Prediction of nipple-areolar complex involvement by breast cancer: role of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI)

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Abstract

Background: Skin-sparing and nipple-sparing mastectomies were considered as alternative techniques for modified radical mastectomy. In patients who are candidates for nipple-sparing mastectomy, preoperative assessment of the nipple-areolar complex (NAC) is essential for adequate surgical planning. Breast MRI is highly sensitive for cancer detection and has an important role in disease staging. The aim of this study was to estimate the role of DCE-MRI in predicting malignant NAC invasion by underlying breast cancer and assess the best predictors on MRI that can suspect malignant NAC invasion.

Results: Out of the 125 patients with breast cancer, 33 patients (26.4%) showed malignant NAC invasion. On basis of multivariate analysis, abnormal nipple enhancement, tumor nipple enhancement, tumor nipple distance ≤ 2 cm, and abnormal and asymmetric nipple morphology were all significant predictors of malignant NAC invasion (P < 0.001) with abnormal unilateral nipple enhancement as the most important independent MRI predictor of malignant NAC invasion (odds ratio = 61.07, 95% CI 12.81–291.22, P < 0.001). When combining more than positive suspicious MRI features, DCE-MRI had 66.6% sensitivity, 76% specificity, 50% PPV, 86.4% NPV, and 73.6% accuracy in prediction of malignant NAC invasion.

Conclusion: DCE-MRI could predict malignant NAC invasion with abnormal unilateral nipple enhancement as the most important independent MRI predictor.

Keywords: Dynamic contrast enhanced, Magnetic resonance imaging, Nipple-areolar complex, Breast cancer

Background

Breast cancer is considered as the second commonest cause of cancer-related death in women [1]. Great efforts were performed in order to introduce more conservative surgeries for the treatment of breast cancer [2]. Skin-sparing mastectomy (SSM) and nipple-sparing mastectomy (NSM) were considered as alternative techniques for modified radical mastectomy (MRM) [3]. They provide better cosmetic outcomes resulting in improved body image and more patient satisfaction with more cosmetic results obtained by NSM due to preservation of the NAC [4]. In SSM, the recurrence rate was equivalent to that of MRM; however, in NSM, a small amount of ductal tissue was left behind the nipple, and this could result in an increased risk of local recurrence [5].

In patients who are candidates for NSM, preoperative assessment of the nipple-areolar complex (NAC) is essential for adequate surgical planning [6]. Several clinical and pathological factors are suspected to be associated with occult invasion of the NAC by the underlying breast cancer such as tumor size, multicentric tumor, central location of the tumor, and proximity of the tumor to the nipple base [7]. Mammography and breast...
ultrasound can be used to predict the malignant invasion of the NAC by underlying breast cancer; however, they
have limited sensitivity and specificity. Breast MRI is highly sensitive for cancer detection and has an important
role in disease staging. It is considered the imaging modality of choice for the assessment of malignant invasion
of the NAC [8].

Several previous studies investigated the role of breast MRI in the prediction of malignant invasion of the NAC
[6–13]. However, there is still debate on what is the most important MRI predictor of malignant NAC invasion
by underlying breast cancer.

Aim of the study
The aim of this work was to estimate the role of DCE-
MRI in predicting malignant NAC invasion by under-
lying breast cancer and assess the best predictors on
MRI that can suspect malignant NAC invasion.

Methods
Patient’s demographic data
This retrospective study was approved by our institu-
tion’s ethics committee. The medical records and the
preoperative MRI studies of 125 female patients with
primary breast cancer and prepared for surgery (MRM,
SSM, or NSM) were reviewed from the period of August
2018 till September 2020. Their age ranged from 28 to
70 years (mean ± SD = 44.8 ± 8.96). Out of the 125 fe-
pemale patients, 77 patients underwent MRM, 30 patients
underwent SSM, and 18 patients underwent NSM. After
reviewing the pathological reports, we found that 33
cases (26.4%) showed malignant NAC invasion and 92
cases (73.6%) showed free NAC. We had 9 cases with
DCIS, 109 cases with IDC, and 7 cases with invasive
lobular carcinoma.

Inclusion criteria
Inclusion criteria included female patients with primary
breast cancer and prepared for surgery (MRM, SSM, or
NSM).

Exclusion criteria
Exclusion criteria included patients who were referred
to other hospitals and their pathological reports were
not available, patients who received neoadjuvant chemotheraphy, and patients with advanced disease stage (stage IV) because they were not amenable for surgery.

MRI technique
MRI breast for 125 female patients was performed using
1.5 T MR imaging unit (Philips Ingenia). All patients
were examined in the prone position by using a dedi-
cated breast coil. All patients underwent the following:
(A) localizing sagittal protocol (scout view); (B) axial
non-fat-suppressed T1W fast spin-echo images, with the
following parameters: TR/TE 450/14 ms, slice thickness
3 mm, field of view (FOV) 300–360 mm, and matrix 307 ×
512; (C) axial non-fat-suppressed T2W turbo spin-
echo images with the following parameters: TR/TE
4500/97 ms, slice thickness 3 mm, and matrix 384 ×
512; (D) axial STIR images with the following parame-
ters: TR/TE 7000–9000/70 ms, T1 150 ms, slice thick-
ness 3–4 mm, inter-slice gap 1 mm, FOV 300–360 mm,
and matrix 307 × 512; and (E) dynamic MR images were
obtained in the axial plane with fat suppression. The
sequence used was FLASH 3-D GRE-T1WI with the
following parameters: TR/ TE 4–8/2 ms, flip angle
20–25, slice thickness 2 mm, no inter-slice gap, FOV
300–360 mm, and matrix 307 × 512. Dynamic MR
images were obtained after injecting a bolus of gado-
pentetate dimeglumine at a dose of 0.2 mmol/kg
using an automated injector at a rate of 3–5 ml/s.
This was followed by a bolus injection of saline (total
of 20 ml at 3–5 ml/s).

Image post-processing includes (A) image subtraction
obtained by subtracting each of the pre-contrast images
from each post-contrast series image and (B) maximum
intensity projection (MIP) images obtained through each
orthogonal plane, producing sagittal, coronal, and axial
projection.

Image interpretation
Using a secondary workstation (Phillips Advantage win-
dows workstation with functional tool software), MR im-
ages were analyzed by two radiologists (ME, DE) with
breast imaging experience for 14 and 9 years. They were
blinded to the clinical and pathological data of the pa-
tients. The two radiologists joined and reached a corres-
pondence for controversial cases.

The assessed signs on dynamic MR images were (A)
malignant mass pattern (mass lesion or non-mass en-
hancement); (B) tumor size (TS) (maximum diameter of
the lesion, if multiple lesions present we took the
maximum diameter of the largest lesion); (C) nipple
morphology (NM) (normal or retracted nipple) was
assessed on axial T1WI and axial STIR image; (D)
symmetry of nipple morphology was assessed on MIP
images; (E) tumor nipple enhancement (TNE) (pres-
ence of enhancement between tumor and nipple base
assessed on early subtraction MR images); (F) tumor
nipple distance (TND) (measured from the tumor
margin to the base of the nipple on early subtraction
MR images); (G) abnormal asymmetric nipple en-
hancement assessed on early subtraction MR images;
and (H) thickening of the periareolar skin when com-
pared with the contralateral NAC, it was assessed on
early subtraction MR images.
Final diagnosis
The pathological reports after surgery were reviewed and the following data were collected: (1) presence of malignant NAC invasion (malignant NAC invasion was defined on pathology as the presence of IDC, DCIS, or invasive lobular carcinoma within the retro-areolar tissue), (2) histologic tumor type, (3) tumor grade, (4) presence of lymphovascular metastasis, (5) presence of lymph node metastasis, and (6) hormone receptor status (ER, PR, Her 2, and Ki67).

Statistical analysis
Data were fed to the computer and analyzed using IBM SPSS Corp., released 2013, IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. Qualitative data were described using number and percent. Quantitative data were described using median (minimum and maximum), interquartile range for non-parametric data, and mean and standard deviation for parametric data after testing normality using the Shapiro-Wilk test. The significance of the obtained results was judged at the (0.05) level. Student t test was used to compare 2 independent groups. The diagnostic performance (accuracy) of a test to discriminate diseased cases from non-diseased cases is evaluated using receiver operating characteristic (ROC) curve analysis. Sensitivity and specificity were detected from the curve. PPV, NPV, and accuracy were calculated through cross-tabulation. The multivariate logistic regression model was done to determine the best combined parameters for the prediction of malignant NAC invasion by generating AUC with 95% confidence intervals.

Results
This retrospective study included 125 female patients with primary operable breast cancer. After reviewing the pathological reports, we found that 33 cases (26.4%) showed malignant NAC invasion and 92 cases (73.6%) showed free NAC (Fig. 1).

On univariate analysis, tumor size, tumor nipple distance, abnormal nipple enhancement, nipple morphology, symmetry of nipple morphology, tumor nipple enhancement, and periareolar skin thickening were all important predictors of malignant NAC invasion (Fig. 2a–c). The mean TS for cases of malignant NAC invasion was 5.5 ± 2.34 cm versus 3.55 ± 1.67 cm for free NAC (P < 0.001). The mean TND for cases of malignant NAC invasion was 2.28 ± 1.94 cm versus 3.89 ± 2.63 cm for free NAC (P = 0.032). Abnormal nipple enhancement was observed in 19 (57.6%) out of 33 cases with malignant NAC invasion; however, it was observed only in 2 (2.2%) cases out of 92 cases with free NAC (P < 0.001). Abnormal nipple morphology was observed in 21 (63.6%) out of 33 cases with malignant NAC; however, it was observed only in 6 (6.5%) cases out of 92 cases with free NAC (P < 0.001). TNE was observed in 24 (72.7%) out of 33 cases with malignant NAC invasion; however, it was observed in 22 (23.9%) out of 92 cases with free NAC. Regarding pathological features, tumor type, HER2 status, and PR state were significant predictors for malignant NAC invasion; P values were 0.006, < 0.001, and 0.014, respectively (Table 1).

Other radiological features as lesion pattern (P = 0.09) and other pathological features as tumor grade (P = 0.105), lymph node status (P = 0.510), Ki67 state (P = 0.970), and ER state (P = 0.262) could not be considered as predictors for malignant NAC invasion (Table 1).

On multivariate analysis, abnormal unilateral nipple enhancement was the most important independent MRI predictor of malignant NAC invasion (odds ratio = 61.07, 95% CI 12.81–291.22, P < 0.001) (Fig. 3). Other MRI predictors as TND ≤ 2 cm, abnormal nipple morphology, asymmetry of nipple morphology, and tumor nipple enhancement were also significant (P < 0.001). Also, HER2 status (P = 0.001) and PR state (P = 0.016) remained significant (Table 2).

Abnormal nipple enhancement had 57.6% sensitivity, 97.8% specificity, and 87.2% accuracy in the prediction of malignant NAC invasion. Abnormal nipple morphology had 63.6% sensitivity, 93.4% specificity, and 85.6% accuracy. The symmetry of nipple morphology had 63.6% sensitivity, 96.7% specificity, and 88% accuracy. TNE had 72.7% sensitivity, 76.1% specificity, and 75.2% accuracy. TND ≤ 2cm had 63.6% sensitivity, 72.8% specificity, and 54.4% accuracy (Table 3).
When combing more than two positive suspicious MRI features, we found that DCE-MRI had 66.6% sensitivity, 76% specificity, 50% PPV, 86.4% NPV, and 73.6% accuracy in the prediction of malignant NAC invasion by underlying breast cancer (Table 4).

Discussion
The incidence of malignant NAC invasion by underlying breast cancer varies in different studies from 5.6 to 24.6% [14–16]. One study showed that malignant invasion of the NAC by underlying breast
|                | Free NAC n = 92 | Malignant NAC invasion n = 33 | Test of significance |
|----------------|-----------------|-----------------------------|----------------------|
| Age/years      | 43.82 ± 9.61    | 45.12 ± 8.42                | t = 0.691 p = 0.491  |
| Mean ± SD      |                 |                             |                      |
| TS/cm          | 3.55 ± 1.67     | 5.51 ± 2.34                 | t = 4.30 p < 0.001*  |
| Mean ± SD      |                 |                             |                      |
| n = 72         |                 | n = 21                      |                      |
| n ≤ 2 cm       | 13 (18.1)       | 0 (0.0)                     | χ² = 4.41 p = 0.036*  |
| > 2 cm         | 59 (81.9)       | 21 (100.0)                  |                      |
| TND/cm         | 3.89 ± 2.63     | 2.28 ± 1.94                 | t = 4.71 p = 0.032*  |
| Mean±SD        |                 |                             |                      |
| ≤ 2 cm         | 25 (27.2)       | 21 (63.6)                   | χ² = 13.88 p < 0.001* |
| > 2 cm         | 67 (72.8)       | 12 (36.4)                   |                      |
| LP             |                 |                             |                      |
| Mass           | 72 (78.3)       | 21 (63.6)                   | χ² = 2.73 p = 0.09    |
| Non-mass       | 20 (21.7)       | 12 (36.4)                   |                      |
| Abnormal nipple enhancement |         |                             |                      |
| Present        | 2 (2.2)         | 19 (57.6)                   | χ² = 53.33 p < 0.001* |
| Absent         | 90 (97.8)       | 14 (42.4)                   |                      |
| NM (Nipple morphology) |         |                             |                      |
| Normal         | 86 (93.5)       | 12 (36.4)                   | χ² = 46.78 p < 0.001* |
| Abnormal (inverted or retracted) | 6 (6.5) | 21 (63.6)                   |                      |
| Sym NM (symmetry of nipple morphology) |         |                             |                      |
| Symmetric      | 89 (96.7)       | 12 (36.4)                   | χ² = 57.07 p < 0.001* |
| Asymmetric     | 3 (3.3)         | 21 (63.6)                   |                      |
| TNE (tumor nipple enhancement) |         |                             |                      |
| Present        | 22 (23.9)       | 24 (72.7)                   | χ² = 24.88 p < 0.001* |
| Absent         | 70 (76.1)       | 9 (27.3)                    |                      |
| PST (peri-areolar skin thickening) |         |                             |                      |
| Present        | 0 (0.0)         | 22 (66.7)                   | χ² = 74.43 p < 0.001* |
| Absent         | 92 (100.0)      | 11 (33.3)                   |                      |
| TT (tumor type) |                 |                             |                      |
| DCIS           | 3 (3.3)         | 6 (18.2) MC                 |                      |
| IDC           | 82 (89.1)       | 27 (81.8)                   |                      |
| Invasive lobular carcinoma | 7 (7.6) | 0 (0.0)                     |                      |
| TG (tumor grade) |               |                             |                      |
| Low or intermediate | 67 (72.8) | 19 (57.6)                   | χ² = 2.63 p = 0.105  |
| High           | 25 (27.2)       | 14 (42.4)                   |                      |
| LNS (lymph node state) |         |                             |                      |
| Positive       | 54 (58.7)       | 17 (51.5)                   | χ² = 0.510 p = 0.475 |
| Negative       | 38 (41.3)       | 16 (48.5)                   |                      |
| PR (progesterone receptor) state |         |                             |                      |
| Positive       | 50 (54.3)       | 26 (78.8)                   | χ² = 6.09 p = 0.014* |
| Negative       | 42 (45.7)       | 7 (21.2)                    |                      |
| HER 2          |                 |                             |                      |
| positive       | 51 (55.4)       | 31 (93.9)                   | χ² = 15.96 p < 0.001* |
| negative or equivocal | 41 (44.6) | 2 (6.1)                     |                      |
| KI 67          |                 |                             |                      |
| High           | 70 (76.1)       | 25 (75.8)                   | χ² = 0.001 p = 0.970 |
| Low            | 22 (23.9)       | 8 (24.2)                    |                      |
| ER (estrogen receptor) state |         |                             |                      |
| Positive       | 63 (68.5)       | 26 (78.8)                   | χ² = 1.26 p = 0.262  |
| Negative       | 29 (31.5)       | 7 (21.2)                    |                      |

χ² Chi-square test, MC Monte Carlo test, t Student’s t test
*Statistically significant
cancer was found in 37 (21.8%) out of 170 mastectomy specimens [16]. Another study showed that malignant NAC invasion was found in 71 (35.5%) out of 200 patients [3]. In this work, malignant NAC invasion by underlying breast cancer was reported in 26.4% of patients.

Several previous studies investigated the role of DCE-MRI in predicting malignant NAC invasion by underlying breast cancer [1, 3, 7–16]. It was stated that both tumor nipple distance and abnormal enhancement extending from the tumor to the nipple base were the most important predictors of malignant NAC invasion on MRI [9, 10]. One stated that TND with cutoff value of 10 mm had high sensitivity and specificity in predicting malignant NAC [3]. Another study stated that Continuity to NAC and unilateral NAC enhancement were all important MRI predictors of malignant NAC invasion [12]. This is in agreement with our study where we found that MRI predictors such as abnormal nipple morphology, asymmetry of nipple morphology, abnormal unilateral nipple enhancement, TNE, and TND ≤ 2cm were all significant predictors of malignant NAC invasion.

In the present study, abnormal unilateral nipple enhancement was the most important independent MRI predictor of malignant NAC invasion (odds ratio = 61.07, 95% CI 12.81–291.22, P < 0.001) (specificity = 97.8% and diagnostic accuracy = 87.2%). This is in agreement with Liao et al. [7] who stated that abnormal unilateral nipple enhancement was the most significant independent image predictor of malignant NAC invasion (odds ratio = 4.86, 95% CI 1.76–13.80, P ≤ .01). Also, our results are in agreement with a study performed by Lee et al. [17], and they found that MR images displaying inhomogeneous and diffuse enhancement in areas of thickened skin and the parenchyma of the NAC were indicative of NAC invasion. Another study performed multivariate logistic regression analysis for pathologic diagnosis of NAC involvement and concluded that NAC enhancement and NAC enhancement thickness were the two most important factors related to NAC invasion (P < .001) [18], and this is in agreement with our results.

The sensitivity and specificity of DCE-MRI in the prediction of malignant NAC invasion is variable among different studies. One study stated that the combination of more than one suspicious MRI feature had 60.5% sensitivity, 87.5% specificity, and 84.6% accuracy in predicting malignant NAC invasion [12]. Another study performed interobserver agreement about the ability of DCE-MRI to predict malignant NAC invasion; the first observer found that DCE-MRI had 71.4% sensitivity, 81.6% specificity, and 80.8% accuracy; and the second observer found that it had 78.6% sensitivity, 88.1% specificity, and 87.4% accuracy [7]. In this study combination of more than two suspicious MRI features, it could result in 66.6% sensitivity, 76% specificity, and 73.6% accuracy in predicting malignant NAC invasion.

The limitations of this study were that its retrospective nature, no interobserver agreement was performed, and also the MRI examinations were performed on 1.5 Tesla MRI.

**Conclusion**

DCE-MRI could predict malignant NAC invasion with abnormal unilateral nipple enhancement as the most important independent MRI predictor.
### Table 2 Multivariate analysis of clinical, pathologic, and MRI findings associated with NAC invasion by underlying breast cancer

|                          | Free NAC n = 92 | Malignant NAC invasion n = 33 | β   | P        | Odds ratio (95% CI) |
|--------------------------|-----------------|-------------------------------|-----|----------|---------------------|
| TS/cm                    |                 |                               |     |          |                     |
| n = 72                   | n = 21          |                               |     |          |                     |
| ≤ 2 cm                   | 13 (18.1)       | 0 (0.0)                       | 20.51 | 0.99    | Undefined           |
| > 2 cm                   | 59 (81.9)       | 21 (100.0)                    |     |          |                     |
| TND/cm                   |                 |                               |     |          |                     |
| n = 7                      | n = 21          |                               |     |          |                     |
| ≤ 2 cm                   | 25 (27.2)       | 21 (63.6)                     | 1.54 | < 0.001* | 4.69 (2.02–10.92)   |
| > 2 cm (R)               | 67 (72.8)       | 12 (36.4)                     |     |          | Reference group     |
| Abnormal nipple enhancement |                 |                               |     |          |                     |
| Present                  | 2 (2.2)         | 19 (57.6)                     | 4.12 | < 0.001* | 61.07 (12.81–291.22) |
| Absent (R)               | 90 (97.8)       | 14 (42.4)                     |     |          | Reference group     |
| NM (nipple morphology)   |                 |                               |     |          |                     |
| Normal (R)               | 86 (93.5)       | 12 (36.4)                     |     |          | Reference group     |
| Abnormal                 | 6 (6.5)         | 21 (63.6)                     | 3.22 | < 0.001* | 25.08 (8.43–74.6)   |
| Sym NM (symmetry of nipple morphology) |  |                                |     |          |                     |
| Symmetric (R)            | 89 (96.7)       | 12 (36.4)                     |     |          | Reference group     |
| Asymmetric               | 3 (3.3)         | 21 (63.6)                     | 3.95 | < 0.001* | 51.92 (13.44–200.58) |
| TT (tumor type)          |                 |                               |     |          |                     |
| DCIS (R)                 | 3 (3.3)         | 6 (18.2)                     | −1.80 | 0.015* | Reference group     |
| IDC                      | 82 (89.1)       | 27 (81.8)                    | −    | 0.99    | 0.165 (0.039–0.704) |
| Invasive lobular carcinoma | 7 (7.6)       | 0 (0.0)                      | 21.89 |          | Undefined           |
| TNE (tumor nipple enhancement) |             |                               |     |          |                     |
| Present                  | 22 (23.9)       | 24 (72.7)                    | 2.14 | < 0.001* | 8.48 (3.44–20.94)   |
| Absent (R)               | 70 (76.1)       | 9 (27.3)                     |     |          | Reference group     |
| PST (peri-areolar skin thickening) |             |                               |     |          |                     |
| Present                  | 0 (0.0)         | 22 (66.7)                    |     |          | Undefined           |
| Absent                   | 92 (100.0)      | 11 (33.3)                    | 23.32 | 0.999   |                     |
| PR (Progesterone receptor state) |           |                               |     |          |                     |
| Positive                 | 50 (54.3)       | 26 (78.8)                    |     |          | 3.12 (1.23–7.91)    |
| Negative (R)             | 42 (45.7)       | 7 (21.2)                     | 1.14 | 0.016* | Reference group     |
| HER 2                    |                 |                               |     |          |                     |
| Positive                 | 51 (55.4)       | 31 (93.9)                    | 2.523 | 0.001* | 12.46 (2.71–55.17)  |
| Negative or equivocal    | 41 (44.6)       | 2 (6.1)                      |     |          | Reference group     |

### Table 3 Diagnostic performances of tumor-nipple enhancement, abnormal nipple morphology, symmetry of nipple morphology, abnormal nipple enhancement and tumor-nipple distance in prediction of NAC invasion by underlying breast cancer

|                          | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Accuracy (%) |
|--------------------------|-----------------|-----------------|---------|---------|--------------|
| Abnormal nipple enhancement | 57.6            | 97.8            | 90.5    | 86.5    | 87.2         |
| Abnormal nipple morphology | 63.6            | 93.4            | 77.7    | 87.7    | 85.6         |
| Symmetry of nipple morphology | 63.6            | 96.7            | 87.5    | 88.1    | 88           |
| TNE (tumor nipple enhancement) | 72.7            | 76.1            | 52.2    | 88.6    | 75.2         |
| TND/cm ≤ 2 cm            | 63.6            | 72.8            | 45.7    | 84.8    | 54.4         |

NPV negative predictive value, PPV positive predictive value
Table 4 Diagnostic performance of DCE-MRI when combing more than two positive MRI features in the prediction of malignant NAC invasion by underlying breast cancer

|                | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Accuracy (%) |
|----------------|-----------------|-----------------|---------|---------|--------------|
| DCE-MRI        | 66.6            | 76              | 50      | 86.4    | 73.6         |

NPV negative predictive value, PPV positive predictive value

Abbreviations
DCE-MRI: Dynamic contrast-enhanced magnetic resonance imaging; NAC: Nipple-areolar complex; TS: Tumor size; TNE: Tumor nipple enhancement; TNID: Tumor nipple distance; NSM: Nipple-sparing mastectomy; SSIM: Skin-sparing mastectomy; IDC: Invasive duct carcinoma; DCIS: Duct carcinoma in situ; MRM: Modified radical mastectomy; ER: Estrogen receptor; PR: Progesterone receptor

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Declarations

Authors’ contributions
AA revised the collected data and the manuscript. DM and ME analyzed the MRI images of all patients. DM wrote the manuscript. ME performed the statistical analysis. The authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
This study was approved by our institution’s ethics committee (Mansoura Faculty of Medicine Institutional Research Board) (ethics committee reference number is R. R.19.05.513), and all patients gave their written informed consent before inclusion in the study.

Consent for publication
This study is a retrospective study, so there is no need for patient consent.

Competing interests
The authors declare that they have no competing interests.

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