Original Article

Patterns, Predictors, and Prognostic Implication of Treatment-Related Amenorrhea in Patients with Breast Cancer: A retrospective study

Korat Akash Hasmukhbhai[1], Soliya Tushar Makanbhai[2], Koradia Shreya Kantilal[3], Jeet Bhavesh Sureja[4]

[1]Assistant Professor, Department of General Medicine, Gmers Medical College & Hospital Junagadh, Gujarat, India. [2]Medical Officer, KJ Cancer and Super Speciality Hospital, Junagadh, Gujarat, India. [3]Senior Resident, Department of General Medicine, Gmers Medical College & Hospital Junagadh, Gujarat, India. [4]Senior Resident, Gmers Medical College & Hospital Junagadh, Gujarat, India.

Abstract

Background: Treatment-related amenorrhea (TRA) is a common consequence of systemic therapy in premenopausal women with breast cancer and may affect fertility, quality of life, and reproductive health. However, predictors of persistent TRA and its prognostic relevance remain uncertain. **Material and Methods:** A retrospective observational study of 200 premenopausal women with histologically confirmed breast cancer treated with systemic therapy at a tertiary cancer centre. Clinical, pathological, and treatment-related variables were extracted from medical records. TRA was assessed longitudinally, with persistent TRA defined as treatment-associated amenorrhea lasting ≥12 consecutive months without documented spontaneous menstrual recovery. Logistic regression was used to identify predictors of TRA and persistent TRA. Disease-free survival (DFS) and overall survival (OS) were evaluated using Cox proportional-hazards models. **Results:** TRA occurred in 124 (62.0%) patients, including 78 (39.0%) with persistent and 46 (23.0%) with transient TRA. Age ≥40 years was independently associated with TRA (adjusted OR [aOR], 2.82; 95% CI, 1.49–5.34; P=0.002) and persistent TRA (aOR, 3.48; 95% CI, 1.58–7.67; P=0.002). Alkylating-agent exposure independently predicted TRA (aOR, 2.21; 95% CI, 1.07–4.58; P=0.033), while ovarian function suppression was associated with both TRA (aOR, 2.34; 95% CI, 1.06–5.17; P=0.035) and persistent TRA (aOR, 2.71; 95% CI, 1.13–6.51; P=0.026). TRA was not significantly associated with DFS (adjusted HR, 0.71; 95% CI, 0.37–1.36; P=0.304) or OS (adjusted HR, 0.61; 95% CI, 0.25–1.49; P=0.278). **Conclusion:** TRA is common among premenopausal women receiving breast cancer therapy. Older age is the strongest predictor of persistent amenorrhea, while treatment-related ovarian suppression contributes substantially to menstrual dysfunction. TRA was not independently prognostic for DFS or OS.

Keywords: Breast cancer, treatment-related amenorrhea, chemotherapy-induced amenorrhea, ovarian function, ovarian function suppression, menstrual recovery, fertility preservation, premenopausal women.

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Introduction

Breast cancer is the most commonly diagnosed malignancy among women worldwide and represents a substantial health burden among premenopausal women. With advances in multimodal treatment, including chemotherapy, endocrine therapy, targeted therapy, and radiotherapy, survival outcomes have improved considerably.[1,2] However, treatment-related toxicities remain an important concern, particularly in younger women for whom preservation of ovarian function, fertility, and long-term quality of life are clinically relevant components of survivorship care.[3,4]

Treatment-related amenorrhea (TRA), defined as the cessation of menstruation following systemic anticancer therapy, is one of the most frequent reproductive toxicities observed in premenopausal women with breast cancer.[5,6] The occurrence and duration of amenorrhea vary substantially according to patient characteristics, treatment exposure, and duration of follow-up. Although menstrual function may resume after completion of cytotoxic therapy, persistent amenorrhea may indicate sustained treatment-related ovarian dysfunction and can have important consequences for fertility, vasomotor symptoms, sexual health, bone health, and psychological well-being.[7,8] Importantly, menstrual status alone does not establish diminished ovarian reserve or premature ovarian insufficiency; therefore, distinguishing transient from persistent TRA is clinically relevant when evaluating treatment-related reproductive outcomes.

The reported incidence of TRA varies widely, ranging from approximately 20% to more than 80%, largely because of differences in patient age, chemotherapy regimen, endocrine treatment, follow-up duration, and definitions used to characterize amenorrhea.[9-11] Age at treatment is consistently among the strongest determinants of menstrual recovery, with older premenopausal women having a substantially higher

Address for correspondence: Dr Soliya Tushar Makanbhai, Medical Officer, Kj Cancer and Super Speciality Hospital, Junagadh, Gujarat, India
E-mail: drtusharsoliya77@Gmail.Com

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likelihood of persistent amenorrhea than younger women.[12,13] Treatment-related factors, including exposure to alkylating agents and anthracycline- and taxane-containing chemotherapy, may further increase the risk of ovarian dysfunction.[5,7,14] Endocrine therapy and pharmacological ovarian function suppression (OFS) may also influence menstrual status, although amenorrhea occurring during intentional ovarian suppression should be interpreted differently from amenorrhea resulting from irreversible gonadal toxicity. These differences highlight the importance of evaluating both patient- and treatment-related predictors when characterizing TRA.[15,16]

Beyond its reproductive and survivorship implications, TRA has been investigated as a potential marker of treatment efficacy and prognosis in breast cancer. In particular, chemotherapy-induced amenorrhea has been associated with improved disease-free and overall survival in some studies, especially among patients with hormone receptor-positive disease.[9,17] One proposed explanation is that treatment-induced ovarian suppression may reduce endogenous estrogen exposure and thereby contribute to endocrine-mediated disease control. However, the prognostic association between TRA and breast cancer outcomes has not been consistent across studies and may be influenced by age, hormone receptor status, treatment regimen, ovarian suppression, and duration of follow-up.[3,9] Consequently, whether TRA independently contributes prognostic information beyond established clinicopathological and treatment-related factors remains uncertain.

In addition to its potential prognostic relevance, the duration and reversibility of treatment-related menstrual dysfunction are important determinants of survivorship outcomes. Women experiencing persistent amenorrhea may face greater concerns regarding fertility, menopausal symptoms, sexual function, and long-term reproductive health than those who subsequently regain menstruation.[4,5] Identifying patients at increased risk of persistent TRA before or during treatment may therefore facilitate individualized counseling, timely fertility-preservation discussions, and appropriate long-term survivorship planning.

Despite the clinical importance of treatment-related reproductive dysfunction, real-world data describing the patterns, predictors, and prognostic implications of TRA in premenopausal women with breast cancer remain limited, particularly in retrospective cohorts receiving contemporary multimodal systemic therapy. Furthermore, the distinction between transient and persistent amenorrhea and the independent contribution of TRA to survival outcomes require further evaluation.

Therefore, this retrospective study aimed to characterize the patterns of treatment-related amenorrhea, identify clinical and treatment-related predictors of TRA and persistent TRA, and evaluate the prognostic implications of TRA for disease-free survival and overall survival among premenopausal women with breast cancer receiving systemic therapy. By integrating reproductive outcomes with clinicopathological and treatment-related factors, this study seeks to provide clinically relevant evidence for individualized counseling, fertility and ovarian-function assessment, and long-term survivorship care.

Materials and Methods

Study Design and Participants: This retrospective observational study included 200 premenopausal women with histologically confirmed breast cancer who received systemic anticancer therapy at a tertiary cancer center. Patients were considered premenopausal if they had spontaneous and regular menstrual cycles before initiation of systemic treatment. Eligible patients had documented menstrual status before treatment and adequate clinical follow-up to determine post-treatment menstrual outcomes.

Patients were excluded if they had a history of hysterectomy or bilateral oophorectomy, documented ovarian insufficiency or menopause before initiation of systemic therapy, pregnancy during the assessment period, or insufficient clinical documentation to determine post-treatment menstrual status. Patients receiving pharmacological ovarian function suppression (OFS) were retained in the primary analysis because OFS represents an important component of contemporary breast cancer treatment. Its potential influence on menstrual status was considered during multivariable analyses.

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Ethics Committee (IEC/116/2026) of the participating institution. As this was a retrospective study involving de-identified clinical data, the requirement for individual informed consent was waived where applicable.

Data Collection and Definitions: Clinical, pathological, and treatment-related data were retrospectively extracted from institutional medical records using a standardized data-collection form. The variables collected included age at diagnosis, body mass index (BMI), clinical stage, histological type and grade, estrogen receptor (ER) and progesterone receptor (PR) status, human epidermal growth factor receptor 2 (HER2) status, molecular subtype, neoadjuvant chemotherapy, chemotherapy regimen, endocrine therapy, OFS, anti-HER2 therapy, radiotherapy, and duration of follow-up.

Chemotherapy exposure was categorized according to the presence or absence of anthracyclines, taxanes, and alkylating agents. Endocrine therapy was recorded according to the treatment received. OFS was defined as pharmacological ovarian suppression administered as part of breast cancer treatment. Because OFS directly suppresses ovarian activity and menstruation, amenorrhea occurring during OFS was interpreted as treatment-related menstrual suppression and was not considered, in isolation, evidence of irreversible ovarian failure.

Treatment-related amenorrhea (TRA) was defined as the absence of spontaneous menstruation for at least 12 consecutive months following initiation of systemic anticancer therapy, in the absence of pregnancy or another documented physiological or surgical cause of amenorrhea. Patients who subsequently resumed spontaneous menstruation after meeting the definition of TRA were classified as having transient TRA, whereas those who remained amenorrheic throughout the available follow-up were classified as having persistent TRA. Menstrual status was

determined from clinical documentation and patient-reported menstrual history recorded during follow-up.

Because menstrual status alone cannot establish diminished ovarian reserve or premature ovarian insufficiency, these conditions were not inferred solely from the presence of persistent TRA unless supported by independent clinical or biochemical evidence.

Outcomes: The primary outcome was the occurrence of treatment-related amenorrhea following systemic anticancer therapy.

Secondary outcomes included the pattern of menstrual recovery, categorized as transient or persistent TRA; demographic, clinicopathological, and treatment-related factors associated with TRA; and factors independently associated with persistent TRA.

For survival analyses, disease-free survival (DFS) was defined as the time from the date of breast cancer diagnosis to the first documented disease recurrence, progression, second primary malignancy, or death from any cause, according to the prespecified clinical definitions. Overall survival (OS) was defined as the time from diagnosis to death from any cause. Patients who did not experience an event were censored at the date of their last documented follow-up.

Statistical Analysis: Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR), and categorical variables as frequencies and percentages. Categorical variables were compared using the chi-square test or Fisher's exact test, while continuous variables were compared using the independent-samples t-test or Mann–Whitney U test, as appropriate. Univariable and multivariable logistic regression analyses were performed to identify factors associated with TRA and persistent TRA, with adjusted odds ratios (ORs) and 95% confidence intervals (CIs) reported. Kaplan–Meier analysis with the log-rank test was used to evaluate menstrual recovery, disease-free survival (DFS), and overall survival (OS). Cox proportional-hazards regression was used to assess the association of TRA with DFS and OS, with hazard ratios (HRs) and 95% CIs reported. A two-sided P value <0.05 was considered statistically significant. Analyses were performed using SPSS version 29.0.

Results

The baseline demographic, clinicopathological, and treatment characteristics of the study population are presented in [Table 1]. Among the 200 premenopausal women with breast cancer, the mean age was 39.8 ± 5.1 years, with 112 (56.0%) patients aged ≥40 years and a mean BMI of 24.7 ± 3.8 kg/m². Most patients had stage II disease (58.0%), invasive ductal carcinoma (88.0%), and grade 2 tumors (56.0%). ER-positive and PR-positive tumors were observed in 66.0% and 58.0% of patients, respectively, while 24.0% were HER2-positive. Regarding treatment characteristics, 46.0% received neoadjuvant chemotherapy, while anthracycline-, taxane-, and alkylating-agent-containing chemotherapy was administered to 82.0%, 88.0%, and 82.0% of patients, respectively. Endocrine therapy was received by 66.0%, ovarian function suppression by 27.0%, anti-HER2 therapy by 22.0%, and radiotherapy by 82.0% of patients.

The incidence and patterns of treatment-related amenorrhea according to baseline and treatment characteristics are summarized in [Table 2]. Overall, TRA occurred in 124 (62.0%) patients, including 78 (39.0%) with persistent TRA and 46 (23.0%) with transient TRA. The incidence of TRA was significantly higher among women aged ≥40 years than among those aged <40 years (73.2% vs 47.7%, P<0.001). TRA was also more frequent among patients receiving anthracycline-containing chemotherapy (65.9% vs 44.4%, P=0.028), taxane-containing chemotherapy (64.8% vs 41.7%, P=0.018), alkylating-agent exposure (65.9% vs 44.4%, P=0.028), endocrine therapy (68.2% vs 50.0%, P=0.019), and ovarian function suppression (77.8% vs 56.2%, P=0.008).

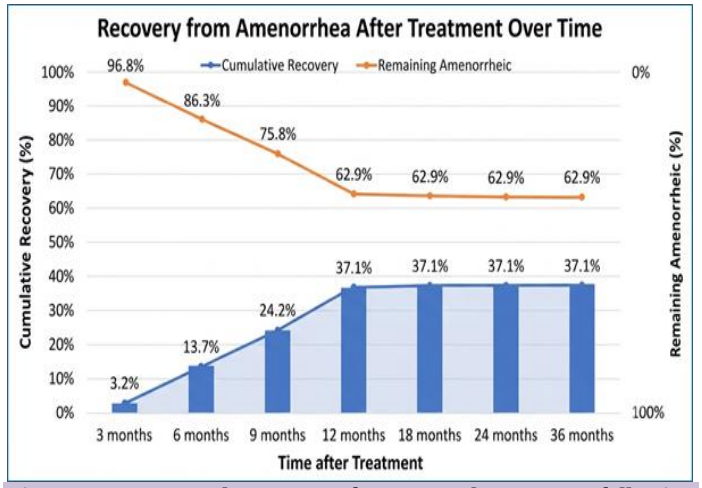


Figure 1: Temporal pattern of menstrual recovery following systemic therapy

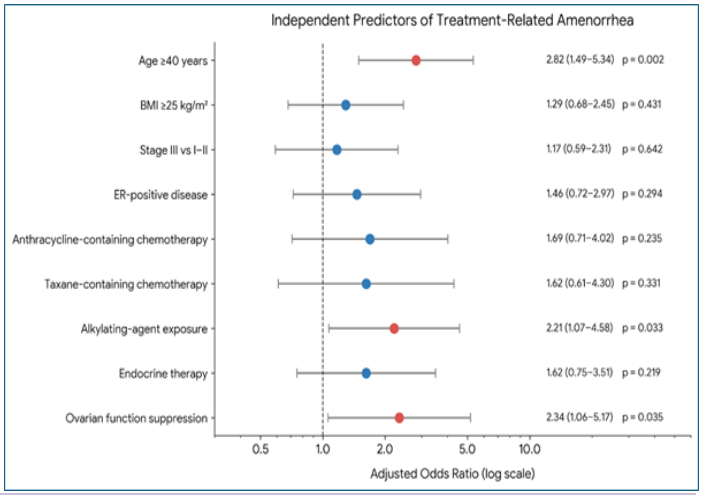


Figure 2: Forest plot of independent predictors of treatment-related amenorrhea

The factors associated with treatment-related amenorrhea are presented in [Table 3]. In multivariable logistic regression, age ≥40 years was independently associated with increased odds of

TRA (adjusted OR [aOR], 2.82; 95% CI, 1.49–5.34; P=0.002). Alkylating-agent exposure (aOR, 2.21; 95% CI, 1.07–4.58; P=0.033) and ovarian function suppression (aOR, 2.34; 95% CI, 1.06–5.17; P=0.035) were also independently associated with TRA. In contrast, BMI, clinical stage, ER status, anthracycline exposure, taxane exposure, and endocrine therapy were not independently associated with TRA after adjustment.

The predictors of persistent treatment-related amenorrhea are shown in [Table 4]. Age ≥40 years was independently associated with persistent TRA (aOR, 3.48; 95% CI, 1.58–7.67; P=0.002), while ovarian function suppression was also significantly associated with persistent TRA (aOR, 2.71; 95% CI, 1.13–6.51; P=0.026). Alkylating-agent exposure showed a significant association in univariable analysis but did not retain statistical significance after adjustment (aOR, 2.29; 95% CI, 0.95–5.52; P=0.065). No significant independent associations were observed for BMI, clinical stage, ER status, anthracycline exposure, taxane exposure, or endocrine therapy.

The association between treatment-related amenorrhea and survival outcomes is presented in [Table 5]. TRA was not significantly associated with either disease-free survival or overall survival. In the adjusted analysis, TRA was associated with DFS with an HR of 0.71 (95% CI, 0.37–1.36; P=0.304) and with OS with an HR of 0.61 (95% CI, 0.25–1.49; P=0.278), indicating that neither association reached statistical significance.

The temporal pattern of menstrual recovery following systemic therapy is illustrated in [Figure 1]. Among the 124 patients who developed TRA, 46 subsequently experienced spontaneous menstrual recovery, whereas 78 had persistent TRA, indicating that a substantial proportion of women with treatment-related amenorrhea eventually regained menstruation. The forest plot of independent predictors of TRA is presented in Figure 2, demonstrating that age ≥40 years, alkylating-agent exposure, and ovarian function suppression were independently associated with increased odds of TRA, with age ≥40 years showing the strongest association. The adjusted probability of persistent TRA according to age at diagnosis is shown in Figure 3. Women aged ≥40 years had a higher adjusted probability of persistent TRA than those aged <40 years, consistent with the multivariable analysis identifying older age as the strongest independent predictor of persistent TRA.

Table 1: Baseline demographic, clinicopathological, and treatment characteristics of the study population

Characteristic	Overall cohort (N = 200)
Demographic characteristics	
Age at diagnosis, years, mean ± SD	39.8 ± 5.1
Age ≥40 years, n (%)	112 (56.0)
BMI, kg/m², mean ± SD	24.7 ± 3.8
BMI ≥25 kg/m², n (%)	74 (37.0)
Tumor characteristics	
Clinical stage, n (%)	
├─ Stage I	24 (12.0)
├─ Stage II	116 (58.0)
└─ Stage III	60 (30.0)
Histological type, n (%)	
├─ Invasive ductal carcinoma	176 (88.0)
└─ Other histological types	24 (12.0)
Histological grade, n (%)	
├─ Grade 1	24 (12.0)
├─ Grade 2	112 (56.0)
└─ Grade 3	64 (32.0)
ER-positive, n (%)	132 (66.0)
PR-positive, n (%)	116 (58.0)
HER2-positive, n (%)	48 (24.0)
Molecular subtype, n (%)	
├─ Luminal A	62 (31.0)
├─ Luminal B	70 (35.0)
├─ HER2-enriched	28 (14.0)
└─ Triple-negative	40 (20.0)
Treatment characteristics	
Neoadjuvant chemotherapy, n (%)	92 (46.0)
Anthracycline-containing chemotherapy, n (%)	164 (82.0)
Taxane-containing chemotherapy, n (%)	176 (88.0)
Alkylating-agent exposure, n (%)	164 (82.0)
Endocrine therapy, n (%)	132 (66.0)
Ovarian function suppression, n (%)	54 (27.0)
Anti-HER2 therapy, n (%)	44 (22.0)
Radiotherapy, n (%)	164 (82.0)

Abbreviations: BMI, body mass index; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; SD, standard deviation.

Table 2: Incidence and patterns of treatment-related amenorrhea according to baseline and treatment characteristics

Characteristic	Total, n	TRA, n (%)	Persistent TRA, n (%)	Transient TRA, n (%)	P value*
Overall cohort	200	124 (62.0)	78 (39.0)	46 (23.0)	—
Age at diagnosis					<0.001
<40 years	88	42 (47.7)	18 (20.5)	24 (27.3)	
≥40 years	112	82 (73.2)	60 (53.6)	22 (19.6)	
BMI, kg/m²					0.214
<25	126	74 (58.7)	44 (34.9)	30 (23.8)	
≥25	74	50 (67.6)	34 (45.9)	16 (21.6)	
Clinical stage					0.318
I–II	140	84 (60.0)	50 (35.7)	34 (24.3)	
III	60	40 (66.7)	28 (46.7)	12 (20.0)	
ER status					0.081
Negative	68	36 (52.9)	22 (32.4)	14 (20.6)	
Positive	132	88 (66.7)	56 (42.4)	32 (24.2)	
Anthracycline-containing chemotherapy					0.028
No	36	16 (44.4)	10 (27.8)	6 (16.7)	
Yes	164	108 (65.9)	68 (41.5)	40 (24.4)	
Taxane-containing chemotherapy					0.018
No	24	10 (41.7)	6 (25.0)	4 (16.7)	
Yes	176	114 (64.8)	72 (40.9)	42 (23.9)	
Alkylating-agent exposure					0.028
No	36	16 (44.4)	8 (22.2)	8 (22.2)	
Yes	164	108 (65.9)	70 (42.7)	38 (23.2)	
Endocrine therapy					0.019
No	68	34 (50.0)	18 (26.5)	16 (23.5)	
Yes	132	90 (68.2)	60 (45.5)	30 (22.7)	
Ovarian function suppression					0.008
No	146	82 (56.2)	46 (31.5)	36 (24.7)	
Yes	54	42 (77.8)	32 (59.3)	10 (18.5)	

Abbreviations: BMI, body mass index; ER, estrogen receptor; TRA, treatment-related amenorrhea.

Table 3: Univariable and multivariable logistic regression analysis of factors associated with treatment-related amenorrhea

Predictor	Univariable OR	95% CI	P value	Adjusted OR	95% CI	P value
Age ≥40 years	3.02	1.66–5.50	<0.001	2.82	1.49–5.34	0.002
BMI ≥25 kg/m²	1.47	0.80–2.71	0.214	1.29	0.68–2.45	0.431
Stage III vs I–II	1.33	0.71–2.49	0.319	1.17	0.59–2.31	0.642
ER-positive disease	1.78	0.93–3.39	0.081	1.46	0.72–2.97	0.294
Anthracycline-containing chemotherapy	2.42	1.10–5.31	0.028	1.69	0.71–4.02	0.235
Taxane-containing chemotherapy	2.58	1.04–6.40	0.041	1.62	0.61–4.30	0.331
Alkylating-agent exposure	2.42	1.10–5.31	0.028	2.21	1.07–4.58	0.033
Endocrine therapy	2.00	1.00–4.00	0.050	1.62	0.75–3.51	0.219
Ovarian function suppression	2.72	1.28–5.78	0.009	2.34	1.06–5.17	0.035

Abbreviations: BMI, body mass index; CI, confidence interval; ER, estrogen receptor; OR, odds ratio; TRA, treatment-related amenorrhea.

Table 4: Univariable and multivariable logistic regression analysis of factors associated with persistent treatment-related amenorrhea

Predictor	Univariable OR	95% CI	P value	Adjusted OR	95% CI	P value
Age ≥40 years	3.91	1.86–8.21	<0.001	3.48	1.58–7.67	0.002
BMI ≥25 kg/m²	1.48	0.74–2.96	0.270	1.34	0.64–2.82	0.437
Stage III vs I–II	1.57	0.76–3.25	0.221	1.39	0.63–3.06	0.410
ER-positive disease	1.53	0.73–3.22	0.263	1.29	0.58–2.86	0.533
Anthracycline-containing chemotherapy	1.62	0.70–3.74	0.259	1.31	0.53–3.24	0.558
Taxane-containing chemotherapy	1.47	0.59–3.67	0.407	1.22	0.46–3.22	0.688
Alkylating-agent exposure	2.61	1.14–5.96	0.023	2.29	0.95–5.52	0.065
Endocrine therapy	2.00	0.99–4.03	0.054	1.62	0.75–3.51	0.219
Ovarian function suppression	3.17	1.40–7.18	0.006	2.71	1.13–6.51	0.026

Abbreviations: BMI, body mass index; CI, confidence interval; ER, estrogen receptor; OR, odds ratio; TRA, treatment-related amenorrhea.

Table 5: Association between treatment-related amenorrhea and survival outcomes

Survival outcome	Univariable HR	95% CI	P value	Adjusted HR	95% CI	P value
Disease-free survival	0.74	0.40–1.36	0.329	0.71	0.37–1.36	0.304
Overall survival	0.63	0.27–1.47	0.286	0.61	0.25–1.49	0.278

Abbreviations: CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; OS, overall survival; TRA, treatment-related amenorrhea.

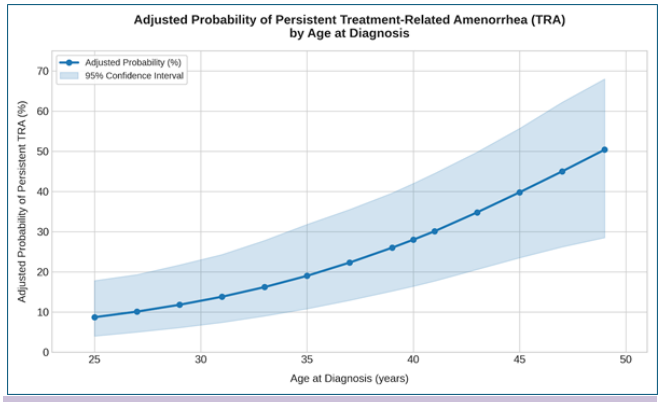


Figure 3: Adjusted probability of persistent treatment-related amenorrhea according to age at diagnosis

Discussion

In this retrospective cohort of 200 premenopausal women with breast cancer, treatment-related amenorrhea (TRA) occurred in 62.0% of patients, with persistent TRA observed in 39.0% and transient TRA in 23.0%. Increasing age was the most consistent determinant of menstrual dysfunction, with women aged ≥40 years having significantly higher rates of TRA and persistent TRA than younger women. In multivariable analysis, age ≥40 years, alkylating-agent exposure, and ovarian function suppression (OFS) were independently associated with the occurrence of TRA, whereas age ≥40 years and OFS were independently associated with persistent TRA. In contrast, TRA was not independently associated with disease-free survival (DFS) or overall survival (OS). Collectively, these findings emphasize that the clinical significance of TRA extends beyond the occurrence of amenorrhea itself and depends on patient age, treatment exposure, reversibility of menstrual suppression, and the context in which ovarian function is being assessed.

The observed TRA rate of 62.0% is consistent with the substantial incidence of treatment-related menstrual dysfunction reported in contemporary breast cancer cohorts, although direct comparisons between studies are complicated by substantial variation in definitions and follow-up duration. In a prospective cohort of 76 premenopausal women, Raveendran et al,[1] reported clinical amenorrhea in 84.2% of patients and biochemical amenorrhea in 78.9%, with clinical amenorrhea defined as cessation of menstruation for at least three months. Their higher incidence compared with our cohort may partly reflect the shorter definition of amenorrhea, prospective menstrual surveillance, and biochemical confirmation of ovarian suppression. Importantly, Raveendran et al,[1] also demonstrated that clinical and biochemical amenorrhea were significantly associated, supporting the clinical relevance of menstrual assessment while simultaneously highlighting the distinction between menstrual status and biochemical ovarian function. Similarly, the updated meta-analysis by Wang et al,[4] comprising 68 studies and 26,585 patients, demonstrated substantial heterogeneity in reported chemotherapy-induced amenorrhea rates, ranging from 15.1% to 98.3%, largely because different studies used definitions ranging from 3 to 12 months of amenorrhea. Thus, the 62.0% incidence observed in our cohort should be interpreted within the context of the definition and follow-up framework used in the present study rather than as a universal estimate of TRA incidence.

Age emerged as the strongest and most consistent predictor of TRA in our study. Women aged ≥40 years had approximately threefold higher adjusted odds of TRA and more than threefold higher adjusted odds of persistent TRA than women younger than 40 years. This finding is biologically plausible because ovarian follicular reserve declines with age, reducing the capacity of the ovary to recover following cytotoxic injury. Our findings are strongly concordant with Wang et al,[4] whose meta-analysis identified younger age as a factor associated with a lower incidence of chemotherapy-induced amenorrhea. Similarly, Kabirian et al,[15] in a large prospective longitudinal cohort of 1,636 premenopausal women, found that chemotherapy-related amenorrhea was more frequent among older women and that late menstrual recovery could occur even after prolonged amenorrhea. The consistency across these substantially different study designs strengthens the evidence that age is one of the most clinically useful predictors of post-treatment menstrual recovery.

The age effect observed in our cohort also supports the concept that menstrual recovery is a dynamic process rather than a binary treatment toxicity. In our cohort, 46 of 124 women with TRA subsequently experienced menstrual recovery, indicating that a substantial proportion of women with treatment-associated amenorrhea may regain ovarian activity. Kabirian et al,[15] similarly reported persistent amenorrhea in 57.1% of women included in their longitudinal quality-of-life analysis, while also documenting late recovery patterns. These findings are clinically important because early post-treatment amenorrhea should not automatically be interpreted as permanent ovarian failure. The distinction is particularly relevant when counseling younger women regarding fertility, contraception, endocrine therapy, and expectations for recovery.

The importance of differentiating menstrual recovery from ovarian reserve is further supported by recent evidence evaluating biochemical markers of ovarian function. Weidlinger et al,.[9] reported a substantial decline in anti-Müllerian hormone (AMH) after chemotherapy, with a pooled mean reduction of 1.61 ng/mL and more than half of breast cancer survivors demonstrating very low ovarian reserve after treatment. However, the same study emphasized that amenorrhea is an unreliable surrogate for infertility because endocrine treatment can independently alter menstrual function,[9] More recently, van Zwol-Janssens et al,[10] using individual patient data from 1,029 women, found that ovarian function resumed in approximately 24%–61% of women depending on follow-up duration and that higher pre-treatment AMH was associated with greater likelihood of ovarian function recovery. Nevertheless, no clinically reliable AMH threshold could be established across assays. These findings reinforce an important interpretation of our study: persistent TRA may identify women at increased risk of sustained reproductive dysfunction, but menstrual status alone cannot establish diminished ovarian reserve or premature ovarian insufficiency.

Treatment exposure also influenced TRA in our cohort. Alkylating-agent exposure was independently associated with any TRA, with an adjusted OR of 2.21, whereas the association with persistent TRA did not reach conventional statistical significance after multivariable adjustment. This pattern is consistent with the established gonadotoxic potential of alkylating chemotherapy. Furlanetto et al,[3] in a prospective analysis of four randomized neoadjuvant/adjuvant breast cancer trials, demonstrated substantial chemotherapy-related ovarian failure in young women, supporting the concept that the intensity and composition of systemic therapy are important determinants of ovarian toxicity. The broader review by Yildiz et al,[6] likewise emphasized the dependence of ovarian dysfunction on patient age and treatment characteristics. Our findings therefore support a clinically relevant distinction between the occurrence of TRA and its persistence: some treatment exposures may increase the probability of menstrual suppression without necessarily being sufficient, after adjustment for age and other factors, to independently predict permanent or prolonged amenorrhea.

The lack of independent associations between anthracycline- or taxane-containing chemotherapy and TRA after adjustment is also noteworthy. In univariable analyses, both exposures were associated with higher rates of TRA; however, these associations were attenuated after adjustment. This may reflect the strong correlation between chemotherapy components and the use of multi-agent regimens in routine breast cancer practice. Wang et al,[4] similarly identified chemotherapy regimen as an important determinant of chemotherapy-induced amenorrhea, but their meta-analysis also demonstrated heterogeneity across treatment regimens. These findings suggest that evaluating individual cytotoxic agents in isolation may underestimate the complexity of ovarian toxicity, which is influenced by cumulative exposure, combination therapy, age, baseline ovarian reserve, and subsequent endocrine treatment.

OFS requires particularly careful interpretation in the present study. OFS was associated with both any TRA and persistent TRA after multivariable adjustment. However, unlike chemotherapy-induced ovarian injury, pharmacological OFS is an intentional therapeutic intervention designed to suppress ovarian function. Therefore, amenorrhea occurring during OFS cannot be equated with irreversible ovarian failure. This distinction is supported by contemporary evidence emphasizing the therapeutic role of OFS in premenopausal hormone receptor-positive breast cancer. Fleege et al,[12] examined ovarian function suppression in premenopausal women receiving concurrent endocrine therapy, while Ma et al,[13] reviewed the clinical indications and survival implications of GnRH agonist-based OFS. The association observed in our cohort should consequently be interpreted as evidence that OFS substantially influences menstrual status rather than as evidence that OFS independently causes permanent gonadal damage.

This distinction is also relevant when interpreting ovarian recovery during endocrine therapy. Lammers et al,[14] in long-term follow-up from the DATA trial, reported ovarian function recovery in 12% of monitored women with chemotherapy-induced ovarian function failure receiving adjuvant anastrozole; ovarian function recovery was associated with numerically poorer DFS and OS outcomes, although the confidence intervals were wide. Their findings emphasize that ovarian recovery can have clinical implications in hormone receptor-positive breast cancer and that apparent post-treatment ovarian failure may not always be permanent. In contrast, our study assessed TRA and subsequent menstrual recovery in a broader real-world population and did not demonstrate a significant association between TRA itself and survival. The different study populations and definitions are important when comparing these results.

Our prognostic findings differ from the favorable survival association reported in earlier pooled evidence. Wang et al,.[4] reported that chemotherapy-induced amenorrhea was associated with improved DFS and OS, with pooled estimates corresponding to substantially lower odds of recurrence and death. In the present cohort, however, TRA was not significantly associated with DFS (adjusted HR, 0.71; 95% CI, 0.37–1.36; P=0.304) or OS (adjusted HR, 0.61; 95% CI, 0.25–1.49; P=0.278). The direction of the point estimates was compatible with a potentially favorable association, but the confidence intervals crossed unity and therefore do not support a statistically significant prognostic effect. Several factors may explain the discrepancy. First, the meta-analysis by Wang et al,[4] included heterogeneous historical treatment cohorts, whereas our cohort reflects contemporary multimodal management. Second, TRA definitions varied substantially across the studies included in the meta-analysis. Third, ovarian suppression and endocrine therapy may influence both menstrual status and breast cancer outcomes, creating complex confounding and mediation that are difficult to eliminate in retrospective analyses. Finally, the relatively small number of survival events in our cohort may have limited statistical power to detect modest associations.

The relationship between ovarian function and prognosis is biologically plausible, particularly in hormone receptor-positive disease, because ovarian estrogen production can influence endocrine responsiveness. However, menstrual status is an imperfect surrogate for estrogen exposure. The final outcomes of the SOFT and TEXT trials reported by Francis et al,[16] further reinforce the importance of effective ovarian suppression in determining outcomes among premenopausal women with hormone receptor-positive early breast cancer. Thus, the absence of a statistically significant prognostic association between TRA and survival in our cohort should not be interpreted as evidence that ovarian function is irrelevant to breast cancer outcomes. Rather, it suggests that amenorrhea as a clinical marker alone may not provide independent prognostic information once established tumor and treatment characteristics are considered.

The distinction between ovarian suppression, ovarian recovery, and ovarian reserve is particularly important for survivorship care. The systematic review by Weidlinger et al,[9] demonstrated a substantial post-chemotherapy decline in ovarian reserve, while van Zwol-Janssens et al,[10] showed that pre-treatment AMH is associated with subsequent ovarian function recovery but that no universally applicable AMH threshold can currently

guide treatment decisions. Together, these findings suggest that clinical menstrual history should be integrated with appropriate reproductive and endocrine assessment rather than used as the sole measure of ovarian health. This has practical implications for patients in whom fertility preservation or future pregnancy is relevant.

The findings also have implications for clinical counseling. The ASCO fertility-preservation guideline update by Su et al,[17] emphasizes the importance of discussing fertility preservation with patients at risk of treatment-related infertility before cancer treatment begins. Our finding that age ≥40 years substantially increases the likelihood of TRA and persistent TRA supports early individualized counseling, particularly when gonadotoxic systemic therapy is planned. At the same time, younger age should not be interpreted as protection against ovarian injury, because substantial ovarian reserve depletion can occur even when menstruation subsequently resumes. Therefore, fertility-preservation discussions should be based on anticipated treatment gonadotoxicity, age, reproductive goals, and available ovarian reserve assessment rather than menstrual status alone.

Our results also complement the quality-of-life findings reported by Kabirian et al,[15] Their large longitudinal study demonstrated that persistent chemotherapy-related amenorrhea was associated with worse insomnia, greater systemic therapy-related symptoms, and impaired sexual functioning. Although quality of life was not directly evaluated in our retrospective cohort, the relatively high proportion of women with persistent TRA highlights the potential survivorship burden of this toxicity. In routine clinical practice, documentation of menstrual recovery should therefore be accompanied by assessment of menopausal symptoms, sexual health, fertility concerns, and psychosocial needs rather than being treated simply as a laboratory or treatment-toxicity endpoint.

Limitations: This study has several limitations. First, its retrospective single-center design introduces the possibility of selection bias, information bias, and residual confounding. Second, menstrual status was derived from clinical documentation rather than standardized prospective menstrual diaries and serial biochemical assessment of ovarian function. Third, we did not have systematic measurements of AMH, FSH, or estradiol; therefore, persistent TRA should not be interpreted as a direct measure of diminished ovarian reserve or premature ovarian insufficiency. Fourth, treatment heterogeneity, particularly the use of endocrine therapy and OFS, complicates the interpretation of amenorrhea as a marker of chemotherapy-induced ovarian injury. Fifth, the sample size and number of survival events may have limited the statistical power of the prognostic analyses. Finally, the observational design prevents causal inference regarding the relationships between individual treatment exposures, menstrual recovery, and survival.

Clinical and Research Implications: Despite these limitations, the present study provides clinically relevant real-world evidence that TRA is common among premenopausal women receiving contemporary breast cancer therapy and that its persistence is strongly influenced by age and treatment-related ovarian suppression. The findings support risk-adapted counseling before treatment, particularly for women approaching 40 years of age and those expected to receive gonadotoxic systemic therapy. Future prospective studies should integrate menstrual history with serial AMH, FSH, estradiol, and fertility outcomes and should distinguish pharmacological ovarian suppression from irreversible chemotherapy-related ovarian dysfunction. Longitudinal multicenter studies with standardized definitions and sufficiently long follow-up are also needed to determine whether persistent TRA has prognostic value independent of ovarian suppression and endocrine therapy.

Conclusion

In this cohort, treatment-related amenorrhea affected nearly two-thirds of premenopausal women with breast cancer, while approximately two-fifths experienced persistent amenorrhea. Older age was the most consistent predictor of both TRA and persistent TRA, whereas alkylating-agent exposure was independently associated with TRA and OFS was associated with both TRA and persistent TRA. However, TRA was not independently associated with DFS or OS. These findings indicate that TRA is primarily an important marker of treatment-related reproductive toxicity rather than a definitive prognostic biomarker. Incorporating age, treatment regimen, ovarian suppression, and individualized fertility goals into pretreatment counseling may improve reproductive risk assessment and survivorship care.

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Conflicts of interest

There are no conflicts of interest.

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