doi.org/10.36721/PJPS.2025.38.6.REG.15239.1

Therapeutic effect of Xihuang capsules in combination with low-power high-intensity focused ultrasound on granulomatous mastitis and its impact on macrophage (CD68) and proliferative (Ki67) markers

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Abstract: Granulomatous mastitis (GM) is a chronic inflammatory breast disease with a high recurrence rate and low effectiveness of the traditional treatments. This randomized controlled trial compared the effectiveness of the combined use of Xihuang Capsules and low-power High-Intensity Focused Ultrasound (HIFU) and their impact on macrophage infiltration (CD68) and cell proliferation (Ki67). Sixty women with histologically proven GM were randomized to experimental (HIFU + Xihuang) or control (HIFU alone) groups (n=30 each group). Follow-up was for 12 weeks and recurrence at 6 months. Compared with controls, the combination group experienced more lesion reduction (3.50±0.79 cm to 0.92±0.42 cm vs. 3.42±0.88 cm to 1.85±0.60 cm, $p<0.001$), improved complete resolution (86.7% vs. 60.0%, $p = 0.023$), earlier resolution (6.2±1.4 vs. 9.1±1.8 weeks, $p<0.001$) and greater pain reduction (VAS: 7.2±1.1 to 1.3±0.6 vs. 7.0±1.3 to 2.8±0.9, $p<0.001$). Immunohistochemistry also demonstrated marked reductions in CD68+ macrophages and Ki67 index, both blindly graded. Recurrence at 6 months reduced with combination therapy (6.7% vs. 20.0%, $p=0.098$). Both treatments were well tolerated. These data indicate that Xihuang Capsules plus low-power HIFU produce faster regression of lesions, disappearance of symptoms and modulation of macrophage infiltration and cell proliferation in GM, with tendency of decreased recurrence.

Keywords: Combination therapy; granulomatous mastitis; Low-power high-intensity focused ultrasound; Macrophage marker (CD68); Proliferation marker (Ki67); Xihuang capsules

Submitted on 19-09-2025 – Revised on 24-09-2025 – Accepted on 27-09-2025

INTRODUCTION

Granulomatous mastitis (GM) is a rare, non-caseating granulomatous breast inflammation with a low prevalence that predominantly affects childbearing women, especially within a few years postpartum (Wang *et al.,* 2025a; Cui *et al.,* 2024). GM clinically presents as an unilateral, hard, tender breast mass with overlying erythema, sinus tract, or abscesses and will usually simulate breast carcinoma clinically and radiologically (Dilaveri *et al.,* 2024). Histopathologically, GM is diagnosed by lobulocentric granulomas composed of epithelioid histiocytes, multinucleated giant cells and lymphoplasmacytic infiltration (Guimaraes *et al.,* 2025). The etiology established is cryptic, albeit autoimmune reactions to milk protein extravasation, endocrinopathies and Corynebacterium kroppenstedtii infections have been culpable (Esmaeil and Salih, 2024).

Treatment of GM is not easy because of its chronicity, very high rate of recurrence and lack of standardized therapy. Traditional therapeutic regimens-like systemic corticosteroids, immunosuppressive drugs (e.g., Methotrexate, Azathioprine) and surgery-are followed by unpredictable results (Wang *et al.,* 2024; Ebadi, 2025a). Corticosteroids are effective in the short term but have high side effect risks and reactivity rates upon withdrawal (Wijesinghe *et al.,* 2024). Surgical removal carries risks of impairing wound healing, breast deformity and subtotal lesion removal, which, in most cases, is followed by residual or recurrent disease (Zhang *et al.,* 2025a). These constraints identify the necessity of new, minimally invasive treatment that decreases local inflammation, supports resolution of the lesion and can potentially preclude recurrence (Shojaeian *et al.,* 2024; Sarmadian *et al.,* 2024; Ebadi, 2025b; Ebadi *et al., 2025).*

Xihuang Capsules, a classical Chinese medicine combination of Niu Huang (Calculus Bovis), She Xiang (Moschus), Ru Xiang (Olibanum) and Mo Yao (Myrrh), exerted anti-inflammatory, anti-proliferative and immunomodulatory activities in pharmacological studies (Lou *et al*., 2024; Ebadi and Selamoglu 2025). They can modulate macrophage function and lymphocyte proliferation, indicating possible application as an adjunct therapy for inflammatory breast diseases like GM (Zhang *et al.,* 2025a; Li *et al.,* 2024a).

High-Intensity Focused Ultrasound (HIFU) is an image-guided non-invasive thermal ablation treatment that causes site-specific tissue necrosis without damaging the structures above (Li *et al.,* 2024a). Low-intensity HIFU was recently employed in benign and inflammatory breast tumors to reduce the lesion size, cause tissue repair and reduce surgical trauma. Marriage between systemic anti-inflammatory treatment and local focused HIFU ablation

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has synergistic effects in GM, e.g., increased inflammatory resolution, inhibition of abnormal cell growth and potentially decreased recurrence (Li *et al.,* 2025; Liang and Zhang, 2025b; Yu *et al.,* 2025).

The justification for using Xihuang Capsules and HIFU is that their mechanisms of action are complementary. Active components like boswellic acids, myrrh resins and muscone were found to block macrophage invasion, suppress pro-inflammatory cytokines and suppress the growth of irregular cells, hence targeting the inflammatory microenvironment of GM. HIFU is effective in lesion destruction but does not completely suppress this dysregulation of immunity, which can lead to recurrence. Synergy is thus hypothesized to be established by the following: HIFU decreases local lesion burden, whereas Xihuang Capsules achieves systemic immune modulation to maintain remission.

Immunohistochemical markers Ki67 and CD68 are both commonly applied for assessing proliferative and immune activity on a local tissue level. CD68 is a pan-macrophage marker of macrophage infiltration and chronic inflammation, whereas Ki67 is a marker of cellular proliferation. To correct things, CD68 does not stain regulatory T cells, contrary to some previous publications. Greater CD68 positive macrophages and Ki67 expression in GM lesions correlate with greater inflammation and risk of recurrence and are therefore important surrogate biomarkers to measure treatment response. (Li *et al.,* 2024b; Lou *et al.,* 2024).

However, while these advances have been made, no RCT to date has assessed the combination of Xihuang Capsules with low-intensity HIFU for GM treatment. The present study thus brings new clinical evidence by being the first prospective RCT to assess whether or not such integrative therapy improves clinical outcome and modulates related biomarkers versus HIFU alone.

With the limitations of available treatments and GM clinical workload, this research was performed to compare the efficacy of Xihuang Capsules plus low-energy HIFU with that of HIFU alone and their effects on CD68 and Ki67 expression. In theory, combination therapy was supposed to enhance clinical effects, inhibit local inflammatory and proliferative activity and reduce recurrence rates compared with monotherapy using HIFU and offer a presumably safe and effective individualized treatment for refractory GM patients.

MATERIALS AND METHODS

Study design

The trial was a prospective, randomized, controlled clinical trial designed to assess the therapeutic value of Xihuang Capsules and low-power High-Intensity Focused Ultrasound (HIFU) in the treatment of granulomatous mastitis (GM) and their impact on macrophage (CD68) and proliferative (Ki67) markers. The research was conducted in the Department of Breast Surgery, Shijiazhuang Fourth Hospital, Hebei Province, China, between January 2023 and December 2024. The Patients were longitudinally followed to measure clinical response, biomarker change, lesion resolution and recurrence.

Participants

Included were female participants aged 18–50 years with histopathologically proven GM, maximum lesion size ≤5 cm and clinical signs and symptoms such as localized tenderness, erythema, or swelling. Lactation history and parity were documented for all the patients and recruitment was restricted to those who had discontinued breastfeeding for ≥6 months. Patients with active infection, such as tuberculosis, fungal, or bacterial mastitis, were excluded according to microbiological examination and clinical assessment. Exclusion reasons included: history of surgical removal, recent corticosteroid or immunosuppressive treatment, suspicion or diagnosis of breast cancer, pregnancy or lactation, systemic autoimmune or inflammatory disease, severe hepatic, renal, or endocrine illness, known hypersensitivity to ingredients of Xihuang Capsule, or inability to follow study protocol. Screening was by clinical breast examination (CBE), breast ultrasonography, core needle biopsy and laboratory studies (CBC, liver and kidney function).

Sample size and randomization

Sample size was determined from pilot data showing a 25% greater incidence of lesion resolution with combination therapy compared to HIFU alone, using two-tailed $\alpha = 0.05$ and 80% power. In that pilot, the mean difference between lesion size reduction at 12 weeks was about 0.9 cm, SD ~1.2 cm. 25 patients would be required in each group based on these numbers to provide sufficient power; since there could be some dropouts, 30 were enrolled in each group (overall n = 60). Of these, 58 finished the study (29 in each group) and 2 patients (one in each group) were lost to follow-up in week 4. These were included in intention-to-treat sensitivity analyses but not in per-protocol analysis. Patients were randomly allocated 1:1 by a computer-generated list to the control (HIFU alone) or experimental (HIFU + Xihuang Capsules) group by an independent statistician. Allocation concealment was ensured by numbered, opaque, sealed envelopes. Xihuang Capsules compliance was assessed by pill counts and diaries every week, with over 90% average compliance. No significant protocol deviations were found.

Blinding

Though patients and clinicians delivering care could not be blinded owing to the intervention nature, outcome assessors remained blinded to group allocation. In particular, blinded study personnel obtained patient self-report VAS pain scores on standardized questionnaires and

standardized forms. Recurrence evaluations (clinical examination and ultrasound review) were obtained by blinded independent breast radiologists and independent breast surgeons. The CD68 and Ki67 evaluation pathologists and the sonographers used to measure the lesion size remained blinded until completion.

Low-power HIFU procedure

HIFU was carried out on the JC200 Focused Ultrasound Tumor Therapeutic System (Chongqing Haifu Medical Technology Co., China). The patients were in prone position and breast to be treated in a degassed water bath. Sonication parameters: power, 50–80 W; frequency, 1.5 MHz; duration per point, 3–5 s. Real-time ultrasonography was used to verify complete lesion coverage with a 5-mm buffer of safety. The treatment time varied from 20 to 40 minutes. Follow-up ultrasonography was noted to have coagulation necrosis and lack of vascular damage (De Maio *et al*., 2023; Wu *et al*., 2025). Power and frequency were chosen from literature experience with benign and inflammatory breast disease and our institution's guidelines, trying to get enough ablation of granulomatous tissue without causing skin burns and collateral tissue damage. These safety–efficacy factors guided the use of the "low-power" method employed in this study.

Administration of Xihuang capsule

Experimental group took oral Xihuang Capsules 0.3 g/capsule, three times a day for eight weeks starting from the day after HIFU. Capsules were provided by Beijing Tong Ren Tang with GMP qualification (Batch No. 2023A01). All the lots were subjected to high-performance liquid chromatography (HPLC) fingerprinting for reproducible confirmation of major active ingredients such as boswellic acids (Boswellia), myrrh resin, muscone (Moschus) and cinnamic acid (Borneolum). The same lot of drug was administered to all the patients to maintain uniformity. Instructions regarding administration, compliance and side effects were provided to the patients. Compliance was checked with weekly pill counts and patient diaries. Side effects were checked and controlled according to intensity. This treatment protocol attempted to increase anti-inflammatory, anti-proliferative and immunomodulatory impacts with tissue repair after HIFU (Ma *et al.,* 2024).

Outcome measures

The main outcome was response at 12 weeks, i.e., ≥50% reduction in ultrasonographic lesion size and disappearance of pain, erythema, or discharge locally. Secondary outcomes were time to lesion resolution, 6-month recurrence rates, quantitative change in CD68 and Ki67 expression, incidence and severity of adverse events, patient pain assessment (VAS) and general satisfaction.

Biomarker analysis

Core needle biopsies at baseline and 12 weeks were done. The tissue sections were incubated with CD68 (mouse anti-human, 1:100, Abcam, UK) and Ki67 (rabbit anti-human, 1:200, Cell Signaling Technology, USA). Five randomly chosen high-power fields were evaluated for percent positive cells and intensity of staining by two blinded pathologists. Scoring: percentage: <10% = 0; 10–25% = 1; 26–50% = 2; 51–80% = 3; >80% = 4; intensity: none = 0; weak = 1; moderate = 2; strong = 3. Agreement between the two observers was evaluated with Cohen's kappa statistic and high reproducibility was demonstrated (κ = 0.82 for CD68 and κ = 0.79 for Ki67). In the event of disagreement between the two pathologists, joint review and consensus were used to resolve them.

Safety evaluation

Safety monitoring involved clinical evaluation on every visit and lab tests (complete blood counts, serum electrolytes, liver and kidney function) at 0 weeks, 4 weeks and 12 weeks. The patients were systematically evaluated for gastrointestinal, dermatologic and systemic side effects on every follow-up with standardized questionnaires. AEs were documented and graded as per the Common Terminology Criteria for Adverse Events (CTCAE v5.0).

Statistical analysis

Data were compared using SPSS version 26.0. Continuous data were reported as mean ± SD and were compared with independent-samples t-tests (between groups) or paired t-tests (within groups). Categorical data were compared with chi-square or Fisher's exact tests. Shapiro–Wilk test was employed to examine normality. Two-tailed $p < 0.05$ was regarded as statistically significant.

RESULTS

Patient flow

Of 78 patients screened, 60 were eligible and were randomized (30 to control and 30 to experimental). Two patients (one from each group) were lost to follow-up after week 4, so 58 completed the study. All 60 patients randomized were included in intention-to-treat analyses and per-protocol analyses excluded the two lost to follow-up. Compliance with Xihuang Capsules was very good, with greater than 90% mean compliance as measured by diaries and pill counts. There were no important protocol deviations.

Patient baseline demographics and characteristics

Sixty female patients with histologically diagnosed granulomatous mastitis were randomly assigned to the control arm (low-power HIFU alone, n = 30) or experimental arm (HIFU + Xihuang Capsules, n = 30). Baseline data on age, BMI, lesion size, disease duration and immunohistochemical parameters (CD68-positive macrophages and Ki67) were relatively comparable between groups, in keeping with successful randomization (Table 1).

Clinical response and lesion size reduction

Mean lesion size decreased from 3.50 ± 0.79 cm to 0.92 ± 0.42 cm for the experimental group and from 3.42 ± 0.88 cm to 1.85 ± 0.60 cm for the control group ($p < 0.001$). Total regression of lesions occurred in 26/30 (86.7%) of the treated patients and 18/30 (60.0%) controls ($p = 0.023$). Mean resolution time was lower for the treated group (6.2 ± 1.4 weeks vs. 9.1 ± 1.8 weeks, $p < 0.001$). The results are illustrated in fig. 1, which shows mean lesion size before and after 12 weeks of treatment (Panel A) and the rate of complete resolution of lesions (Panel B). For added strength to reliability, reduction in lesion size was also reported with 95% confidence intervals (Table 2).

Pain reduction and symptom improvement (VAS Scores)

VAS pain scores declined significantly in both groups with greater reduction in the experimental group (7.2 ± 1.1 → 1.3 ± 0.6) than controls (7.0 ± 1.3 → 2.8 ± 0.9; $p < 0.001$). Median time to resolution of local signs of inflammation was shorter in the experimental group too (4.1 vs. 6.7 weeks; $p = 0.008$) (Fig. 2, Table 3). Pain was assessor-reported with VAS and data recorded by blinded staff.

Reduction in CD68 and Ki67 expression

CD68-positive macrophages decreased from 41.4 ± 7.1% to 15.8 ± 4.2% in the experimental group vs. 42.1 ± 6.8% to 26.5 ± 5.3% in the control group ($p < 0.001$). The Ki67 index decreased from 32.3 ± 5.8% to 9.4 ± 3.6% in the experimental group vs. 31.6 ± 5.4% to 18.2 ± 4.1% in the control group ($p < 0.001$) (Table 4, Fig. 3). Figs. 3A1–3D2 illustrate decreased macrophage invasion (CD68-positive cells) and proliferation (Ki67-positive nuclei) following combined treatment compared with HIFU alone. Quantitation was obtained by blinded scoring of positive staining within two independent pathologists, with high inter-observer concordance ($\kappa = 0.82$ for CD68; $\kappa = 0.79$ for Ki67).

Reduction in CD68 and Ki67 expression

CD68-positive macrophages decreased from 41.4 ± 7.1% to 15.8 ± 4.2% in the experimental group vs. 42.1 ± 6.8% to 26.5 ± 5.3% in the control group ($p < 0.001$). The Ki67 index decreased from 32.3 ± 5.8% to 9.4 ± 3.6% in the experimental group vs. 31.6 ± 5.4% to 18.2 ± 4.1% in the control group ($p < 0.001$) (Table 4, Fig 3). Figs. 3A1–3D2 illustrate decreased macrophage invasion (CD68-positive cells) and proliferation (Ki67-positive nuclei) following combined treatment compared with HIFU alone. Quantitation was obtained by blinded scoring of positive staining within two independent pathologists, with high inter-observer concordance ($\kappa = 0.82$ for CD68; $\kappa = 0.79$ for Ki67).

6-Month recurrence rate

During follow-up, 2/30 (6.7%) patients in the experimental group and 6/30 (20.0%) in the control group experienced recurrence ($p = 0.098$). Although the difference did not reach statistical significance, the experimental group showed a numerically lower recurrence rate. Longer-term follow-up is needed to determine whether this effect is durable (Table 5).

Safety and adverse events

Treatment was well tolerated. 3/30 (10%) experimental patients had mild gastrointestinal upset, which resolved spontaneously within 48–72 hours without the necessity for intervention. Mild local edema following HIFU in 5/30 (16.7%) controls and 6/30 (20%) experimental patients ($p = 0.74$). No hematologic, electrolyte, dermatologic, or systemic toxicities were observed. All of the adverse events were grade 1–2 according to CTCAE v5.0 and no grade ≥3 event was observed. Liver function test, renal function test, complete blood count and serum electrolytes were within the normal range in all the patients throughout the study (Table 6).

DISCUSSION

Granulomatous mastitis (GM) is a subacute inflammatory breast condition characterized by painful nodules, erythema and discharge, which greatly deteriorate the quality of patients' lives (Zhang *et al.,* 2025a; Parperis *et al.,* 2024). GM is difficult to cure since there is no single accepted therapy. Some frequently employed treatments, including corticosteroids, immunosuppressants, antibiotics, or surgery, tend to pose risks of side effects, incomplete resolution, or recurrence (Azzam *et al.,* 2023). Thus, less invasive operations coupled with adjunctive treatments are being increasingly investigated as alternatives for the purpose of maximizing efficacy with less complication (Shojaeian *et al.,* 2024). In the current study, 60 patients (30 in each group) completed the trial and were analyzed, which yielded proper statistical power but still restricts generalizability.

The prospective randomized trial assessed the efficacy of Xihuang Capsules combined with low-power high-intensity focused ultrasound (HIFU) for GM. As compared with HIFU monotherapy, the combination treatment had higher lesion reduction, higher complete resolution rates and better symptom relief speed. For example, median time to inflammatory symptom resolution was decreased by more than two weeks and pain improvement on VAS appeared more obvious in the experimental group. These results provide preliminary evidence that integrative therapies could enhance outcomes in refractory GM, but are subject to confirmation in bigger, multicenter trials with longer follow-up (Cui *et al.,* 2024; Hua *et al.,* 2024).

Importantly, immunohistochemical analysis detected greater reduction in CD68-positive macrophages and Ki67 labeling index in the combination group. CD68 is a marker of macrophage expression for immune cell infiltration and chronic inflammation, while Ki67 indicates proliferative activity.

Table 1: Baseline patient demographics and clinical features

Variable	Control (n = 30)	Experimental (n = 30)
Age (years)	32.8 ± 6.2	33.4 ± 5.7
BMI (kg/m²)	23.7 ± 2.8	23.2 ± 3.1
Lesion size (cm)	3.42 ± 0.88	3.50 ± 0.79
Disease duration (weeks)	10.3 ± 3.4	9.9 ± 3.1
CD68-positive macrophages (%)	42.1 ± 6.8	41.4 ± 7.1
Ki67-positive cells (%)	31.6 ± 5.4	32.3 ± 5.8

Note: Values are given as mean ± SD. No statistical comparisons were made of the baseline characteristics in line with CONSORT guidelines.

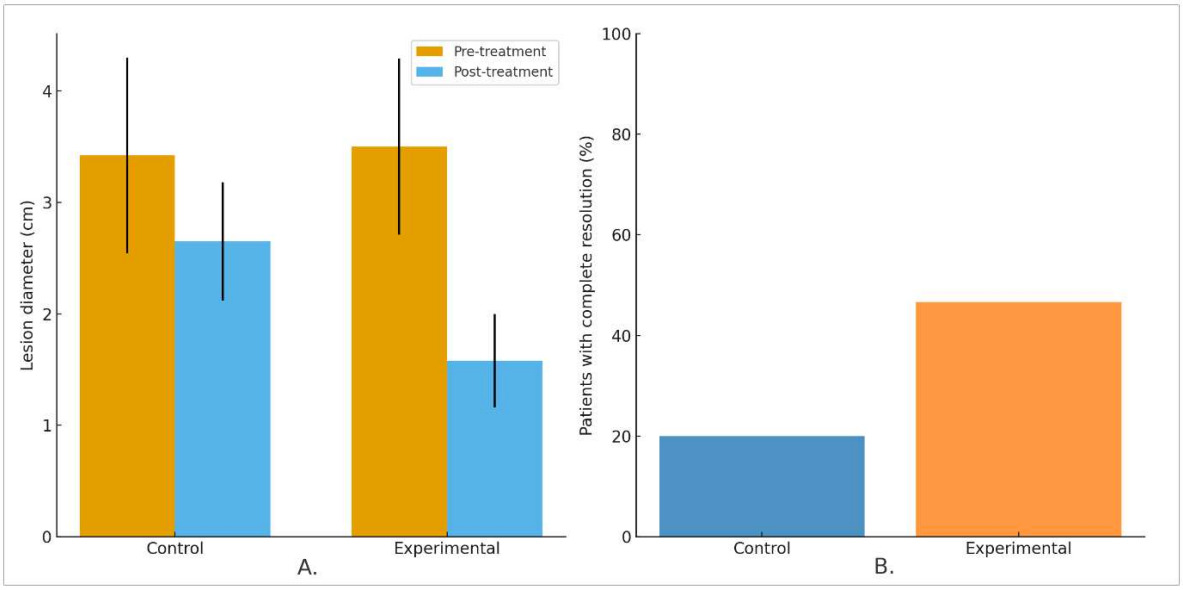

Fig. 1: Clinical response and lesion size reduction. (A) Mean lesion diameter at baseline and after 12 weeks of treatment. (B) Proportion of patients with complete lesion resolution at 12 weeks. Results are expressed as mean ± SD with 95% confidence intervals. All the measurements were performed by blinded outcome assessors to ensure accuracy.

Table 2: Lesion size reduction and complete resolution

Parameter	Control (n = 30)	Experimental (n = 30)	p-value
Pre-treatment lesion size (cm)	3.42 ± 0.88 (95% CI: 3.05–3.79)	3.50 ± 0.79 (95% CI: 3.18–3.82)	0.73
Post-treatment lesion size (cm)	1.85 ± 0.60 (95% CI: 1.57–2.13)	0.92 ± 0.42 (95% CI: 0.72–1.12)	<0.001
Complete lesion resolution, n (%)	18 (60.0)	26 (86.7)	0.023
Time to resolution (weeks)	9.1 ± 1.8	6.2 ± 1.4	<0.001

Note: Values are mean ± SD unless otherwise specified. 95% confidence intervals are provided for continuous variables. p-values are generated using independent t-tests for continuous variables and χ^2 tests for categorical variables.

Table 3: Relief of symptoms and improvement of pain

Symptom	Control (n=30)	Experimental (n=30)	p-value
VAS pain score (pre → post)	7.0 → 2.8	7.2 → 1.3	<0.001
Median time to symptom resolution (weeks)	6.7	4.1	0.008

Table 4: CD68 and Ki67 expression pre- and post-treatment

Marker	Control	Experimental	p-value
CD68 (%)	42.1 → 26.5	41.4 → 15.8	<0.001
Ki67 (%)	31.6 → 18.2	32.3 → 9.4	<0.001

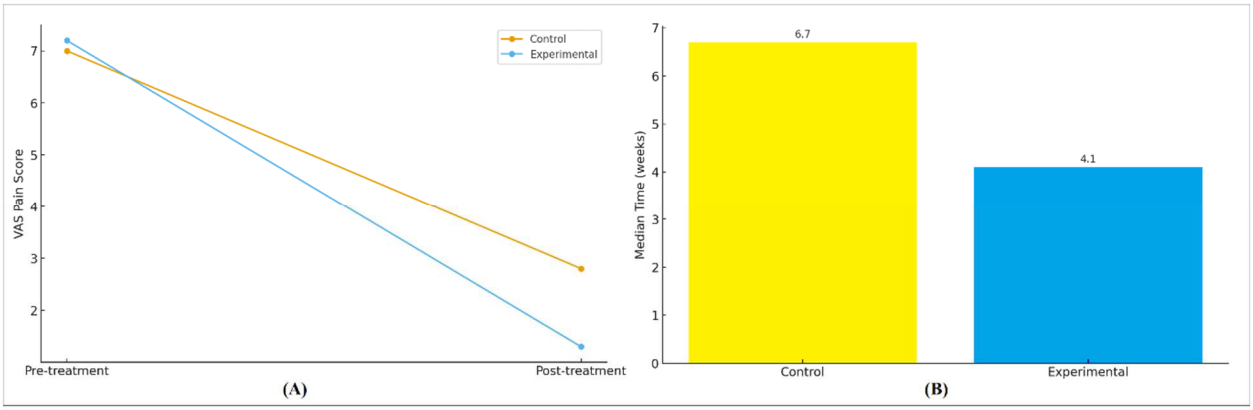

Fig. 2: Pain relief and symptomatic improvement. (A) Control and experimental group post-treatment and baseline visual analog scale (VAS) pain scores. (B) Median time to resolution of inflammatory symptoms. Data are expressed as mean ± SD (VAS) and medians (time to resolution). Symptom resolution and pain scores were captured by blinded outcome assessors.

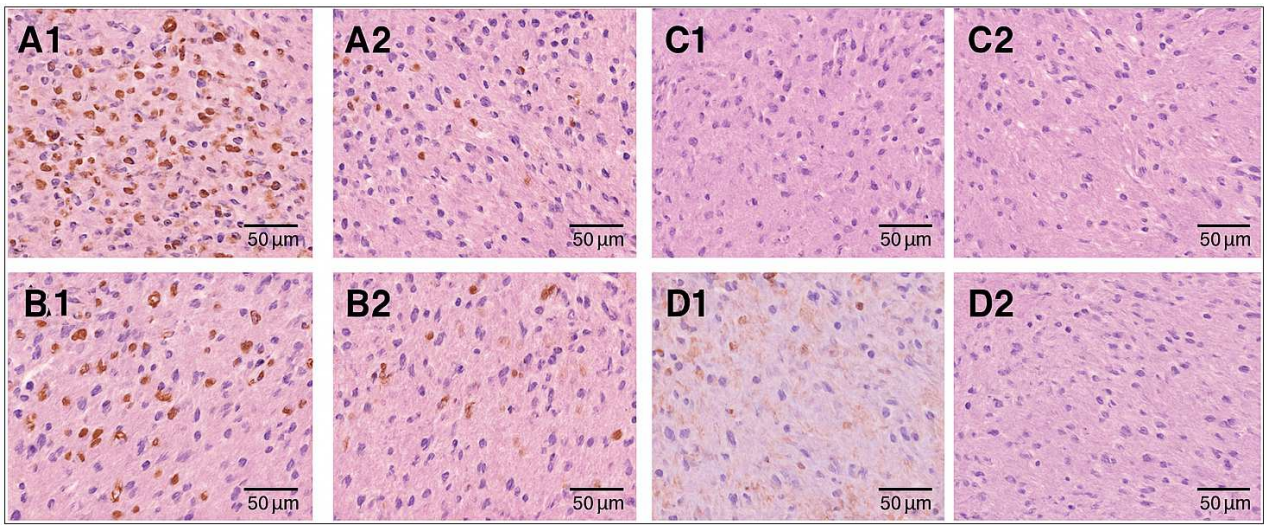

Fig. 3: Representative immunohistochemistry (IHC) of CD68 and Ki67 expression in granulomatous mastitis. (A1-A2) CD68 staining of the control group before and after treatment; (B1–B2) CD68 staining of the experimental group (HIFU + Xihuang Capsules) before and after treatment; (C1–C2) Ki67 staining of the control group before and after treatment; (D1–D2) Ki67 staining of the experimental group before and after treatment; Representative images indicate inhibited macrophage infiltration (CD68-positive cells) and decreased cellular proliferation (Ki67-positive nuclei) following combined treatment compared with HIFU only. Quantitation was done using blinded analysis of positive staining by two independent pathologists

Table 5: Recurrence during 6-month follow-up

Group	Recurrence n (%)	p-value
Control	6 (20.0)	0.098
Experimental	2 (6.7)	—

Table 6: Safety and adverse events

Adverse event	Control (n=30)	Experimental (n=30)	p-value
Gastrointestinal discomfort	0	3 (10%)	0.077
Local edema post-HIFU	5 (16.7%)	6 (20%)	0.74
Liver/renal dysfunction	0	0	—

To correct, CD68 is not specific to regulatory T cells, as sometimes misinterpreted in previous reports. Overall, these results suggest that Xihuang Capsules may exert complementary anti-inflammatory and anti-proliferative effects besides the ablative effect of HIFU. Although the underlying mechanisms are not clearly understood, previous pharmacological research supports that bioactive constituents of Xihuang Capsules modulate immune cell activity and angiogenesis (Lou *et al.,* 2024). Our results provide early clinical proof that such effects may be transferred to improved disease control.

Though the six-month recurrence was lower in the combination arm (6.7% vs. 20.0%), this was not statistically significant and should be interpreted with caution. The larger populations with longer follow-up will be needed to define if the observed numerical difference represents a durable advantage. In our study, all the patients were followed up for a minimum of 6 months, during which time recurrence was noted. While follow-up for this period of time is useful to ascertain short-term information, we recognize that late recurrences could possibly be missed. To truly assess long-term outcome, therefore, longer follow-up (12-24 months) is continued.

Both treatments were well tolerated overall. Mild gastrointestinal upset occurred in 3/30 (10%) Xihuang Capsules patients, grade 1-2 in severity, spontaneously resolving within 48-72 hours without needing treatment. Local edema at the treatment site for HIFU occurred in both groups and resolved spontaneously. No events of grade ≥3 were observed and laboratory monitoring (liver/renal function tests, hematocrit/hemoglobin and electrolytes) remained static during follow-up. These findings indicate that the combined approach is not only feasible but also safe within the clinical context (Zhang *et al.,* 2025a; Parperis *et al.,* 2024).

There are several limitations of this study. First, it was conducted at one center, which, although allowing for standardized treatment protocols and uniform follow-up, might cause selection bias and limit generalizability. The relatively small sample size, although arrived at by an a priori power calculation from pilot work, even more firmly suggests guarded interpretation of findings. Furthermore, since such a small sample size was used, the resulting effect sizes (e.g., reduction in lesions and relief of pain) are likely to be spurious and must be confirmed in larger populations. Second, the relatively rigorous exclusion criteria led to a homogeneous patient population that may not even be representative of real GM patients since most have either comorbidities or prior steroid exposure (Li *et al.,* 2025; Liang and Zhang, 2025b; Yu *et al.,* 2025).

Our rationale was to have a uniform cohort for this initial randomized controlled trial such that confounding variables are kept to a minimum and treatment effects can be more readily interpreted. Future multicenter trials will have to enroll more heterogeneous populations in order to maximize external validity. Third, patients and treatment providers could not be blinded due to the nature of the intervention, but outcome measurers (radiologists, surgeons and pathologists) were blinded to minimize bias. Fourth, primary endpoint of reduction in lesion size was assessed at 12 weeks, chosen to reflect early response to treatment. However, granulomatous mastitis is prone to relapse after this time. To address this more directly, we also reported recurrence at 6 months as a secondary endpoint but need additional follow-up for validation of durability. We do acknowledge that 6 months may still be too short to establish long-term benefit since GM often recurs after one year or more. This is being extended with longer follow-up out to 12-24 months to address this limitation (Cui *et al.,* 2024; Hua *et al.,* 2024).

Fifth, although we did include immunohistochemical markers, these were limited to CD68 (macrophage infiltration) and Ki67 (proliferation). Misuse of these markers in settings outside their validated functions should be avoided. Furthermore, beyond VAS pain scores, more detailed patient-related outcomes and quality-of-life measurements were not consistently obtained and thus the entire patient-focused effect of therapy cannot be determined. Future prospective studies should include validated quality-of-life measures to improve clinical utility. Future multicenter studies with larger sample size, extended follow-up, mechanistic studies and integration of patient-reported endpoints such as quality of life and cost-effectiveness will be important in a comprehensive evaluation of the clinical worth of this regimen (Liu *et al.,* 2025; Zuo *et al.,* 2021). Comparative trials with other integrative or immunomodulatory therapies may continue to maximize treatment in GM.

CONCLUSION

In summary, combining low-power HIFU with Xihuang Capsules is a safe and promising therapeutic regimen for granulomatous mastitis. Compared to HIFU monotherapy, combination therapy was associated with faster relief of symptoms, greater regression of lesions and better suppression of inflammatory (CD68) and proliferative (Ki67) markers. The rate of recurrence at 6 months nonsignificantly tended to reduce, which should be verified using longer follow-up. By bringing the local ablative effect of HIFU and the systemic anti-inflammatory and immunomodulatory action of Xihuang Capsules together, this approach offers a potentially valuable treatment adjunct. But because of small sample size, single-site design and short follow-up, these findings have to be considered preliminary. Longer follow-up and multicenter trials of larger sizes are required before the approach can be used in routine clinical practice.

Acknowledgement
Not applicable.

Authors' contributions

Xiaolong Li and Hang Li contributed to the study conception and design. Wei Liu and Qianqian Du supervised the study, coordinated patient recruitment and were responsible for manuscript drafting. Yi Shang and Qingru Han performed the data collection, biomarker analysis and statistical analysis. All authors critically reviewed the manuscript, provided intellectual input and approved the final version for publication.

Funding

This work was supported by the 2024 Annual Research Project Plan of Hebei Provincial Health Commission (No.20240458). The funding agency had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Data availability statement

All data generated or analysed during this study are included in this published article.

Ethical approval

The study protocol was reviewed and approved by the Institutional Ethics Committee of Shijiazhuang Fourth Hospital, Hebei Province, China (Approval No. SFH-IEC-2023-041). All participants provided written informed consent prior to enrollment and the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Conflict of interest

The authors declare that they have no conflicts of interest relevant to this study.

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