first diagnosis. Moreover, there were no statistically significant differences in the occurrence of distant metastasis, TNM stages III and IV, or histological grade 3. MBC treatment was not assessed in this study. Data from randomized controlled trials are needed to guide the treatment of patients with MBC.

Abbreviations: CI = confidence interval, DFS = disease-free survival, HR = hazard ratio, MBC = metaplastic breast cancer, OR = odds ratio, OS = overall survival, TNBC = triple-negative breast cancer.

Keywords: clinicopathological characteristics, meta-analysis, metaplastic breast cancer, prognosis, triple-negative breast cancer

1. Introduction

Metaplastic breast cancer (MBC) is a clinically rare breast cancer subtype, accounting for <1% of all breast cancers,[1] and was first described by Huvos AG et al[2] in 1973. However, it was not until 2000 that MBC was officially recognized as an independent pathological diagnosis. It is a poorly differentiated heterogeneous tumor that arises from epithelial and mesenchymal cells and exhibits a wide range of histopathological features. According to the World Health Organization, MBC is classified into the following subtypes: squamous cell carcinoma, metaplastic carcinoma with mesenchymal differentiation, low-grade adenosquamous carcinoma, spindle cell carcinoma, fibromatosis-like metaplastic carcinoma, mixed metaplastic carcinoma, and myoepithelial carcinoma.[3]

Numerous studies have demonstrated that the immunohistochemistry of MBC is mostly estrogen receptor and progesterone receptor negative and does not overexpress human epidermal growth factor receptor-2 (HER-2),[4,5] which is consistent with the diagnosis of triple-negative breast cancer (TNBC). Due to the immunohistochemical features of MBC, which are compatible with TNBC, many investigators believe that MBC is a specific type of TNBC. MBC and TNBC are, therefore, commonly contrasted when discussing the prognosis and clinicopathological characteristics of MBC. The prognosis and clinicopathological characteristics of patients with MBC are unclear owing to the rarity of this cancer subtype. Currently, only cohort or case-control studies with small sample sizes are available, and large-sample retrospective analyses remain lacking.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] Department of Breast Cancer Center, the Fourth Hospital of Hebei Medical University, Shijiazhuang, China.

** Correspondence: Tao Zhou, Department of Breast Cancer Center, the Fourth Hospital of Hebei Medical University, No. 12, Jian-Kang Road, Shijiazhuang 050011, China (e-mail: 13930462390@163.com).*

How to cite this article: Yang X, Tang T, Zhou T. Prognosis and clinicopathological characteristics of metaplastic breast cancer: A meta-analysis. Medicine 2022;101:49(e32226).

Received: 18 August 2022 / Received in final form: 17 November 2022 / Accepted: 17 November 2022

http://dx.doi.org/10.1097/MD.0000000000032226

Therefore, to clarify the prognostic and clinicopathological features of MBC, this study retrieved studies comparing the prognosis and pathology of MBC and TNBC and performed a meta-analysis.

2. Methods

2.1. Ethics approval

The present investigation was based on data from previously published studies; as such, ethics approval was not required.

2.2. Information sources

No MBC-related items were found in the MeSH database. As such, the search terms "Metaplastic breast carcinoma," "Metaplastic carcinoma of the breast," "Squamous cell carcinoma," "Metaplastic carcinoma with mesenchymal differentiation," "Spindle cell carcinoma," "Fibromatosis-like metaplastic carcinoma," "Mixed metaplastic carcinoma," and "Myoepithelial carcinoma" were used as keywords to comprehensively search the PubMed, EMBASE, Ovid, and Web of Science databases. The results were limited to the search strategy for controlled clinical trials designed and provided by the Harvard Library. Relevant studies addressing the prognosis and clinicopathological characteristics of MBC, published from inception of the database to June 2022, were retrieved and selected in accordance with the inclusion criteria.

2.3. Inclusion criteria

Published cohort and case-control studies fulfilling the following criteria were included: pathological diagnosis of the observation group conformed to the definition of MBC; pathological diagnosis of the control group conformed to the definition of TNBC; and available statistical indicators including clinical or pathological characteristics and prognostic data.

2.4. Data extraction

The literature search and data extraction were independently performed by 2 investigators. Inconsistencies between the 2 reviewers were resolved through discussion and consultation with a third party.

The following data were extracted from the included studies: first author; year of publication; published country; clinicopathological characteristics (age, tumor size, lymph node metastasis status, distant metastasis status, TNM stage, and histological grade); and survival outcomes.

2.5. Evaluation of study quality

The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the included studies, based mainly on 8 items in 3 categories: selection, comparability, and outcome. The maximum possible NOS score is 9 points, and studies with a score of ≥6 were regarded to be good quality.[6]

2.6. Statistical analyses

Review Manager version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration) was used to conduct the meta-analysis. The I^2 statistic was used to evaluate the heterogeneity of effects between studies, and $I^2 > 50$ or a Q test $P < .1$ indicated significant heterogeneity. The random-effects model was used in cases of considerable heterogeneity, and the fixed-effects model was used for low heterogeneity. A sensitivity analysis was performed by excluding a single studies one at a time (i.e., "leave one out" method) to determine whether the effect values changed considerably. Publication bias was assessed using Begg test, in which $P < .05$ was considered significant publication bias.[7] Stata version 17.0 (StataCorp LLC, College Station TX) was used to assess publication bias.

Overall survival (OS) was defined as the time from diagnosis to death from any cause. For subjects lost to follow-up before death, the last follow-up was defined as the time of death. Disease-free survival (DFS) was defined as the time from diagnosis to disease recurrence (local or distant recurrence). For subjects lost to follow-up before recurrence, the last follow-up time was defined as the time at which a recurring event occurred. The hazard ratio (HR) was used to evaluate survival outcomes (i.e., OS and DFS), and the odds ratio (OR) was used to compare clinicopathological characteristics (age, tumor size, lymph node metastasis status, distant metastasis status, TNM stage, and histological grade) of patients with MBC and those with TNBC. Differences with $P < .05$ were considered to be statistically significant.

3. Results

3.1. Literature search results

The initial literature search retrieved 612 studies, of which 83 duplicates were excluded. Of the remaining 529 studies, 508 deemed irrelevant after review of titles and abstracts were further excluded. After reading the full text of the remaining 21 studies, 12 were excluded because 3 lacked the necessary statistical data and the control groups in the 9 others did not consist of patients with TNBC. Ultimately, 9 studies[8–16] were included in the meta-analysis. The literature search process is illustrated in Figure 1 and details of the 9 included studies are summarized in Table 1.

3.2. Quality evaluation of the included studies

Quality evaluation of the 9 included studies according to the NOS scale is summarized in Table 1, with all studies scoring ≥ 6.

3.3. Meta-analysis results

Five studies reported HRs and corresponding 95% CIs for 5-year DFS and OS. The heterogeneity test results for DFS were $P = .26$ and $I^2 = 25\%$, demonstrating no significant heterogeneity in these studies. A fixed-effects model was used for data integration. The overall HR value for DFS in MBC patients versus TNBC patients was 1.64 (95% CI 1.36–1.98; $P < .001$), demonstrating that patients with MBC had a shorter 5-year DFS than those with TNBC (Fig. 2). The heterogeneity test results for OS were $P = .36$ and $I^2 = 9\%$. Therefore, a fixed-effects model was used to assess the HR for 5-year OS, which revealed an overall HR of 1.52 (95% CI 1.27–1.81; $P < .001$). Similarly, the 5-year OS for MBC patients was shorter than that of TNBC patients (Fig. 3).

Additionally, most patients with MBC were ≥50 years of age (OR 1.63 [95% CI 1.45–1.84]; $P < .001$), fewer had tumor diameters ≤5 cm (OR 0.29 [95% CI 0.14–0.58]; $P < .001$), and most had negative lymph node status (OR 1.46 [95% CI 1.13–1.88]; $P = .003$) at diagnosis compared to those with TNBC. In contrast to TNBC, MBC is often characterized by age ≥50 years, tumor diameter >5 cm, and negative lymph node status at the time of diagnosis (Fig. 4). There were no statistical differences in the occurrence of distant metastasis (OR 1.59 [95% CI 0.89–2.81]; $P = .11$), TNM stage III and IV (OR 1.49 [95% CI 0.80–2.77]; $P = .21$), and histological grade 3 (OR 2.25 [95% CI 0.85–5.97]; $P = .10$) (Fig. 5).

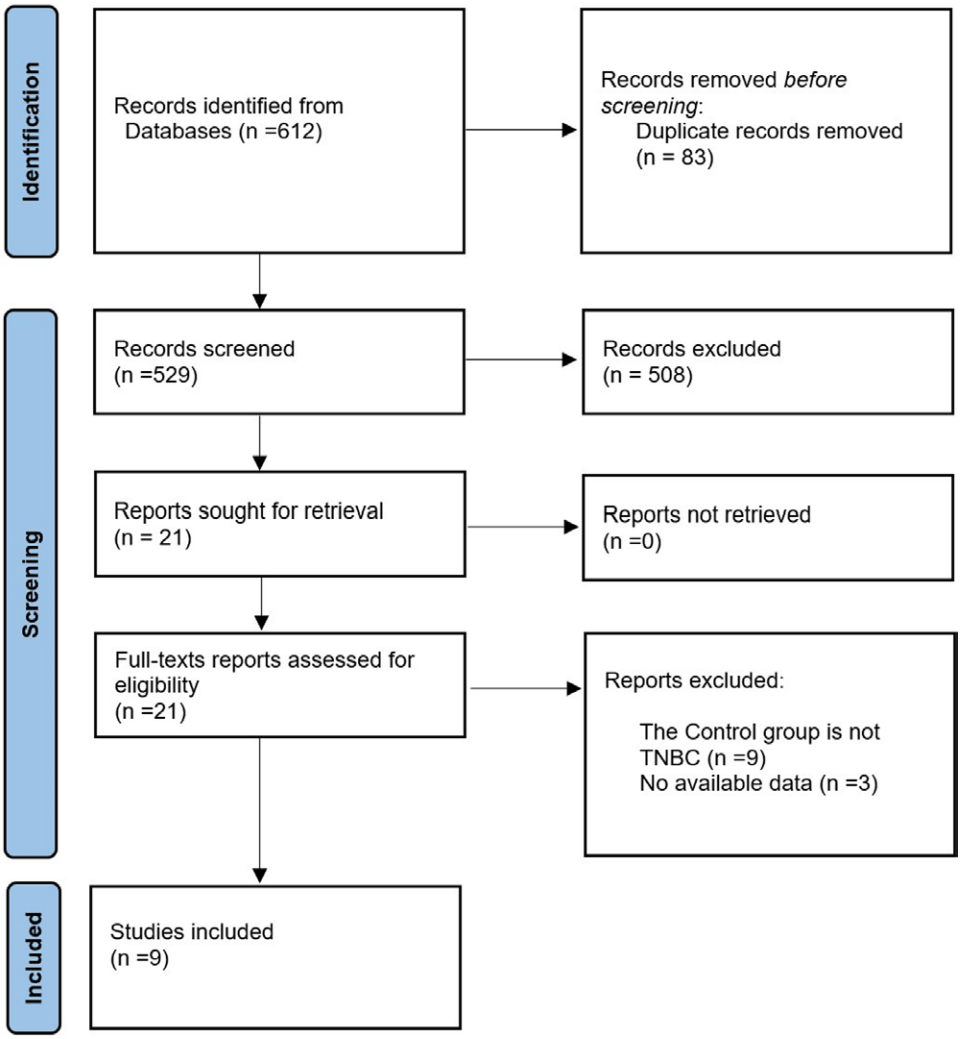

Figure 1. Flowchart of literature search.

3.4. Sensitivity analysis

Sensitivity analysis, in which studies were removed one at a time, was performed to evaluate the stability of results. Results of analysis revealed that no individual study significantly influenced the overall HRs and ORs, suggesting that the results of the present meta-analysis were credible.

3.5. Publication bias

The Begg test indicated that no publication bias affected the HRs for DFS and OS. The *P* values for HRs for 5-year DFS and 5-year OS were 0.462 and 0.086, respectively. Figures 6 and 7 show the Begg's funnel plots of HRs for 5-year DFS and 5-year OS, respectively.

4. Discussion

In this meta-analysis, 5 studies were included in the prognostic analysis. We used a fixed-effects model because there was no significant heterogeneity among the 5 studies. However, we found that the study by Li Y et al[14] was the largest, much larger than the other 4 studies, and accounted for more significant weight. To obtain a small sample weight, we additionally used the random-effects model. This is because the study weights are more uniform (i.e., similar to one another) under the random-effects model than under the fixed-effects model. Large studies were assigned a lower relative weight, and small studies were assigned a higher relative weight compared to the fixed-effects model.[17] Other than that, the random-effects model is more likely to fit the actual sampling distribution. Using the random-effects model, the overall HR for DFS was 1.81 (95% CI 1.36–2.41; $P < .001$) and the overall HR for OS was 1.58 (95% CI 1.26–1.98; $P < .001$) for patients with MBC versus those with TNBC. The 5-year DFS and OS for patients with MBC were shorter than those with TNBC in both the random-effects and fixed-effects models. It is well known that patients with TNBC tend to relapse earlier and have a shorter survival time than other molecular subtypes. However, we found that the prognosis of MBC was worse in terms of DFS and OS than that of nonspecific TNBC. This suggests that MBC is a highly malignant subtype of breast cancer.

We also found that MBC is often lymph node-negative compared with nonspecific TNBC. In general, invasive breast cancer typically spreads to the axillary lymph nodes first, and individuals with positive lymph nodes usually have a poor prognosis. However, we found that patients with MBC had a poor prognosis despite having negative lymph nodes. Many investigators have speculated that the poor prognosis of patients with MBC is due to the tendency of MBC to develop hematogenous rather than lymphatic metastases.[18] However, our study did not find an increased incidence of distant metastases among patients with MBC.

Table 1

Literature included in the study.

Author	Publication	Histology	Observation indicators																		Score
			Age (yrs)		Tumor size (cm)		N status (±)		M status (±)		TNM stage		Histological grade		DFS			OS			
Aydiner A, et al[8]	Turkey 2015	MBC n = 55	<50 n = 33	*P* .97	≤5 n = 37	*P* .68	+ n = 27	*P* .37	--		I and II n = 38	*P* .65	--		--			--			8☆
			≥50 n = 21		>5 n = 14		- n = 23				III and IV n = 13										
		TNBC n = 51	<50 n = 31		≤5 n = 38		+ n = 23				I and II n = 36										
			≥50 n = 20		>5 n = 13		- n = 28				III and IV n = 15										
Bae SY, et al[9]	Korea 2011	MBC n = 47	--		≤5 n = 44	*P* .14	+ n = 13	*P* .16	--		I and II n = 44	*P* .78	1or2 n = 12	*P* .05	--			--			6☆
					>5 n = 3		- n = 34				III and IV n = 3		3 n = 28								
		TNBC n = 218			≤5 n = 211		+ n = 82				I and II n = 190		1or2 n = 36								
					>5 n = 7		- n = 136				III and IV n = 28		3 n = 175								
El zein D, et al[10]	USA 2017	MBC n = 46	--		--		--		--		--		--		HR= 1.99	*P* .05		HR= 1.50	*P* .25		7☆
		TNBC n = 508																			
He X, et al[11]	China 2019	MBC n = 1112	<50 n = 227	*P* <.001	--		+ n = 269	*P* <.001	+ n = 60	*P* .96	--		--		--			--			7☆
			≥50 n = 885				- n = 837		- n = 1052												
		TNBC n = 21321	<50 n = 6430				+ n = 7810		+ n = 1143												
			≥50 n = 14891				- n = 13441		- n = 20178												
Jung SY, et al[12]	Korea 2010	MBC n = 35	--		≤5 n = 23	*P* <.001	+ n = 10	*P* .93	+ n = 3	*P* .02	I and II n = 27	*P* .01	1or2 n = 2	*P* <.001	HR= 3.99	*P* .01		HR= 3.14	*P* .02		6☆
					>5 n = 10		- n = 24		- n = 32		III and IV n = 6		3 n = 23								
		TNBC n = 473			≤5 n = 444		+ n = 161		+ n = 10		I and II n = 401		1or2 n = 246								
					>5 n = 28		- n = 307		- n = 463		III and IV n = 63		3 n = 201								
Lee. H, et al[13]	Korea 2012	MBC n = 67	--		≤5 n = 48	*P* <.001	+ n = 28	*P* .59	+ n = 7	*P* .003	I and II n = 43	*P* <.001	1or2 n = 2	*P* <.001	HR= 2.53	*P* .005		HR= 2.56	*P* .017		6☆
					>5 n = 17		- n = 37		- n = 60		III and IV n = 24		3 n = 40								
		TNBC n = 520			≤5 n = 476		+ n = 204		+ n = 12		I and II n = 427		1or2 n = 253								
					>5 n = 44		- n = 314		- n = 508		III and IV n = 93		3 n = 240								
Li Y, et al[14]	China 2019	MBC n = 586	<50 n = 123	*P* <.01	≤5 n = 452	*P* <.01	+ n = 152	*P* <.01	+ n = 38	*P* .79	I and II n = 464	*P* <.01	1or2 n = 101	*P* <.01	HR= 1.48	*P* <.01		HR= 1.42	*P* <.01		8☆
			≥50 n = 463		>5 n = 134		- n = 431		- n = 548		III and IV n = 122		3 n = 465								
		TNBC n = 18797	<50 n = 5582		≤5 n = 16208		+ n = 6429		+ n = 1271		I and II n = 14862		1or2 n = 3323								
			≥50 n = 13215		>5 n = 2588		- n = 12312		- n = 17526		III and IV n = 3934		3 n = 15324								
Morgan E, et al[15]	USA 2020	MBC n = 44	--		--		--		--		--		--		HR= 1.64	*P* .22		HR= 1.64	*P* .26		8☆
		TNBC n = 130																			
Song Y, et al[16]	China 2013	MBC n = 55	--		≤5 n = 27	*P* <.001	+ n = 15	*P* .001	--		I and II n = 34	*P* <.001	1or2 n = 29	*P* .285	--			--			8☆
					>5 n = 22		- n = 35				III and IV n = 16		3 n = 20								
		TNBC n = 131			≤5 n = 113		+ n = 69				I and II n = 113		1or2 n = 77								
					>5 n = 5		- n = 50				III and IV n = 8		3 n = 41								

DFS = disease-free survival, HR = hazard ratio, MBC = metaplastic breast cancer, OS = overall survival, TNBC = triple-negative breast cancer, USA = The United States of America.

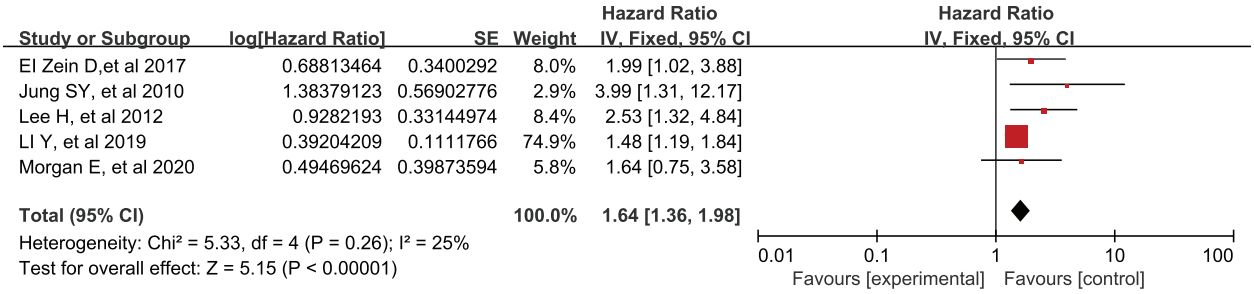

Figure 2. Hazard ratio value for disease-free survival of MBC patients versus TNBC patients.MBC = metaplastic breast cancer, TNBC = triple-negative breast cancer.

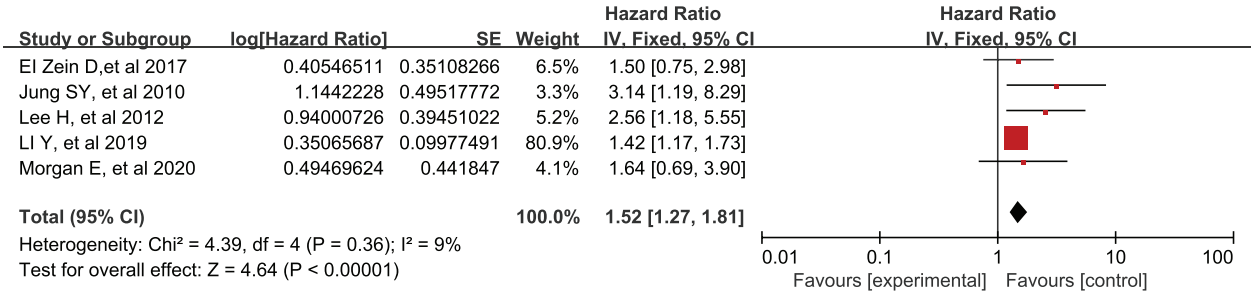

Figure 3. Hazard ratio value for overall survival of MBC patients versus TNBC patients. MBC = metaplastic breast cancer, TNBC = triple-negative breast cancer.

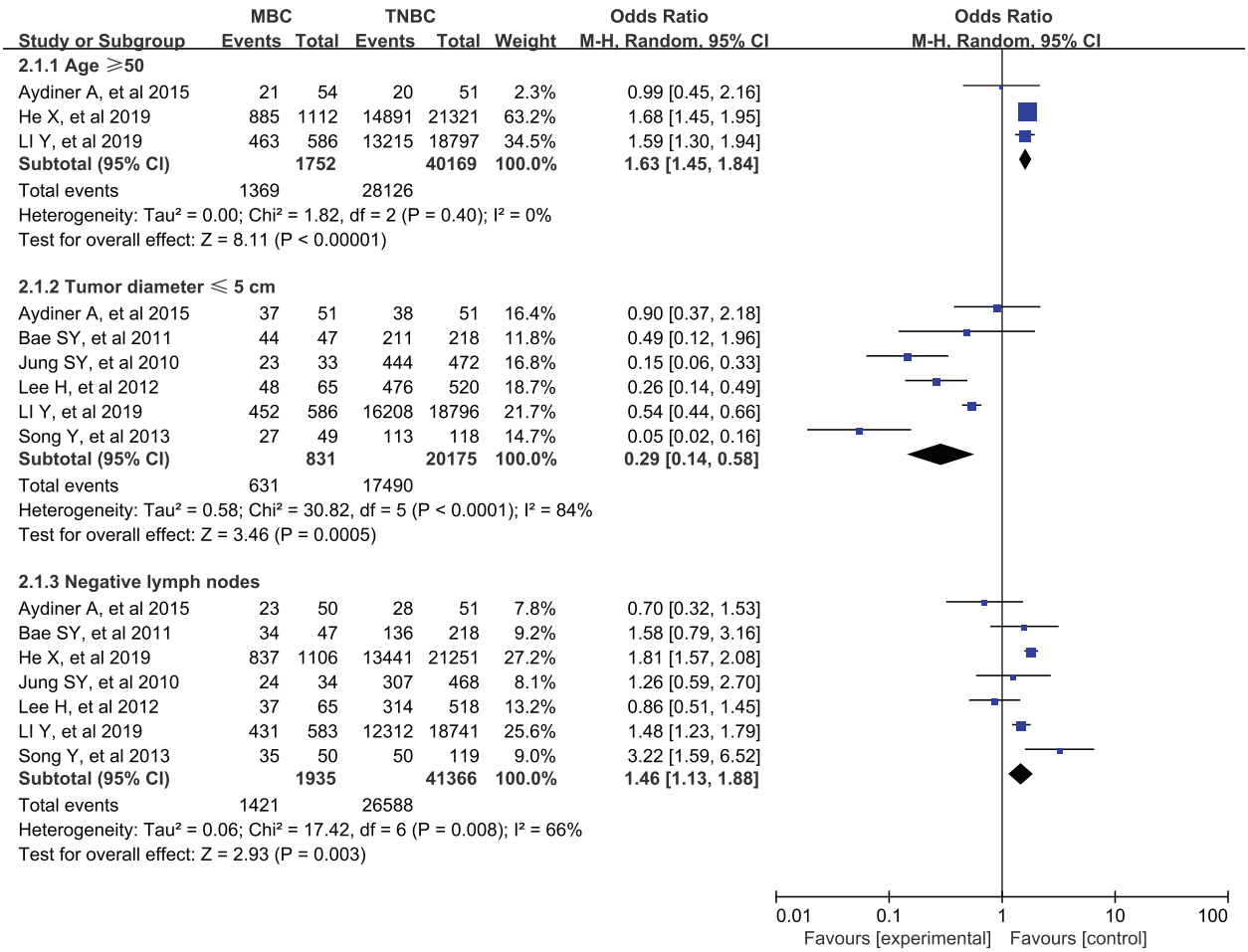

Figure 4. Statistically significant clinicopathological characteristics.

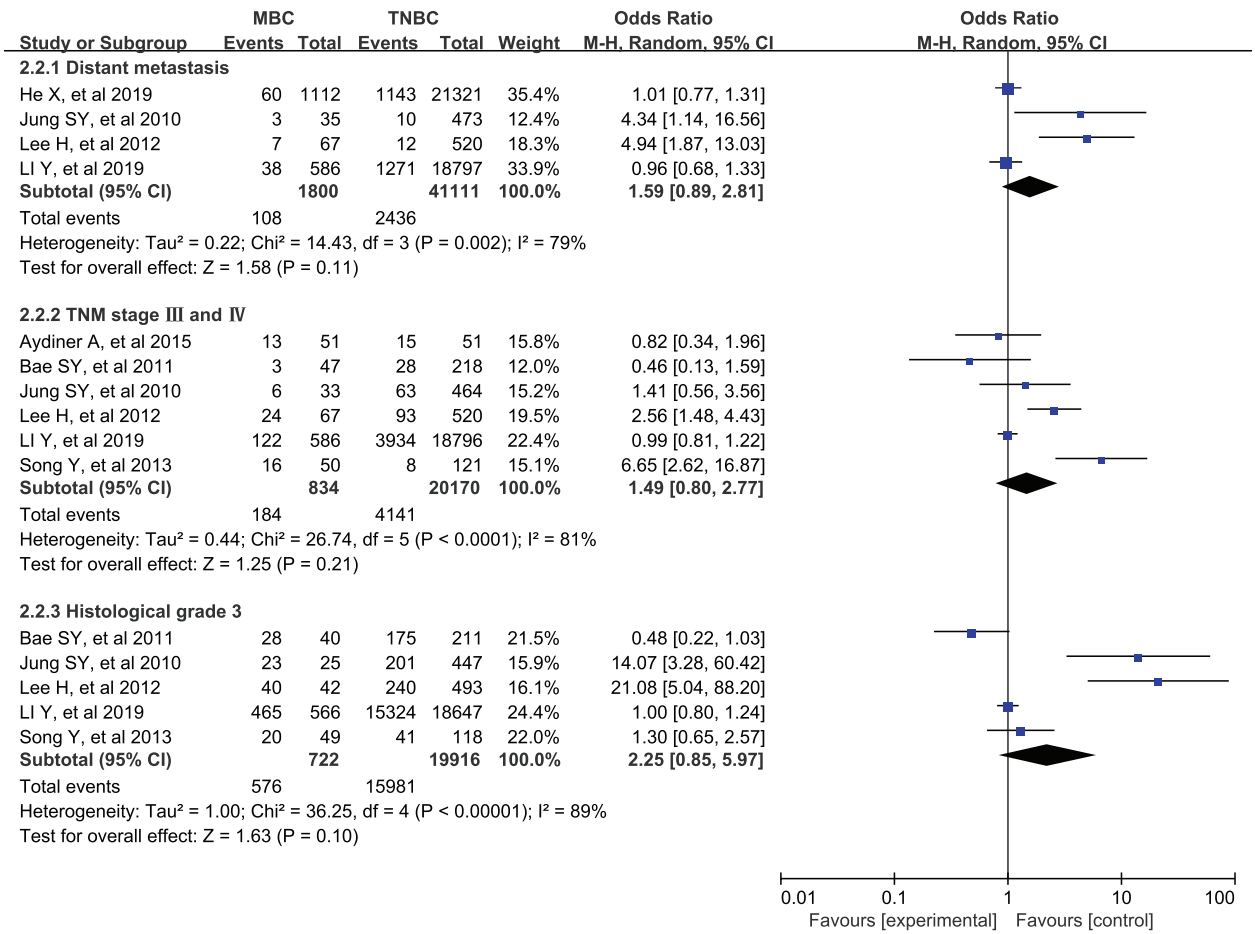

Figure 5. No statistically significant clinicopathological characteristics.

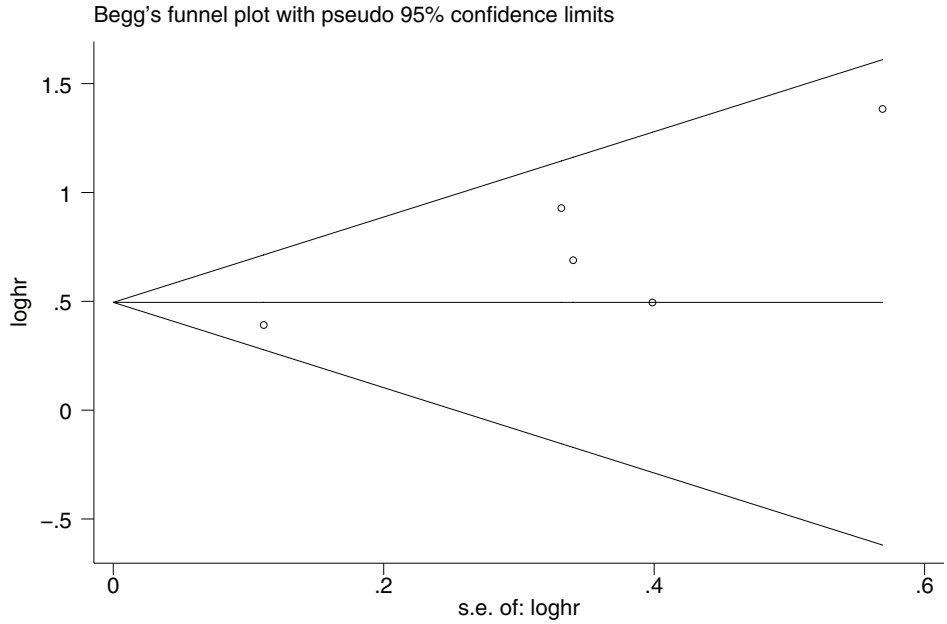

Figure 6. Begg's funnel plots of HR for 5-year DFS. DFS = disease-free survival, HR = hazard ratio.

It remains unclear why patients with MBC have a poor prognosis; however, we believe that 1 factor may be the lack of standardized and efficient therapy for this patient population. Currently, there are no clinical guidelines for the treatment of MBC. Therapy for MBC is frequently referred to as the treatment of TNBC.[19] However, our study found that the clinicopathological characteristics and prognosis of MBC were not exactly the same as those of TNBC. As such, when treating

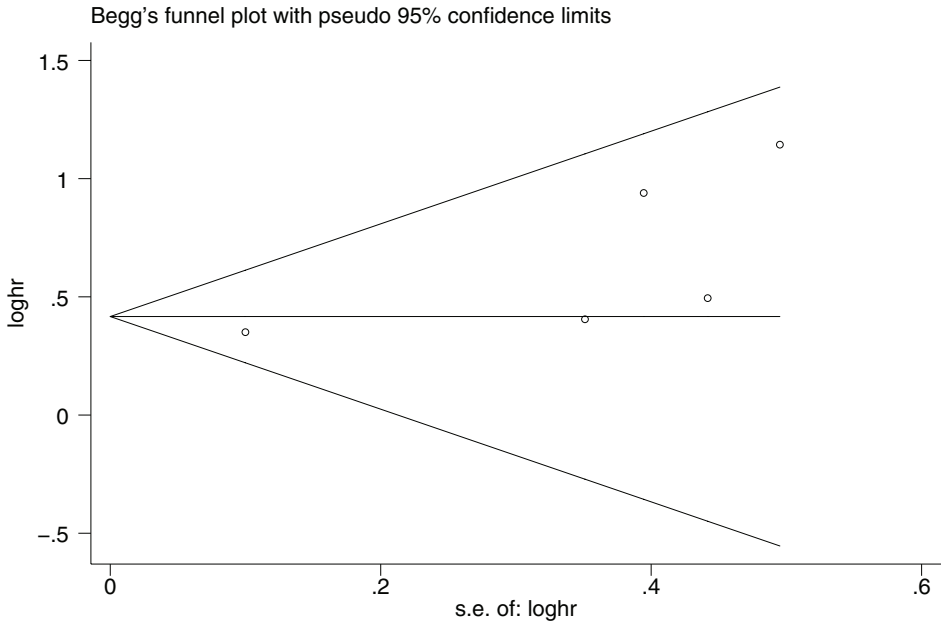

Figure 7. Begg's funnel plots of HR for 5-year OS. HR = hazard ratio, OS = overall survival.

patients with MBC, it may not be advisable to follow the exact treatment guidelines for TNBC. According to a retrospective analysis, only 17.6% of patients undergoing paclitaxel-based chemotherapy regimens exhibited a partial response, indicating that MBC did not respond well to systemic treatment.[20] Another study revealed that individuals with MBC could benefit better from platinum-based chemotherapy regimens.[21] Other studies reported that radiation increases OS and DFS in individuals with MBC, regardless of their surgical treatment.[19,22] However, these are small sample, single-center, retrospective studies. Because few studies have directly investigated MBC therapy, the treatment aspect was not covered in our study and, as such, can be considered a limitation.

5. Conclusion

Our study is the first meta-analysis to include patients with MBC. We believe that our study has improved physicians' comprehension of MBC. According to our results, patients with MBC had a worse prognosis than those with TNBC in terms of OS and DFS. Moreover, in terms of clinicopathological characteristics, MBC patients mostly presented at > 50 years of age, with tumor diameter >5 cm, and negative lymph nodes when first diagnosed. There were no statistically significant differences in the occurrence of distant metastasis, TNM stages III and IV, or histological grade 3. However, because few studies have directly addressed MBC therapy, our analysis was limited to prognostic and clinicopathological characteristics, and lacked information regarding treatment. Data from randomized controlled trials are required to inform the treatment of patients with MBC.

Author contributions

Conceptualization: Tao Zhou.
Formal analysis: Xiaolu Yang.
Investigation: Tao Zhou.
Methodology: Xiaolu Yang.
Supervision: Tao Zhou.
Validation: Xiaolu Yang, Tiantian Tang.
Writing – original draft: Xiaolu Yang.
Writing – review & editing: Tiantian Tang.

References

[1] Wright PG, Davis AT, Koehler TJ, et al. Hormone receptor status does not affect prognosis in metaplastic breast cancer: a population-based analysis with comparison to infiltrating ductal and lobular carcinomas. Ann Surg Oncol. 2014;21:3497–503.
[2] Huvos AG, Lucas JC Jr, Foote FW Jr. Metaplastic breast carcinoma. Rare form of mammary cancer. N Y State J Med. 1973;73:1078–82.
[3] Sinn HP, Kreipe H. A brief overview of the WHO classification of breast tumors, 4th edition, focusing on issues and updates from the 3rd edition. Breast Care (Basel). 2013;8:149–54.
[4] Beatty JD, Atwood M, Tickman R, et al. Metaplastic breast cancer: clinical significance. Am J Surg. 2006;191:657–64.
[5] Pezzi CM, Patel-Parekh L, Cole K, et al. Characteristics and treatment of metaplastic breast cancer: analysis of 892 cases from the national cancer data base. Ann Surg Oncol. 2007;14:166–73.
[6] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25:603–5.
[7] Macaskill P, Walter SD, Irwig L. A comparison of methods to detect publication bias in meta-analysis. Stat Med. 2001;20:641–54.
[8] Aydiner A, Sen F, Tambas M, et al. Metaplastic breast carcinoma versus triple-negative breast cancer: survival and response to treatment. Medicine (Baltim). 2015;94:e2341.
[9] Bae SY, Lee SK, Koo MY, et al. The prognoses of metaplastic breast cancer patients compared to those of triple-negative breast cancer patients. Breast Cancer Res Treat. 2011;126:471–8.
[10] El Zein D, Hughes M, Kumar S, et al. Metaplastic carcinoma of the breast is more aggressive than triple-negative breast cancer: a study from a single institution and review of literature. Clin Breast Cancer. 2017;17:382–91.
[11] He X, Ji J, Dong R, et al. Prognosis in different subtypes of metaplastic breast cancer: a population-based analysis. Breast Cancer Res Treat. 2019;173:329–41.
[12] Jung SY, Kim HY, Nam BH, et al. Worse prognosis of metaplastic breast cancer patients than other patients with triple-negative breast cancer. Breast Cancer Res Treat. 2010;120:627–37.
[13] Lee H, Jung SY, Ro JY, et al. Metaplastic breast cancer: clinicopathological features and its prognosis. J Clin Pathol. 2012;65:441–6.
[14] Li Y, Zhang N, Zhang H, et al. Comparative prognostic analysis for triple-negative breast cancer with metaplastic and invasive ductal carcinoma. J Clin Pathol. 2019;72:418–24.
[15] Morgan E, Suresh A, Ganju A, et al. Assessment of outcomes and novel immune biomarkers in metaplastic breast cancer: a single institution retrospective study. World J Surg Oncol. 2020;18:11.
[16] Song Y, Liu X, Zhang G, et al. Unique clinicopathological features of metaplastic breast carcinoma compared with invasive ductal carcinoma and poor prognostic indicators. World J Surg Oncol. 2013;11:129.

[17] Borenstein M, Hedges LV, Higgins JP, et al. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods. 2010;1:97–111.
[18] Park HS, Park S, Kim JH, et al. Clinicopathologic features and outcomes of metaplastic breast carcinoma: comparison with invasive ductal carcinoma of the breast. Yonsei Med J. 2010;51:864–9.
[19] Shah DR, Tseng WH, Martinez SR. Treatment options for metaplastic breast cancer. ISRN Oncol. 2012;2012:706162.
[20] Chen IC, Lin CH, Huang CS, et al. Lack of efficacy to systemic chemotherapy for treatment of metaplastic carcinoma of the breast in the modern era. Breast Cancer Res Treat. 2011;130:345–51.
[21] Liu J, Yu Y, Sun JY, et al. Clinicopathologic characteristics and prognosis of primary squamous cell carcinoma of the breast. Breast Cancer Res Treat. 2015;149:133–40.
[22] Tseng WH, Martinez SR. Metaplastic breast cancer: to radiate or not to radiate? Ann Surg Oncol. 2011;18:94–103.