

Prognostic Factors for Advanced Breast Cancer

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Abstract: Breast cancer is one of the most frequent malignancies affecting women's health and is the second leading tumor in terms of prevalence globally. However, advanced breast cancer remains incurable, and the prognosis is unfavorable. Identifying prognostic factors in advanced breast cancer is crucial for clinical practice. In this paper, we aim to summarize significant risk factors affecting the prognosis of patients suffering from advanced breast carcinoma, including age, sites of metastasis, molecular typing, and local treatments. Additionally, this paper explores the methods and functions of prediction models for advanced breast cancer, aiming at offering new insights for clinicians and researchers. In the future, with a large body of research, we hope clinical researchers will develop prediction models for advanced breast cancer that are widely applicable in clinical practice. These models could enable patients to have a clearer and more in - depth understanding of their conditions and assist physicians in implementing individualized treatments and precision medicine, ultimately prolonging patient survival.

Keywords: Advanced breast cancer, Prognostic factors, Survival

1. Background

Breast cancer, a prevalent malignancy afflicting women on a global scale, has witnessed a year - on - year upsurge in its incidence. Genetics, family history, a menstrual duration of more than 40 years, premature menarche (< 12 years old) or delayed menopause (> 55 years old), infertility, late childbearing, non-lactation, prolonged utilization of exogenous estrogen, menopause-related obesity, long-term undue alcohol consumption, and other factors may induce breast cancer [1]. Breast cancer usually presents as an indolent breast mass, and 90% of breast lumps are benign in nature. It may present with a firm, immobile, irregular, or fixed lump in the breast and/or armpit; breast engorgement or changes in shape and size; skin erythema, dimples, ulcers, and cellulitis; and nipple inversion or discharge [2]. With the gradual refinement of breast cancer surgery and treatment methods in recent years, the mortality rate has decreased, and the 5-year survival rate of breast cancer patients in China has witnessed a remarkable upsurge, reaching 83.2%. However, advanced breast cancer remains incurable, which seriously threatens the health of patients. On April 14, 2023, the China Center for Disease Control and Prevention released a report analyzing female breast cancer data from 2003 till 2017. By 2030, there will be more than 400,000 newly diagnosed cases and over 100,000 deaths in the country. The age-standardized morbidity rate of breast cancer in women over 20 years old in China increased from 46.34 per 100,000 in 2003 to 68.78 per 100,000 in 2017.

Today, the therapy of advanced breast cancer has stepped into the era of “precise classification and precise stratification,” and precision therapy is becoming the dominant treatment method for breast cancer in the advanced stage. Chemotherapy remains an important treatment, but more new options are being developed to provide patients with more choices. For example, for patients with advanced triple-negative breast cancer, in addition to chemotherapy, there are antibody-drug conjugates, targeted therapies, immunotherapies, and combinations of TROP2-targeting ADC drug Dedatuzumab and immunotherapy, providing new options [3]. For patients with HR+ advanced breast cancer, the combination of CDK4 and CDK6 inhibitors and endocrinotherapy has been found to significantly improve prognosis [4]. Additionally, antibody-drug conjugates, PI3K/Akt inhibitors, and mTOR inhibitors may have potential applications for HR+ advanced breast cancer. The therapy of HER-2+ advanced breast cancer has also made significant progress, and tucatinib in combination with T-DM1 second-line therapy and trastuzumab (T-DXd) may have therapeutic effects on HER-2+ advanced breast cancer[5].

At present, the factors that mainly affecting the prognosis of advanced breast cancer include molecular typing, treatment methods, distant metastasis of vital organs, age, and other factors. Among these, the molecular types of breast cancer primarily include hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) positive, triple-negative breast cancer, Luminal A, and Luminal B types. Triple-negative breast cancer has the highest heterogeneity and is highly susceptible to long-term metastasis at an advanced stage, resulting in the worst prognosis. Additionally, among patients with advanced breast cancer, those having bone metastases tend to have a better prognosis compared to those without bone metastases. However, the survival rates of patients afflicted with brain metastases, liver metastases, and lung metastases are significantly lower compared to those without metastases in these organs [2], with patients having isolated bone metastases having the best prognosis and those with brain metastases having the poorest prognosis [6]. The prognosis of advanced breast cancer in young women versus older patients remains controversial due to the lack of research comparing advanced breast cancer in older and younger women, the absence of targeted treatments, and the failure of nearly half of elderly patients to comply with clinical recommendations [1]. This article will primarily focus on these aspects. It is hoped that the article will inspire clinicians and researchers to further advance treatment options for advanced breast cancer in the future.

2. Age

There are many theories about the prognosis of older patients with advanced breast cancer compared to younger patients. In accordance with 2008 data, 16.6% of breast cancer patients in China are 65 and above, and it is anticipated that this proportion will increase to 27.0% by 2030 [7].

Compared to younger patients, the rate of elderly patients with Luminal type breast cancer is higher. However, there are few studies on Luminal types in elderly patients, and most of them have low organ function, often suffer from multiple comorbidities, have poor surgical tolerance, and may be non-compliant with medical instructions, all of which can lead to a poor prognosis in older patients [7]. Currently, the most commonly used surgical regimens are breast-sparing surgery with sentinel node biopsy and modified radical breast resection, both of which reduce surgical trauma and facilitate recovery in elderly patients. For elderly patients, special attention must be given to changes in cardiac function and the timely adjustment of treatment regimens [8].

Younger patients with breast cancer tend to be more biologically active than older patients and may present with more adverse pathological features, such as high-grade tumors, lymphovascular invasion, and aggressive subtypes. These features contribute to higher rates of recurrence and psychosocial morbidity, which may cause a less optimistic prognosis in younger patients with advanced breast cancer than for older patients. However, this does not mean that young breast cancer

patients are necessarily more severe or have a worse prognosis; detecting early, diagnosing early, and treating early can enhance their quality of life effectively [9].

3. Molecular Typing

Breast cancer is a heterogeneous disease with various subcategories, each exhibiting a varied incidence rate and prognosis. The molecular classification of breast cancer is mainly divided into HER2+ type, HER2- type, triple-negative mammary cancer(TNBC), Luminal A type, and Luminal B type. Among these, Luminal A and Luminal B types are primarily treated with endocrine therapy and generally have a better prognosis. Prior to the era of HER2-targeted therapy, HER2+ breast cancer was invasive, recurred rapidly, and had a worse survival rate than HER2- breast cancer. However, with the use of anti-HER2-targeted drugs such as trastuzumab, the survival rate of HER2+ breast cancer patients has improved. In patients presenting with metastatic breast cancer, the survival rate for HER2+ patients is higher than that for HER2- breast cancer patients [10]. Among the aforementioned molecular classifications, TNBC constitutes 10 - 15% of all documented breast cancer cases. It is highly invasive, has the greatest heterogeneity, and is extremely prone to long-term metastasis in its later stages, leading to the worst prognosis. Moreover, owing to the absence of estrogenic and progestational receptors and low HER2 expression, TNBC is difficult to treat effectively with hormone therapy or anti-HER2 therapy. However, TNBC is more sensitive to chemotherapy, and although the use of chemotherapy is limited, it remains the standard treatment for this subtype [11]. Despite recent progress in treatment methods, the median survival period for TNBC is still approximately 5 years shorter than that for ER-positive or HER2-positive breast cancer patients [12].

4. Metastasis Sites

Among the distant metastases of breast cancer, those most commonly involving the bone, lung, liver, and brain are of great concern. Research has demonstrated that 30-60% of breast cancer metastases occur in the bone, 4-10% in the brain, 15-32% in the liver, and 21-32% in the lungs [13]. In general, skin, subcutaneous, bone, and lymph node metastases, along with nodular lung metastases, are associated with a better prognosis, slower tumor growth, and longer survival. Conversely, brain, liver, and multiple lung metastases, lymphangitis carcinomatosa, or large tumor-induced lymphangitis are strongly associated with worse outcomes. In a study by Bernardo et al., the median survival was only 28 months for the entire patient population, and even less if skin and/or soft tissue metastases were detected [10].

Bone metastases are usually the earliest site of metastasis and the most common one of metastasis breast cancer, particularly for the HER2+ subcategory. Although Milano et al. (2012) found that the risk of death from osseous abnormalities was four times lower than from other sites of metastasis. It was not as good for patients who had bone metastases. This is because bone migration substantially augment the peril of dire complications, such as fractures and spinal cord compression. The pain is often excruciatingly intense and virtually insufferable, which gravely impairs patients' lives, disrupting their daily routines and severely diminishing their quality of life [14]. Patients, who have metastases only to the lungs, have a poor prognosis, and their median survival is only 25 months.[13]. Currently, surgery (segmentectomy, lobectomy, or lung resection) is a widely accepted treatment [14]. Among all the loci of breast cancer metastasis, the liver ranks third most prevalently affected, trailing only the osseous tissue and the pulmonary organ. In patients with de novo stage IV breast cancer, the liver serves as the site of metastasis in 13.3% of cases. Liver metastasis is generally related to poorer survival results, especially for the HER2+ subtype [10]. The average survival for patients suffering from liver metastasis is 1.15 years, while the average survival for patients with nodular lung

metastases is 2.21 years. Without treatment, survival may be as low as 4 to 8 months. However, liver surgery can significantly increase patient survival [14]. Breast cancer brain metastases (BCBMs) occur later, but nearly 25% of patients with advanced breast cancer develop brain metastases, specifically those with triple-negative and HER2+ subtypes, greatly reducing their well-being and overall survival [15, 16].

In general, the more substantial the quantity of distant organ metastases, the more detrimental the prognosis for patients [17]. The 2-year survival rate is 54.12% if only one organ is metastasized, while this percentage decreases to 39.01% when metastases involve multiple organs. In previous studies of patients having metastatic breast cancer (MBC), including bone metastases, median overall survival (OS) was close to 2.6 years when bone was the only metastatic site, and decreased to one year if a second metastatic site was present. Data from a previous study by Insa et al. suggest that patients in the single - site metastasis group have a median overall survival (OS) of 30 months. This figure drops to 22 months for those in the two - site metastasis group. In cases where there are three or more metastatic sites, the median OS is only 11 months. In contrast, the EORTC comprehensive analysis demonstrated that patients with liver involvement alone had an OS of 22 to 26 months, while the OS for patients with metastases across multiple sites was 14 to 16 months [14].

5. Local Treatment

Patients with advanced breast cancer often have systemic metastasis, which are mainly divided into primary breast cancer and recurrent breast cancer. Both are considered systemic diseases and are generally regarded as incurable. Traditionally, treatment has been carried out using a systemic approach. It is commonly believed that topical therapy is used only to prevent or alleviate symptoms and makes no significant difference to advanced breast cancer patients' survival.

However, recent studies, such as those by D. Kay Blanchard et al. [18] and Gildy V. Babiera et al. [19], have indicated that, by comparing patients who underwent surgical resection of the primary breast tumor with those who did not, such surgical intervention for primary breast tumors can improve both overall survival and progression - free survival in patients with stage IV breast cancer. Rapiti et al. [14] also concluded from a population-oriented retrospective analysis that compared to women who did not, women who underwent surgery for the primary tumor had a 40% reduction in breast cancer mortality. However, the survival benefit was limited specifically to those with negative surgical margins, and it was particularly evident for patients with only bone metastases. On the other hand, patients who underwent adjuvant or neoadjuvant treatment, particularly those treated with anthracyclines, tended to have worse survival results. While in the research conducted by Marleen Rosche et al. [20], they suggested that overall survival or progression - free survival in patients with advanced breast cancer was not affected by surgery for the primary tumor.

In patients with recurrent advanced breast cancer, surgical resection may be most appropriate if one or more lesions occur at a single organ site [21]. Surgery (segmentectomy, lobectomy, or lung resection) is a commonly recognized treatment option for patients having lung-only metastases [14]. It has been found that if patients receive systemic therapy, their 10 - year survival rate is only 6.5%, but if they undergo surgery, it is significantly improved to 40%. For patients with liver metastases, combining liver surgery with preoperative systemic therapy is pivotal in determining the outcome following liver resection and disease progression prior to surgery is notably linked to a decline in overall survival rates. A disease-free period of fewer than one year between the initial diagnosis and liver metastasis, as well as a positive resected margin after operation, both were connected with worse prospects for long-term survival [14]. The effectiveness of systemic treatment is low for patients suffering from brain metastases, and treatment is usually a combination of radiotherapy, surgery, or both. The triple-negative phenotype and progressive extracranial disease negatively affect the survival of breast cancer patients having brain metastases after receiving stereotactic radiosurgery

(SRS) [14]. In addition, stereotactic body radiation therapy (SBRT) can minimize morbidity while locally controlling target injuries in the liver, lungs, spine, and multiple sites [21]. For bone metastases, SBRT has shown better therapeutic effects. In one study, 39 patients with osteoblastic metastases (OMBC) out of a total of 121 patients received SBRT, and none of the irradiated bone lesions recurred [14].

6. Prediction Model

Today, model maps have been widely used in early breast cancer, but they are still in the research stage for advanced breast cancer, with no corresponding clinical applications available. Many researchers are now attempting to build models to forecast prognosis and related factors in advanced breast cancer patients.

Shanyao Lin et al. selected data from the database of the National Cancer Center, which included 4039 patients were certified to be suffering from breast cancer during the years from 1987 through 2019. They recruited 2263 participants with advanced breast cancer (ABC) and assigned them randomly to the training and verification sets at a ratio of 3:1. On the basis of independent predictors determined by single-variable and multivariable Cox regression analysis, age, Eastern Cooperative Oncology Group score, T stage, N stage, cancer subtype, distant metastases, local treatment, first-line treatment effect, and metastasis-free interval (MFI) were all significantly correlated with overall survival (all $P < 0.05$). Combining these factors into a nomogram can forecast the 2- and 3-year overall survival for patients with ABC, providing a prognostic prediction and helping guide physicians in making personalized treatment decisions[22].

To Shunrong Li et al., the National Cancer Database (NCDB) was searched for patients diagnosed with stage IV breast cancer from 2010 to 2013 and 7199 patients were included in the nomogram to predict overall survival. The median duration of follow-up was 25.7 months, and it was 80.6% and 52.5% that the one - and the three - year OS rate reached, respectively. They found that there were many elements which were dramatically connected with OS, such as ethnicity, age, comorbidity status, T stage, hypotype, ER/PR/Her 2 status, distant metastases, operation, radiation therapy, and chemotherapy. Prognostic factors including the diagnosis year, tumor position(quadrant), and tumor sidedness were, in theory, independent of survival. However, the comparison between N2 and N0, as well as different histological types (invasive ductal carcinoma [IDC], invasive lobular carcinoma [ILC], and others), showed no association with overall survival (OS). This model can also identify high-risk subgroups that may require more intensive therapy and low-risk patients who may gain from less aggressive therapy, aiding in clinical diagnosis. However, the model did not include information about hormonal therapy or HER2-targeted therapy, and it could not distinguish between treatment-naïve patients with advanced breast cancer and those advancing to stage IV after adjuvant therapy. Other studies have shown that survival differs between these two subgroups, with the latter having more variables. Therefore, future in - depth investigations into diverse treatment regimens and the corresponding responses of patients to these therapies have the potential to enhance this model significantly. [23].

Lee et al. [24] devised a nomogram to forecast the lifespan duration for females afflicted with advanced breast cancer. The model was built using data from two first - line chemotherapy trials (ANZ693 and ANZ8101) with 8,614 patients in the training cohorts. It was put to the test in two other trials (ANZ0001 and ANZ9311) with 324 and 233 patients separately. Prognostic factors such as age, function status, estrogen receptor state, quantity of organs including (lung, liver, and brain), hemoglobin level, neutrophil number, and serum ALP were considered. The concordance index for the nomogram predicting OS was 0.65 (95% CI, 0.62-0.67). Once the new baseline survival function was recalibrated for each validation cohort, the probabilities of 18 - month survival, both the actual and those predicted by the model, showed a high degree of consistency. This nomogram can serve to

individualize treatment and classify patients in future randomized tests. In addition, Lee et al. [25] developed a PMOS system using multicenter data from Korean hospitals that forecasts survival in metastatic breast cancer patients by taking into account the features of the original primary tumor (e.g., tumor grading, hormone receptor condition, and Ki-67 expression degree) as well as the features of distant metastatic manifestations (e.g., length of disease-free interval, metastasis position, and existence or nonexistence of metastasis-related symptoms) as autonomous prognostic determinants. Both researches concentrated on forecasting survival after a distant metastatic event in primary breast cancer patients some time after treatment. However, these patients differ from those with new-onset advanced breast cancer, as there are reports suggesting they obtain more beneficial results[26].

7. Conclusion

In general, advanced breast cancer has a poor prognosis and represents a major threat to female's health. Predicting the prognosis of patients using various prognostic factors can guide clinical treatment and contribute to the growth of more effective approaches for advanced breast cancer. Currently, few studies have focused on prediction models for advanced breast cancer, and none have been widely applied. Further research is needed to develop a model that can be effectively used in medical practice.

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