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Impact of de novo metastatic breast cancer on survival of patients: A comparative retrospective observational study

Mahmut Ucar[a,*], Mukaddes Yilmaz[a], Eda Erdis[b], Birsen Yucel[b]

[a] *Sivas Cumhuriyet University, Faculty of Medicine, Department of Medical Oncology, Sivas, Türkiye*
[b] *Sivas Cumhuriyet University, Faculty of Medicine, Department of Radiation Oncology, Sivas, Türkiye*

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Abstract

Aim: The aim is to compare the characteristics of de nova metastatic BC (dnMBC) and recurrent metastatic BC (rMBC).

Materials and Methods: The study included female patients diagnosed with histologically dnMBC and rMBC who received treatment at a tertiary care center from 2010 to 2019. Medical records were utilized to collect information regarding the patients' tumors, alongside clinical and demographic characteristics. Each patient's overall survival (OS) was determined starting from the moment they were diagnosed with MBC. The patients with dnMBC and rMBC were compared statistically based on their clinical and sociodemographic features.

Results: Out of the 322 patients, 213 (66.1%) had rMBC, and 109 (33.9%) had dnMBC. Patients with dnMBC were older ($p<0.001$), and had a worse Eastern Cooperative Oncology Group Performance Score ($p<0.001$), a higher number of postmenopausal patients ($p<0.001$). Multicentricity/multifocality ($p=0.017$), human epidermal growth factor receptor 2 positivity ($p=0.010$), T-stage, N-stage ($p<0.001$), and tumor marker levels ($p<0.05$) showed significant differences between the groups. However, neither the median OS (29.0 months vs 21.0 months, respectively; $p=0.152$) nor the metastatic spread patterns ($p>0.05$) differed significantly between the groups.

Conclusion: There was no difference in OS. Clinic subtype, tumor grade, and treatment modalities may confuse the survival outcomes in BC patients.

Introduction

Breast cancer (BC) ranks among the most commonly diagnosed cancers globally [1, 2]. In addition, the incidence of BC progressively rises [3]. Early-stage BC mortality rates have decreased, distant disease-free survival rates have increased [4] and metastatic BC (MBC)-related survival trends have improved in recent years [5].

MBC diagnosis is established either at the time of or shortly after BC diagnosis (de novo MBC [dnMBC]) or at the time of recurrence in non-metastatic cancer (recurrent MBC [rMBC]) [6-8]. Patients with dnMBC represent 5%-15% of all BC cases, while 20%-30% of early BC patients develop rMBC following standard treatment [1, 6].There is no study to date on the probable survival differences between dnMBC and rMBC patient populations [4]. Previous studies have suggested that dnMBC and rMBC patients represent two distinct populations with diverse histological and molecular profiles, e.g., metastatic site, demographic characteristics, e.g., age at metastatic diagnosis and socioeconomic status, and clinical risks, e.g., intrinsic BC subtypes, all of which likely influence prognosis [1, 4, 6]. Survival outcomes of rMBC patients are generally worse than those of dnMBC patients yet are known to vary depending on patient- and tumor-related features [4, 9]. Large-scale studies including diverse populations are essential to clarify the influence of the type of metastasis on BC prognosis.

The objective of this investigation was to analyze the clinicopathological traits of patients suffering from dnMBC and rMBC, as well as to identify the risk factors that impact their survival outcomes.

Materials and Methods

Study design and patients selection

It was carried out as a comparative retrospective observational analysis. The study protocol received approval from the local ethics committee (Sivas Republic University, ethical committee for non-invasive clinical research, approval

*Corresponding author:
Email address: dr.mahmutucar@gmail.com (Mahmut Ucar)

on November 16, 2023, decision no: 2023-11/12). The research was conducted following the ethical principles in the Declaration of Helsinki. Because of the retrospective design of the study and the patients' anonymity, written informed consent could not be obtained.

The study included female patients aged 18 and older with histologically confirmed dnMBC and rMBC, treated at the Oncology Center of Cumhuriyet University in Sivas, Turkey, from 2010 to 2019. Patients with non-metastatic disease, bilateral BC, other malignancies, local recurrence limited to regional lymph nodes and/or chest wall, and incomplete demographic, clinical, and tumor data were excluded from the study. Overall, 322 MBC patients took part in the study.

For BC staging, the 7th AJCC guideline was followed, and stage IV disease was grouped as dnMBC and rMBC [10]. Distant metastasis found at admission or within three months of the diagnosis is classified as dnMBC [7, 8]. Metastatic disease identified more than three months after the diagnosis is classified as rMBC [6].

Data collection

Patients' sociodemographic, i.e., age, body mass index (BMI), menopausal status, and familial BC history, the Eastern Cooperative Oncology Group (ECOG) performance status, tumor markers at the time of metastatic BC dignosis, tumor characteristics, i.e., side, size, T and N staging, histological type and grade, human epidermal growth factor receptor 2 (HER2), progesterone receptor (PR), estrogen receptor (ER) positivity, Ki-67 value, location and type of organ metastasis, and treatment details were gathered from the medical records accessible in the hospital's information system.

Positive nuclear immunohistochemical staining of at least 1% of the tumor cells was considered to indicate ER and PR positivity [1]. Patients with strong HER2 (+3) staining on immunohistochemical staining were considered HER2-positive. The preparations of patients with moderate (+2) staining were checked for HER2-positivity by fluorescence in situ hybridization. ER, PR, and HER2 positivity were used to identify the intrinsic BC subtypes. The luminal-A subtype was identified in patients with low Ki-67, ER and PR positive, and HER2 negative, while the luminal-B subtype was defined as patients who were HER2 negative ER or PR positive but high Ki-67. Furthermore, patients with HER2 and ER and/or PR positive were classified as having the luminal-B HER2 subtype. Only HER2 positive cases were included in the HER2 positive subtype. The triple-negative subtype was defined as patients who were negative for ER, PR, and HER2 [6].

Imaging and/or pathology results supported the diagnosis of metastatic disease based on clinical signs of metastases associated with the affected organ or system. We categorized BC cases as oligo- ($\leq$5) or polymetastatic (>6) based on the number of metastases [11]. The metastases were also categorized according to their site, i.e., bones, lung/pleura, liver, distant lymph node, and central nervous system, e.g., parenchymal brain metastasis and/or leptomeningeal metastasis [1].

Treatments

In line with the standard treatment approaches for MBC, patients with luminal BC subtypes were started on systemic treatment along with chemotherapy as well as hormonal treatment, provided that there was no visceral crisis, patients with HER2 positivity were started on anti-HER2 treatment along with chemotherapy, and patients with triple-negative BC subtype were started on chemotherapy.

Statistical analysis

For the statistical analysis of collected data, we employed the JASP 0.17.3 software (Jeffreys' Amazing Statistics Program, version 0.17.3, 2023, available at https://jasp-stats.org), Jamovi project 2.3.28 (Jamovi, version 2.3.28, 2023, available at https://www.jamovi.org), and SPSS version 23 (IBM Corp., Armonk, New York, USA). When α=0.05, β=0.10, 1-β=0.98, it was decided to include 322 individuals, and the power of the test was determined as 0.98844. In the G Power program (version 3.1.9.7), the power of the study was calculated by selecting effect size=0.5. For continuous variables that conformed to a normal distribution, the descriptive statistics derived from the data were expressed as mean ± standard deviation (SD) values. For continuous variables that deviated from normal distribution, they were represented as medians along with minimum and maximum values. Categorical variables were presented as numbers (n) and percentage values (%). The normal distribution properties of continuous variables were assessed using the Shapiro-Wilk, Kolmogorov-Smirnov, and Anderson-Darling tests. Fisher's Exact Test was applied when the expected count of cells in 2x2 tables was less than five; Pearson's chi-square test was utilized when the expected count of cells in 2x2 tables was five or more; and the Fisher-Freeman-Halton test was employed when the expected count of cells in RxC tables was less than five. These tests were used to compare the differences in categorical variables across groups. In the chi-square test, a Bonferroni adjustment was applied to identify the variable that influenced the multiple counts of cells in tables such as 2x3 and 2x4. The Mann-Whitney U test and independent samples t-test were used to compare two independent groups based on continuous data.

Each patient's overall survival (OS) was determined starting from the moment they were diagnosed with metastatic BC. As a result, OS denoted the interval between the diagnosis of MBC and the date of death or the most recent follow-up [12]. The survival curves were plotted using the Kaplan-Meier survival method. Using the log-rank test, we evaluated the groups' differences in survival outcomes.

Statistical significance was defined as probability (p) statistics of < 0.05.

Results

Between 2010 and 2019, 1198 patients were admitted to Sivas Cumhuriyet University Oncology Center with breast carcinoma and 322 (27%) had metastatic disease. Of the 322 patients included in the study, 109 (33.9%) had dnMBC, and 213 (66.1%) had rMBC. The median metastasis development time in the rMBC group was 37.0 (range:

Table 1. Sociodemographic and clinical characteristics of the study groups.

	Group dnMBC (n=109)	Group rMBC (n=213)	p-values
Age †	57.0 [18.0 – 83.0]	47.0 [25.0 – 77.0]	<0.001**
Age groups ‡			
<65 years	80 (73.4)	188 (88.3)	0.001*
≥65 years	29 (26.6)	25 (11.7)	
BMI (kg/m^2) †	29.2 ± 5.9	29.9 ± 5.5	0.456***
Menopause status ‡			
Pre	34 (31.2)	112 (52.6)	<0.001*
Post	75 (68.8)	101 (47.4)	
Family history of breast cancer ‡	20 (18.3)	41 (19.2)	0.964*
ECOG Performance status ‡			
0[a]	28 (25.7)	111 (52.1)	
1	45 (41.3)	73 (34.3)	<0.001*
2 or more[a]	36 (33.0)	29 (13.6)	
Comorbidities ‡			
Hypertension	31 (28.4)	53 (24.9)	0.580*
Diabetes mellitus	18 (16.5)	31 (14.6)	0.765*
Coronary artery disease	7 (6.4)	14 (6.6)	0.999*

†: median [min-max], ‡: n (%). dnMBC: de novo metastatic breast cancer, rMBC: recurrent metastatic breast cancer, BMI: body mass index, ECOG: the Eastern Cooperative Oncology Group. *. Pearson Chi-Square test. **. Mann-Whitney U test. ***. Independent Samples T-Test. [a]: variables that make a difference between groups after bonferroni adjustment.

4-218) months. In approximately two-thirds (67.0%) of the rMBC patients, metastasis was diagnosed 24 months or later after the initial BC diagnosis. Table 1 shows the comparison of sociodemographic and clinical characteristics of the groups. There were statistically significant differences between the groups in terms of age, menopausal status and performance status (<0.05 for all cases). Table 2 shows how the study groups' tumoral features were distributed at the time of the initial BC diagnosis. Multicentricity/multifocality, HER2 positive, T-stage tumor, and N-stage tumor rates showed significant variations across the groups (p<0.05 for all cases). There were significant differences between the groups in CEA and CA 15-3 levels and in the rates of patients with high and normal CEA and CA 15-3 levels (Table 3). There was no significant difference between the groups in the characteristics of metastatic disease, i.e., site and number of metastases (p>0.05) (Table 4). In this study, median follow-up was 22 (1-186) months. Median OS was 31.0 months in the dnMBC group and 25.0 months in the rMBC group (Figure 1). Kaplan-Meier survival analysis using the Log-Rank test revealed no significant difference in OS between the groups (p=0.393).

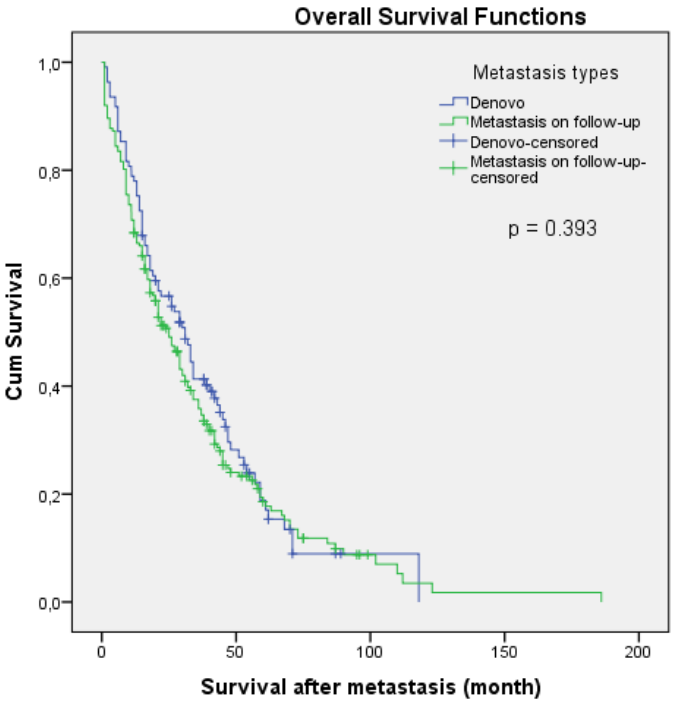

Figure 1. Kaplan-Meier Analysis of Overall Survival after Metastasis in Group dnMBC and Group rMBC.

Discussion

Our findings indicated significant differences in demographic and clinical characteristics, such as age, menopausal status, and ECOG performance status, between BC patients with dnMBC and rMBC. Accordingly, older, postmenopausal patients with higher ECOG performance status were more likely to have dnMBC than rMBC. Tumors with higher T and N stages and elevated tumor markers were significantly associated with dnMBC. Yet, no significant difference was found between the patients with dnMBC and rMBC in terms of survival outcomes. There are similar studies in the literatüre. the observations of our clinic in this regard will be discussed.

There is some controversy about the definition of dnMBC. BC patients who develop metastasis within three months

Table 2. Tumoral characteristics of the patients at the diagnosis of breast cancer in Groups dnMBC and rMBC.

	Group dnMBC (n=109)	Group rMBC (n=213)	p-values
Side ‡			
Right	61 (56.0)	95 (44.6)	0.070*
Left	48 (44.0)	118 (55.4)	
Tumor diameter (cm) †	3.0 [0.0 – 52.0]	3.3 [0.0 – 85.0]	0.939**
Multi-centricity/focality ‡	17 (34.0)	35 (17.5)	**0.017***
Histology grades ‡			
1	22 (20.2)	42 (19.7)	
2	54 (49.5)	101 (47.4)	0.893*
3	33 (30.3)	70 (32.9)	
Histopathology ‡			
Ductal	97 (89.0)	170 (79.8)	
Lobular	3 (2.8)	11 (5.2)	0.227*
Mixed	6 (5.5)	17 (8.0)	
Others	3 (2.8)	15 (7.0)	
ER status ‡, *Positive*	77 (70.6)	138 (64.8)	0.352*
PR status ‡, *Positive*	62 (56.9)	124 (58.2)	0.912*
HER2 status ‡, *Positive*	48 (44.0)	60 (28.8)	**0.010***
HER2 IHC results ‡			
0 and 1[a]	49 (45.0)	130 (61.0)	
2	22 (20.2)	38 (17.8)	**0.012***
3[a]	38 (34.9)	45 (21.1)	
Ki-67 (%) †	30.0 [0.0 – 90.0]	29.0 [0.0 – 100.0]	0.338**
Molecular subtypes ‡			
Luminal A	22 (20.2)	48 (23.1)	
Luminal B HER2 negative	25 (22.9)	56 (26.9)	
Luminal B HER2 positive	31 (28.4)	41 (19.7)	0.077*
HER2 positive	17 (15.6)	19 (9.1)	
Triple negative	14 (12.8)	44 (21.2)	
Lymphovascular invasion ‡	33 (62.3)	123 (65.4)	0.793*
Perineural invasion ‡	18 (47.4)	85 (51.8)	0.752*
T stage ‡			
T1	15 (13.8)	29 (13.6)	
T2[a]	25 (22.9)	123 (57.7)	
T3	14 (12.8)	39 (18.3)	**<0.001***
T4	17 (15.6)	20 (9.4)	
TX[a]	38 (34.9)	2 (0.9)	
T staging groups ‡			
T1-3	54 (76.1)	191 (90.5)	**0.004***
T4	17 (23.9)	20 (9.5)	
N stage ‡			
N0[a]	4 (3.7)	41 (19.2)	
N1[a]	7 (6.4)	38 (17.8)	
N2[a]	17 (15.6)	77 (36.2)	**<0.001***
N3	38 (34.9)	55 (25.8)	
NX[a]	43 (39.4)	2 (0.9)	
N staging groups ‡			
N0	4 (6.1)	41 (19.4)	**0.017***
N 1-3	62 (93.9)	170 (80.6)	

†: median [min-max], ‡: n (%). dnMBC: de novo metastatic breast cancer, rMBC: recurrent metastatic breast cancer, ER: estrogen receptor, PR: progesterone receptor, HER2: human epidermal growth factor receptor 2, IHC: immunohistochemical. *. Pearson Chi-Square, Fisher's Exact or Fisher Freeman Halton test. **. Mann-Whitney U test. [a]: variables that make a difference between groups after bonferroni adjustment.

Table 3. Laboratory investigations of the patients at the diagnosis of metastasis.

	Group dnMBC (n=109)	Group rMBC (n=213)	p-values
CEA (ng/dL) †	3.8 [0.4 – 921.3]	1.9 [0.2 – 1444.0]	**<0.001****
CA 15-3 (U/mL) †	28.2 [2.1 – 2894.6]	22.5 [0.9 – 600.0]	**0.017****
CEA groups ‡			
Normal (<2.5 ng/mL)	58 (61.7)	146 (79.8)	**0.002***
High (≥2.5 ng/mL)	36 (38.3)	37 (20.2)	
CA 15-3 groups ‡			
Normal (<30 U/mL)	43 (44.8)	109 (58.0)	**0.047***
High (≥30 U/mL)	53 (55.2)	79 (42.0)	

†: median [min-max], ‡: n (%). dnMBC: de novo metastatic breast cancer, rMBC: recurrent metastatic breast cancer, CEA: carcinoembryonic antigen. *. Pearson Chi-Square, Fisher's Exact or Fisher Freeman Halton test. **. Mann-Whitney U test.

Table 4. Clinical findings associated with the metastatic disease.

	Group dnMBC (n=109)	Group rMBC (n=213)	p-values*
Site of metastasis ‡			
Distant lymph node	19 (17.4)	35 (16.4)	0.945
Bone	78 (71.6)	149 (70.0)	0.865
Liver	34 (31.2)	68 (31.9)	0.994
Lung/pleura	33 (30.3)	77 (36.2)	0.354
Central nervous system	31 (28.4)	64 (30.0)	0.865
Skin	5 (4.6)	15 (7.0)	0.535
Grouping for metastatic sites ‡			
Non-visceral	34 (31.2)	63 (29.6)	
Visceral	21 (19.3)	48 (22.5)	0.793
Both	54 (49.5)	102 (47.9)	
Oligometastasis ‡	18 (16.5)	19 (8.9)	0.066
Number of metastatic sites ‡			
1	40 (36.7)	84 (39.4)	
2	49 (45.0)	73 (34.3)	0.120
3	20 (18.3)	56 (26.3)	
Overall survival			
The 2-year (%)	57	51	
The 5-year (%)	17	19	0.393
Median (month±SE†)	31±4.37	25±2.47	

‡: n (%). dnMBC: de novo metastatic breast cancer, rMBC: recurrent metastatic breast cancer. *. Pearson Chi-Square test. †: SE: standard error.

after the initial diagnosis are generally considered to have dnMBC [3,7,8,13]. In contrast, several authors considered only patients with confirmed distant metastatic BC at the time of diagnosis [14] or within 120 days of initial diagnosis [6,15] to have dnMBC, whereas others characterized dnMBC by the development of metastases before or shortly after the identification of a primary breast tumor and did not specify the interval [12,16-18]. Yamamura et al. [19] characterized rMBC by the development of distant metastasis after the removal of the primary BC following standard adjuvant treatment, excluding locoregional recurrences. De Maar et al. [20] excluded the patients with distant metastasis within three months of the primary diagnosis from their sample. The incidence or prevalence of dnMBC among all breast or metastatic BC patients reported in the literature varies significantly, ranging between 8.8% and 71.9%, due to differences in the definition of dnMBC and patient populations [1,6,8,12,13,14,16-18]. Gilbert et al. [9] reported that 71.9% of BC patients were diagnosed with MBC within the first four months after the initial diagnosis. The rate of patients with dnMBC in this study was 33.9%, comparable to the patient populations in previously published studies. In contrast, in a study conducted in Turkey, Dogan et al. [7] reported that almost half (47.7%) of their patients had dnMBC. In the said study, although metastasis within three months after the initial diagnosis was defined as dnMBC, as in our study, the rates of patients with DnMBC were higher than in our study. The differences between the studies in the prevalence of dnMBC or rMBC may be attributed to the

varying diagnostic imaging capacities of the institutions in visualizing MBC.

Previous studies reported significant differences between the patients with dnMBC and rMBC in demographic and clinical characteristics, including different patterns of metastatic spread. In a large cohort study conducted in France, Marshall et al. [12] reported that dnMBC patients were significantly older than rMBC patients, and there were significantly more postmenopausal patients in dnMBC patients than in rMBC patients, as in this study. Similarly, another study reported that the dnMBC patients were significantly older than rMBC patients [6,7,20]. Triple-negative tumors and high grades were reportedly related to rMBC [12]. Several studies found no significant difference between dnMBC and rMBC patients [9,15,19]. In our study, no significant difference was found between dnMBC and rMBC patients in molecular subtypes, histological grades, and metastatic spread patterns. In our study, no significant difference was found between dnMBC and rMBC patients in terms of molecular subtypes, histologic grades and metastatic spread patterns. However, it was also observed that they did not have exactly the same clinicopathologic features. Patients with dnMBC exhibited older median age, more patients with postmenopause, worse performance status, more multi-centricity/focality, more advanced T and N stages, more HER2-positivity, and higher tumor markers than rMBC. In contrast, rMBC had more triple negative disease. The higher rate of HER2-positivity in the dnMBC group compared to the rMBC group, as in McKenzie's [14] and de Maar's studies [20], might be associated with improved survival outcomes secondary to anti-HER2 medications [13].

Although several authors speculated that dnMBC and rMBC are distinct patterns of MBC based on the differences in clinicopathological characteristics and survival [3,13,20], it is generally accepted that better survival outcomes in dnMBC are associated with higher HER-2-positivity rates [7,13]. Hence, the discrepancies between the studies may be attributed to the heterogeneity in clinical and tumoral characteristics of MBC.

The survival outcomes in metastasic BC vary depending on whether it is dnMBC or rMBC [4,9]. It has been speculated that the patients with rMBC may be followed up better than those with dnMBC, given the higher possibility of diagnosing metastasis at an earlier stage [9,12]. In contrast, several studies reported that dnMBC patients had better prognosis after metastasis development than rMBC patients [2,6-8,12,14-16,19,21]. Better prognosis in patients with dnMBC compared to patients with rMBC may be due to having treatment-naive oligometastatic BC featuring only bone metastasis, higher rates of hormone positivity, lower rates of resistance to the first systemic palliative therapy, and the use of more aggressive first-line treatment [9,15-18]. The improvement in prognosis is reportedly more pronounced if MFS is less than 24 months [18]. Although there were more patients with oligo-and bone metastasis in the dnMBC group than in the rMBC group, we did not detect a significant difference in prognosis between the groups.

Others speculated that dnMBC diagnosis is associated with adverse tumor features [14]. In a systematic review [4], Lord et al. stated that population-level improvements have been observed in the OS of dnMBC patients since 1995. In parallel, we found that the OS of the patients with dnMBC was more prolonged, albeit not significantly, compared to those with rMBC. Several other studies have found similar findings regarding the OS of dnMBC and rMBC patients [17,18] as in this study. These results suggest that de novo type metastasis is not an independent prognostic factor of OS in MBC patients [7]. Studies with larger sample sizes may be needed to offset the variations in population characteristics, study periods, and follow-up durations when assessing the prognostic differences between dnMBC and rMBC.

Limitations

The fact that the study featured real-life practice patterns from a tertiary center over ten years is its primary strength. The study did have many drawbacks, though, the main one being that it was retrospective in nature. Secondly, the fact that the impact of treatment characteristics, such as the treatment duration and patient compliance, has not been addressed may be considered another limitation of the study.

Conclusion

Patients with dnMBC exhibited older median age, more patients with posmenopause, worse performance status, more multi-centricity/focality, more advanced T and N stages, more HER2-positivity, and higher tumor markers than rMBC. In contrast, rMBC had more triple negative disease. However, no significant difference in OS was detected between dnMBC and rMBC patients.

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Ethics Committee Approval

The present study was conducted in accordance with the principles of the Declaration of Helsinki. On November 16, 2023, the Ethics Committee of Sivas Cumhuriyet University granted approval (decision no: 2023-11/12).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

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Authors' Contributions

MU: Conception, Design, Writing- Original draft preparation; MY: Data collection, Writing- Original draft preparation, Analysis and interpretation; EE: Conception, Materials, Data collection; BY: Writing- Reviewing and Editing, Supervision, Critical Review.

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