Clinical Correlates and Nonlinear Effects Associated With Short-Term Surgical Outcomes After Breast-Conserving Surgery for Breast Cancer: A Single-Center Retrospective Study

Ann. Ital. Chir., 2026 97, 9: 1653–1664
https://doi.org/10.62713/aic.4744

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AIM: To explore clinical correlates of short-term surgical outcomes after breast-conserving surgery for breast cancer, and to examine whether the association between preoperative ultrasound tumor size and these outcomes is nonlinear.

METHODS: This single-center retrospective cohort study included 150 patients with breast cancer who underwent first breast-conserving surgery with curative intent between January 2021 and December 2025. Preoperative clinical, imaging, core needle biopsy, and laboratory data were collected. The primary outcome was a short-term adverse surgical outcome, defined as reoperation for margin-related reasons within 90 days, a strict positive margin, or a clinically meaningful close/indeterminate margin or suspected residual disease identified on postoperative pathology or imaging-pathology review when available, according to documented postoperative margin-related assessment. All association analyses were performed using Firth penalized logistic regression. A prespecified multivariable model was constructed with preoperative ultrasound tumor size as the main exposure, and restricted cubic spline (RCS) analysis was used as an exploratory analysis to examine potential nonlinearity.

RESULTS: Among 150 patients, 15 (10.0%) experienced a short-term adverse surgical outcome. Compared with the no-adverse-outcome group, patients with the adverse outcome had larger preoperative ultrasound tumor size and a higher frequency of multifocal/multicentric disease on imaging. Univariable Firth regression showed that each 5 mm increase in preoperative ultrasound tumor size was associated with the adverse outcome (odds ratio (OR) = 2.32, $p < 0.001$). Multifocal/multicentric disease on imaging was also associated with the outcome (OR = 4.68, $p = 0.026$), whereas a ductal carcinoma *in situ* (DCIS) component on core biopsy showed borderline statistical significance (OR = 2.87, $p = 0.050$). In the prespecified primary model adjusted for mammographic microcalcifications and a DCIS component on core biopsy, preoperative ultrasound tumor size remained associated with the outcome (OR = 2.16, $p = 0.001$). RCS analysis showed an overall association and suggested potential nonlinearity, but the spline findings were exploratory. Exploratory subgroup analyses suggested a stronger association among patients without mammographic microcalcifications and a similar exploratory pattern among those without a DCIS component on core biopsy.

CONCLUSIONS: Preoperative ultrasound tumor size may be associated with poorer short-term surgical outcomes, and this association may not be fully explained by a linear relationship. Multifocal/multicentric disease on imaging and a DCIS component on core biopsy may also be relevant risk-related features. For lesions characterized by microcalcifications or accompanied by a DCIS component, preoperative evaluation based on ultrasound tumor size alone may be insufficient. Therefore, imaging findings and pathological information should still be interpreted in an integrated manner. These exploratory findings require validation in larger cohorts.

Keywords: breast neoplasms; segmental mastectomy; excision margins; mammography; mammary ultrasonography

Introduction

Breast cancer is the most common malignant tumor in women worldwide. In 2022, there were about 2.3 million new cases and 670,000 deaths globally [1]. By 2040, the number of new cases may exceed 3 million [2]. With wider screening coverage and advances in early diagnosis, more patients are now identified at an operable stage. Breast-conserving surgery followed by radiotherapy has become one of the standard treatment options. Current evidence indicates that, in appropriately selected patients, breast-conserving surgery combined with radiotherapy is not inferior to mastectomy in terms of long-term survival [3,4].

However, margin management remains a key issue that affects the quality of breast-conserving surgery. Consensus guidelines from surgical and radiation oncology societies indicate that, for invasive breast cancer treated with whole-breast irradiation, "no ink on tumor" can be accepted as a negative margin. For ductal carcinoma *in situ* (DCIS), a margin width of 2 mm is generally considered appropriate [5,6]. Even so, positive margins and reoperation cannot be completely avoided in clinical practice, and reoperation rates continue to vary considerably across centers [7]. Re-

Submitted: 7 May 2026 Revised: 5 June 2026 Accepted: 22 June 2026
Published: 15 September 2026
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Editor: Gianluca Franceschini

operation not only increases patient anxiety and financial burden, but may also affect cosmetic outcome and delay subsequent treatment [8].

Previous studies on margin status and reoperation after breast-conserving surgery have suggested that tumor size, imaging features, a DCIS component, and histological type are important factors [9,10]. Tumor size is a key preoperative variable, and larger tumors have been associated with a higher risk of positive margins [11]. On imaging, mammographic microcalcifications and multifocal or multicentric disease have also been linked to margin-related problems [12]. From a pathological perspective, a DCIS component identified on core biopsy may indicate a higher risk of positive margins after surgery [13]. Nevertheless, most previous studies have used either "positive margins" or "reoperation" as a single endpoint, which may not fully reflect the overall quality of the initial breast-conserving procedure. In addition, continuous variables have often been categorized directly, which may obscure potential nonlinear associations. For DCIS-dominant lesions or lesions characterized mainly by microcalcifications, radiological underestimation of the true disease extent has not been adequately addressed [14,15,16].

Against this background, we conducted a single-center retrospective cohort study in patients undergoing breast-conserving surgery for breast cancer. Using Firth penalized logistic regression, which is more robust in the setting of sparse events, we analyzed the preoperative factors associated with short-term surgical outcomes, evaluated the association between preoperative ultrasound tumor size and the outcome, explored potential nonlinearity using restricted cubic splines, and performed exploratory subgroup analyses in a limited number of clinically relevant strata.

Methods

Study Design

This was a single-center retrospective cohort study. Clinical data were retrospectively collected from patients with breast cancer who underwent breast-conserving surgery at the Department of Breast Surgery, Yongkang Women and Children's Health Hospital, from January 2021 to December 2025. This retrospective study was based on medical records generated during routine clinical care and involved no additional diagnostic or therapeutic interventions. Therefore, it fell within the scope of exemption from Ethics Review. The study was reviewed and granted an exemption by the Ethics Committee of Yongkang Women and Children's Health Hospital. The requirement for informed consent was waived because of the retrospective nature of the study and the use of de-identified data.

Study Population

Patients with breast cancer who underwent first breast-conserving surgery with curative intent at the Department of Breast Surgery, Yongkang Women and Children's Health Hospital during the study period were consecutively included (Fig. 1). Inclusion criteria were as follows: (1) female, age ≥18 years; (2) malignancy clearly identified on preoperative core needle biopsy and confirmed as malignant breast tumor on final postoperative pathology; (3) receipt of first breast-conserving surgery with curative intent; (4) completion of routine preoperative breast assessment, including physical examination, breast ultrasonography, mammography, and core needle biopsy pathology; and (5) availability of complete postoperative pathological margin data and follow-up information on reoperation within 90 days after surgery. Exclusion criteria were as follows: (1) receipt of neoadjuvant therapy before surgery; (2) recurrent breast cancer, synchronous bilateral breast cancer, or distant metastasis; (3) prior surgery for malignant disease in the ipsilateral breast that might affect assessment of the current margin status; and (4) missing key study variables, including preoperative ultrasound tumor size, mammographic microcalcifications, multifocal/multicentric disease on imaging, key core needle biopsy pathological information, postoperative margin status, or reoperation information within 90 days after surgery.

All patients in this study underwent inpatient surgery. Standardized perioperative evaluation was completed before surgery, and postoperative pathology as well as short-term follow-up information could be retrieved from the inpatient record system and outpatient follow-up records. Detailed intraoperative margin-management strategies were not systematically recorded in the retrospective dataset and were therefore not included in the present analysis. Therefore, no missing data were found for the key variables in this study, and no imputation was performed.

Data Collection and Variable Definitions

All data were obtained from the electronic medical record system, imaging reporting system, pathology reporting system, and perioperative records.

Preoperative Clinical and General Data

The following variables were collected: age, body mass index (BMI), menopausal status, tumor laterality, family history of breast cancer, presence of a palpable mass, and comorbidities including hypertension, diabetes mellitus, cardiovascular disease, and anemia.

Preoperative Imaging Data

The maximum tumor diameter recorded in the preoperative breast ultrasound report was collected and defined as the largest diameter of the main lesion on the last preoperative ultrasound assessment. Whether mammography showed microcalcifications and whether imaging suggested multifocal/multicentric disease were also recorded. Multifocal/multicentric disease on imaging was defined as more than one suspicious malignant focus in the ipsilateral breast identified on preoperative ultrasonography or mammogra-

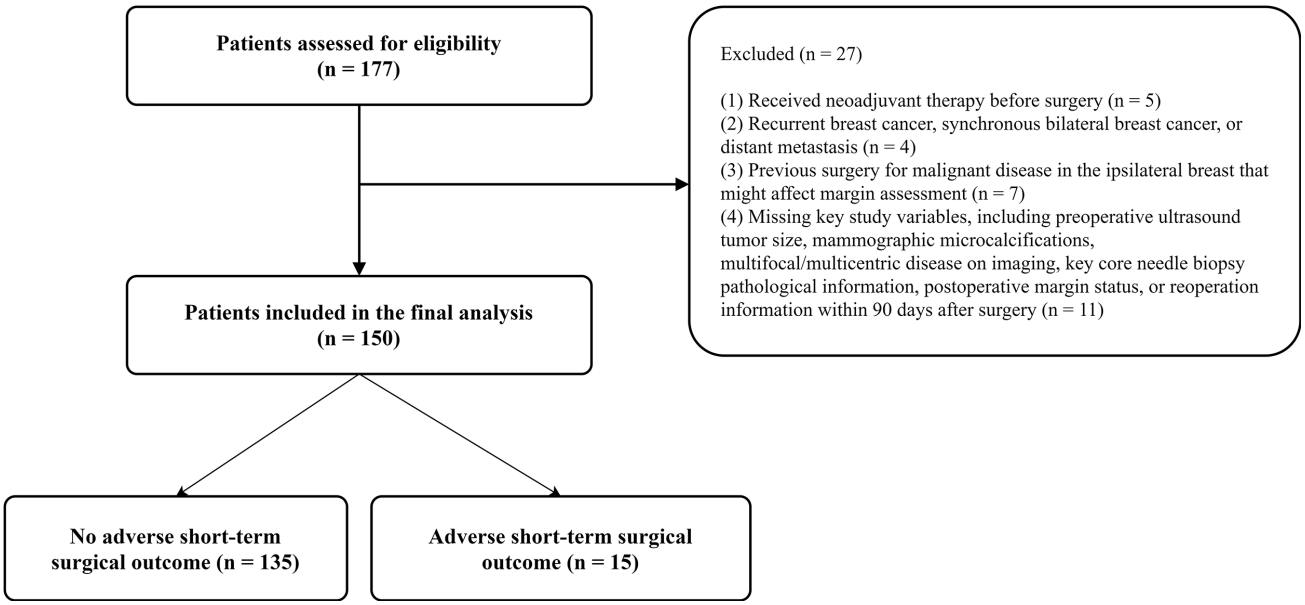

Fig. 1. Flowchart of patient selection for the present study.

phy. Tumor quadrant was determined based on preoperative imaging findings and the surgical record. The localization method was categorized as either image-guided localization or palpation-guided localization.

Preoperative Core Needle Biopsy Pathology

Histological type on core needle biopsy was recorded, including DCIS, invasive ductal carcinoma (IDC), and invasive lobular carcinoma (ILC). Whether the core biopsy showed a DCIS component was also recorded. Estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status, as well as the Ki-67 index, were collected.

Preoperative Laboratory Data

The most recent routine laboratory results before surgery were collected, including hemoglobin, white blood cell count, platelet count, albumin, creatinine, blood urea nitrogen, fasting plasma glucose, alanine aminotransferase, aspartate aminotransferase, total bilirubin, cancer antigen 15-3 (CA15-3), and carcinoembryonic antigen (CEA). All laboratory variables were obtained from the final preoperative results used for the perioperative assessment before the first surgery.

Postoperative Pathology and Short-Term Outcome Data

Final pathological tumor size, margin status, and reoperation within 90 days after surgery were collected. Final pathological tumor size was abstracted from the final pathology report. For invasive carcinoma, it generally referred to the largest diameter of the invasive focus. For pure DCIS or lesions in which the *in situ* component represented the main disease extent, the main lesion extent recorded by the pathologist was used. In multifocal/multicentric disease, the size of the largest or main focus was used rather than the sum of all foci, and multifocal/multicentric disease on imaging was recorded separately.

Outcome Definition

The primary outcome of this study was a short-term adverse surgical outcome, defined as the occurrence of any of the following after surgery: (1) reoperation within 90 days for margin-related reasons, including re-excision or other salvage procedures; (2) a strict positive margin on final routine pathology; or (3) although not meeting the definition of a strict positive margin and not leading to reoperation, a clinically meaningful close margin, suspected residual disease, or indeterminate margin assessment identified on postoperative pathology or imaging-pathology review when available and judged in the postoperative record to carry a risk of local residual disease.

For clarity, a strict positive margin was defined as the presence of tumor cells at the inked margin on final pathology examination. For invasive cancer, margin status was interpreted according to the “no ink on tumor” principle. For DCIS, the 2-mm negative margin consensus standard was used to identify clinically meaningful close margins, rather than to automatically classify all close margins as strict positive margins [5,6]. The third component of the composite outcome was coded only when the postoperative record documented that the finding was clinically meaningful in relation to possible residual disease or margin-related management. Specifically, these cases required documentation of at least one of the following: a close margin considered to carry residual-disease concern, an indeterminate margin assessment because of pathological or specimen-related uncertainty, suspected residual disease on imaging-pathology review when available, residual suspicious calcifications or

lesions, radiology-pathology discordance, or a documented recommendation for additional margin-related evaluation or management. Close margins without documented concern for residual disease were not coded as outcome events.

To avoid double counting, the component events of the composite outcome were classified hierarchically and reported as mutually exclusive categories: reoperation first, then strict positive margin, and then clinically meaningful close/indeterminate margin or suspected residual disease. Because this study included both invasive breast cancers and lesions with or without a DCIS component, adverse outcome events were determined comprehensively on the basis of the final pathology report, imaging-pathology review when available, and documented postoperative margin-related clinical decision-making. Reoperation within 90 days was defined as re-excision or other salvage procedures performed within 90 days after the initial surgery. This 90-day time window was based on definitions commonly used in previous studies of reoperation after breast-conserving surgery [17,18].

Because the components of the composite outcome differ in clinical severity and objectivity, the component distribution was reported descriptively, and the composite endpoint was interpreted as a pragmatic short-term surgical outcome rather than as a single homogeneous pathological endpoint.

Statistical Analysis

All statistical analyses were performed using R software (version 4.3.0; R Foundation for Statistical Computing, Vienna, Austria). The distribution of continuous variables was assessed using the Shapiro–Wilk test together with visual inspection of histograms and Q–Q plots. Variables with an approximately normal distribution were expressed as mean ± standard deviation (SD) and compared using the independent-samples *t*-test. Variables with a skewed distribution were expressed as median (quartile 1, quartile 3) and compared using the Mann-Whitney U test. Categorical variables were expressed as numbers (percentages) and compared using the chi-square test or Fisher's exact test. To describe the difference between preoperative ultrasound tumor size and final pathological tumor size in the overall cohort, paired measurements were compared using the Wilcoxon signed-rank test and displayed in a paired violin/box plot.

Short-term adverse surgical outcome was used as the dependent variable in the regression analyses. To reduce small-sample bias and unstable estimation in the setting of sparse events, all regression analyses were performed using Firth penalized logistic regression. Multivariable models were constructed on the basis of prespecified clinical considerations rather than purely data-driven selection. Candidate preoperative variables were first examined in univariable Firth regression analyses. Preoperative ultrasound tumor size was then entered as the main exposure in multivariable models. Model 1 was unadjusted. Model 2, prespecified as the primary model, was adjusted for mammographic microcalcifications and DCIS component on core biopsy. Model 3 was exploratory and additionally adjusted for multifocal/multicentric disease on imaging. Variance inflation factor (VIF) was used to assess multicollinearity, and VIF <5 was considered acceptable.

To explore the potential nonlinear association between preoperative ultrasound tumor size and short-term adverse surgical outcomes, restricted cubic spline (RCS) analysis was further performed. The BIC values for the 3-, 4-, and 5-knot models were 98.78, 96.35, and 101.13, respectively; therefore, the 4-knot model, which had the lowest BIC, was selected as the final model, with knots placed at the 5th, 35th, 65th, and 95th percentiles of ultrasound tumor size. Exploratory subgroup analyses were limited to a small number of key clinicopathological factors, and interaction terms were tested separately. Given the limited number of outcome events, the RCS analysis and subgroup interaction analyses were considered exploratory. A two-sided $p < 0.05$ was considered statistically significant.

Results

Baseline Characteristics

A total of 150 patients undergoing breast-conserving surgery for breast cancer were included, of whom 135 experienced no short-term adverse surgical outcomes, and 15 experienced at least one short-term adverse surgical outcome. Compared with the no-adverse-outcome group, patients in the adverse-outcome group had a larger preoperative ultrasound tumor size [(23.47 ± 6.70) mm vs. (17.55 ± 5.84) mm, $p < 0.001$] and a higher frequency of multifocal/multicentric disease on imaging (26.67% vs. 7.41%, $p = 0.049$). A DCIS component on core biopsy was also more common in the adverse-outcome group, although the difference did not reach statistical significance (53.33% vs. 28.15%, $p = 0.087$). No statistically significant differences were observed in the remaining demographic, clinicopathological, comorbidity, or preoperative laboratory variables (Table 1 and **Supplementary Table 1**).

Postoperative Pathological Findings and Short-Term Surgical Outcomes

Postoperative descriptive findings are shown in Table 2. Compared with the no-adverse-outcome group, the adverse-outcome group had a larger final pathological tumor size [26.00 (22.50, 33.00) mm vs. 20.00 (16.50, 26.50) mm, $p = 0.002$]. Among the 15 short-term adverse surgical outcome events, 3 were classified as reoperation within 90 days for margin-related reasons, 5 as strict positive margins, and 7 as clinically meaningful close/indeterminate margins or suspected residual disease. These component events were classified hierarchically and reported solely to describe the composition of the composite outcome; no inferential comparison was performed for these component variables. In the overall cohort, final pathological tumor

Table 1. Preoperative baseline characteristics according to short-term adverse surgical outcomes.

Variable	Total (n = 150)	No adverse short-term surgical outcome (n = 135)	Adverse short-term surgical outcome (n = 15)	Statistic	*p* value
Age (years), mean ± SD	52.30 ± 10.07	52.43 ± 10.29	51.13 ± 7.96	$t = 0.47$	0.638
BMI (kg/m^2), median (Q1, Q3)	23.90 (21.95, 26.98)	23.90 (22.00, 27.00)	25.00 (22.10, 25.70)	Z = –0.13	0.893
Tumor laterality, n (%)				$\chi^2 = 0.44$	0.507
Left	88 (58.67)	78 (57.78)	10 (66.67)		
Right	62 (41.33)	57 (42.22)	5 (33.33)		
Menopausal status, n (%)				$\chi^2 = 0.01$	0.912
Postmenopausal	88 (58.67)	79 (58.52)	9 (60.00)		
Premenopausal	62 (41.33)	56 (41.48)	6 (40.00)		
Palpable mass, n (%)				$\chi^2 = 0.25$	0.616
No	59 (39.33)	54 (40.00)	5 (33.33)		
Yes	91 (60.67)	81 (60.00)	10 (66.67)		
Family history of breast cancer, n (%)				$\chi^2 = 0.00$	1.000
No	129 (86.00)	116 (85.93)	13 (86.67)		
Yes	21 (14.00)	19 (14.07)	2 (13.33)		
Tumor quadrant, n (%)				Fisher's exact test	0.907
Central	23 (15.33)	20 (14.81)	3 (20.00)		
Lower inner quadrant	26 (17.33)	23 (17.04)	3 (20.00)		
Lower outer quadrant	19 (12.67)	18 (13.33)	1 (6.67)		
Upper inner quadrant	25 (16.67)	22 (16.30)	3 (20.00)		
Upper outer quadrant	57 (38.00)	52 (38.52)	5 (33.33)		
Localization method, n (%)				$\chi^2 = 0.25$	0.618
Image-guided localization	89 (59.33)	81 (60.00)	8 (53.33)		
Palpation-guided	61 (40.67)	54 (40.00)	7 (46.67)		
Ultrasound tumor size (mm), mean ± SD	18.14 ± 6.17	17.55 ± 5.84	23.47 ± 6.70	$t = –3.67$	<0.001
Mammographic microcalcifications, n (%)				$\chi^2 = 1.06$	0.303
No	98 (65.33)	90 (66.67)	8 (53.33)		
Yes	52 (34.67)	45 (33.33)	7 (46.67)		
Multifocal/multicentric disease on imaging, n (%)				$\chi^2 = 3.86$	0.049
No	136 (90.67)	125 (92.59)	11 (73.33)		
Yes	14 (9.33)	10 (7.41)	4 (26.67)		
Core needle biopsy histology, n (%)				Fisher's exact test	0.326
DCIS	17 (11.33)	14 (10.37)	3 (20.00)		
IDC	121 (80.67)	109 (80.74)	12 (80.00)		
ILC	12 (8.00)	12 (8.89)	0 (0.00)		
DCIS component on core biopsy, n (%)				$\chi^2 = 2.93$	0.087
No	104 (69.33)	97 (71.85)	7 (46.67)		
Yes	46 (30.67)	38 (28.15)	8 (53.33)		
ER positivity, n (%)				$\chi^2 = 0.41$	0.520
Negative	35 (23.33)	33 (24.44)	2 (13.33)		
Positive	115 (76.67)	102 (75.56)	13 (86.67)		
PR positivity, n (%)				$\chi^2 = 0.03$	0.869
Negative	63 (42.00)	57 (42.22)	6 (40.00)		
Positive	87 (58.00)	78 (57.78)	9 (60.00)		
HER2 positivity, n (%)				$\chi^2 = 0.53$	0.465
Negative	125 (83.33)	114 (84.44)	11 (73.33)		
Positive	25 (16.67)	21 (15.56)	4 (26.67)		
Ki-67 index (%), mean ± SD	26.86 ± 11.17	27.06 ± 11.16	25.05 ± 11.43	$t = 0.66$	0.509

Note: Data are presented as mean ± SD, median (Q1, Q3), or n (%). *p* values were derived from student's *t*-test, Mann–Whitney U test, chi-square test, or Fisher's exact test, as appropriate.

Abbreviations: BMI, body mass index; DCIS, ductal carcinoma *in situ*; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2.

Table 2. Postoperative pathological tumor size and descriptive components of short-term adverse surgical outcomes.

Variable	Total (n = 150)	No adverse short-term surgical outcome (n = 135)	Adverse short-term surgical outcome (n = 15)	Statistic	*p* value
Final pathological tumor size (mm), median (Q1, Q3)	21.00 (17.00, 27.00)	20.00 (16.50, 26.50)	26.00 (22.50, 33.00)	Z = –3.05	0.002
Reoperation within 90 days, n (%)				—	—
No	147 (98.00)	135 (100.00)	12 (80.00)		
Yes	3 (2.00)	0 (0.00)	3 (20.00)		
Strict positive margin, n (%)				—	—
No	145 (96.67)	135 (100.00)	10 (66.67)		
Yes	5 (3.33)	0 (0.00)	5 (33.33)		
Clinically meaningful close /indeterminate margin or suspected residual disease, n (%)				—	—
No	143 (95.33)	135 (100.00)	8 (53.33)		
Yes	7 (4.67)	0 (0.00)	7 (46.67)		

Note: Data are presented as median (Q1, Q3) or n (%). The *p* value for final pathological tumor size was derived from the Mann–Whitney U test. Reoperation within 90 days, strict positive margin, and clinically meaningful close/indeterminate margin or suspected residual disease were components of the primary composite outcome. To avoid double counting, these component events were classified hierarchically and reported as mutually exclusive categories. The symbol "—" indicates that no inferential test was performed because these variables were components of the composite outcome and were reported descriptively.

size was descriptively larger than preoperative ultrasound tumor size (Fig. 2; Wilcoxon signed-rank test, $p < 0.001$). This paired comparison should be interpreted cautiously because preoperative ultrasound and final pathology may capture different dimensions of disease extent, particularly in lesions with DCIS extension, microcalcifications, or multifocal/multicentric disease.

Univariate Association Analysis

Univariable Firth penalized logistic regression showed that increasing preoperative ultrasound tumor size was associated with higher odds of the adverse outcome. For each 5 mm increase in ultrasound tumor size, the odds of the adverse outcome increased by 2.32-fold (odds ratio (OR) = 2.32, 95% CI: 1.44–4.02, $p < 0.001$). Multifocal/multicentric disease on imaging was also associated with the outcome (OR = 4.68, 95% CI: 1.23–16.00, $p = 0.026$). In addition, a DCIS component on core biopsy showed a borderline association with the outcome (OR = 2.87, 95% CI: 1.00–8.43, $p = 0.050$). Hemoglobin level and anemia showed marginal associations but did not reach the conventional threshold for statistical significance (hemoglobin: OR = 0.96, 95% CI: 0.91–1.00, $p = 0.072$; anemia: OR = 3.13, 95% CI: 0.94–9.54, $p = 0.062$). No statistically significant associations were observed in age, body mass index, Ki-67, laterality, menopausal status, family history of breast cancer, mammographic microcalcifications, core biopsy histology, hormone receptor status, HER2 status, palpable mass, tumor quadrant, localization method, routine laboratory variables, tumor markers, or other comorbidities (all $p > 0.05$) (Table 3).

Multivariable Association Analysis

Multivariable Firth penalized logistic regression results are shown in Table 4. In the unadjusted model, preoperative ultrasound tumor size was associated with the short-term adverse outcome. In Model 2, prespecified as the primary model and adjusted for mammographic microcalcifications and DCIS component on core biopsy, preoperative ultrasound tumor size remained associated with the outcome (per 5 mm increase: OR = 2.16, 95% CI: 1.33–3.73, $p = 0.001$). In the exploratory Model 3, which additionally included multifocal/multicentric disease on imaging, the association remained in the same direction (OR = 2.02, 95% CI: 1.2–3.50, $p = 0.005$). These results suggest a consistent positive association across the prespecified primary model and the exploratory extended model. However, the effect estimates should be interpreted with caution because of the limited number of outcome events.

Nonlinear Association Analysis

Restricted cubic spline analysis showed an overall association between preoperative ultrasound tumor size and short-term adverse surgical outcomes and suggested a potential departure from a strictly linear relationship. In the unadjusted model, the overall association test and the nonlinearity test were $p = 0.003$ and $p = 0.037$, respectively. After adjustment for mammographic microcalcifications and DCIS component on core biopsy, the corresponding values were $p = 0.005$ and $p = 0.040$. However, the confidence intervals were wide, particularly at the lower and upper extremes of ultrasound tumor size. Given the limited number of outcome events relative to the complexity of the spline model, the nonlinearity test may be unstable and should be

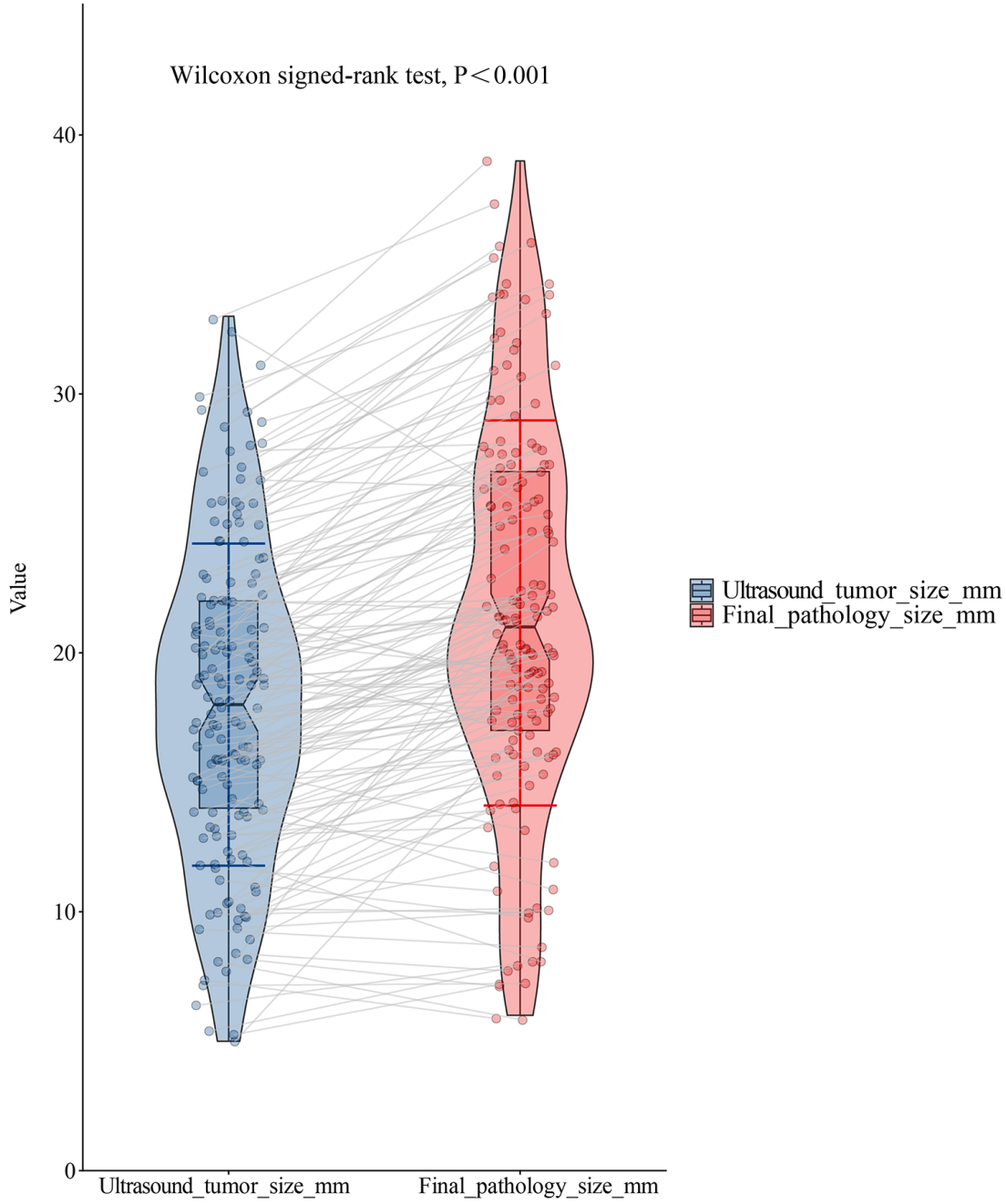

Fig. 2. Paired comparison of preoperative ultrasound tumor size and final pathological tumor size in the overall cohort. Each line represents paired measurements from the same patient. Final pathological tumor size was descriptively larger than preoperative ultrasound tumor size (Wilcoxon signed-rank test, Z = −8.85, $p < 0.001$). This paired comparison should be interpreted cautiously because ultrasound and pathological measurements may reflect different dimensions of disease extent.

interpreted with particular caution. Therefore, the spline curve should be interpreted as an exploratory indication of potential nonlinearity rather than as strong evidence for a specific threshold or a clear increase in risk at larger tumor sizes (Fig. 3).

Subgroup Analysis

Exploratory subgroup analyses are shown in Table 5. The association between preoperative ultrasound tumor size and the outcome appeared stronger in patients without mammographic microcalcifications (OR = 4.58, 95% CI: 2.04–13.78, $p < 0.001$) than in those with microcalcifications (OR = 1.31, 95% CI: 0.73–2.50, $p = 0.369$), with a nominal interaction signal (P for interaction = 0.014). A similar exploratory pattern was observed after stratification by a DCIS component on core biopsy. The association appeared stronger among patients without a DCIS component (OR = 3.54, 95% CI: 1.70–9.07, $p < 0.001$) than among

Table 3. Univariable Firth penalized logistic regression analysis of preoperative factors associated with short-term adverse surgical outcomes.

Variable	β	SE	Z	*p* value	OR (95% CI)
Age (years)	–0.013	0.026	–0.480	0.637	0.99 (0.94–1.04)
BMI (kg/m^2)	0.009	0.081	0.106	0.917	1.01 (0.85–1.18)
Ultrasound tumor size (per 5 mm increase)	0.842	0.255	3.306	<0.001	2.32 (1.44–4.02)
Ki-67 (per 10% increase)	–0.156	0.240	–0.650	0.521	0.86 (0.52–1.37)
Hemoglobin (g/L)	–0.043	0.024	–1.772	0.072	0.96 (0.91–1.00)
White blood cell count (×10^9/L)	–0.103	0.188	–0.549	0.588	0.90 (0.62–1.31)
Platelet count (×10^9/L)	0.008	0.006	1.388	0.175	1.01 (1.00–1.02)
Alanine aminotransferase (U/L)	0.011	0.036	0.304	0.772	1.01 (0.93–1.08)
Aspartate aminotransferase (U/L)	0.020	0.040	0.493	0.638	1.02 (0.93–1.10)
Total bilirubin (μmol/L)	0.006	0.061	0.094	0.927	1.01 (0.88–1.13)
Albumin (g/L)	–0.055	0.072	–0.768	0.446	0.95 (0.82–1.09)
Creatinine (μmol/L)	–0.012	0.022	–0.536	0.598	0.99 (0.94–1.03)
Blood urea nitrogen (mmol/L)	0.052	0.224	0.234	0.818	1.05 (0.67–1.66)
Fasting plasma glucose (mmol/L)	0.168	0.344	0.489	0.631	1.18 (0.59–2.34)
CA15-3 (U/mL)	0.012	0.029	0.408	0.698	1.01 (0.94–1.07)
CEA (ng/mL)	0.232	0.164	1.420	0.171	1.26 (0.90–1.73)
Laterality: Right vs Left	–0.335	0.554	–0.605	0.540	0.72 (0.22–2.06)
Menopausal status: Pre vs Post	–0.038	0.538	–0.071	0.944	0.96 (0.32–2.73)
Family history of breast cancer: Yes vs No	0.101	0.731	0.138	0.891	1.11 (0.21–4.05)
Mammographic microcalcifications: Yes vs No	0.562	0.533	1.055	0.295	1.76 (0.60–5.03)
Multifocal/multicentric disease on imaging: Yes vs No	1.543	0.642	2.402	0.026	4.68 (1.23–16.00)
Core biopsy histology: DCIS vs IDC	0.749	0.666	1.124	0.285	2.11 (0.50–7.27)
Core biopsy histology: ILC vs IDC	–1.049	1.473	–0.712	0.408	0.35 (0.003*–2.98)
ER positive vs negative	0.568	0.717	0.793	0.403	1.76 (0.50–9.32)
PR positive vs negative	0.068	0.538	0.127	0.899	1.07 (0.38–3.22)
HER2 positive vs negative	0.734	0.604	1.216	0.244	2.08 (0.58–6.49)
DCIS component on core biopsy: Yes vs No	1.054	0.536	1.967	0.050	2.87 (1.00–8.43)
Palpable mass: Yes vs No	0.244	0.555	0.440	0.657	1.28 (0.44–4.07)
Tumor quadrant: Central vs UOQ	0.488	0.732	0.668	0.511	1.63 (0.35–6.73)
Tumor quadrant: LIQ vs UOQ	0.352	0.727	0.484	0.633	1.42 (0.31–5.82)
Tumor quadrant: LOQ vs UOQ	–0.256	0.960	–0.267	0.785	0.77 (0.08–4.25)
Tumor quadrant: UIQ vs UOQ	0.395	0.729	0.542	0.592	1.48 (0.32–6.09)
Localization method: Palpation-guided vs image-guided	0.277	0.531	0.522	0.603	1.32 (0.45–3.76)
Hypertension: Yes vs No	0.193	0.643	0.301	0.767	1.21 (0.29–3.94)
Diabetes: Yes vs No	1.018	0.674	1.510	0.158	2.77 (0.64–9.69)
Cardiovascular disease: Yes vs No	0.853	0.666	1.281	0.227	2.35 (0.55–8.05)
Anemia: Yes vs No	1.141	0.580	1.965	0.062	3.13 (0.94–9.54)

Note: Firth penalized logistic regression was used because only 15 adverse outcome events were observed. Ultrasound tumor size was modeled per 5 mm increase, and Ki-67 was modeled per 10% increase. *Additional decimal places were retained for this value to avoid rounding a nonzero value to 0.00. Ultrasound tumor size was modeled per 5 mm.

Abbreviations: CA15-3, cancer antigen 15-3; CEA, carcinoembryonic antigen; OR, odds ratio; UOQ, upper outer quadrant; LIQ, lower inner quadrant; LOQ, lower outer quadrant; UIQ, upper inner quadrant.

those with a DCIS component (OR = 1.35, 95% CI: 0.74–2.68, $p = 0.335$), with a borderline exploratory signal for interaction (p for interaction = 0.058). Because only 15 outcome events were observed, including 8 and 7 events in the microcalcification-negative and microcalcification-positive subgroups, respectively, these subgroup findings should be interpreted only as exploratory signals and not be used to support firm clinical recommendations.

Discussion

This study examined short-term surgical outcomes after breast-conserving surgery for breast cancer. Preoperative ultrasound tumor size was positively associated with short-term adverse surgical outcomes in the univariable analysis, the prespecified primary model, and the exploratory extended model. Multifocal/multicentric disease on imaging was also associated with the outcomes in the univari-

Table 4. Effect estimates for preoperative ultrasound tumor size across Firth penalized logistic regression models for short-term adverse surgical outcomes.

Variable	Model 1 OR (95% CI)	*p* value	Model 2 OR (95% CI)	*p* value	Model 3 OR (95% CI)	*p* value
Ultrasound tumor size (per 5 mm increase)	2.32 (1.44, 4.02)	<0.001	2.16 (1.33, 3.73)	0.001	2.02 (1.23, 3.50)	0.005

Note: All estimates were obtained using Firth penalized logistic regression. Model 1 was unadjusted. Model 2, prespecified as the primary model, was adjusted for mammographic microcalcifications and DCIS component on core biopsy. Model 3 was exploratory and additionally adjusted for multifocal/multicentric disease on imaging. Ultrasound tumor size was modeled per 5 mm increase. The VIF values for all variables in models 2 and 3 were less than 3.

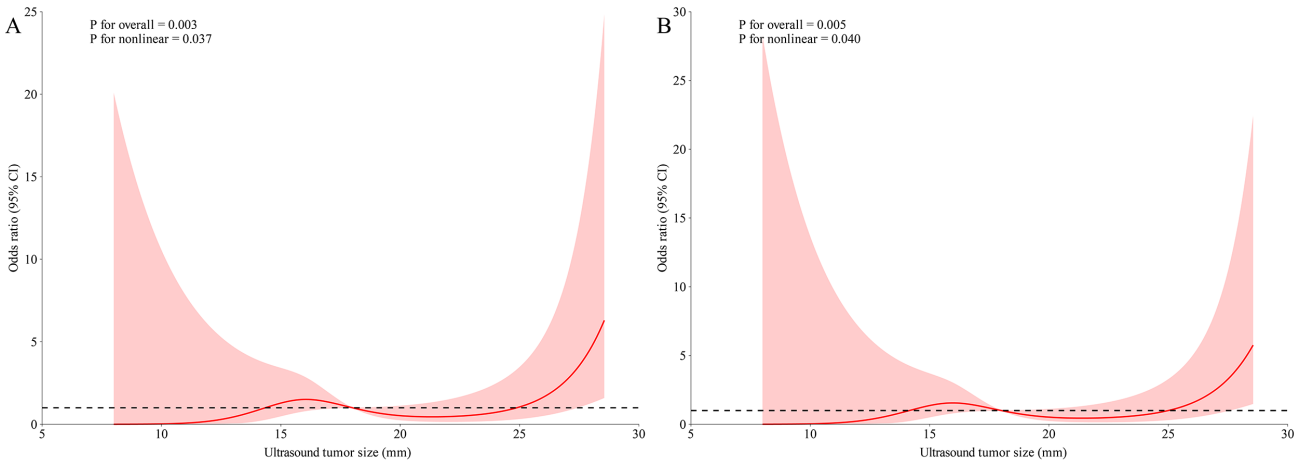

Fig. 3. Restricted cubic spline curves for the association between preoperative ultrasound tumor size and short-term adverse surgical outcomes. (A) Unadjusted restricted cubic spline analysis. (B) Restricted cubic spline analysis adjusted for mammographic microcalcifications and ductal carcinoma *in situ* (DCIS) component on core biopsy (same covariates as Model 2). *Note:* The final restricted cubic spline (RCS) model used 4 knots selected according to the Bayesian information criterion. Knots were placed at the 5th, 35th, 65th, and 95th percentiles of ultrasound tumor size (8.0, 16.0, 20.0, and 28.55 mm). The solid line denotes the estimated odds ratio, and the shaded area denotes the 95% confidence interval.

Table 5. Exploratory subgroup analyses for the association between preoperative ultrasound tumor size and short-term adverse surgical outcomes.

Subgroup	Level	N	Events	OR (95% CI)	*p* value	*p* for interaction
Mammographic microcalcifications	No	98	8	4.58 (2.04, 13.78)	<0.001	0.014
	Yes	52	7	1.31 (0.73, 2.50)	0.369	
DCIS component on core biopsy	No	104	7	3.54 (1.70, 9.07)	<0.001	0.058
	Yes	46	8	1.35 (0.74, 2.68)	0.335	

Note: Exploratory subgroup analyses were performed using Firth penalized logistic regression, with preoperative ultrasound tumor size modeled per 5 mm increase. Interaction *p* values were obtained from separate interaction models. Because of the sparse-event setting, subgroup-specific estimates and interaction *p* values should be interpreted as exploratory signals.

able analysis, whereas a DCIS component on core biopsy showed borderline statistical significance. Restricted cubic spline analysis suggested possible departure from a strictly linear relationship. However, given the limited number of outcome events, the nonlinear and subgroup findings should be interpreted as exploratory and hypothesis-generating rather than as definitive evidence of nonlinear effects or effect modification.

Preoperative ultrasound tumor size was one of the more consistent preoperative correlates in this study. This finding is consistent with a previous report that larger lesions are more likely to be associated with margin-related problems [19], and Liu et al. [20] also included tumor size as an important input variable in their preoperative model. From a surgical perspective, larger lesions may require a wider initial excision and leave less tolerance for boundary-estimation error, particularly when breast volume is limited or lesion margins are indistinct. Furthermore, restricted cubic spline analysis suggested that the association between preoperative ultrasound tumor size and short-term adverse

surgical outcomes may not be fully captured by a simple linear relationship. This observation is consistent with previous concerns that lesion extent may be underestimated in selected clinical settings, particularly in DCIS-dominant lesions or those characterized by microcalcifications [16,21]. However, the confidence intervals of the spline curve were wide, particularly at the lower and upper extremes of ultrasound tumor size. Therefore, the spline findings should not be interpreted as evidence of a precise threshold or a clear increase in risk at larger tumor sizes.

Mammographic microcalcifications and a DCIS component may also define the interpretive boundary of ultrasound tumor size. Microcalcifications are among the characteristic mammographic findings of DCIS and may reflect ductal extension rather than a compact mass with a clearly measurable contour [22]. Previous studies have shown that radiological underestimation in lesions related to DCIS or microcalcifications is associated with positive margins [15,23], and underestimation of DCIS diagnosed by core needle biopsy has also been well documented [24]. Therefore, the attenuated association in microcalcification-positive or DCIS-component-positive lesions should not be interpreted as indicating a lower-risk pattern. Rather, it suggests that ultrasound size alone may be insufficient to characterize disease extent in these lesions. Multifocal/multicentric disease on imaging was also associated with the outcome in this study. Multifocal or multicentric disease may increase the difficulty of complete excision and accurate margin assessment and may affect the chance of completing breast-conserving surgery successfully at the first operation [12]. Invasive lobular carcinoma has also been reported to show a more diffuse infiltrative growth pattern and a higher risk of positive margins [25,26,27], further supporting the importance of careful preoperative assessment of disease extent. Because of the sparse-event setting, these findings should be interpreted as clinically meaningful exploratory correlates and require confirmation in larger cohorts. Similarly, the paired comparison between preoperative ultrasound tumor size and final pathological tumor size should be interpreted descriptively, because these measurements may reflect different dimensions of disease extent, particularly in lesions with DCIS extension, microcalcifications, or multifocal/multicentric disease.

From a clinical perspective, the value of this study lies not in proposing a new breast-conserving technique, but in offering practical information for preoperative risk recognition and surgical planning before the initial breast-conserving procedure. Accordingly, for lesions dominated by microcalcifications, accompanied by a DCIS component, or showing multifocal/multicentric disease on imaging, preoperative ultrasound size should be interpreted in conjunction with mammographic, pathological, and other surgical findings. Previous studies have suggested that, in high-risk patients, cavity shave margins, systematic intraoperative margin assessment, or more appropriate localization strategies may help reduce positive margins and reoperation rates [28,29,30]. Recent national follow-up data on DCIS have also suggested that the relationship between margin width and recurrence is not simply linear, highlighting the need to interpret pathological detail alongside the overall clinical context [31,32]. Thus, rather than using any single variable to determine surgical appropriateness, the practical implication is earlier recognition of patients who may require more careful margin management. Such recognition may help optimize the initial resection plan, localization strategy, and intraoperative margin handling and reduce repeat decision-making and the cosmetic or psychological burden associated with repeated operations [33,34]. These implications should be considered hypothesis-generating and require validation in larger multicenter cohorts.

This study has several limitations. First, it was a single-center retrospective analysis and, therefore, can only identify associations rather than establish causality. Second, although the composite short-term outcome may better reflect the clinical concept of "completion quality" after the first breast-conserving procedure than a single positive-margin endpoint, the component events are not of equal clinical importance, and some close/indeterminate margin events still involved a degree of clinical judgment. To address this issue, the component events were classified hierarchically and reported descriptively, and the composite endpoint was interpreted as a pragmatic measure of short-term surgical outcome rather than as a single homogeneous pathological endpoint. Third, only 15 adverse outcome events were observed, which limited the stability of the multivariable models and the reliability of the nonlinear and subgroup analyses. These findings should therefore be regarded primarily as hypothesis-generating and informative for risk assessment rather than as broadly generalizable. Finally, we did not further incorporate potentially relevant factors such as intraoperative margin-assessment method or inter-surgeon variation, and their influence remains to be clarified. However, the study retains practical value because the included variables are routinely available before surgery, and the analysis may help generate clinically relevant hypotheses regarding nonlinear associations and potential heterogeneity in preoperative risk patterns.

Conclusions

The findings of this study suggest that, among patients undergoing breast-conserving surgery for breast cancer, preoperative ultrasound tumor size may be associated with poorer short-term surgical outcomes, and this association may not be fully explained by a linear relationship. Multifocal/multicentric disease on imaging and a DCIS component on core biopsy may also be relevant risk-related features. For lesions dominated by microcalcifications or accompanied by a DCIS component, preoperative evaluation based solely on ultrasound tumor size may be insufficient, highlighting the need for integrated interpretation of imag-

ing and pathological findings. These exploratory findings warrant further validation in larger, multicenter studies.

Availability of Data and Materials

The data analyzed are available from the corresponding author upon reasonable request.

Author Contributions

CYC designed the research study. CYC and SCY performed the research. CYC and SCY analyzed the data. CYC drafted the article. Both authors have been involved in revising the manuscript critically for important intellectual content. Both authors gave final approval of the version to be published. Both authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

This retrospective study was based on medical records generated during routine clinical care and involved no additional diagnostic or therapeutic interventions. Therefore, it fell within the scope of exemption from Ethics Review. The study was reviewed and granted an exemption by the Ethics Committee of Yongkang Women and Children's Health Hospital. The requirement for informed consent was waived because of the retrospective nature of the study and the use of de-identified data. The study was conducted in accordance with the Declaration of Helsinki.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.62713/aic.4744.

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