Original Article

Prognostic factors for patients with metastatic breast cancer: a literature review

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Background: To treat metastatic breast cancer (MBC) more precisely, many efforts have been made to identify prognostic factors of MBC in many studies. This review aims to qualitatively summarize these studies and to provide a reference for the research of MBC.

Methods: Relevant papers were searched on PubMed, with the search terms including MBC, prognostic factors and prognosis, and the studies aimed at exploring prognostic factors for patients with histologically confirmed MBC, including stage IV at initial diagnosis and metastatic recurrence, were included.

Results: A total of 30 papers were included at last. An analysis of prognostic factors frome those studies was conducted. Age at primary diagnosis (6 studies), performance status (4 studies), histological grade (4 studies), hormonal receptor (HR) status (9 studies) and site of metastasis (12 studies) were universally acknowledged prognostic factors. There were four studies revealing that short DFS was significantly associated with better OS, while there was one study not revealing this association. There were various results in different studies with a reference to efficacy. Surgery and endocrine therapy were related to a better prognosis (3 studies). Targeted therapies could also conduce to the prognosis. However, there was still a contention on the role of radiotherapy. In particular, a model was brought out to calculate the risk of death in MBC. Meanwhile, it was found that some biomarkers are related to prognosis as well as per the latest findings in some studies.

Conclusions: In summary, intrinsic characteristics of tumors such as HR status and histological grade are the main factors affecting the prognosis of patients with MBC. Besides traditional factors, some new drugs and biomarkers are also associated with the prognosis of patients with MBC. In the future, the focus of studies shall be on the construction of a practical and high-quality model to predict the risk of death in MBC patients.

Keywords: Breast cancer (BC); metastasis; prognostic factor; review

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Introduction

Breast cancer (BC) is one of the most common malignant tumors and the leading cause of cancer death among women (1,2). Metastasis is the main reason causing death in patients with BC (3). Metastasis would occur in approximately 5% to 10% of patients with BC. Besides, about 30% of women will finally develop relapsed BC after the initial diagnosis at early stages (4,5). Despite of medical advances, the 5-year survival rate of patients with metastatic breast cancer (MBC)

is still less than 30% (6).

In order to treat MBC more precisely, many efforts have been made to identify prognostic factors of MBC in many studies. It has been found in some studies that patient characteristics such as age and performance status are associated with the prognosis of patients with MBC (1,7). Moreover, it has been found in other studies that characteristics of tumors such as molecular type and histological grade are related to the survival of these patients (8,9). According to molecular type and other prognostic factors, specific treatment strategies, such as anti-HER2 therapy and endocrine therapy, could be adopted to improve the outcome of patients.

Due to the fact that the prognosis of MBC is affected by various factors, it is significant to better evaluate the prognosis of individual patients through combining those factors together. There are various results on prognostic factors of MBC from different studies involving different subtypes. This review aims to make a summarization of these studies and give some suggestions on future studies, so that researchers could easily find the specific prognostic factors and relevant information about different subtypes of MBC, thus providing a reference for the research of MBC. We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-2119).

Methods

Literature search and selection criteria

Relevant papers were searched on PubMed, with the search terms including MBC (title), prognostic factors (title) and prognosis (title). Abstracts from the selected papers were reviewed by an assessor at first. Then the full papers were further evaluated according to the selection criteria by another assessor. The studies included should aim at exploring prognostic factors for patients with histologically confirmed MBC, including stage Ⅳ at the initial diagnosis and metastatic recurrence. The studies were excluded in case of any of the following criteria was met: (I) the publication type was comment, letter or review; (II) there was any other malignant tumor with the patients; (III) the paper was published before 1990.

Data extraction and analysis

Data extraction was performed independently by two assessors. Information on patient selection, sample size and endpoints were extracted for each study (*Table 1*). Prognostic factors of MBC in each study were summarized (*Table 2* and *Figure 1*) and analyzed. Results from different subtypes of BC were demonstrated and discussed separately.

The endpoints included overall survival (OS), breast cancer specific survival (BCSS), disease-free survival (DFS), or progression-free survival (PFS) in these studies. OS was defined as the time from the diagnosis to death or the last visit for patients presenting primary metastatic breast cancer (PMBC) and the time from the metastasis to death or the last visit for patients presenting BC metastatic recurrence. BCSS was defined as the BC related survival time. DFS was defined as the time from the diagnosis of BC to the metastatic recurrence. PFS was defined as the disease progression after the diagnosis of BC metastatic recurrence.

Results

Selection and characteristics of studies

The search strategy identified 113 English-language papers in total. After the screening of the title and abstract, a total of 69 papers were selected. Throug the text review, 39 papers were further excluded. Finally, 30 papers were determined as per the inclusion criteria.

These 30 included studies were published between 1998 and 2019, in which Kaplan-Meier method and Cox proportional hazard regression model were adopted to analyze the effect of different clinicopathological characteristics on the prognosis of patients diagnosed with MBC (*Table 1*). There were 7 studies including patients diagnosed with either the PMBC or initial stage III subsequently developing metastatic disease (8,10-15). Among them, there was 1 study identifying patients diagnosed with bone as only metastasis site (13) and were 2 studies focusing on human epidermal growth factor receptor 2 oncogene (HER2) positive patients (11,14). There were 10 studies focusing on BC patients with metastatic recurrence (1,2,7,9,16-21), in which there was 1 study focusing on bone metastasis (BM) (16), 1 study focusing on central nervous system (CNS) metastasis (17), 1 study focusing on brain metastasis (20) and 1 study focusing on patients older than 70 years old, respectively (19). There were 3 studies including patients diagnosed with PMBC (22-24), in which there was 1 study focusing on hormone receptor (HR) positive patients. There were 10 studies focusing on the effect of specific factors, such as drugs and

Table 1 Characteristics of the included studies on prognostic factors of metastatic breast cancer

No.	First author	Year	Patients	Country	Number	Inclusion	Exclusion	Endpoints	Methods
1	Coleman	1998	Bone metastasis	UK	367	Bone metastasis as first recurrence	Incomplete data	OS	K-M, Cox
2	Insa	1999	MBC	Spain	439	Metastatic recurrence	PMBC, neoadjuvant chemotherapy	OS	K-M, Cox
3	Altundag	2007	CNS metastasis	US	420	CNS recurrence	Incomplete data	OS	K-M, Cox
4	Largillier	2008	MBC	France	1,038	Metastatic recurrence	neo-adjuvant chemotherapy	OS	K-M, Cox
5	Puente	2010	MBC	Spain	2,322	Operable, metastatic recurrence	Stage IV, isolated local recurrence, other neoplasm, secondary PBC	OS	K-M, Cox
6	Liu	2010	MBC	China	135	Metastatic recurrence	Incomplete data	OS, DFS	K-M, Cox
7	Kawano	2013	HR+ PMBC	Japan	69	PMBC	Incomplete data	OS	K-M, Cox
8	Dorien	2013	MBC	Netherland	798	MBC	Incomplete data	OS	K-M, Cox
9	Tazhibi	2013	MBC	Iran	996	Metastatic recurrence	Incomplete data	DFS	K-M, Cox
10	Khanfir	2013	MBC	Tunisia	332	MBC	Incomplete data	OS	K-M, Cox
11	Kwast	2014	MBC	Netherland	2,001	Metastatic recurrence	ER–, PR+, not tumor-free after treatment	OS	K-M, Cox
12	Follana	2014	>70 years	France	401	Metastatic recurrence	distant secondary lymph node metastasis, neoadjuvant chemotherapy	BCSS	K-M, Cox
13	Ren	2014	MBC	US	194	PMBC	Incomplete data	OS	K-M, Cox
14	Yamamura	2015	Brain metastasis	Japan	75	Brain recurrence	Incomplete data	OS	K-M, Cox
15	Andrew	2015	MBC	US	570	MBC	Incomplete data	OS, PFS	K-M, Cox
16	Qin	2015	HER2+ MBC	China	243	MBC	Incomplete data	OS	K-M, Cox
17	Bringolf	2016	HER2+ MBC	Switzerland	81	MBC, HER2-targeted therapy	Incomplete data	OS, PFS	K-M, Cox
18	Esaie	2017	MBC	France	594	MBC	Incomplete data	OS	K-M, Cox
19	Chen	2017	MBC	US	4,932	PMBC, distant lymph node metastasis	Not enough follow-up time	OS, BCSS	K-M, Cox

Table 1 (*continued*)

Table 1 (*continued*)

No.	First author	Year	Patients	Country	Number	Inclusion	Exclusion	Endpoints	Methods
20	Parkes	2018	Bone metastasis	US	1,445	Bone as first and only metastasis site	Coexisting malignant neoplasma	OS	K-M, Cox
21	Richard	2016	HR+HER2−	America	666	HR+HER2−	Receiving prior systemic therapy for advanced disease	PFS	Log-rank test, K-M, Cox
22	Hortobagyi	2016	HR+HER2−	America	668	HR+HER2−, postmenopausal	Receiving prior systemic therapy for advanced disease	PFS	Log-rank test, K-M, Cox
23	Goetz	2017	HR+HER2−	America	493	HR+HER2−	Receiving prior systemic therapy for advanced disease	PFS	Log-rank test, Cochran-Mantel-Haenszel test
24	Robson	2017	HER2−	Amercica	302	HER2−, BRCA mutation	More than 2 previous cytotoxic regimens	PFS	Log-rank, K-M
25	Jennifer	2018	HER2−	America	431	HER2−, BRCA mutation	More than 3 previous cytotoxic regimens	PFS	Log-rank test, K-M, Cox
26	Dieras	2017	HER2+	France, America	991	HER2+, pretreated with trastuzumab and a taxane	Pretreated with T-DM1 or lapatinib or capecitabine	OS	K-M, Cox
27	Michela	2016	MBC	Italy	56	MBC, regardless of previous therapy	Without histological sample	PFS, OS	K-M, Cox
28	Botteri	2010	MBC	Italy	80	MBC	More than two previous lines of chemotherapy	PFS, OS	K-M, Cox
29	Mostert	2015	MBC	Netherland	197	MBC	Already start first-line therapy	Time-to-treatment failure	K-M, Log-rank
30	Sander	2019	HER2+	Sweden	46	HER2+, treated with trastuzumab	Receiving previous anti-HER2 treatment	PFS, OS	K-M, Cox

MBC, metastatic breast cancer; PMBC, primary metastatic breast cancer; CNS, central nervoue system; OS, overall survival; PFS, progression free survival; DFS, disease free survival; BCSS, breast cancer specific survival; HR, hormonal receptor; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; T-DM1, ado-trastuzumab emtasine 1.

Table 2 Prognostic factors of metastatic breast cancer in each study

No.	First author	Year	Patients	Number	Prognostic factors
1	Coleman	1998	Bone metastasis	367	Age at diagnosis, histological grade, ER, bone disease at initial presentation, DFS
2	Insa	1999	MBC	439	Site of metastasis, axillary lymph node status at diagnosis, ER, DFS
3	Altundag	2007	CNS metastasis	420	Age at diagnosis, ER
4	Largillier	2008	MBC	1,038	Age at diagnosis, HR, site of metastasis, primary tumor size, histological grade, adjuvant chemotherapy
5	Puente	2010	MBC	2,322	Age at diagnosis, HR, lymph node, site of metastasis, chemotherapy, number of hormonal therapy in metastasis, response to first line therapy
6	Liu	2010	MBC	135	Performance status, chemotherapy
7	Kawano	2013	HR+ PMBC	69	PR, response to first/second endocrine therapy
8	Dorien	2013	MBC	798	Molecular subtype, site of metastasis, DFS
9	Tazhibi	2013	MBC	996	Lymph node
10	Khanfir	2013	MBC	332	Age at diagnosis, performance status, visceral metastasis
11	Kwast	2014	MBC	2,001	Age at metastatic diagnosis, HR, histological grade, Her 2, DFS, site of metastasis, surgery, chemotherapy, endocrine treatment
12	Follana	2014	>70 years	401	HR, lymph node, site of metastasis, DFS
13	Ren	2014	MBC	194	Race, ER
14	Yamamura	2015	Brain metastasis	75	Molecular subtype, performance status, single brain metastatic tumor
15	Andrew	2015	MBC	570	Race, BMI, stage, molecular subtype, site of metastasis, adjuvant hormones, local therapy, adjuvant radiotherapy
16	Qin	2015	HER2+ MBC	243	Surgery, endocrine therapy, anti-Her2 therapy, performance status, brain metastasis
17	Bringolf	2016	HER2+ MBC	81	Primary brain metastasis
18	Esaie	2017	MBC	594	Age at metastasis, molecular subtype, histological grade, first metastatic site
19	Chen	2017	MBC	4,932	Age at diagnosis, race, T stage, molecular subtype, surgery, radiotherapy, visceral metastasis
20	Parkes	2018	Bone metastasis	1,445	Multiple bone metastasis, both axial and appendicular skeleton metastasis
21	Richard	2016	HR+HER2−	666	Palbociclib combined with letrozole (*vs.* AI)
22	Hortobagyi	2016	HR+HER2−	668	Ribociclib combined with letrozole (*vs.* AI)
23	Goetz	2017	HR+HER2−	493	Abemaciclib combined with AI (*vs.* AI)
24	Robson	2017	HER2−	302	Olaparib (*vs.* single chemotherapy)
25	Jennifer	2018	HER2−	431	Talazoparib (*vs.* single chemotherapy)
26	Dieras	2017	HER2+	991	T-DM1 (*vs.* lapatinib plus capecitabine)
27	Michela	2016	MBC	56	Circulating tumor cell
28	Botteri	2010	MBC	80	Circulating tumor cell
29	Mostert	2015	MBC	197	Circulating tumor cell
30	Sander	2019	HER2+	46	*ERBB2* and *PTPN2* gene copy numbers

MBC, metastatic breast cancer; PMBC, primary metastatic breast cancer; CNS, central nervoue system; DFS, disease free survival; HR, hormonal receptor; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; T-DM1, ado-trastuzumab emtasine 1; BMI, body mass index; AI, Aromatase inhibitor.

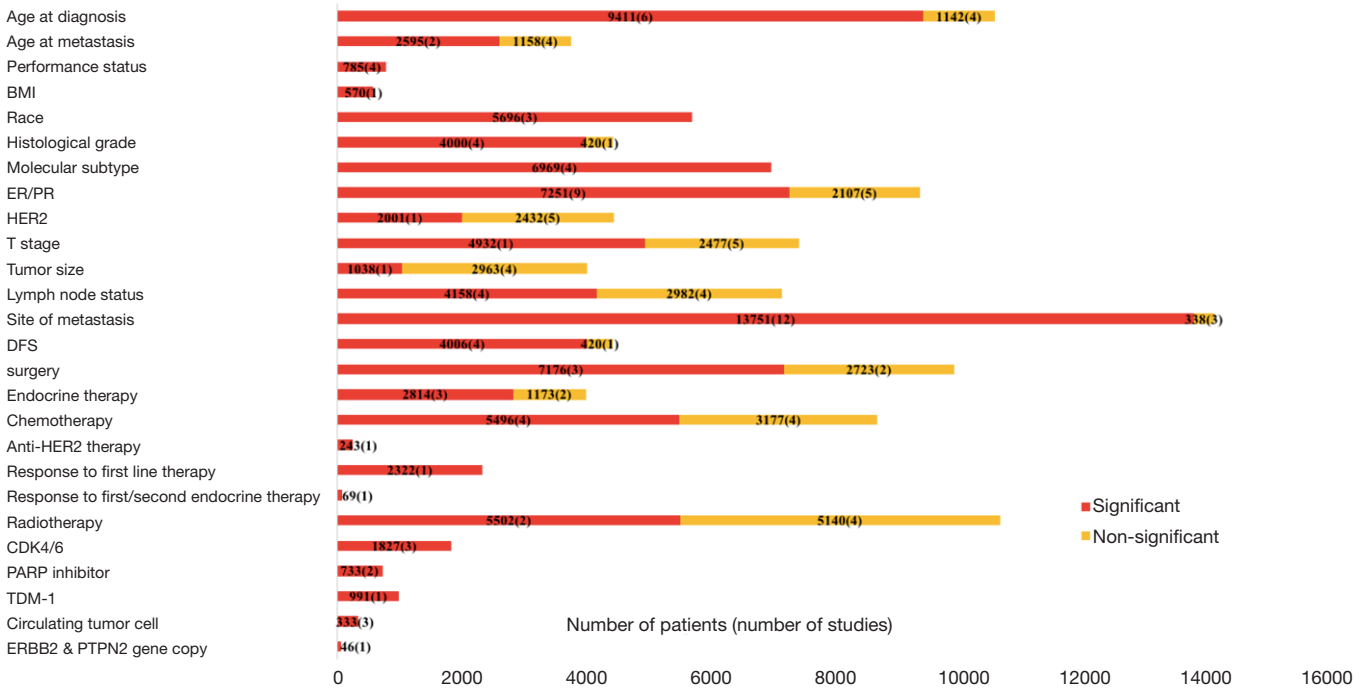

Figure 1 Prognostic factors of MBC identified in at least one study. BMI, body mass index; ER, estrogen receptor; PR, progesterone receptor; DFS, disease free survival; HER2, human epidermal growth factor receptor 2; CDK4/6, cyclin-dependent kinase 4/6; PARP, poly (adenosine diphosphate–ribose) polymerase; T-DM1, ado-trastuzumab emtasine 1; MBC, metastatic breast cancer.

biomarkers, on prognosis (25-34).

Study results

Prognostic factors of MBC, including PMBC and metastatic recurrence

Khanfir *et al.* (15) analyzed 332 patients with histologically confirmed PMBC and metastatic recurrence BC in Tunisia. They found that good performance status (PS), non-visceral metastatic recurrence and ≤70 years old were related to better OS (*Table 2*). Marshall *et al.* (12) conducted research into 594 patients from the only registry specialized BC center in France. The results showed that molecular subtypes, histological grade, metastasis site and age at diagnosis were independent prognostic factors of the OS in MBC, while there was no significant difference in OS between patients with PMBC and metastatic recurrence. Lobbezoo *et al.* (8) conducted a research into 798 patients in eight hospitals in the Netherlands. They divided the patients into four groups according to HR and HER2 status of primary tumor or metastatic lesion, and found that patients with the HR+/HER2+ subtype had better OS than the patients with other subtypes. Meanwhile, it was found that ≤50 years old at primary diagnosis, DFS ≥24 months, adjuvant endocrine therapy, and absence of visceral, brain and multiple metastases were favorable prognostic factors. In another study, Bishop *et al.* (10) identified 570 MBC patients treated at MD Anderson. They defined a complete response according to RECIST criteria as no-evidence-of-disease (NED). They found attaining NED status was not related to OS, but it would influence the survival at 2 and 3 years.

Patients with BC metastatic recurrence

Largillier *et al.* (18) reported a study of 1038 patients diagnosed with metastatic recurrence and not receiving adjuvant chemotherapy in France. They found that age, size of primary tumor, histological grade, HR status, metastasis site and adjuvant chemotherapy were independent prognostic factors of MBC, while DFS was not significantly associated with OS. Similarly, in other three studies (2,7,21), researchers identified the prognostic factors of patients with metastatic recurrence in Spain, China and Iran respectively. However, in the study from Spain, DFS remained

independently associated with OS after the first recurrence. In the study from China, it was found that PS was related to OS besides the mentioned factors, while there was no such relation for DFS. There was another study evaluating patients in Spain (1), which included more population compared with the study in Spain. This study collected the clinical data of 2,322 patients from 50 hospitals. In this study, it was found that age, tumor characteristics and treatment were related to prognosis, but DFS appeared not to be associated with prognosis as per the multivariate analysis.

Patients with PMBC

Ren *et al.* (23) identified 194 patients with distant metastasis at the time of diagnosis in the United States. They found race and HR status could exert impact on OS. In another study from the United States (24), researchers aimed to identify clinical characteristics related to distant metastasis by age groups in a large population. They found that age, HR and other factors such as T stage and the site of metastasis, could affect OS and BCSS of these patients. In a study from Japan, Kawano *et al.* (22) conducted an analysis of 69 HR positive PMBC patients. They found that progesterone receptor status and clinical benefit rate from the first-line endocrine therapy were independent prognostic factors of OS.

Prognostic factors of MBC with bone metastasis

There were two studies discovering the factors affecting prognosis of MBC patients with BM. Coleman *et al.* (16) identified 367 patients with the first recurrence site in bone. They found that age at diagnosis, histology, HR status, DFS, bone disease at presentation would affect the prognosis. From another point of view, Parkes *et al.* (13) described the association among bone pain, location, number, type of BM and OS in MBC patients with BM. They conducted an analysis of 1445 patients with bone as the only metastatic site, and found that multiple bone metastases and both appendicular and axial skeleton metastases were risk factors for decreased OS in these patients. Patients with both appendicular and axial metastases had a 69% (hazard ratio, 1.69; 95% CI, 1.31–2.19) and 65% (hazard ratio, 1.65; 95% CI, 1.26–2.17) of increased hazard of death compared to patients with metastasis confined to appendicular and axial skeleton respectively.

Prognostic factors of MBC with CNS metastasis

Altundag *et al.* (17) retrospectively evaluated data from 420 patients with BC and CNS metastasis. CNS metastasis was defined as a metastasis in the brain and/or leptomeningeal disease. The results showed that patients with ER positive (hazard ratio, 0.69; 95% CI, 0.55–0.87) and younger age (hazard ratio, 1.01; 95% CI, 1–1.02) had better outcome, while other factors, such as PR status, histological grade, tumor size and lymph node classification, were not significantly associated with the survival. In this study, there were only 248 patients with known information of HER2 status. Patients with HER2 positive lived longer than those with negative HER2 (median time 11 *vs.* 6 months). Yamamura *et al.* (20) conducted research into 75 early BC patients subsequently developing brain metastasis. The results indicated that luminal HER2 cancer, favorable PS and single metastatic brain tumor independently affected the prognosis of those patients.

Prognostic factors of MBC with positive HER2

Qin *et al.* (11) assessed 243 MBC patients with HER2 positive in southern China. They found that anti-HER2 therapy (trastuzumab or lapatinib), endocrine therapy and surgical intervention were favorable independent prognostic factors for OS in these patients, while poor PS and brain metastasis were unfavorable factors. In another study, Bringolf *et al.* (14) identified 81 patients with HER2 positive, among whom there were 25 receiving HER2-targeted therapy in Switzerland. They found that only primary brain metastasis was an unfavorable prognostic factor, while other factors were not significantly associated with the prognosis of these patients. Median OS of patients with primary brain metastasis was 1.9 years (95% CI, 1.7–2.2 years), while median OS of all patients with brain metastasis was 26 months (95% CI, 19.9–32.0 months).

Latest findings on prognostic factors of MBC

Besides the mentioned traditional clinicopathological factors, the effects of new drugs and biomarkers on the prognosis of MBC patients were explored in some studies. Cyclin - dependent kinase 4/6 (CDK 4/6) inhibitor is a newly developed drug to overcome the intrinsic or acquired resistance to endocrine therapy in patients with HR positive/HER2 negative patients (31). Finn *et al.* (25) found that in untreated patients with HR positive/HER2 negative patients, palbociclib combined with letrozole would result in a significantly longer PFS than that with letrozole alone (24.8 *vs.* 14.5 months). In other two clinical trials, it was also demonstrated that drugs targeting CDK4/6 combined with aromatase inhibitor (AI) could

improve PFS compared to that with AI alone (26,35). Recently, the role of poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitor in HER2 negative especially triple negative MBC has been identified. Robson *et al.* (28) found that among HER2 negative patients with BRCA mutation, the median PFS of patients treated with Olapalib was 2.8 months, which was longer than that with standard single agent chemotherapy. Similarly, it was demonstrated that talazoparib, another PARP inhibitor, could provide more significant benefits in terms of PFS than standard chemotherapy in another phase III clinical trial (30). Ado-trastuzumab emtasine (T-DM1) is a compound consisting of anti-HER2 drug trastuzumab and cytotoxic emtasine, which provides a treatment for patients who have received trastuzumab for MBC or have disease progression after adjuvant trastuzumab therapy (29). In a phase III clinical trial, Diéras *et al.* conducted research into HER2 positive MBC patients who have been pretreated with trastuzumab and a taxane, and they found that median OS was longer with T-DM1 than with lapatinib plus capecitabine (29.9 *vs.* 25.9 months) (27).

Circulating tumor cells (CTC) are tumor cells shed in blood from primary tumors and might represent the risk of metastasis. Fehm *et al.* found PFS and OS would decreased as the increase of CTC at baseline (36). Bulfoni *et al.* found CD45 negative CTC co-expressing epithelial and mesenchymal markers were significantly related to poor PFS and OS (37). In another study, it was demonstrated that a 16-gene CTC profile had a better prognostic performance than CTC count in MBC patients (38).

In patients treated with anti-HER2 therapy, trastuzumab resistance is a frequent challenge while there is relapsing or metastatic disease. HER2-associated PI3K/Akt signalling pathway may play a critical role in trastuzumab resistance. In a recent study, Ellegard *et al.* discovered that high-grade ERBB2 gene amplification level of more than 6 copies could improve OS and PFS, and more than 3 copies of *PTPN2* gene were related to shorter OS and PFS in HER2 positive patients who received trastuzumab for treatment (32).

Discussion

In this review, an exploration on the prognostic factors of MBC from 30 studies has been carried out from different aspects. As per the results, it can be seen that age at primary diagnosis, tumor size, histological grade, HR status, HER2 status, lymph node involvement, site and number of metastasis are universally acknowledged prognostic factors (*Figure 1*), which reflects that the intrinsic characteristics of tumor are main factors affecting the prognosis of patients with MBC.

In previous studies, DFS was considered as a strong prognostic factor of MBC (39-41). In this study, however, there is still a contention on the relationship between DFS and OS. It was revealed in some studies that short DFS was significantly associated with worse OS (2,8,9,16,19); however, there were some studies not revealing this association (1,7,18). There are several possible reasons for those studies not showing the significant association between DFS and OS. Firstly, as per the study of Largillier *et al.* (18), DFS appears to be related to OS in the univariate analysis, but other parameters like tumor size are more powerful in the prediction of the specific survival in multivariate Cox model, which would eliminate the efficacy of DFS. Secondly, as per the study of Liu *et al.* (7), a prognostic tool named Nottingham Prognostic Index, along with DFS and other factors, has been included in the analysis. The Nottingham Prognostic Index has been constructed via histological grade, ER status, site of metastasis and DFS (42) and DFS indeed could exert an impact on this index. Finally, all the mentioned factors do not show a significant influence on OS except for Nottingham Prognostic Index. Since there is a relationship between Nottingham Prognostic Index and other factors, the results may not be persuasive enough. As we know, DFS reflects the aggressiveness of tumor. If there is a relationship between DFS and OS, DFS would be a useful factor to predict the survival time of patients and maybe a more powerful ajuvant treatment should be applied to patients to prolong the duration of DFS. Of course, a further investigation shall be made in the future.

Owing to advances in early detection and modern systemic therapy, the survival of patients with MBC improves over time (43) and the risk of death decreases by 1% in each year (44). It is suggested that the improvement in survival is related to treatment as per the results from a large multicenter study (43). Referring to the efficacy, there are various outcomes in different studies in this review. It could be found in some studies that adjuvant therapies, including chemotherapy, endocrine therapy, targeted therapy and radiotherapy, could prolong the survival time of patients with MBC, while there still are some studies not revealing the significant benefits on survival from systemic treatment (1,2,7,8,18-21,24). However, due to the fact that most studies included are single-center studies, it is

inevitable for the existence of patient selection bias, which would disturb the results. Nevertheless, in this review, there are two studies carried out in eight and fifty hospitals respectively (1,8). As per the results from these two studies, the adjuvant treatment can be regarded as a favorable prognostic factor of MBC. These results are relatively more convincing. A prospective study should be conducted to testify the impact of adjuvant therapy on survival.

Bone is the most common site of metastasis in BC. It is suggested that about 70% of patients with BC will develop BM (45). Bone metastasis are mainly distributed to axial skeleton, due to the possible fact that malignant cells could migrate through the axial bone marrow circulation which is connected with low-pressure valveless vertebral-venous plexus (16). As per the study of Parkes *et al.*, 36% of patients would have BM in the axial skeleton, 11% of patients would have BM in the appendicular skeleton, and 54% of patients would have BM in both the axial and appendicular skeleton. These results could confirm the theory mentioned above. In this study, metastasis in both axial and appendicular skeleton would result in worse outcome than in either axial or appendicular skeleton, which could help us to stratify the risk of death within patients diagnosed with BM and provide them with a more appropriate treatment.

CNS is one of the most common sites of metastasis and accounts for about 30% of all MBC (46). It has been assumed that the incidence of CNS metastasis would be higher in young, ER negative (47) and HER2 positive patients (48). As per the study of Altundag *et al.* (17), there is a better prognosis of MBC with CNS metastasis for young and ER positive patients. Although young patients are more likely to develop CNS metastasis, they tend to have better outcomes than old patients. However, for patients with ER negative, the prognosis is not optimistic due to both higher risk of developing CNS metastasis and poor prognosis after CNS metastasis. It has also been found by the authors that patients with HER2 positive tend to live longer than those with HER2 negative, which is consistent with the results from Yamamura *et al.* (20). Anti-HER2 therapy may be the main factor that could improve the prognosis of patients with HER2 positive.

HER2 proto-oncogene amplification can be found in about 25–30% of patients with BC (49) and has been thought to be related with poor prognosis in patients with BC. The treatment with anti-HER2 therapy dramatically alters the role of HER2 and improves the outcomes of patients with HER2-positive BC, which is even better than those with HER2-negative BC (34,50,51). In this review, Qin *et al.* (11) has found that anti-HER2 treatment, such as trastzumab and lapatinib, could increase survival time of patients with HER2 positive, which is in line with the results from previous studies. As per another study by Bringolf *et al.* (14), it has been found that primary brain metastasis could exert impacts on the prognosis of patients with HER2 positive. Therefore, brain metastasis may be a useful prognostic factor in HER2 positive MBC in anti-HER2-therapy era. However, there are certain limitations in this study. Owing to the fact that only 6 patients have been diagnosed with primary brain metastasis and 34 patients with secondary brain metastasis, the statistical comparison between the primary and secondary brain metastasis has been made indirectly in this review. Therefore, their results are not statistically significant and not persuasive enough.

It would be beneficial to identify factors affecting prognosis for clinical management strategies. Furthermore, it would conduce to guiding the treatment and follow-up more precisely via constructing a practical prognostic index. In the previous studies, there is one study proposing an index to calculate the risk of death in MBC (1). The researchers have collected data of patients with MBC from fifty hospitals. Through Cox proportional hazards model, a prognostic index has been constructed. 962 patients with complete data of all prognostic variables have been divided into the high, intermediate and low risk groups based on the index score. Finally, cumulative survival rate of each group has been calculated to validate the index. In this study, a useful tool has been provided to identify MBC patients with high risk of death who need more aggressive treatment. However, there are certain limitations in this study. First and most importantly, the qualification of a predictive model depends on the area under the ROC curve (AUC). The AUC value in this study is only 0.69, which is not enough to distinguish patients with absolutely high risk. Second, the data are collected from the same database to validate the index in this study. It would be more convincing if the data can be collected from another database to validate the index. Despite all limitations, it is extremely meaningful to make an attempt to construct a practical model with the aim of predicting the risk of death in patients with MBC.

Conclusions

In this review, some prognostic factors of MBC have been discussed from different aspects. In summary, such

intrinsic characteristics of tumors as tumor size and histological grade are main factors affecting the prognosis of patients with MBC. However, there is still a contention on the relationship between DFS and OS, which shall be investigated in the future. Stratified by molecular type and metastatic site, there are specific prognostic factors for different types of MBC. Besides traditional factors, some new drugs and biomarkers are also associated with the prognosis of patients with MBC. It would be beneficial to identify factors affecting prognosis for developing clinical management strategies, and furthermore, it would conduce to guiding the treatment more precisely via constructing a practical prognostic index. In the future, the research focus would be on the construction of a practical and high-quality model with the aim of predicting the risk of death in patients with MBC.

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