Effect of Huaier granule on prognosis of breast cancer: A single-center propensity score matching retrospective study

Qianqian Guo[1], Yuting Peng[2], Ge Zhang[3,4,5,6,7], Huan Lin[1], Qianjun Chen[1,8]

[1]Breast Department, Guangdong Provincial Hospital of Chinese Medicine, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangdong Provincial Academy of Chinese Medical Sciences, Guangzhou, Guangdong 510006, China;
[2]The Second Clinical College, Guangzhou University of Chinese Medicine, Guangzhou, Guangdong 510006, China;
[3]Law Sau Fai Institute for Advancing Translational Medicine in Bone and Joint Diseases (TMBJ), School of Chinese Medicine, Hong Kong Baptist University, Hong Kong 999077, China;
[4]Guangdong-Hong Kong-Macao Greater Bay Area International Research Platform for Aptamer-based Translational Medicine and Drug Discovery (HKAP), Hong Kong 999077, China;
[5]Institute of Precision Medicine and Innovative Drug Discovery (PMID), School of Chinese Medicine, Hong Kong Baptist University, Hong Kong 999077, China;
[6]Institute of Integrated Bioinformedicine and Translational Science (IBTS), School of Chinese Medicine, Hong Kong Baptist University, Hong Kong 999077, China;
[7]Northwestern Polytechnical University-Hong Kong Baptist University United Research Center of Space Musculoskeletal Health, Shenzhen, Guangdong 518063, China;
[8]State Key Laboratory of Traditional Chinese Medicine Syndrome, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangdong Provincial Hospital of Chinese Medicine, Guangdong Provincial Academy of Chinese Medical Sciences, Guangzhou, Guangdong 510006, China.

Abstract

Background: Huaier granule is an important medicinal fungus extract widely used in cancer treatment. Previous retrospective studies have reported its effectiveness in breast cancer patients, but the imbalanced baseline characteristics of participants could have biased the results. Therefore, this retrospective study aimed to examine the efficacy of Huaier granule on the prognosis of breast cancer patients.

Methods: In this single-center cohort study, breast cancer patients diagnosed and treated at the Guangdong Provincial Hospital of Chinese Medicine between 2009 and 2017 were selected. The data were retrospectively analyzed and divided into two groups according to whether the patients received Huaier granules. The propensity score matching (PSM) method was used to eliminate selection bias. The disease-free survival (DFS) and overall survival (OS) for these groups were compared using the Kaplan–Meier method and the Cox regression.

Results: This study included 214 early invasive breast cancer patients, 107 in the Huaier group and 107 in the control group. In the Kaplan–Meier analysis, the 2-year and 5-year DFS rates were significantly different in the Huaier group and control group (hazard ratio [HR], 0.495; 95% confidence interval [CI], 0.257–0.953; $P = 0.023$). The 2-year and 5-year OS rates were also significantly different (HR, 0.308; 95% CI, 0.148–0.644; $P = 0.001$). On multivariable Cox regression, Huaier granule was associated with improved DFS (HR, 0.440; 95% CI, 0.223–0.868; $P = 0.018$) and OS (HR, 0.236; 95% CI, 0.103–0.540; $P = 0.001$).

Conclusion: In this retrospective study, Huaier granules improved the DFS and OS of early invasive breast cancer patients, providing real-world evidence for further prospective studies on treating breast cancer with Huaier granules.

Keywords: Breast cancer; Prognosis; Huaier granule; Propensity score matching; Retrospective study; Clinical study

Introduction

In 2022, breast cancer was the most common female cancer in China, and there is an estimated 429,105 new cases.[1–2] For early, non-metastatic breast cancer, conventional treatments can be applied to improve disease-free survival (DFS) and overall survival (OS) of patients.[3] Chinese medicine (CM), developed over thousands of years in China, has played an adjunctive role during breast cancer treatment to alleviate adverse symptoms during conventional treatments and improve the quality of life of patients.[4]

Huaier (*Trametes robiniophila Murr.*) is a sandy-beige mushroom commonly used in CM for over 1600 years.[5] Previous studies have indicated that Huaier has potential anticancer effects[6] and it has been shown to inhibit cancer cell growth among different kinds of cancers.[7–9]

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Qianqian Guo and Yuting Peng contributed equally to this work.

Correspondence to: Qianjun Chen, Breast Department, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangdong Provincial Hospital of Chinese Medicine, Guangdong Provincial Academy of Chinese Medical Sciences, 55 Inner Ring West Road, Panyu District, Guangzhou, Guangdong 510006, China
E-Mail: cqj55@163.com

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Further, Huaier could inhibit the proliferation of breast cancer stem cells, induce programmed cell death, and reverse breast cancer stem cells by regulating multiple key signaling pathways.[10] Huaier granule (the aqueous product of Huaier extract) has been evaluated for its effectiveness for various cancers,[11] such as hepatocellular carcinoma[8,12,13] and gastric cancer.[14]

The effect of Huaier granule administration may depend on the molecular phenotype of the breast cancer being treated. For example, one prospective clinical study examined the use of Huaier granules among triple-negative breast cancer (TNBC) patients without showing statistical differences.[15] However, Huaier aqueous extract has been reported to suppress breast cancer cell proliferation by inhibiting estrogen receptor (ER)-α signaling.[16] There is currently insufficient evidence regarding whether Huaier granules benefit breast cancer patients, regardless of the hormone receptor status. Zhang *et al*[17] conducted a retrospective study involving 284 breast cancer patients with or without Huaier granules and demonstrated that patients with Huaier granules achieved longer DFS.

Further research is needed to confirm the Huaier's efficacy among breast cancer patients. Here, we conducted a retrospective real-world study and used the propensity score matching (PSM) to minimize the impact of confounding while examining the effect of Huaier granules combined with conventional treatment on the survival and prognosis of breast cancer patients.

Methods

Ethical approval

This single-center retrospective cohort study was approved by the Ethics Committee of the Guangdong Provincial Hospital of Chinese Medicine (GPHCM) (No. YE2021-187-01) before the commencement of the study. According to the requirements of the ethics committee, the annual follow-up review report and the final summary report of project completion should be submitted. The requirement for written informed consent was waived due to the retrospective nature of this study.

Patient selection

Patients with pathologically diagnosed breast cancer in GPHCM from January 1, 2009 to August 30, 2017 were considered. The inclusion criteria were as follows: (I) females aged 18–75 years; (II) pathologically diagnosed invasive breast cancer; (III) receipt of standard conventional treatment after breast cancer surgery; (IV) availability of complete medical records. The exclusion criteria were as follows: (I) patients diagnosed with a prior history of cancers; (II) those diagnosed with advanced breast cancer, carcinoma *in situ*, bilateral breast cancer, inflammatory breast cancer, malignant lobulated tumor, and angiosarcoma; (III) patients receiving Huaier granule but for less than 18 weeks (three courses);[18] (IV) lack of follow-up data.

Huaier granule, also known as Jinke Huaier granule, is a traditional CM approved by the National Medical Products Administration in cancer treatment in 1992. The prescription is 20 g orally three times a day for six weeks as a course of treatment for the adjuvant treatment of breast cancer. Eligible patients who met the inclusion and did not met the exclusion criteria were divided into the Huaier granule group and control group (without Huaier granule) according to whether the patients used Huaier granule (at least 18 weeks, equivalent to three courses) during cancer treatment.

Data collection and collation

Data were extracted from the hospital's internal medical records system in excel format. The extracted variables included age, clinical stage, histological grade, hormone receptor status (ER and progesterone receptor [PR] statuses), human epidermal growth factor receptor 2 (HER2) status, and conventional treatment settings (chemotherapy, radiation therapy, targeted therapy, and endocrine therapy).

The clinical staging of breast cancer is based on the American Joint Committee on Cancer 8th Edition Breast Cancer Staging System.[19] The definition for hormone receptor-positive is that the cancer cell is positive for one or both of the receptors (ER and PR), whereas the definition for ER positive or PR positive is that they have immunohistochemical (IHC) ≥1%.[20] However, the American Society of Clinical Oncology and the College of American Pathologists changed the cut-off of ER and PR positive definition from 10% to 1% in 2010.[21] Therefore, the status of these two markers was checked to ensure accuracy. HER2 positive (HER2$^+$) is defined as IHC (3+) with more than 10% complete membrane staining or confirmed with *in situ* hybridization.[22]

Further, whether the patients were prescribed the Huaier granules was also exported from the hospital's internal system, with the duration and dose information listed if the patients received Huaier granules. The patients included in our study have used Huaier granules since 2009.

Data were checked and normalized. If some mistake record was identified, the original medical record would be checked. Some variables were normalized, such as the histological grade was normalized into 0 (grade 1), 1 (grade 2), and 2 (grade 3) for further analysis. The proportion of missing data ranged from 1.7% to 17.3%. Multiple imputations were applied since these missing data were assessed as missing completely at random data.[23]

After data screening and collating, the follow-up information was exported from the Research Electronic Data Capture (REDCap, Tennessee, the United States) electronic system that we used to record follow-up information of breast cancer patients.

Study outcome and follow-up

The DFS and OS were assessed to evaluate the efficacy of Huaier granules. DFS was defined as the time from breast

cancer surgery to the first appearance of recurrence (including local and regional recurrence), metastasis, or death. OS was defined as the time from the surgical intervention of breast cancer to patient death from any cause.

The follow-up period started on the date of the breast cancer surgery and ended in March 2022. Methods of the follow-up approach included a review of the inpatient and outpatient medical records and telephone calls. The follow-up is conducted annually for the patients, and the specific follow-up date is calculated according to the surgery date of each patient. If the patient fails to answer the phone call three times, then the medical record system is checked to determine whether the patient has an event (such as metastasis lesions in imaging examination or pathologically confirmed metastasis lesions). In the second year, the phone call is still made; further, the medical records are checked. Loss of follow-up is defined as if the patients cannot obtain follow-up information through phone calls and medical record checks. Follow-up contents include whether the patients have recurrence or metastasis, or whether the patients have death events. Patients without follow-up data were excluded from this study.

Statistical analysis

Data were screened and analyzed by authors Qianqian Guo and Yuting Peng independently and then double-checked to ensure accuracy. PSM is a method of matching that attempts to allow for the assessment of the effect of an intervention in the absence of randomization.[24] PSM can be applied in observational cohort studies to reduce the effect of confounding bias.[24] The subjects in the two groups were selected based on the similar probability that came up after PSM.[24] The variables included in this PSM were histological grade, clinical stage, hormone receptor status, HER2 status, receipt of chemotherapy, receipt of radiation therapy, receipt of targeted therapy, and receipt of endocrine therapy. Patients were matched 1:1 using a caliper value of 0, and the option of "give priority to exact matches" in SPSS 26.0 (IBM Corp., Armonk, NY, USA) software was chosen, representing an exact match between the two groups.

For the baseline characteristics, the normality of the continuous variables (e.g., age) was examined by the Kolmogorov–Smirnov test. *t*-test and Wilcoxon rank sum test were conducted depending on whether the data represented a normal distribution. Binary variables were compared by chi-squared test. After PSM, DFS and OS were determined by Kaplan–Meier analysis and Cox proportional hazard regression model, and the survival outcomes of the Kaplan–Meier analysis were compared using the log-rank test. Hazard ratio (HR) and 95% confidence interval (CI) were reported, and P value <0.05 was considered statistically significant.

The software SPSS was applied for data analysis (including baseline analysis, PSM analysis, Kaplan–Meier analysis, and Cox regression), and the DFS and OS survival curve was performed using GraphPad Prism (Version 9.4.1; GraphPad Software Inc., San Diego, CA, USA).

Results

In total, medical records of 3901 patients with breast cancer were exported from the hospital, and 1862 patients were excluded according to the exclusion criteria [Figure 1]. Two hundred and forty-eight patients with missing follow-up data were also excluded. The median follow-up time was 86 months. After PSM, 214 patients were included, with 107 in the Huaier group and 107 in the control group. The baseline characteristics of the patients before and after PSM are summarized in Table 1. The histological grade, clinical stage, hormone receptor status, HER2 status, and treatment significantly differed between the Huaier group and the control group, but showed no significant differences after PSM.

After PSM, the 2-year DFS rate was 98.1% in the Huaier group and 93.5% in the control group, and the 5-year DFS rate was 94.4% in the Huaier and 85.0% in the control groups, with statistically significant differences (P = 0.023) [Figure 2A]. The 2-year OS rate was 99.1% in the Huaier group and 93.5% in the control group, and the 5-year OS rate was 98.1% in the Huaier group and 86.6% in the control group, which were also statistically significant (P = 0.001) [Figure 2B].

The multivariate Cox regression analysis showed that the patients who received Huaier granules were associated with improved DFS (HR = 0.440; 95% CI [0.223–0.868], P = 0.018) and OS (HR = 0.236; 95% CI [0.103–0.540], P = 0.001).

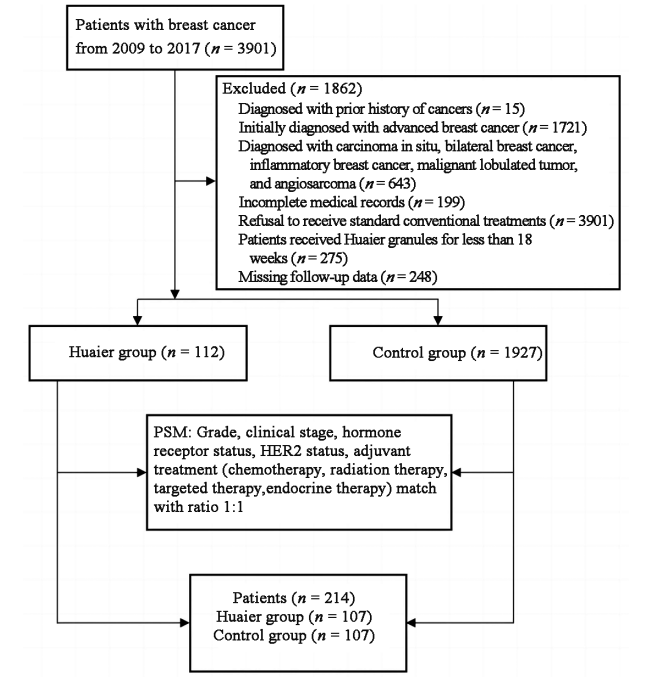

Figure 1: Flow diagram of participant selection. A total of 2039 patients were enrolled according to the predefined inclusion and exclusion criteria. Following PSM, 214 patients were included in the analysis, comparing 107 in the Huaier group and 107 in the control group. HER2: Human epidermal growth factor receptor 2; PSM: Propensity score matching.

Table 1: Baseline characteristics of breast cancer patients before and after PSM for the Huaier group and control group.

Characteristics	Before PSM				After PSM			
	Huaier group ($n = 112$)	Control group ($n = 1927$)	χ^2	*P* values	Huaier group ($n = 107$)	Control group ($n = 107$)	χ^2	*P* values
Age (years)	51.54 ± 9.60	50.00 ± 10.48	–1.152*	0.249	51.56 ± 9.55	51.96 ± 9.46	–0.138*	0.890
Grade			23.242	<0.001			0.000	1.000
1	5 (4.5)	157 (8.1)			3 (2.8)	3 (2.8)		
2	43 (38.4)	1101 (57.1)			42 (39.3)	42 (39.3)		
3	64 (57.1)	669 (34.7)			62 (57.9)	62 (57.9)		
Clinical stage			28.234	<0.001			0.000	1.000
Stage I	26 (23.2)	662 (34.4)			26 (24.3)	26 (24.3)		
Stage II	42 (37.5)	903 (46.9)			40 (37.4)	40 (37.4)		
Stage III	44 (39.3)	362 (18.8)			41 (38.3)	41 (38.3)		
Hormone receptor status			137.350	<0.001			0.000	1.000
Negative	73 (65.2)	359 (18.6)			69 (64.5)	69 (64.5)		
Positive	39 (34.8)	1568 (81.4)			38 (35.5)	38 (35.5)		
HER2 status			19.480	<0.001			0.000	1.000
Negative	65 (58.0)	1474 (76.5)			61 (57.0)	61 (57.0)		
Positive	47 (42.0)	453 (23.5)			46 (43.0)	46 (43.0)		
Chemotherapy			8.149	0.017			0.000	1.000
No	4 (3.6)	232 (12.0)			4 (3.7)	4 (3.7)		
Neoadjuvant	9 (8.0)	184 (9.5)			7 (6.5)	7 (6.5)		
Adjuvant	99 (88.4)	1511 (78.4)			96 (89.7)	96 (89.7)		
Radiation therapy			4.914	0.027			0.000	1.000
No	42 (37.5)	930 (48.3)			39 (36.4)	39 (36.4)		
Yes	70 (62.5)	997 (51.7)			68 (63.6)	68 (63.6)		
Targeted therapy			24.437	<0.001			0.000	1.000
No	72 (64.3)	1596 (82.8)			69 (64.5)	69 (64.5)		
Yes	40 (35.7)	331 (17.2)			38 (35.5)	38 (35.5)		
Endocrine therapy			114.923	<0.001			0.000	1.000
No	70 (62.5)	375 (19.5)			67 (62.6)	67 (62.6)		
Yes	42 (37.5)	1552 (80.5)			40 (37.4)	40 (37.4)		

Data are expressed as *n* (%) or mean ± SD. HER2: Human epidermal growth factor receptor 2; PSM: Propensity score matching; SD: Standard deviation. *Z score results from the Wilcoxon rank sum test.

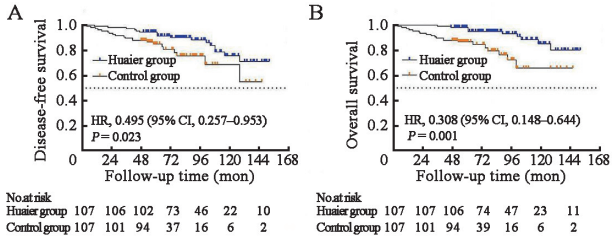

Figure 2: Kaplan–Meier survival curve of early invasive breast cancer patients after PSM. The 2-year and 5-year DFS and OS rates were significant differences between the Huaier group and the control group. (A) DFS survival and (B) OS survival. CI: Confidence interval; DFS: Disease-free survival; HR: Hazard ratio; OS: Overall survival; PSM: Propensity score matching.

Discussion

This study applied the PSM method to explore the efficacy of Huaier granules among breast cancer patients using the PSM method. After PSM, the DFS and OS showed a significant difference between the Huaier group and the control group. Before PSM, the Huaier group had more grade III, stage III, hormone receptor negative, and HER2+ patients. After PSM, the baseline characteristics, including pathology characteristics and the treatment options, showed no significant difference, minimizing the confounding effects of them.

The specific regimen and duration of the chemotherapy, radiation therapy, targeted therapy, and endocrine therapy were not extracted since these treatments are tailored according to the pathological subtypes[25] and the patient's situation. Involving too many detailed indicators in PSM may lead to invalid matches and reduce the sample size. Indicator selection is critical in PSM,[26] but also challenging. The research team has discussed this issue thoroughly and referenced existing published literature.[27] Therefore, it is critical to balance including enough relevant factors to reduce bias and not including too many factors that may lead to invalid matches.

Previous studies have suggested that Huaier extract could increase the antitumor effect of paclitaxel therapy in breast cancer cells,[28] sensitize breast cancer cells to radiation therapy,[29] and potentially inhibit angiogenesis by targeting tumor-associated macrophages.[30] A meta-analysis that included 27 trials involving 2562 patients with breast cancer indicated that the combination of conventional treatment and Huaier granule prolonged 2-year and 5-year DFS and OS,[31] similar to our study's DFS and OS

results. This meta-analysis also mentioned the significant heterogeneity among the included trials, and the duration of the treatment may be one reason. The duration of the included studies varied from three weeks to two years, indicating that the duration of Huaier granules for breast cancer has not been well defined. Further, this meta-analysis reported that the immune function of patients was also enhanced by increased percentages of cluster of differentiation 3^+ ($CD3^+$), cluster of differentiation 4^+ ($CD4^+$), and natural killer cells and $CD4^+$ cell/ cluster of differentiation 8^+ ($CD8^+$) cell ratio.

TNBC is regularly related to a poor prognosis compared to other breast cancer subtypes.[32] Preclinical study suggested that Huaier could induce immunogenic cell death by promoting cell surface calreticulin exposure in TNBC.[33] Further, the polysaccharides of Huaier (the major components of Huaier) could inhibit epithelial–mesenchymal transition in TNBC cells by inducing autophagy to degrade Snail protein.[34] Wang *et al*[15] conducted a clinical study that involved 201 TNBC patients. Patients were randomly allocated to Huaier granules or a control group (without receiving any traditional CM preparations), and the 5-year DFS and OS were not statistically significant. However, subgroup analysis indicated that the stage III patients benefited from Huaier granules. Further, this study divided the 101 patients in the Huaier group to receive Huaier granules for six months and 18 months, and found that patients in the longer duration (18 months of medication) showed a lower possibility of disease progression. As mentioned, how long the Huaier granules could benefit breast cancer is unknown, and the effective duration needs further exploration.

Effective maintenance therapy for TNBC has been previously reported. For example, the Sun Yat-sen University Cancer Center-001 (SYSUCC-001) study[35] indicated that 1-year low-dose capecitabine could significantly improve 5-year DFS in early stage TNBC who received standard treatment. Although the low-dose capecitabine maintenance was well tolerated, the patients still experienced side effects, including hand-foot syndrome, diarrhea, and leukopenia. The adjuvant olaparib was associated with longer survival free of recurrent invasive or distant disease among patients with high-risk, $HER2^-$ early breast cancer with *BRCA* 1 or *BRCA* 2 mutation,[36] but also with grade 3 or higher adverse events, including anemia, neutropenia, and leukopenia. For Huaier granules, Chen *et al*[12] have reported that the main adverse event was liver dysfunction, but without significant differences when compared to the control group (no further treatment). Further, this study[12] also reported that 98.5% of patients in the Huaier group had good compliance. Therefore, whether Huaier granule is an option for TNBC needs further research. A large prospective randomized clinical study, such as the clinical trial conducted by Fudan University (No. NCT04790305), is anticipated. Further, developing more efficient molecular targets and novel biomarkers for TNBC treatment is also urgent for oncologists.[37]

Some strengths and limitations should be acknowledged. This study applied the PSM method to adjust the imbalance baseline, thereby reducing the effect of confounding. However, the sample size was reduced after PSM, precluding an assessment of the efficacy of Huaier granules at different durations. Some approaches, such as oversampling and replacement methods, can be applied to mitigate the influence of a small sample size after PSM.[38] Previous research also recommended that the PSM can be used with any algorithm and one-to-one matching ratio in moderately small samples (N = 100–300), and this study's sample size is in this range.[39] Besides, the nature of the retrospective study and the single-center data also limited the generalizability of the results. Huaier granule is commonly used in breast cancer treatment with standard duration, but it is challenging to observe patient compliance and the safety of using Huaier granules with a retrospective nature. Whether the patients used the drug according to the prescription is unclear. Further, the interpretation of PSM results should be cautious since the unmatched information may result in imprecise estimates and loss of statistical power.[40] Therefore, this study provided real-world evidence for future study, and a well-designed prospective study is needed.

In conclusion, our results indicated that Huaier granules improved the DFS and OS of early invasive breast cancer patients and suggested the potential benefit of Huaier granules among these populations. This study provided real-world data support for future prospective studies, and further study about optimizing the utilization of Huaier granules among breast cancer patients is essential.

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Conflicts of interest

None.

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