



Investigating Clinical Risk Factors Contributing to the Recurrence of Idiopathic Granulomatous Mastitis

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Abstract

Background: Granulomatous mastitis (GM) is a chronic inflammatory disorder affecting breast tissue, with a high recurrence rate.

Objectives: Regarding this impotence, this paper aims at proposing a retrospective approach to compile an extensive dataset of clinical information as well as to identify potential risk factors associated with GM recurrence.

Methods: For this purpose, data on pathologically-confirmed cases of GM were retrospectively collected from the medical archives of the Shahid Beheshti Cancer Research Center, Iran, from March 2020 to February 2023. Then, the descriptive statistics were utilized to analyze demographic information, disease-related variables, patient-related variables, and details regarding treatment modalities. Evaluation of disease recurrence occurred 24 months following the initial GM diagnosis through clinical assessments, ultrasound, or mammography. Among the 100 accessible patients, 33 experienced recurrences within 24 months.

Results: According to the obtained results, factors significantly associated with recurrence included body mass index (28.31 vs. 26.05), history of breastfeeding and its duration (22.44 months vs. 16.95 months) (90.9% vs. 72.7%), abortion, pain (72.7% vs. 46.3%), erythema nodosum (51.5% vs. 16.4%), hypertension (18.2% vs. 3%), thyroid disease (33.3% vs. 14.9%), rheumatologic disease (69.7% vs. 13.4%), dermal involvement (51.5% vs. 10.9%), joint involvement (85.9% vs. 39.4%), and the combined treatment modalities (45.5% vs. 11.9%). Moreover, the predictive model exhibited an overall accuracy of 83.3%.

Conclusions: Finally, it can be concluded that abortion history, breastfeeding and its duration, combined treatment, pain, erythema nodosum, hypertension, thyroid or rheumatologic disease, dermatologic or joint signs, and Body Mass Index (BMI) could be the significant factors related to the recurrence of GM. Thus, special attention to these factors and management of baseline disease may have a predictive effect on the relapse of idiopathic granulomatous mastitis (IGM).

Keywords: Idiopathic Granulomatous Mastitis, Recurrence, Clinical Risk Factors

1. Background

Granulomatous mastitis (GM) is a rare and chronic inflammatory disease that predominantly affects women in their reproductive age, impacting breast tissue. It is characterized by the development of granulomas, which can lead to pain, swelling, and palpable masses. These findings may be an initial presentation or precursor to more severe lesions, such as abscesses and fistulas. The estimated prevalence of

GM stands at approximately 2.4 cases per 100 000 women aged between 20 and 40 years (1). Some investigations suggest a higher incidence and prevalence of idiopathic granulomatous mastitis (IGM) in specific geographical areas (2). According to the number of patients within papers, Turkey, Iran, and China had the highest number (3), encountering daily challenges with the treatment of patients with IGM and their episodes of recurrence.

Multiple factors have been pinpointed as potential IGM risk factors. These encompass responses to various agents such as oral contraceptive pills, infectious ailments, and autoimmune disorders triggered by immunological stimuli elicited by milk flow within epithelial lobules. The definitive diagnostic criterion for IGM is breast biopsy, which remains the gold standard in clinical practice (4, 5). The etiopathogenesis of IGM remains elusive, but autoimmune processes are implicated in its development. Speculations have arisen regarding local trauma, local irritants, or viral agents serving as potential triggers for this immune cascade (6, 7).

No well-established, effective diagnostic protocol, or treatment paradigm exists for IGM (8). One of the significant challenges in managing GM is the potential for recurrence. Research has revealed recurrence rates ranging from 11.7% to 47.5% (6, 7, 9, 10). The recurrence of GM syndrome carries significant implications, encompassing both psychological and physical side effects. Moreover, it imposes substantial economic and logistical burdens due to the necessity for repeated treatments such as corticosteroids, antibiotics, and surgery. These demands can overwhelm patients and the healthcare system (1).

While several factors have been identified as potential contributors to recurrence, comprehensive data on these factors and their significance remain limited. These factors may encompass race, pregnancy, breastfeeding history, use of contraceptive hormones, hyperprolactinemia, obesity, involvement of breast skin, corynebacterial infection, lower serum vitamin B12 levels, multicentricity, accompanying rheumatologic complications, and the treatment modality employed for primary GM (6, 8, 11-13). Historically, the primary approaches for managing GM involved surgical interventions and antibiotic regimens. However, a noteworthy revelation emerged from tissue biopsies, revealing the prevalence of T-cells within the affected tissues. Concurrently, the efficacy of immunomodulators in treating GM implies an underlying inflammatory component (14-16). Addressing GM poses a formidable challenge due to limited awareness, the absence of standardized guidelines, and alarmingly high relapse rates ranging from 5% to 50% (17). Consequently, it is crucial to identify risk factors capable of discerning patients at heightened risk of relapse.

Based on what was mentioned above, the main contribution of this paper is that this knowledge empowers clinicians to judiciously allocate resources and offer vigilant monitoring to those most in need.

This underscores the critical importance of long-term follow-up and ongoing monitoring for individuals diagnosed with GM. Through vigilant disease surveillance and the implementation of appropriate management protocols, healthcare providers can mitigate the risk of recurrence, thus enhancing long-term outcomes for GM patients. The study adopted a retrospective approach to attain a more comprehensive grasp of GM, amassing a substantial volume of clinical data.

2. Objectives

The primary objective was to identify factors associated with GM recurrence, intending to generate novel insights that may inform future treatment strategies.

3. Methods

3.1. Study Design

From March 2020 to February 2023, data were retrospectively collected from the medical archive at Shahid Beheshti Cancer Research Center in Tehran, Iran. G*Power software was used to estimate the sample size. The input parameters to calculate the sample size include the hypothesis having 2 ranges, the average value of the estimated odds ratio (Odds ratio) equal to 2, the alpha error level (α err prob) equal to 0.05 and the statistical power [Power ($1-\beta$ err prob)] equal to 75% was selected as software input. Based on the calculations, the total sample size for the two groups was 101 people. In this research, the inclusion criteria are the patients' demographic, clinical, radiological, treatment, and recurrence of IGM-related characteristics after removing the incomplete samples. Only the patients who were histopathologically diagnosed with IGM were included in this study. Exclusion criteria included male patients, patients with breast carcinoma who coexisted with IGM, and non-IGM patients. Patients with tuberculous mastitis were not included in the study. History of pulmonary tuberculosis, evidence of histologically tuberculous mastitis, positive staining with Ziehl-Neelsen or acid-fast or positive tissue cultures, and chest X-ray findings consistent with previous tuberculosis findings with positive tuberculin test were excluded in this study. The return of a sign, symptom, or disease after a remission was accepted as recurrence. All patients' data in the pathology departments of the Cancer Research Centers of SBMU with the diagnosis of IGM in the last 3 years (from 2020 to 2023) were evaluated. The statistical analysis was finally performed with a volume of 100 samples. The demographic criteria

Table 1. The Demographic Criteria^a

Variables	Non-recurrent	Recurrent
Education		
Less than high school	31 (50.8)	17 (51.5)
End of high school	14 (23)	12 (36.4)
University degree	16 (26.2)	4 (12.1)
Occupation		
Household	49 (73.1)	32 (97)
Employed	7 (10.4)	1 (3)
Age (y)	41.55 ± 10.58	38.12 ± 8.44

^a Values are expressed as No. (%) or mean \pm SD.

including age, education, and occupation are separately mentioned in **Table 1** for recurrent and non-recurrent groups. **Table 2** presents the required sample size determined a priori.

Table 2. A Priori Sample Size Calculation

Analysis	Values
Input	
Study(s)	Two
Odds ratio	2
$Pr(Y=1 X=1) H_0$	0.2
α err prob	0.05
Power (1- β err prob)	0.75
R^2 other X	0
X distribution	Normal
X parm μ	0
X parm σ	1
Output	
Critical z	1.9599640
Total sample size	101
Actual power	0.7533357

This study comprised female patients initially diagnosed with GM based on histopathological examination of core needle or excisional biopsy specimens. Antibiotics were given to all mastitis patients for 10 days. In cases with no or minimal clinical improvement, a core biopsy was done to diagnose IGM. The treatment method was categorized into 3 groups; first, patients who had received surgery alone; second, patients who had only received oral agents (corticosteroid, antibiotics) and, third, the combination therapy (medical and surgical). Here, it should be mentioned that this cross-sectional study aimed at evaluating risk factors for recurrence and the type of treatment was also compared in the groups. Descriptive statistics were employed to analyze demographic data,

disease-related variables, patient-related information, and details regarding treatment modalities. During 24 months from the initial diagnosis of GM, disease recurrence was assessed through clinical evaluation, supplemented by ultrasound or mammography patients were divided into 2 groups: Recurrence and patients with non-recurrence.

Data that were analyzed including education, occupation, history of breastfeeding, menopause, laterality, nipple discharge, anatomical nipple retraction, erythema nodosum, breast trauma, smoking, history of breast cancer, family history of breast cancer, diabetes, thyroid disease, high prolactin level above 25 μ g/L, rheumatologic disease (Rheumatoid Arthritis), psychiatric disease receiving medication, skin involvement, oral contraceptive usage, and management method were compared between two groups.

The other studies ($n = 60$)¹⁷ with rather large series in the literature were those, in which some demographic characteristics could be related to IGM (18), but our study is among Iranian patients with similar ethnicity and all from the same geographical region; so, only occupation education and age were evaluated.

3.2. Statistical Analysis

In the analysis section, SPSS version 28 was utilized for data analysis. Descriptive statistics described the variables, including frequency, percentage, mean, and standard deviations. The relationship between variables and the recurrence of GM was explored, using Fisher's exact test for 2×2 relationships, the chi-square test, and an independent *t*-test for quantitative variables. Finally, a two-sided binary logistic regression analysis was conducted to predict the recurrence of GM (recurrent or non-recurrent) based on the predictor variables. In this

endeavor, logistic regression emerges as a valuable statistical tool. It aims at estimating the relationship between one or more independent (predictor) variables and a binary dependent (outcome) variable. A binary variable can assume only 2 distinct values or levels. Logistic regression offers a dual function: First, it enables the prediction of the outcome variable for new combinations of predictor variables. Second, it facilitates an in-depth exploration of the study area by quantifying the relative contribution of each predictor variable to the outcome variable. Importantly, logistic regression is especially well-suited for models involving dichotomous outcomes, which is frequently the case in health science studies, where the focus is often on disease states (diseased/healthy) and decision-making processes (yes/no). In logistic regression, the logarithm of the odds of a positive outcome (where "positive" aligns with the encoding of the outcome variable, i.e., Y = 1) is computed. Subsequent algebraic manipulation transforms this into the probability of the desired outcome.

4. Results

Out of the 104 available files, data for 100 patients were accessible after 24 months. Therefore, the study sample consisted of 100 individuals diagnosed with GM, of whom 67 had not experienced recurrence, and 33 had a history of recurrence after 24 months from the primary diagnosis. Table 3 describes the study variables by recurrence status. The significance of the relationship between variables and the recurrence of GM was also examined using the chi-square and Fisher's exact tests.

Table 3. Description of Variables by Recurrence Status of Granulomatous Mastitis and Comparison of Variables Between the Two Groups

Variables	Non-recurrent	Recurrent	χ^2	P-Value
Education			3.40	0.183
Less than high school	31 (50.8)	17 (51.5)		
End of high school	14 (23)	12 (36.4)		
University degree	16 (26.2)	4 (12.1)		
Occupation			2.28	0.249
Household	49 (73.1)	32 (97)		
Employed	7 (10.4)	1 (3)		
History of abortion			11.79	0.003
0	2 (3)	6 (18.2)		
1	45 (68.2)	25 (75.8)		
2	19 (28.8)	2 (6.1)		
Menopause at disease onset			1.44	0.321
No	54 (85.7)	3 (193.9)		
Yes	9 (14.3)	2 (6.1)		
Breastfeeding			4.35	0.040

Variables	Non-recurrent	Recurrent	χ^2	P-Value
No	18 (27.3)	3 (9.1)		
Yes	48 (72.7)	30 (90.9)		
Laterality			3.79	0.150
Right	33 (49.3)	20 (60.6)		
Left	32 (47.8)	10 (30.3)		
Both	2 (3)	3 (9.1)		
Nipple discharge			2.09	0.215
No	53 (79.1)	21 (65.6)		
Yes	14 (20.9)	11 (34.4)		
Nipple retraction			0.74	0.463
No	52 (77.6)	23 (69.7)		
Yes	15 (22.4)	10 (30.3)		
Pain			6.25	0.018
No	36 (53.7)	9 (27.3)		
Yes	31 (46.3)	24 (72.7)		
Erythema nodus			13.51	0.001
No	56 (83.6)	16 (48.5)		
Yes	11 (16.4)	17 (51.5)		
Breast trauma			1.64	0.331
No	63 (94)	30 (90.9)		
Yes	2 (3)	3 (9.1)		
Smoker			0.32	0.567
No	56 (86.2)	27 (81.8)		
Yes	9 (13.8)	6 (18.2)		
History of breast cancer			1.35	0.373
No	55 (82.1)	30 (90.9)		
Yes	12 (17.9)	3 (9.1)		
FH of breast cancer			0.99	0.387
No	58 (86.6)	26 (78.8)		
Yes	9 (13.4)	7 (21.2)		
FH of other cancers			0.29	0.624
No	52 (77.6)	24 (72.7)		
Yes	15 (22.4)	9 (27.3)		
DM			0.05	1
No	60 (89.6)	30 (90.9)		
Yes	7 (10.4)	3 (9.1)		
HTN			6.94	0.015
No	65 (97)	27 (81.8)		
Yes	2 (3)	6 (18.2)		
Thyroid disease			4.52	0.040
No	57 (85.1)	22 (66.7)		
Yes	10 (14.9)	11 (33.3)		
High PRL			0.54	0.597
No	65 (97)	31 (93.9)		
Yes	2 (3)	2 (6.1)		
Rheumatologic disease			32.17	0.000
No	58 (86.6)	10 (30.3)		
Yes	9 (13.4)	23 (69.7)		
Psychiatry disorder			0.17	0.773
No	57 (85.1)	27 (81.8)		
Yes	10 (14.9)	6 (18.2)		
Skin involvement			19.25	0.000
No	57 (89.1)	16 (48.5)		

Variables	Non-recurrent	Recurrent	χ^2	P-Value
Before GM	55 (85.9)	13 (39.4)		
During GM	8 (12.5)	16 (48.5)		
After GM	1 (1.6)	4 (12.1)		
OCP			1.19	0.375
No	55 (87.3)	26 (78.8)		
Yes	8 (12.7)	7 (21.2)		
Surgery alone			0.33	0.681
No	63 (94)	30 (90.9)		
Yes	4 (6)	3 (9.1)		
Oral agent alone			0.12	0.826
No	43 (64.2)	20 (60.6)		
Yes	24 (35.8)	13 (39.4)		
Combined treatment			14.02	0.000
No	59 (88.1)	18 (45.5)		
Yes	8 (11.9)	15 (45.5)		

Abbreviations: GM, granulomatous mastitis; HTN, hypertension.

The results in [Table 3](#) indicate significant differences in several variables between GM's recurrence and non-recurrence groups ($P < 0.05$). The analysis of significant relationships showed that the recurrence group had a higher frequency of breastfeeding history than the non-recurrence group (90.9% vs. 72.7%). The rate of surgical intervention alone for primary GM was not significantly higher in the recurrence group (9.1% vs. 6%). The use of oral agents was also not significantly higher in the recurrence group (39.4% vs. 35.8%). Conversely, the combination of surgical intervention and oral agents was significantly higher in the recurrence group (45.5% vs. 11.9%). The recurrence group had a higher pain incidence than the non-recurrence group (72.7% vs. 46.3%). The recurrence group also had a higher incidence of erythema (51.5% vs. 16.4%). The prevalence of hypertension (HTN) was higher in the recurrence group compared to the non-recurrence group (18.2% vs. 3%). The prevalence of thyroid disease was significantly higher in the recurrence group (33.3% vs. 14.9%). Rheumatologic diseases were significantly more prevalent in the recurrence group (69.7% vs. 13.4%). The recurrence group had a higher incidence of skin symptoms (51.5% vs. 10.9%), while the non-recurrence group had a higher incidence of joint symptoms before GM diagnosis (85.9% vs. 39.4%) and a lower incidence of joint symptoms after the diagnosis (12.5% vs. 48.5%).

[Table 4](#) describes the quantitative variables between the recurrent and non-recurrent GM groups. The average values of these variables were compared between the two groups, using an independent *t*-test. The results of [Table 4](#) indicate a significant difference between the recurrent and non-recurrent groups in two

variables: Body Mass Index (BMI) and lactation period ($P < 0.05$). According to the results, the mean BMI in the recurrent group was significantly higher (28.31 vs. 26.05), as was the mean lactation period (22.44 months vs. 16.95 months).

The results of the logistic regression analysis to predict the recurrence of GM are presented in [Table 5](#). The table shows the accuracy of the model in classifying the samples. It is important to note that 72 samples with complete data were included in the logistic regression analysis. The results in [Table 5](#) indicate that based on the predictor variables of the model, it is possible to predict relapse in patients with GM with an accuracy rate of 84.4%. The model's accuracy is above 50%, which is considered acceptable. The overall accuracy of the model in correctly classifying samples is 83.3%. According to the results, out of 32 individuals who experienced relapse, 27 were correctly identified, and only 5 were misclassified.

Omnibus tests were used to evaluate the overall fit of the logistic regression model. The chi-square value was 76.45 ($P < 0.001$), indicating that the model's overall fit was acceptable, and the logistic regression model aimed at predicting the recurrence of GM had a good fit. The determination coefficients in logistic regression showed that the range of these coefficients was between a minimum of 0.47 for the Nagelkerke R Square coefficient and a maximum of 0.63 for the Cox & Snell R Square coefficient. This indicates that the predictor variables of the model were able to explain between 47% and 63% of the variance in the recurrence outcome variable, indicating good explanatory power for the model.

[Table 6](#) presents the logistic regression analysis results to identify recurrence predictors in GM. It is worth mentioning that the assumption of linearity between the predictor variables was checked, using the variance inflation factor (VIF), and all values were found to be less than 5, indicating no severe multicollinearity issues among the predictor variables. Only the significant variables from [Tables 2](#) and [3](#) were included in the logistic regression model, resulting in 11 variables being included. The results of [Table 6](#) showed that among the predictor variables in the model, the effects of 6 variables on the recurrence of GM were confirmed ($P < 0.05$). The findings indicated that individuals who experienced recurrence had higher levels of erythema, skin, and joint symptoms. The prevalence of rheumatologic diseases was higher in the recurrence group compared to the non-recurrent group. Additionally, individuals who experienced relapse had higher BMI and more extended lactation periods.

Table 4. Description of Quantitative Variables Along with Independent *t*-Test for Comparing the Means of Variables Between the Two Groups

Variables	Non-recurrent	Recurrent	<i>t</i>	P-Value
Age (y)	41.55 ± 10.58	38.12 ± 8.44	1.52	0.133
BMI (kg/m ²)	26.05 ± 4.41	28.31 ± 3.90	2.32	0.023
Number of pregnancies	2.34 ± 1.37	2.24 ± 0.94	0.43	0.669
The interval between disease to last pregnancy (mo)	92.95 ± 1.3049	60.66 ± 53.59	171	0.093
Duration of breastfeeding (mo)	16.95 ± 5.62	22.44 ± 5.47	3.72	0.000
Interval between disease to last breastfeeding (mo)	76.34 ± 99.10	42.69 ± 51.76	1.82	0.074

Table 5. Evaluation of the Accuracy of the Regression Model in Classifying the Sample Based on the Recurrence Status of Granulomatous Mastitis

Variables	Prediction of Recurrence ^a		Total	True Prediction (%)
	Non-recurrent	Recurrent		
Recurrence status				
Non-recurrent	33 (82.5)	7 (12.5)	40	82.5
Recurrent	5 (15.62)	27 (84.4)	32	84.4
Total	38 (100)	34 (100)	72	83.3

^aValues are expressed as No. (%).

5. Discussion

Recurrence poses a significant challenge in the treatment of GM. Studies have reported recurrence rates of GM ranging from 11.7% up to 47.5% (7, 10-14). In the study, the recurrence rate of GM was 33%, placing it within the mid-range. This underscores the fact that a considerable proportion of GM cases experience one or more recurrences, even after initial treatment. Recurrence complicates the long-term management of the disease and the achievement of remission, putting patients at risk of ongoing symptoms, complications, and the need for continuous surveillance. Various factors may influence the recurrence of GM, including patient-related, disease-related, and treatment-related factors. In this survey, an evaluation of multiple available factors based on previous studies and collective experience that might potentially contribute to GM recurrence was conducted.

In our study regarding demographic and patient-related factors, the level of education and occupation were not significantly related to GM recurrence, which is following the results of the study by Basim et al. (9). The studies of The other studies (n = 60) with rather a large series in the literature were those, in which some demographic characteristics could be related to IGM (18). This is because our study was conducted between the same race and all were Iranian from the same

geographical regions only age while education and occupation were not significantly related to recurrence.

However, a significant association between higher BMI and a higher recurrence rate was discovered when assessing the effect of BMI on recurrence. In the study, the average BMI for the non-recurrent group was 26.05 kg/m², while for the recurrent group, it was 28.31 kg/m² (P = 0.023), although BMI does not show the breast volume and fat tissue extent but this may be because of the faster spread of inflammation in adipose tissue (19). This contradicts Basim et al.'s (9) findings but aligns with two other studies by Yilmaz et al. (20) and Huang and Wu (10), which concluded that BMI is associated with GM recurrence. Various gynecological and obstetric factors that were supposed to influence GM recurrence, including the number of pregnancies, history of abortion, history, and duration of breastfeeding, and intervals between disease onset and the last pregnancy or lactation, were examined. Among these factors, only the duration of lactation was significantly associated with GM recurrence, with an average time of 16.95 months for the non-recurrent group and 22.44 months for the recurrent group (P = 0.000). This contrasts with the results of a systematic review involving 4 735 patients, which suggested that both lactation history and pregnancy history were related to GM recurrence (7). Yilmaz et al. (20) and Basim et al. (9) reported conflicting findings on this matter, possibly due to variations in sample size or other

Table 6. Coefficient Table of Logistic Regression Test for Predicting the Recurrence of Granulomatous Mastitis

Predictor Variable	Unstandardized Coefficient	Standard Deviation	Wald Statistic	P-Value	Odds Ratio
Abortion	-0.998	0.622	2.576	0.109	0.369
Breastfeeding	-1.149	1.656	0.481	0.488	0.317
Combined treatment	2.838	2.367	1.437	0.670	0.663
Pain	0.579	0.518	1.249	0.264	1.78
Redness	1.437	0.523	7.547	0.006	4.210
HTN	2.060	1.547	1.774	0.183	7.848
Thyroid disease	0.882	0.818	1.164	0.281	2.416
Rheumatologic disease	2.182	0.603	13.112	0.000	8.868
Skin sign	1.602	0.582	7.584	0.006	4.962
Joint sign	1.508	0.489	9.501	0.002	4.519
BMI	0.136	0.062	4.794	0.029	1.146
Duration of breastfeeding	0.159	0.062	6.517	0.011	1.172

Abbreviations: HTN, hypertension; BMI, Body Mass Index.

underlying serological disturbances, such as high serum prolactin levels, which have been implicated in GM recurrence in some studies (10, 21). It should be mentioned that breast lobules secret milk (protein-rich liquid) during lactation, due to prolactin stimulation, and the ducts remain dilated. Moreover, prolonged breastfeeding would lead to long-term distention of acini and ducts, facilitating rupture and injury of these structures as well as resulting in a granulomatous inflammatory response (22).

Granulomatous mastitis is classified among autoimmune diseases, so its relationship with and co-occurrence with rheumatologic diseases like rheumatoid arthritis and diabetes mellitus could yield valuable insights into GM recurrence. Consistent with similar studies, rheumatologic and thyroidal diseases were more prevalent among GM recurrence cases, with P-values of 0.000 and 0.040, respectively. However, after logistic regression analysis, the thyroidal disease could not significantly predict GM recurrence ($P = 0.281$) (Table 6) (9). A recent review article by Parperis et al. (23) concluded that GM is associated with various autoimmune rheumatologic diseases (ARDs), including sarcoidosis, systemic lupus erythematosus, granulomatosis with polyangiitis, psoriasis/psoriatic arthritis, familial Mediterranean fever, ankylosing spondylitis, Sjogren's syndrome, rheumatoid arthritis, and erythema nodosum, with the most common being granulomatous mastitis-erythema nodosum-arthritis syndrome (GMENA), granulomatosis with polyangiitis (Wegener's), and sarcoidosis (23). This finding may prompt healthcare providers to more closely monitor patients with a history of ARDs to detect GM recurrence.

Regarding disease signs and symptoms, neither pain nor nipple discharge were related to GM recurrence, consistent with the findings of a study conducted by Basim et al. (9). Instead, cutaneous manifestations, including GMENA, were more prevalent in recurrent cases, in line with several other studies (8, 9, 14, 20). This may be because of no differentiation by nipple discharge.

There were conflicting results in various studies regarding the role of treatment modality (medical, surgical, combination, or observation) in GM recurrence. While some studies suggested that surgical intervention could result in a higher recurrence rate, others indicated that surgical and combination therapies led to better outcomes, including a lower recurrence rate (11, 14, 24, 25). Although not statistically significant, it was observed that patients undergoing combination treatment experienced more recurrence than other groups. This observation could be attributed to the small sample size of each group and the inherently more aggressive nature of primary GM in patients, who received combination therapies, which is a limitation of retrospective observational studies. A recent review article by Fattahi et al. (7) with a large sample size concluded that the choice between surgery or immunosuppression should be based on disease severity, patient preferences, and treatment complications. They also suggested that antibiotic therapy and observation could be sufficient for primary GM with fewer symptoms.

Finally, a logistic regression model was designed to predict GM recurrence, with an accuracy of 84.4% for recurrent patients and 83.3% for all patients. In this study, we used factors including abortion history,

breastfeeding and its duration, combined treatment, pain, erythema nodosum, hypertension, thyroid or rheumatologic disease, dermatologic or joint signs, and BMI to design the prediction model. Basim et al. (9) also developed a predictive model, finding that factors such as serum vitamin B12 levels, accompanying rheumatologic disease, fistula, number of complaints, erythema nodosum, multicentricity of GM, and treatment modality could be utilized to predict GM recurrence with an accuracy of 85%, similar to the conclusion reached here. Yilmaz et al. (20) introduced a scoring system based on data from 53 patients, which included the number of births, duration of lactation, BMI, luminal inflammation, presence of fistula, and abscess collection to predict GM recurrence accurately.

5.1. Conclusions

Granulomatous mastitis is a chronic inflammatory disorder affecting breast tissue and its recurrence rate of GM is reported to range between 11.7% and 47.5. Regarding this impotence, this paper aims at employing a retrospective approach to compile an extensive dataset of clinical information to identify potential risk factors associated with GM recurrence. For this purpose, data on pathologically confirmed cases of GM are retrospectively collected from the medical archives of the Shahid Beheshti Cancer Research Center from March 2020 to February 2023. Then, the descriptive statistics are utilized to analyze demographic information, disease-related variables, patient-related variables, and details regarding treatment modalities. Given the rarity of GM, we could conduct this study with a sample size of 100, which was quite great. We concluded that abortion history, breastfeeding, and duration, combined treatment, pain, erythema nodosum, hypertension, thyroid or rheumatologic disease, dermatologic or joint signs, and BMI could be significant factors related to the recurrence of GM. On the contrary, single modality treatment, occupation or level of education, nipple discharge, smoking, and history of breast cancer were unrelated to GM recurrence. Future studies especially systematic review articles with larger sample sizes over multiple centers as well as longer follow may lead to obtaining improved prediction models.

Footnotes

Authors' Contribution: Study concept and design: S. E. and A. A.; Analysis and interpretation of data: M. E. A. and M. F. T.; Drafting of the manuscript: D. F.; Critical revision of the manuscript for important intellectual content: N. H.; Statistical analysis: A. A.

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References

- Irkorucu O, Shorbagi Al, Alwardat DM, Parlakgümüş A, Peköz BC, Taş ZA. An Update on Granulomatous Lobular Mastitis: It is Time to Tell the Untold. *Erciyes Med J.* 2023;45(2):115-22. <https://doi.org/10.14744/etd.2023.53929>.
- Leonardo NM, McNeil J. Behcet's Disease: Is There Geographical Variation? A Review Far from the Silk Road. *Int J Rheumatol.* 2015;9:945262. [PubMed ID: 26798344]. [PubMed Central ID: PMC4698787]. <https://doi.org/10.1155/2015/945262>.
- Metanat S, Soleimani Jobaneh Y, Noori M, Sadeghi F, Mirzapour A, Mashhoori N, et al. Global Distribution of Idiopathic Granulomatous Mastitis: A Scoping Review: IGM Global Distribution. *Arch Breast Cancer.* 2022;9(3-SI):261-71. <https://doi.org/10.32768/abc.20229SI261-271>.
- Hamsho S, Alaswad M, Alsmadi H, Sleiay M, Hoha G, Alcheikh S. Idiopathic granulomatous mastitis with extramammary manifestations: a case report. *Ann Med Surg (Lond).* 2023;85(12):6192-5. [PubMed ID: 38098607]. [PubMed Central ID: PMC10718323]. <https://doi.org/10.1097/MS9.0000000000001397>.
- Altintoprak F, Kivilcim T, Ozkan OV. Aetiology of idiopathic granulomatous mastitis. *World J Clin Cases.* 2014;2(12):852-8. [PubMed ID: 25516860]. [PubMed Central ID: PMC4266833]. <https://doi.org/10.12998/wjcc.v2.i12.852>.
- Martinez-Ramos D, Simon-Monterde I, Suelves-Piquerres C, Queralt-Martin R, Granel-Villach L, Laguna-Sastre JM, et al. Idiopathic granulomatous mastitis: A systematic review of 3060 patients. *Breast J.* 2019;25(6):1245-50. [PubMed ID: 31273861]. <https://doi.org/10.1111/tbj.13446>.
- Fattah A, Amini G, Sajedi F, Mehrad-Majd H. Factors Affecting Recurrence of Idiopathic Granulomatous Mastitis: A Systematic Review. *Breast J.* 2023;2023:9947797. [PubMed ID: 37794976]. [PubMed Central ID: PMC10547579]. <https://doi.org/10.1155/2023/9947797>.
- Azizi A, Prasath V, Canner J, Gharib M, Sadat Fattah A, Naser Forghani M, et al. Idiopathic granulomatous mastitis: Management and predictors of recurrence in 474 patients. *Breast J.* 2020;26(7):1358-62. [PubMed ID: 32249491]. <https://doi.org/10.1111/tbj.13822>.
- Basim P, Argun D, Argun F. Risk Factors for Idiopathic Granulomatous Mastitis Recurrence after Patient-Tailored Treatment: Do We Need an Escalating Treatment Algorithm? *Breast Care (Basel).* 2022;17(2):172-9. [PubMed ID: 35707181]. [PubMed Central ID: PMC9149487]. <https://doi.org/10.1159/000517399>.
- Huang Y, Wu H. A retrospective analysis of recurrence risk factors for granulomatous lobular mastitis in 130 patients: more attention should be paid to prolactin level. *Ann Palliat Med.* 2021;10(3):2824-31. [PubMed ID: 33549007]. <https://doi.org/10.21037/apm-20-1972>.
- Yabanoglu H, Colakoglu T, Belli S, Aytac HO, Bolat FA, Pourbagher A, et al. A Comparative Study of Conservative versus Surgical Treatment

Protocols for 77 Patients with Idiopathic Granulomatous Mastitis. *Breast J.* 2015;21(4):363-9. [PubMed ID: 25858348]. <https://doi.org/10.1111/tbj.12415>.

12. Rakhshan A, Akbari A, Ahadi M, Zham H, Moradi A, Karimi Toudeshki K, et al. Clinicopathological Evaluation of Idiopathic Granulomatous Mastitis: A Retrospective Analysis of Sixty Women at Shohada-e-Tajrish Hospital from 2010 to 2019. *Int J Cancer Management.* 2023;In Press(In Press). <https://doi.org/10.5812/ijcm-139543>.

13. Tsai MJ, Huang WC, Wang JT, Wang MY, Lee YH, Lin SW, et al. Factors associated with treatment duration and recurrence rate of complicated mastitis. *J Microbiol Immunol Infect.* 2020;53(6):875-81. [PubMed ID: 32327329]. <https://doi.org/10.1016/j.jmii.2020.03.028>.

14. Lermi N, Ekin A, Ocak T, Bozkurt ZY, Otegeceli MA, Yagiz B, et al. What predicts the recurrence in idiopathic granulomatous mastitis? *Clin Rheumatol.* 2023;42(9):2491-500. [PubMed ID: 37301771]. <https://doi.org/10.1007/s10067-023-06651-3>.

15. Chiu IW, Goodwin K, Vohra P, Amerson E. Cystic Neutrophilic Granulomatous Mastitis Regression with the Tumor Necrosis Factor-alpha Inhibitor, Adalimumab. *Eur J Breast Health.* 2022;18(1):94-101. [PubMed ID: 35059598]. [PubMed Central ID: PMC8734519]. <https://doi.org/10.4274/ejbh.galenos.2021.2021-7-2>.

16. Pereira FA, Mudgil AV, Macias ES, Karsif K. Idiopathic granulomatous lobular mastitis. *Int J Dermatol.* 2012;51(2):142-51. [PubMed ID: 22250621]. <https://doi.org/10.1111/j.1365-4632.2011.05168.x>.

17. Kehribar DY, Duran TI, Polat AK, Ozgen M. Effectiveness of Methotrexate in Idiopathic Granulomatous Mastitis Treatment. *Am J Med Sci.* 2020;360(5):560-5. [PubMed ID: 32635989]. <https://doi.org/10.1016/j.amjms.2020.05.029>.

18. Uysal E, Soran A, Sezgin E, Granulomatous Mastitis Study G. Factors related to recurrence of idiopathic granulomatous mastitis: what do we learn from a multicentre study? *ANZ J Surg.* 2018;88(6):635-9. [PubMed ID: 28749045]. <https://doi.org/10.1111/ans.14115>.

19. Makki K, Froguel P, Wolowczuk I. Adipose tissue in obesity-related inflammation and insulin resistance: cells, cytokines, and chemokines. *ISRN Inflamm.* 2013;2013:139239. [PubMed ID: 24455420]. [PubMed Central ID: PMC3881510]. <https://doi.org/10.1155/2013/139239>.

20. Yilmaz TU, Gurel B, Guler SA, Baran MA, Ersan B, Duman S, et al. Scoring Idiopathic Granulomatous Mastitis: An Effective System for Predicting Recurrence? *Eur J Breast Health.* 2018;14(2):112-6. [PubMed ID: 29774320]. [PubMed Central ID: PMC5939974]. <https://doi.org/10.5152/ejbh.2018.3709>.

21. Ma G, Zhu L, Wang W, Hong X, Li W. Burden of ischaemic heart disease and attributable risk factors among Nanjing adults in China from 2011 to 2017. *J Public Health.* 2024. <https://doi.org/10.1007/s10389-024-02194-2>.

22. Verfaillie G, Breucq C, Sacre R, Bourgain C, Lamote J. Granulomatous lobular mastitis: a rare chronic inflammatory disease of the breast which can mimic breast carcinoma. *Acta Chir Belg.* 2006;106(2):222-4. [PubMed ID: 16761483]. <https://doi.org/10.1080/00015458.2006.11679876>.

23. Parperis K, Achilleos S, Costi E, Vardas M. Autoimmune rheumatic diseases associated with granulomatous mastitis. *Rheumatol Int.* 2023;43(3):399-407. [PubMed ID: 36418558]. <https://doi.org/10.1007/s00296-022-05251-9>.

24. Gopalakrishnan Nair C, Jacob P, Menon RR; Hiran; Misha. Inflammatory diseases of the non-lactating female breasts. *Int J Surg.* 2015;13:8-11. [PubMed ID: 25447605]. <https://doi.org/10.1016/j.ijsu.2014.11.022>.

25. Shin YD, Park SS, Song YJ, Son SM, Choi YJ. Is surgical excision necessary for the treatment of Granulomatous lobular mastitis? *BMC Womens Health.* 2017;17(1):49. [PubMed ID: 28738795]. [PubMed Central ID: PMC5525244]. <https://doi.org/10.1186/s12905-017-0412-0>.