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ORIGINAL RESEARCH

Long-Term Outcomes of Traditional Chinese Medicine in the Treatment of Granulomatous Lobular Mastitis: A Two-Year Follow-Up Study on Recurrence and New Occurrence Rates with Analysis of Risk Factors

Ciyi Hua [ID][1], Feifei Li [ID][1], Youyang Shi[2], Yuan Xu[1], Mengdie Zhu[1], Yang Wang[1], Xiqiu Zhou[2], Sheng Liu[1,3]

[1]Institute of Chinese Traditional Surgery, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, People's Republic of China; [2]Department of Breast Surgery, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, People's Republic of China; [3]Graduate School, Shanghai University of Traditional Chinese Medicine, Shanghai, People's Republic of China

Correspondence: Sheng Liu, Institute of Chinese Traditional Surgery, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, 200032, People's Republic of China, Tel +86 18917763005, Fax +86-64385700, Email shengliu@shutcm.edu.cn

Background: Patients with clinically cured granulomatous lobular mastitis (GLM) still face a high probability of recurrence and new occurrence.

Purpose: To evaluate the long-term efficacy of traditional Chinese medicine (TCM) in treating GLM and to hypothesize potential risk factors for recurrence or new occurrence.

Patients and Methods: A retrospective analysis was conducted on GLM patients treated with TCM at Longhua Hospital affiliated with Shanghai University of Traditional Chinese Medicine from January 2016 to July 2021. We analyzed general data, two-year recurrence and new occurrence rates, and 12 risk factors associated with recurrence or new occurrence.

Results: This cross-sectional study included 261 GLM patients with an average age at onset of 31.95 years (primarily aged 31–40). The two-year recurrence rate for GLM was 1.53%, and the new occurrence rate was 4.21%. Univariate and multivariate conditional logistic regression analyses revealed that a history of inverted nipples was associated with the risk of both recurrence and new occurrence of GLM (HR = 8.672, 5.375, $P < 0.05$), and menstrual irregularity was related to a higher risk of recurrence (HR = 13.172, $P < 0.001$).

Conclusion: A history of inverted nipples is identified as a potential risk factor associated with the long-term recurrence and new occurrence of GLM, while menstrual irregularity is associated with recurrence. Despite this, patients with GLM undergoing TCM demonstrate low rates of long-term recurrence and new occurrence after achieving clinical cure, underscoring the effectiveness of TCM. This study lays the groundwork for a long-term effectiveness strategy to guide future GLM treatments.

Keywords: granulomatous lobular mastitis, GLM, recurrence, new occurrence, risk factor

Introduction

Granulomatous lobular mastitis (GLM) is a benign chronic inflammatory breast disease that primarily affects non-lactating women of childbearing age, which was first described by Kessler and Wolloch.[1] A characteristic pathological feature of GLM is the presence of non-caseous granulomatous lesions located around the terminal duct lobular units, which are predominantly infiltrated by neutrophils, lymphocytes, and giant cells.[2,3] Clinical manifestations of GLM typically include a painful breast mass, erythema and swelling of the breast skin, nipple retraction, nipple discharge, and enlargement of axillary lymph nodes.[4] Current treatments for GLM, such as antibiotic therapy, surgical intervention, corticosteroids, and immunosuppressive agents, have shown limited effectiveness and are linked to potential adverse

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effects. Furthermore, there is a risk of disease relapse upon discontinuation of these therapies.[5,6] Given the extensive lesion involvement, chronic nature of the disease, and high rate of recurrence, GLM places a significant psychological burden on affected patients.

Traditional Chinese Medicine (TCM) has a well-established history of treating chronic inflammatory conditions due to its unique perspectives on disease and therapeutic principles.[7] Clinical practice has shown promising therapeutic effects of TCM in the treatment of GLM.[8] A previous study indicated that a nine-month course of TCM treatment resulted in a cure rate of 63%, comparable to the 68% cure rate achieved with surgical treatment. Additionally, the recurrence rate within one year post-recovery for the TCM treatment group was significantly lower at 6.2% compared to 18% for surgical treatment.[9] The effectiveness of integrating TCM with surgical procedures has been supported by recent studies.[10] Current scientific investigations have utilized network pharmacology and molecular docking techniques to explore the multi-target and multi-pathway properties of TCM.[11] In vivo experiments have also demonstrated the anti-inflammatory and antioxidant effects of specific Chinese herbal ingredients in treating GLM,[12] providing a scientific basis for TCM treatment. Consequently, TCM treatment offers new insights into enhancing treatment efficacy and reducing side effects. However, a subset of patients may experience recurrence (in the previous lesion) or new occurrence (in the new lesion) after initial recovery, especially within 2 years. Given that the observation period after clinical cure of GLM typically ranges from six months to one year, it is essential to monitor over a longer timeframe.

In this cross-sectional study, a retrospective analysis was used to collect and analyze data from 261 GLM patients who achieved clinical cure after TCM treatment for over 2 years. This study was conducted to assess the rate of recurrence or new occurrence in GLM patients treated with TCM after long-term clinical recovery and to determine the potential risks associated with recurrence or new occurrence. The aim of this study is to provide a feasible basis for the long-term efficacy of TCM in treating GLM, thereby expanding the range of clinical treatment options.

Materials and Methods
Study Design and Participants

A retrospective cross-sectional study was conducted to ascertain the two-year recurrence and new occurrence rates of GLM patients receiving TCM treatment after clinical cure. Female patients diagnosed with GLM who sought treatment at Longhua Hospital affiliated with the Shanghai University of Traditional Chinese Medicine between January 2016 and July 2021 were enrolled through strict inclusion and exclusion criteria in this study. The procedures followed the principles outlined in the Declaration of Helsinki. As this study was retrospective, the Ethics Committee waived the need for patient consent. We also declared that all patient data will be kept confidential and will not compromise the interests of the patients.

Inclusion criteria: (1) Pathologically diagnosed with GLM (based on the pathological diagnosis of Shanghai Longhua Hospital); (2) Patients who received exclusively TCM treatment; (3) Clinically cured patients, as defined by the "Consensus on Traditional Chinese Medicine Diagnosis and Treatment of Granulomatous Lobular Mastitis (2021 Edition)",[13] where clinical symptoms have resolved, the original inflammatory lesions are not palpable, and ulcers or wounds have healed, although scattered minuscule lesions may still be visible on imaging (based on the ultrasound imaging of Shanghai Longhua Hospital); (4) Patients who have been clinically cured 2 years and more.

Exclusion criteria: (1) Patients who were clinically uncured and discontinued TCM therapy; (2) Patients who have been clinically cured for less than 2 years; (3) Patients enrolled in other drug trials.

Recurrence criteria: In patients who clinically cured, the original lesion reappears with symptoms such as redness, swelling, heat, pain, pus formation, ulceration or the lesion is visible on ultrasound, and other causes other than GLM are excluded; New occurrence criteria: In patients who clinically cured, a new lesion outside the original lesion area in the breast (including the contralateral breast), which is not the result of direct spread from the original lesion area, and which excludes causes other than GLM.[13]

The formula of traditional Chinese medicine is (addition and subtraction of homemade formula): Radix Bupleuri 6 g, Radix Scutellariae 9 g, Radix Curcumae 12 g, Radix Paeoniae Alba 12 g, Rhizoma Smilacis Glabrae 15 g, Radix Semiaquilegiae 15 g, Radix Camellia sinensis 15 g, raw Crataegi Folium 15 g, Herba Taraxaci 30 g, Radix Pulsatillae 15

g, Caulis Lonicerae 15 g, Herba Violae 15 g, Herba Artemisiae Scopariae 9 g, and Herba Sedi 30 g. Oral application of traditional Chinese medicine continued until recovery.

Data Collection

The researchers retrospectively accessed information collected during the previous medical visits of the included GLM patients, including onset-related information, historical treatment data, and medical records after clinical recovery. The clinical data consisted of three components: (1) General information of patients, including age (years), administrative regions (distinguished according to the seven geographical divisions of China), height (m), and weight (kg), reproductive history; (2) Primary observation items, such as instances of recurrence or new occurrence, the timing of initial disease occurrence, frequency of recurrence or new occurrence, and the duration of each treatment course; (3) Risk factors related to the recurrence or new occurrence of GLM, including Body mass index (BMI) (calculated as weight (kg)/ [height (m)]^2), history of inverted nipples, history of nipple discharge, breastfeeding status (including lactation difficulties and history of lactation massage), course of the disease (including history of breast trauma), prolactin levels, menstrual situation (abnormalities of the menstrual cycle, menstrual periods), duration of Traditional Chinese patent medicine usage after clinical recovery, history of past drug use and history of other diseases.

Statistical Analysis

In this study, the collected data of GLM patients were analyzed using the IBM SPSS Statistics 26.0 software. The descriptive statistics were employed to analyze the clinical data of patients, with measurement data presented as mean ± standard deviation (mean ± s). The count data was summarized as frequency and percentage. A Chi-square test was utilized to analyze the recurrence or new occurrence rate. A multivariate logistic regression analysis was conducted to explore the association between the risk factors for recurrence or new occurrence. Adjusted HRs and their corresponding 95% CIs were obtained using binary conditional multivariable logistic regression analysis. $P<0.05$ from two-tailed tests was considered statistically significant.

Results

Characteristics of Patients

Data from 475 patients were evaluated, and patients who had met any of the exclusion criteria were excluded (n = 142), patients who had missing data related to risk factors were excluded (n = 72). Based on these rigorous selection criteria, a total of 261 GLM patients were ultimately identified for subsequent analyses. The patients' selection process is shown in Figure 1. The clinical data, including age, administrative regions, BMI, history of inverted nipples, history of nipple discharge, reproductive history, breastfeeding status, history of lactation massage, hyperprolactinemia (HPRL), history of breast trauma, duration of Traditional Chinese patent medicine usage after first clinical recovery and duration of first treatment course are summarized in Table 1.

The average age of patients who first diagnosed with GLM in our study was 31.95 ± 4.54 years and a majority of patients (58.6%) fell within the 31–40 age range. All the patients with recurrence and new occurrence of GLM were before the age of 40. Most of the patients (n = 242) were from East China, 8 were from Southwest China, 4 each from Central China and Northwest China, and 1 each from North China, Northeast China, and South China. Among them, all of the patients who had recurrence and new occurrence were from East China.

Approximately 66.7% of the patients had a BMI below 24. The prevalence of nipple inversion was similar between patients with and without this symptom, and only 77 (29.5%) patients reported a history of nipple discharge. Only 8 patients (3.1%) had never given birth, while the majority had a history of childbearing. One patient had a recurrence, and two patients had a new occurrence after the second birth. Among the patients, 59.4% reported having problems with breastfeeding, and 32.2% of them had the history of lactation massage to facilitate milk ejection. The prevalence of HPRL was found to be low (7.3%), with the majority of them (93.1%) maintaining regular menstrual cycles. As a primary etiological factor, the history of breast trauma was identified as the cause of GLM in 117 patients in this
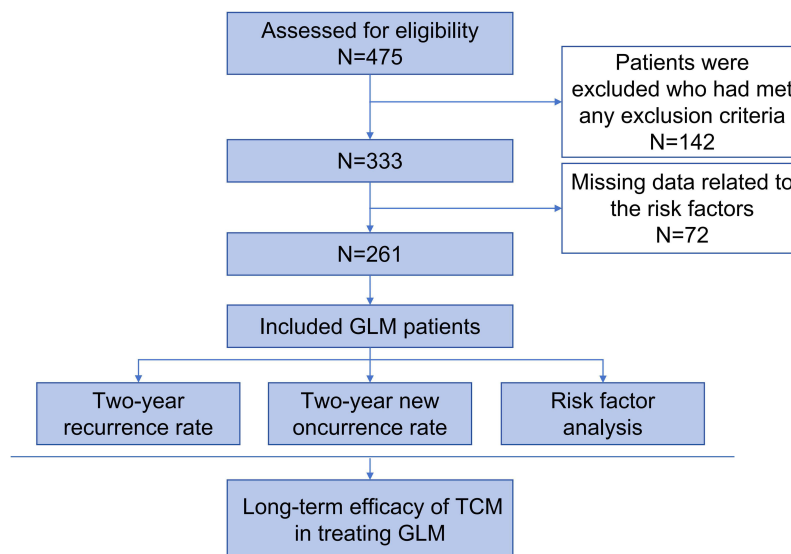
Figure 1 Flow chart of the study.

study. The time of first TCM treatment course in our hospital was 12.10 ± 7.25 months, 108 patients (41.4%) continued the treatment of Traditional Chinese patent medicine to consolidate their condition after clinical recovery.

The Two-Year Recurrence and New Occurrence Rates of Patients with GLM

Among the 261 patients, the recurrence rate was 3.45%, and the new occurrence rate was 6.13% (Figure 2A). Specifically, 4 patients (1.53%) experienced a recurrence and 11 patients (4.21%) had a new occurrence within two years. The number of patients who relapsed or presented with new occurrence two years after clinical recovery was 5

Table 1 Characteristics of Patients

	All N=261 (%)	Non-Recurrence and New Occurrences N=236 (%)	Recurrence N=9 (%)	New Occurrence N=16 (%)
Age (Mean± SD)	31.95 ± 4.54	31.99 ± 4.59	32 ± 4.18	31.36 ± 4.44
≤ 30	101 (38.7%)	94 (39.8%)	2 (22.2%)	5 (31.2%)
31–40	153 (58.6%)	130 (55.1%)	7 (77.8%)	11 (68.8%)
≥ 40	7 (2.7%)	12 (5.1%)	0	0
Administrative regions				
East	242 (92.7%)	217 (92.0%)	9 (100%)	16 (100%)
North	1 (0.4%)	1 (0.4%)	0	0
Northeast	1 (0.4%)	1 (0.4%)	0	0
Central	4 (1.5%)	4 (1.7%)	0	0
South	1 (0.4%)	1 (0.4%)	0	0
Southwest	8 (3.1%)	8 (3.4%)	0	0
Northwest	4 (1.5%)	4 (1.7%)	0	0
BMI				
≤ 23.9	174 (66.7%)	161 (68.2%)	5 (55.6%)	8 (50%)
≥ 24	87 (33.3%)	75 (31.8%)	4 (44.4%)	8 (50%)
History of inverted nipples				
Yes	129 (49.4%)	111 (47.0%)	8 (88.9%)	13 (81.3%)
No	132 (50.6%)	125 (53.0%)	1 (11.1%)	3 (18.7%)

(Continued)

Table 1 (Continued).

	All N=261 (%)	Non-Recurrence and New Occurrences N=236 (%)	Recurrence N=9 (%)	New Occurrence N=16 (%)
History of nipple discharge				
Yes	77 (29.5%)	68 (28.8%)	2 (22.2%)	7 (43.8%)
No	184 (70.5%)	168 (71.2%)	7 (77.8%)	9 (56.2%)
Reproductive history				
0	8 (3.1%)	7 (3.0%)	1 (11.1%)	0
1	203 (77.8%)	184 (78.0%)	6 (66.7%)	13 (81.3%)
≥ 2	50 (19.1%)	45 (19.0%)	2 (22.2%)	3 (18.7%)
Lactation difficulties				
Yes	155 (59.4%)	143 (60.6%)	6 (66.7%)	6 (37.5%)
No	106 (40.6%)	93 (39.4%)	3 (33.3%)	10 (62.5%)
History of lactation massage				
Yes	84 (32.2%)	80 (33.9%)	1 (11.1%)	3 (18.7%)
No	177 (67.8%)	156 (66.1%)	8 (88.9%)	13 (81.3%)
Hyperprolactinemia				
Yes	19 (7.3%)	19 (7.3%)	1 (11.1%)	2 (33.3%)
No	242 (92.7%)	242 (92.7%)	8 (88.9%)	14 (66.7%)
History of breast trauma				
Yes	120 (46%)	108 (45.8%)	2 (22.2%)	10 (62.5%)
No	141 (54%)	128 (54.2%)	7 (77.8%)	6 (37.5%)
Menstrual irregularity				
Yes	18 (6.9%)	13 (5.5%)	4 (44.4%)	1 (6.2%)
No	243 (93.1%)	223 (94.5%)	5 (55.6%)	15 (93.8%)
Duration of Traditional Chinese patent medicine usage				
< 6 months	153 (58.6%)	136 (57.6%)	6 (66.7%)	11 (68.8%)
≥ 6 months	108 (41.4%)	100 (42.4%)	3 (33.3%)	5 (31.2%)
Duration of first treatment course (Mean± SD)	12.10 ± 7.25	12.23 ± 7.41	11.98±4.25	10.24±6.18

(1.92%) (Figure 2B). The recurrence-free survival probability of patients with GLM after clinical recovery within two years was initially high at 98%, gradually decreasing to approximately 95% within 24 months, indicating the majority of patients sustained a lasting response to treatment over the two years period (Figure 2C). The probability of new occurrence-free survival decreases from the initial 97% to approximately 87% at 24 months (Figure 2D). These findings suggest a progressive decline in survival probabilities over time, indicating an elevated risk of disease recurrence or new occurrence with the passage of time since clinical recovery.

Risk Factor Analysis of Recurrence and New Occurrence

The univariate logistic regression analysis identified potential risk factors that were associated with the recurrence of GLM patients who achieved clinical cure after TCM treatment. Notably, a history of inverted nipples emerged as a significant risk factor in univariate analysis (HR = 11.998, 95% CI: 1.129–127.539, P=0.039). This association remained statistically significant after further adjustment in the multivariate model (HR = 8.672, 95% CI: 1.028–73.162, P=0.047), indicating a strong correlation with recurrence. Menstrual irregularity also emerged as a significant predictor in both univariate (HR = 25.614, 95% CI: 3.369–194.747, P=0.002) and multivariate analyses (HR = 13.172, 95% CI: 2.962–58.571, P<0.001), suggesting a notable increase in the risk of recurrence (Table 2).

As for the new occurrence, a history of inverted nipples was still associated with a heightened risk of new occurrence (HR = 5.375, 95% CI: 1.384–20.875, P = 0.015) in the univariate analysis. This association persisted in the multivariate
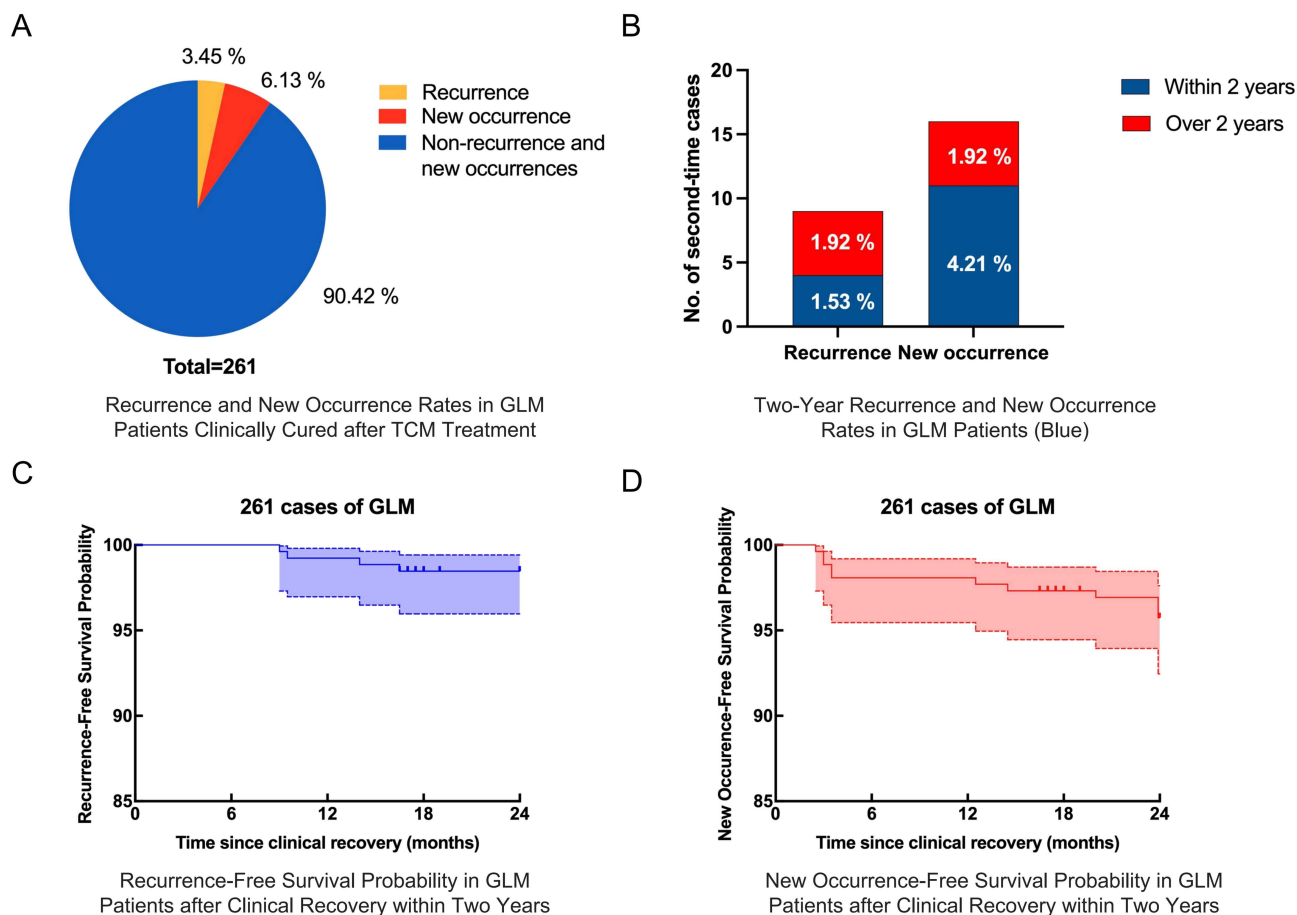
A

Recurrence and New Occurrence Rates in GLM
Patients Clinically Cured after TCM Treatment

B

Two-Year Recurrence and New Occurrence
Rates in GLM Patients (Blue)

C

Recurrence-Free Survival Probability in GLM
Patients after Clinical Recovery within Two Years

D

New Occurrence-Free Survival Probability in GLM
Patients after Clinical Recovery within Two Years

Figure 2 The recurrence and new occurrence rate of clinical cure GLM patients who received TCM treatment (**A**), the two-year recurrence and new occurrence rates of patients with GLM (blue) (**B**), the recurrence-free survival probability (**C**) and the new occurrence-free survival probability (**D**) of GLM patients after clinical recovery within two years.

analysis, indicating an independent predictor (HR = 4.949, 95% CI: 1.366–17.926, *P* = 0.015). Although lactation difficulties did not reach statistical significance in the univariate model (HR = 0.428, 95% CI: 0.121–1.507, *P* = 0.186), the multivariate model suggested a potential trend towards significance (HR = 0.382, 95% CI: 0.132–1.104), with a *P*-value just above the conventional threshold for significance (*P* = 0.076) (Table 3).

Evaluation for Safety

Patients with abnormalities in blood counts, liver and kidney function have been excluded before treatment. During the TCM treatment period, no obvious adverse reactions were found in all patients.

Discussion

GLM is a persistent chronic inflammatory breast disease with a notable incidence rate and a prevalence of approximately 3.5% in China.[4,14] It is characterized by frequent recurrences, posing a significant challenge to effective management. The patient population affected by GLM predominantly comprises women of childbearing age, many of whom have a history of pregnancy and lactation.[15] Our findings offer a detailed analysis of patient characteristics, highlighting the demographic and clinical profiles that predominate in GLM presentations. The GLM patients average age in our study was 32 years old, only 8 patients (3.1%) had never given birth. These results are consistent with those previously reported. Although our study observed that patients experiencing recurrence and new occurrence of GLM were all from the East China region, it is important to note that due to geographical location, the majority of our patient base originates

Table 2 Univariate and Multivariate Logistic Regression Analysis for Predictors of GLM Recurrence

Variables	Recurrence			
	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (y)	0.97 (0.809–1.162)	0.737		
BMI	1.319 (0.235–7.404)	0.753		
History of inverted nipples	11.998 (1.129–127.539)	0.039*	8.672 (1.028–73.162)	0.047
History of nipple discharge	0.669 (0.1–4.463)	0.678		
Reproductive history	0.902 (0.175–4.639)	0.902		
Lactation difficulties	4.587 (0.625–33.647)	0.134		
History of lactation massage	0.261 (0.027–2.572)	0.25		
Hyperprolactinemia	0.597 (0.043–8.217)	0.7		
History of breast trauma	0.453 (0.075–2.736)	0.388		
Menstrual irregularity	25.614 (3.369–194.747)	0.002*	13.172 (2.962–58.571)	<0.001
Duration of Traditional Chinese patent medicine usage	0.439 (0.072–2.671)	0.372		
Duration of first treatment course	0.951 (0.822–1.099)	0.493		

Note: *P < 0.05 in all risk factors.

Table 3 Univariate and Multivariate Logistic Regression Analysis for Predictors of GLM New Occurrence

Variables	New Occurrence			
	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (y)	0.947 (0.836–1.074)	0.397		
BMI	2.49 (0.808–7.673)	0.112		
History of inverted nipples	5.375 (1.384–20.875)	0.015*	4.949 (1.366–17.926)	0.015
History of nipple discharge	1.548 (0.491–4.879)	0.455		
Reproductive history	1.367 (0.462–4.045)	0.573		
Lactation difficulties	0.428 (0.121–1.507)	0.186	0.382 (0.132–1.104)	0.076
History of lactation massage	0.487 (0.102–2.321)	0.366		
Hyperprolactinemia	1.065 (0.176–6.421)	0.946		
History of breast trauma	1.868 (0.588–5.936)	0.289		
Menstrual irregularity	0.654 (0.067–6.38)	0.715		
Duration of Traditional Chinese patent medicine usage	0.689 (0.202–2.35)	0.552		
Duration of first treatment course	0.937 (0.85–1.033)	0.19		

Note: *P < 0.05 in all risk factors.
Abbreviations: GLM, Granulomatous lobular mastitis; TCM, Traditional Chinese Medicine; BMI, body mass index; HPRL, hyperprolactinemia.

from this area. The number of patients from other regions is inherently limited, which restricts our ability to assess whether the geographical location influences the long-term efficacy of TCM treatment for GLM.

There is currently no clear consensus on the treatment approach for GLM. Conservative treatments primarily include the use of antibiotics or corticosteroids. However, antibiotic therapy has been linked to unfavorable outcomes, while the use of corticosteroids is hindered by potential adverse effects and a high risk of recurrence after cessation, limiting its long-term efficacy.[16,17] Consequently, surgical intervention remains one of the principal treatment modalities for GLM for its shorter treatment duration, while it may result in compromised cosmetic outcomes and a risk of recurrence.[5] In the literature, recurrence rates of GLM were reported 15.4–24.8%.[18,19] Consequently, many young women of childbearing age consider surgery as a final option, leading to an interest in TCM as an alternative for treating GLM. Our group have demonstrated that TCM offers unique benefits in terms of recurrence rate (6.2%), quality of life, incidence of adverse reactions, breast aesthetics, and patient satisfaction through a 1-year follow-up study.[9] In later clinical practice, it has

been observed that despite achieving clinical recovery, recurrence and new occurrence (usually in the contralateral breast) persist, especially within 2 years. This cross-sectional study provides a preliminary overview of the long-term outcomes of TCM interventions in the management of GLM.

There is a lack of a certain definition of GLM in ancient literatures. Based on its unique clinical manifestations and pathogenesis, Professors Gu Bohua and Lu Deming of the Shanghai School of Gu's Surgery proposed the name "acne breast carbuncle" in 1980.[18] The disease initially presents with nipple deformities or mammary ductal dilation, leading to structural changes. Subsequently, repressed emotions result in liver Qi stagnation and impaired Qi-blood circulation, culminating in mass formation. Chronic stagnation then transforms into heat, causing tissue necrosis and suppuration, and eventually rupturing. The conservative TCM therapeutic approach primarily entails "soothing the liver" to vent liver Qi and clear liver fire, as well as 'dispelling stasis and activating blood, resolving phlegm and dispersing masses' to promote the resolution of the nodules. Our TCM formula is built on this principle of treatment.

GLM is generally recognized as an autoimmune disease involving humoral and cell-mediated immunity.[2,20] Damage to the epithelium lining of ducts (possibly secondary to retention of ductal secretions) may lead to the efflux of ductal contents from the lumen into the surrounding lobular connective tissue, causing local inflammation. This process facilitates the migration of lymphocytes and macrophages to the periductal zones, resulting in the formation of non-caseating granulomas.[21] Recent experimental studies have unveiled the therapeutic efficacy of TCM in treating GLM through modulating immune functions and resisting inflammation. Specifically, these studies have indicated that TCM can reduce autoimmune and inflammatory responses by regulating the $CD4^+/CD8^+$ ratio in local inflammatory tissues;[22,23] correcting the body's immune disorders by rectifying the dysfunctional balance of Th1/Th2 cells, which can help to clear inflammation and control disease progression;[24,25] and exerting anti-inflammatory effects by down-regulating the expression of inflammatory factors such as IL-6, IL-18, and IL-1β.[25,26] Most of the drugs used in TCM for the treatment of GLM are heat-clearing and detoxifying drugs, and the majority of the herbs in our study have the functions of inhibiting inflammation and regulating immunity. Specifically, the active components of Radix Bupleuri can inhibit the activation of inflammatory cells by regulating the dynamic balance of Th1/Th2/Treg, and enhance the phagocytosis of macrophages to improve the inflammatory state.[27,28] Baicalin has been shown to modulate the balance of Th17/Treg cells, and inhibits mRNA expression of TNF-α, IL-6, and IL-13 by alleviating inflammation.[29,30] These mechanisms of other herbs have been experimentally validated to suppress autoimmune diseases and inflammatory responses.[31–33] The molecular mechanisms of these drugs provide a scientific basis while being consistent with the concept of TCM formulation.

In our study, all patients achieved clinical cure of GLM with TCM treatment, demonstrating a significantly lower two-year recurrence rate of 1.53% compared to conventional treatment modalities documented in existing literature.[19,34] A parallel retrospective analysis of 102 cases with GLM also revealed that treatments comprising oral corticosteroids, antibiotics therapy, surgical drainage of open abscesses, and percutaneous needle aspiration resulted in an aggregate recurrence rate of 11.8% over a median follow-up period of 14 months.[35] This suggests that TCM may have a certain efficacy in preventing the recurrence of GLM in long-term. It is worth noting that there is very limited data on the new occurrence of GLM after clinical recovery. Our study showed a higher new occurrence in the unaffected breast (6.13%), with a two-year new occurrence rate standing at 4.21%. This unique finding may serve as a marker for people to assess the effectiveness of disease management strategies after GLM is clinically cured.

This study also investigates the potential risk factors that may lead to recurrence and new occurrence. Our findings suggest that a history of inverted nipples may serve as a risk factor for both recurrence and new occurrence in this patient population, aligning with existing literature.[36]

Inverted nipple is a congenital structural abnormality that aggravates the obstruction of the milk ducts. Even after clinical cure, the existence of this structure will still increase the risk of recurrence or new recurrence. Multivariate analysis highlights the increased susceptibility to recurrence in patients with menstrual irregularities. These patients are tend to have abnormalities in the menstrual cycle and menstrual periods. Menstrual disorders are linked to endocrine dysregulation and may play a role in the etiology of GLM.[15] Additionally, among patients experiencing a new occurrence, 62.5% reported lactation difficulties. Inadequate breastfeeding can lead to the accumulation of residual

milk in the mammary ducts, while nipple inversion can worsen ductal obstruction and tension, ultimately triggering an inflammatory immune response and causing GLM.

HPRL has been correlated with the occurrence of GLM and has been identified as a risk factor for its recurrence.[37,38] Existing literature highlights that patients with HPRL are more likely to experience relapse.[38] However, our study did not establish a direct correlation between HPRL and the recurrence or new occurrence of GLM, as only 19 (7.3%) patients exhibited HPRL. These patients received extended bromocriptine therapy and maintained the treatment regimen after achieving clinical recovery. The reason for the unobserved correlation may be attributed to incomplete monitoring of prolactin levels due to missing historical data, with many patients not having a prolactin assessment at the time of their first visit. Furthermore, continuous bromocriptine therapy may have consistently normalized PRL levels, potentially reducing its likelihood as a recurring risk factor.

Breast trauma has been identified as an independent triggering factor for GLM.[15] In our study, although 62.5% of patients with a new occurrence reported a history of breast trauma, it did not demonstrate statistical significance in multivariate regression analysis. Interestingly, a majority of patients without a history of breast trauma reported experiencing emotional disturbances. Although only 3 (33.3%) patients with recurrence attributed the sudden emergence of nodules to work-related stress and depressed mood, this observation is consistent with existing literature that links emotional dysregulation to the development of GLM.[15]

Initial research conducted by our group suggests that following clinical recovery of GLM, extended treatment with traditional Chinese patent medicine for a duration of six months or more can significantly reduce the rate of recurrence.[39] In this study, 66.7% of recurrence patients did not complete 6 months of treatment, and 68.8% new occurrence patients failed to reach this treatment duration. Although these findings did not reach statistical significance, it could be due to the patients enrolled from 2016 to 2021, who were not systematically managed with this treatment. Other variables such as age, BMI, history of nipple discharge, reproductive history, and history of lactation massage did not show statistical significance in this study.

Our study is the first to observe the long-term efficacy of TCM in treating GLM over an extended period, specifically using a two-year timepoint. Furthermore, we have conducted a statistical analysis that distinguishes between recurrence and new occurrence of GLM. Notably, our analysis of new occurrence cases provides novel data that has not been previously reported in published studies.

However, this study still has some limitations. Firstly, this is a retrospective study, most of the patients were from China (more in East China), and due to the long treatment period of TCM, some patients discontinued visits upon experiencing the lumps shrunk and symptom resolution, potentially introducing common biases. Secondly, while this study focused exclusively on observing the long-term profiles of TCM treatment without comparison to other therapeutic approaches, our findings are corroborated by our previous research[9] and previous literature, lending credibility to the long-term effectiveness of TCM. Thirdly, the cross-sectional design of this study limits our ability to establish causal relationships. To address these limitations and validate our conclusions, future research should employ prospective, multi-center cohort studies with propensity score matching to enhance the robustness of the results. Additionally, incorporating more comprehensive data, such as patients' imaging indicators and emotional state assessments, would facilitate a deeper exploration of the interactions among risk factors.

Conclusion

In summary, our retrospective study on patients with GLM who received TCM treatment identified potential factors related to recurrence and new occurrence. Notably, a history of inverted nipples plays a significant role in the development of both recurrence and new occurrence. Endocrine disorders associated with menstruation should also be of concern after clinical cure. Moreover, a two-year recurrence rate of 1.53% and a two-year new occurrence rate of 4.21% are both lower than most reported reports. As more and more patients are more inclined to seek conservative treatments, our study provides data on the long-term efficacy of the treatment of GLM with TCM, and valuable prognostic insights into the disease trajectory following TCM treatment. Future clinical diagnoses and treatments should also consider factors such as emotional disturbances and lactation difficulties. Meanwhile, the mechanism of the TCM formula (especially in this study) in treating GLM should be clarified through experimental studies.

Ethics Approval

This study was approved by the Medical Ethics Committee of Longhua Hospital, Shanghai University of Traditional Chinese Medicine (2024LCSY100) with a waived requirement for patient informed consent because the study was retrospective. Patient data remained confidential and this study was conducted in accordance with the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The author(s) reported no conflicts of interest in this work.

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