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Oncologic safety of nipple-sparing mastectomy in patients with short tumor-nipple distance

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Abstract

Background: There is a tendency to avoid nipple-sparing mastectomy (NSM) when a tumor-nipple distance (TND) is <2 cm due to the risk of occult nipple involvement. The purpose of the study was to determine whether the patients who undergo NSM with immediate reconstruction are oncologically safe when TND is <2 cm.

Methods: Patients who underwent NSM followed by immediate reconstruction for breast cancer were retrospectively analyzed. Patients who are negative for nipple-base in either frozen-section or paraffin histopathology were included. MRI was used to obtain TNDs to compare local-recurrence-free and disease-free survival in group I (TND <2 cm) and group II (TND ≥2 cm). Disease-free survival rates were determined to assess the outcome.

Results: Of the 214 cases with malignancy on MRI, 21 cases diagnosed with pure ductal carcinoma in situ were excluded. Among the 193 NSM cases diagnosed with invasive cancer, TND was <2.0 cm in 59 (30.56%) cases and ≥2.0 cm in 134 (69.43%) cases. No significant differences were found between groups in regards to ER, PR, HER2-neu status, and nodal involvement (P = 0.34, P = 0.41, P = 0.54, and P = 0.12 respectively). In a median follow-up time of 62 months (range; 13-114), patients in group I had four local recurrences, whereas group II was found to have five local and three distant metastases. No significant differences were observed between groups concerning disease-free survival (10-year DFS 93.2% vs 96.3%; P = 0.368 respectively).

Conclusions: Patients who have invasive cancer diagnosis with a TND <2 cm are eligible to undergo therapeutic NSM with immediate reconstruction.

KEYWORDS
breast cancer, mastectomy, nipple-sparing mastectomy

1 | INTRODUCTION

Removal of the nipple has been standard in the surgical management of breast cancer for many years. With the evolvement of nipple-sparing mastectomy (NSM), the patient's psychological and aesthetic outcomes were improved, apparently without increasing local recurrence rates (LRR).[1] However, the success of NSM depends on the selection of patients whose cancer does not involve the skin flap or nipple-areolar complex (NAC). Initially, NSM was attempted only in breasts with small, peripheral tumors, but it may now include larger tumors close to the NAC.[2,3] There are controversial issues regarding performing NSM for a tumor near NAC. However, there is a consensus to consider NSM as safe when a negative frozen section/paraffin examination of retroareolar tissues was achieved. Recently, a few studies have reported that patients could be considered eligible for NSM when the tumor is located within 2.0 cm of the NAC.[4,5]

Nevertheless, many surgeons are still reluctant to perform NSM when the tumor-nipple distance (TND) is <2.0 cm owing to the risk for LRR at the NAC.

Even in the series excluding patients with tumors that are large or close to the NAC on imaging, the risk of an occult tumor in the nipple is still 5%-15%.[6] Occult nipple involvements by in situ or invasive carcinoma or a Paget's disease is very difficult to detect by clinical or mammographic examination alone.[7,8] Furthermore, mammography and ultrasound may often underestimate the tumor size. On the contrary, MRI provides valuable information on tumor size and distance from the NAC.[9,10] The purpose of the study was to determine whether the patients who undergo NSM with immediate reconstruction are oncologically safe when TND is <2.0 cm in preoperative imaging including MRI.

2 | METHODS

The institutional data base was utilized to analyze patients who underwent NSM and immediate reconstruction with silicone or tissue expander for operable breast cancer from January 2007 to November 2017. Patients were eligible for the study when a biopsy of the nipple/subareolar margin revealed no in situ or invasive cancer by either in frozen or paraffin section analyses. Preoperative MRI was mainly used to assess the TND to categorize group I (TND < 2 cm) and group II (TND ≥ 2) in order to compare the oncological outcome. Cases with clinical evidence of NAC involvement (nipple retraction, Paget's changes, and pathologic nipple discharge), neoadjuvant chemotherapy, and inflammatory breast cancer were excluded.

2.1 | Surgical technique

Since periareolar incisions with or without medial-lateral extensions result in a slightly higher rate of nipple necrosis after NSMs followed by immediate reconstruction, lateral incisions far from the nipple at least 2 cm were preferred in the majority of our cases. Infra-mammary fold incisions to achieve more cosmetic success or satisfaction were less often used. Furthermore, in sporadic cases with huge ptotic breasts, periareolar and skin-reducing incisions were used. In our surgical practice, NAC and skin isolation was performed by hydro-dissection: a 200 cc saline solution containing 2.5 μg/mL of adrenaline is injected into the deep sub-areolar dermis and the subdermal plane containing cooper ligaments between fatty and glandular tissue to obtain complete detachment.

The preservation of the skin envelope and the NAC implies the necessity of immediate breast reconstruction. Permanent silicone implant or tissue expander was used immediately for the reconstruction by plastic surgeons. In order to cover and support the inferior aspect of the breast pocket, an acellular dermal matrix was used if needed.

The retro-areolar specimen was sent for intraoperative frozen section and evaluated with permanent histology. If the histopathology revealed positive for carcinoma, the NAC was removed. Occult nipple involvement was defined as the finding of invasive ductal or lobular carcinoma or ductal carcinoma in situ (DCIS) in the retro-areolar margin section. The presence of lobular carcinoma in situ (LCIS) or atypical hyperplasia was not counted as involvement. Tumor size and TND were measured mainly on 3.0 T-diffusion weighted MRI along with mammography and ultrasound by a dedicated radiologist who was blinded to nipple involvement. Distance from the nipple was defined as the shortest distance from the base of the nipple to the closest edge of a tumor. The present study has some limitations, namely its retrospective nature, which is in part addressed by having all MRI examinations reviewed blinded to surgical and histopathological data. Different methods for measuring TND were not compared, as this was not within the scope of the present study. Even though MRI was the primary imaging modality to measure TND in our study, in some patients with pure DCIS, it was challenging to assess the extent of malignant micro-calcifications and TND. The disease extent shown on MRIs could be a more accurate predictor of occult disease of the nipple because DCIS is the most common form of nipple involvement. Overestimation of tumor size on MRI is partially due to the DCIS component of the tumor. The presence of tumor-induced angiogenesis causes enhancement of malignant tumors on MRI. DCIS has been shown to have an increased amount of stromal microvessels, which increase blood flow, resulting in higher contrast enhancement. Thus, MRI tumor size measurements have the potential to represent the extent of DCIS, in addition to the invasive components.[11] For this reason, the patients diagnosed with DCIS were excluded from the study.

2.2 | Adjuvant treatment

Agents generally used in the adjuvant chemotherapy protocols included 5-fluorouracil, epirubicin, cyclophosphamide, and taxotere. Postmastectomy RT was indicated for early-stage breast cancer patients who present with risk factors for recurrence after NSM. All suggested risk factors were tumor size, lymph node involvement, extra-capsular extension, lymphovascular space invasion, positive surgical margins, triple negative tumor, multicentric tumor, and age. Cases with close margins such as 1 or 2 mm on surgical margins with negative sentinel lymph node biopsy had PMRT according to the decision making of multidisciplinary breast oncology conference.

2.3 | Statistical analysis

Patient characteristics were compared using independent *t*-tests for continuous variables. Associations between categorical variables were assessed using Pearson's chi-square test or Fisher's exact test as appropriate. The Kaplan-Meier product limit method was used to estimate survival outcomes and groups were compared using a log-rank test. *P* values <0.05 were considered statistically significant; all tests were two-sided. Statistical analyses were carried out with SPSS 16 (Chicago, IL).

3 | RESULTS

Retrospectively, 214 patients with preoperative MRI who underwent immediate reconstruction following therapeutic NSM were enrolled in the study. Of those, 21 patients diagnosed with pure DCIS were excluded. Of the remaining 193 NSM patients diagnosed with invasive cancer, TND was <2 cm (group I) in n = 59 (30.56%) cases and ≥2 cm (group II) in n = 134 (69.43%) cases (Figures 1 and 2). There was no statistical significance in the distribution of tumor size and nodal involvement categories including T1-3 and N0-2 in between-group analyses (P = 0.33, and P = 0.16, respectively; Table 1). Bilateral breast cancer was recorded in n = 7 cases (n = 3, n = 4, respectively), whereas contralateral prophylactic NSMs without sentinel lymph node biopsies were performed in 49 cases (n = 15, n = 34; respectively). Furthermore, there were no significant differences in regards to ER, PR, and HER-2 status (P = 0.34, P = 0.41, and P = 0.54 respectively). The most common histopathology was invasive ductal carcinoma, which also showed a similar distribution in both groups (P = 0.23). The clinicopathological characteristics of both groups are summarized in Table 1.

3.1 | Recurrences, distant metastases, and survival rates

At a median follow-up time of 62.0 months (range 13; 114), patients in Group I (TND <2.0 cm) developed four local recurrences, whereas group II (TND ≥2.0 cm) had five local and three distant metastases. In group I, one patient has a recurrent invasive cancer with a diameter of 5 mm that invaded the NAC, and the others were both located under the skin with a diameter of 12, 15, and 22 mm and a TND of 28, 30, and 46 mm. Therefore, the NAC recurrence rate was only 1.69% (1/59) even the LRR was 6.7% in group I. The first case underwent only NAC excision with local anesthesia, but the others underwent a modified radical mastectomy due to skin involvement and fear of recurrence. All of them are still cancer-free in the follow-up. In-group II, five local recurrences were detected with an LRR rate of 3.73%, which invade the NAC in two cases (1.49%) and skin in three, and three cases with liver, kidney, or bone metastases were recorded which causes multi-organ failure with mortality. All the patients with NAC recurrences in either group received radiation therapy to the reconstruction site. Those patients with NAC recurrences had similar histopathologic type as invasive ductal cancer. There were no significant differences between the two groups in regards to LRRs, NAC recurrence rates, and disease-free survival (10-year DFS 93.2% vs 96.3%; P = 0.368, respectively) (Table 2; Figures 1 and 2).

3.2 | Complications

Early wound complications that occurred in the first month for both groups included wound dehiscence in five cases (2.90%), and surgical site infections in six cases (3.48%). Total nipple necrosis was recorded in four cases (2.32%) in both groups, three in group I and 1 in group II, who subsequently underwent NAC excision under local anesthesia. Furthermore, partial flap necrosis was observed in five patients (2.90%), who also underwent local excision. Factors predisposing to nipple or flap necrosis were found to be large breast volume, ptotic breast, smoking, and periareolar incision (skin reducing NSMs). Late complications that occurred after one month were

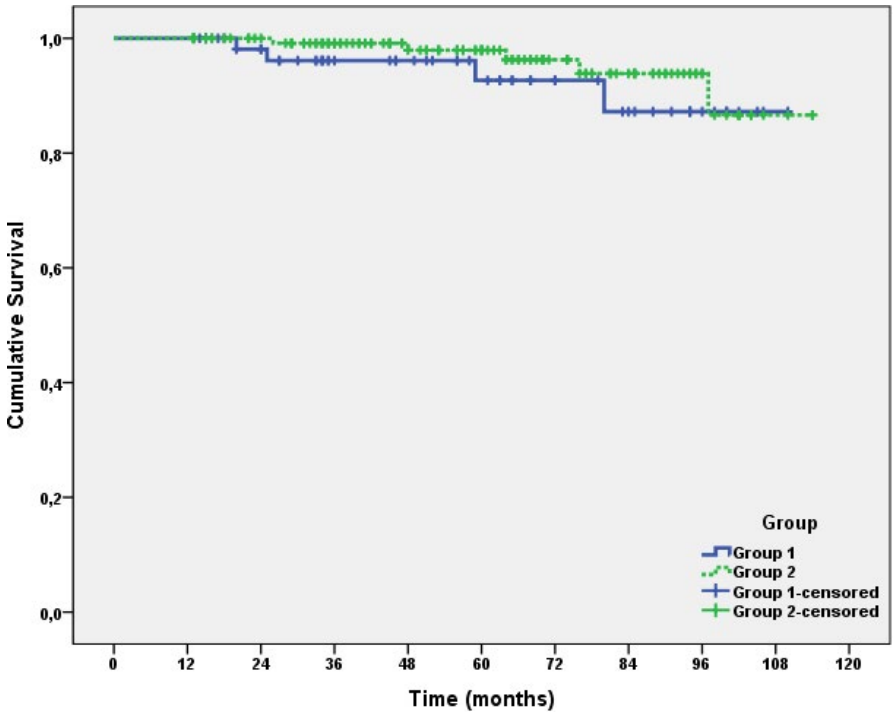

FIGURE 1 Kaplan-Meier analysis of disease-free survival (DFS) between two groups [Color figure can be viewed at wileyonlinelibrary.com]

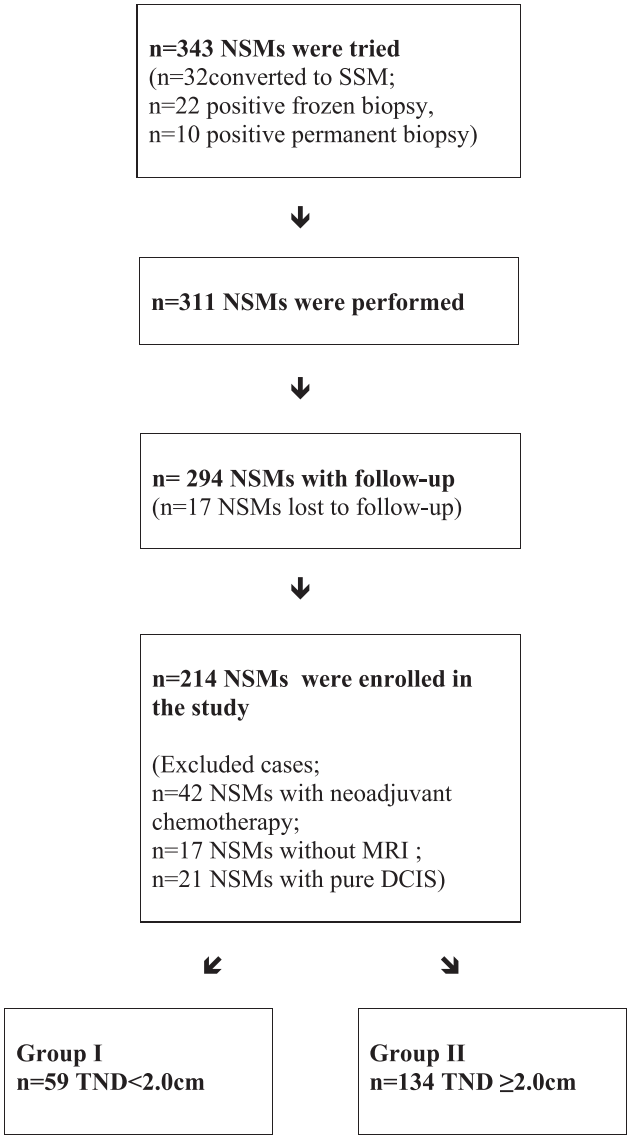

FIGURE 2 Study protocol

capsular contracture in four patients (2.32%), and implant loss in four patients (2.7%). All complications were shown in Table 3. Group I was more likely to have total nipple necrosis as a postoperative complication when compared to group II ($P = 0.028$).

4 | DISCUSSION

Patient selection to undergo NSM has been crucial to achieving better oncologic or aesthetic outcomes. The National Comprehensive Cancer Network recommended therapeutic NSM in only carefully selected patients treated by experienced multidisciplinary teams.[12] NSM is indicated in order to treat extensive or multicentric DCIS and LCIS, multifocal/multicentric invasive ductal or lobular carcinomas (more than 2 cm distant from nipple, without skin involvement and/or pathologic nipple discharge) and BRCA1/2 mutation carriers. Beyond the oncological indications, the conventional NSM procedure is suitable for small-medium breasts only (NAC-inframammary fold distance <8 cm), when breast-conserving surgery is likely to result in unsatisfactory cosmetic results or according to patient's preference.[13] Conversely, carcinoma infiltrating the skin and/or NAC (cancer within 2 cm from the base of the nipple), inflammatory

TABLE 1 Clinicopathological characteristics of patients

	TND <2 cm (n = 59)	TND ≥2 cm (n = 134)	*P* value
Mean age, years (±SD)	42.2 (±7.34)	44.6 (±7.12)	0.210
Mean follow-up, months (range)	61 (13-108)	63 (12-114)	
Lympho-vascular invasion	10	19	0.604
Nuclear grade			
Low	14	24	0.326
Intermediate	28	67	
High	17	43	
Median TND, cm (range)	1.3 (0.5-1.7)	3.5 (2.0-8.2)	
Invasive tumor type			
Ductal	51	122	0.172
Lobular	3	5	
Mixed	3	4	
Others	2	3	
Pathologic T stage			
T0	0	0	0.123
T1	37	79	
T2	19	50	
T3	3	5	
Pathologic N stage			
N0	43	102	0.267
N1	11	26	
N2	5	6	
N3	0	0	
ER status			
Positive	45	112	0.516
Negative	14	22	
PR status			
Positive	35	103	0.306
Negative	24	31	
Her2-neu status			
Amplified	16	25	0.569
Not amplified	43	109	
Adjuvant treatment			
Chemotherapy	39	98	0.414
Radiotherapy	18	32	0.510
Hormonal therapy	43	111	0.299

TABLE 2 Kaplan-Meier analysis of disease-free survival (DFS) between two groups

	n	LR (−) (%)	LR (+) (%)	Mean survival time (95% CI)	*P*
Group 1	59	55 (93.2)	4 (6.8)	103.21 (96.89, 109.53)	0.368[a]
Group 2	134	129 (96.3)	5 (3.7)	109.47 (105.62, 113.33)	
Total	193	184 (95.3)	9 (4.7)	108.68 (105.33, 112.030)	

Abbreviations: N, number of patients; LR, local recurrence; CI, confidence interval.
[a]Log-rank test.

TABLE 3 Postoperative complications in patients who underwent nipple-sparing mastectomy with immediate reconstruction

Complications	Total (N = 193)	Group I (TND <2 cm, n = 59)	Group II (TND ≥2 cm, n = 134)	*P*-value
Wound dehiscence	2.90% (5/172)	3.38% (2/59)	2.23% (3/134)	0.465
Surgical site infection	3.48% (6/172)	3.38% (2/59)	2.98% (4/134)	0.586
Total nipple necrosis	2.32% (4/172)	5.08% (3/59)	0.74% (1/134)	0.028
Partial flap necrosis	2.90% (5/172)	3.38% (2/59)	2.23% (3/134)	0.465
Capsular contracture	2.32% (4/172)	3.38% (2/59)	1.49% (2/134)	0.285
Implant loss	2.32% (4/172)	3.38% (2/59)	1.49% (2/134)	0.285

TABLE 4 Published studies regarding the oncologic safety of NSM with immediate reconstruction

Study	Year	Number of NSMs for breast cancer	Stage	Median follow-up	LRR rate (%)	NAC recurrence rate (%)	Median TNDs (cm)	Number of TND <2.0 cm
Sacchini[15]	2006	68	0-III	25	2.9	0		11
Benediktsson[32]	2008	216	0-III	156	21	0		
Gerber[16]	2009	61	0-I	101	11.7	1.6		
Petit[13]	2009	579	0-I	19	0.9	0		
Paepke[18]	2009	109	T0-3, N0	34	1.0	0		33
Kim[17]	2010	152	0-IIIa	60	2	1.3		
Jensen[19]	2011	99	NA	60	3.0	0		
Warren[20]	2012	428	0-III	28	2.6	0		20
Sakurai[21]	2013	788	0-IV	78	7.8	3.7		
Coopey[4]	2013	315	0-III	22	2.6	0	4	28
Adam[22]	2014	69	0-IV	35	0	0	4.95	5
Stanec[3]	2014	288	0-III	63	4.1	1.2		
Poruk[5]	2015	105	0-IV	26	0.9	0	3.58	5
Balci (present study)	2018	193	0-III	62	4.6	1.5	2.5	59

carcinoma, pathologic nipple discharge, and Paget's disease are considered absolute contraindications to NSM.

The oncologic safety of the NSM in TND <2 cm has been controversial due to the limited literature without sufficient long-term follow-up or local recurrence. The reported involvement of the NAC is minimal and can be managed appropriately with preoperative MRI and intraoperative frozen assessment of the retroareolar tissue.[6,9] In our study, we found no significant difference between groups in regards to local or NAC recurrence. The oncologic safety was confirmed in both groups with 10 years DFS over 90%. Rates of ischemic complications of the NAC and flap were low in both; however, isolated NAC necrosis is slightly higher in-group I. This might be due to the impaired vascular structure after critical dissections with concerns to achieve negative retroareolar margin in these patients.

Routine removal of the nipple in mastectomies has been performed on the base of the risk of occult nipple involvement. Studies have shown that occult NAC involvement in patients with invasive carcinoma varies from 0% to 58%, but some of these studies mainly reflect results in old series with large tumors.[11] In more recent studies, in which the tumor was small and distant from the nipple, the risk of nipple involvement by cancer cells is far less frequent.[4] Table 4 summarizes the published studies concerning the oncological safety

of NSM with immediate breast reconstruction. The LRR is approximately 0%-11% in most series.[3-5,13,15-22] These results are similar to the rates of loco-regional recurrence after skin-sparing or conventional mastectomy.[17,22] Some surgeons remain concerned about NAC recurrence as a result of occult nipple involvement; however, as shown in Table 4, NAC recurrences were only 0%-3.7%. Despite a large number of patients with a TND <2 cm were recruited for the first arm of our study, we found only 1.5% NAC recurrence in total. Therefore, therapeutic NSMs with immediate reconstructions could be performed without fear of NAC recurrence.

In a retrospective analysis of 2323 cases, Weidong et al. found that tumor size, TND, central location, HER-2 amplification, lymph node status, LVI, multicentric, or multifocal tumor were shown to be predictive of nipple involvement.[23] NAC preservation is suggested in HER-2 negative, axillary lymph node, and LVI negative patients with small, solitary tumors located on the periphery of the breast. Several previous studies of NSM have excluded patients if tumor size was 3.0-3.5 cm.[24,25] Others have excluded patients from TNDs 1.0-2.5 cm.[26,27] However, tumor size or TND was not an exclusion criterion for our patients since there has been no precise data or consensus, which confirms oncological inferiority when TNDs are <2.0 cm in comparison to TNDs equal or over 2.0 cm.

Initially, Warren et al[20] excluded NSM in cases in which the TND was <2 cm on preoperative MRI. The authors performed NSM, provided that preoperative MRI demonstrates no clear tumor involvement of the NAC. Although twenty nipple specimens contained tumor, more than half the cases revealed negative margins on repeating excision. Others were managed with NAC radiation without nipple excision. Median follow-up was 28 months. The rate of LRR was 2.6%, and no local recurrence at the NAC was reported.

Coopey et al[4] stated that their institution did not exclude patients by tumor size and TND. The mean TND was found to be 4 cm (range 0-10.7) in their series. Of the 315 NSMs for breast cancer, 28 patients (8.9%) had a TND <2 cm on MRI, and frozen biopsy results were negative for tumor cells at the nipple base. After a mean follow-up time of 22 months, an LRR of 2.6% in was reported. Of note, no local recurrence at the NAC was observed in their series.

In a 2001 meta-analysis, Cense et al[28] found that the main factors related to NAC involvement were tumor size and TND. NAC involvement was seen in an average of 50% of patients when the TND was <2 cm compared with 20% or less when the distance was more than 2 cm on histopathology.[28] In a study of prediction based on mammographic images, Schecter et al[29] reported that tumors involving the NAC were significantly closer to the NAC (1.8 cm vs 4.2 cm) and significantly larger (2.9 cm vs 1.5 cm) than tumors not involving the NAC. Loewen et al[30] described 116 mammographic studies, 11 with histopathologic NAC involvement, and found that distance from the tumor to NAC of 4.96 cm was the only statistically significant predictor of NAC involvement with 82% sensitivity. D'Alonzo et al[31] found that TND of <1 cm predicted NAC involvement with a negative predictive value of 94% for mammography and 100% for MRI. These findings do not correlate with our findings, since our patients who were diagnosed with invasive cancer with a TND <2.0 cm on MRI, had similar LRR in comparison to the control group with a TND ≥2.0 cm. We also believe that NSM can be performed safely for any tumor size as long as there is no clinical or imaging evidence of NAC involvement or skin involvement.

In conclusion, our results suggest that patients with TND <2 cm on MRI are eligible for NSM if there is no visible clinical or radiological evidence of NAC involvement and no malignancy in frozen section evaluation. Prospective studies, however, with a more significant number of cases and longer follow-up are warranted in the future.

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Authors have no conflict of interest. All the patients enrolled in the study had written informed consent. The Institutional Review Board of Acibadem University approved the study. The article was an original work, has not been published before, and was not being considered for publication elsewhere in its final form, in either printed or electronic media. The data, analytic methods, and study materials are available as full and encrypted files in Acibadem University Research and Data Center. The study was not preregistered with or without an analysis plan in an independent, institutional registry.

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