

RESEARCH ARTICLE

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Performance of Radiomic Features in Stir Sequences in Predicting Histopathological Outcomes of Breast Cancer

Meme Kanserinin Histopatolojik Sonuçlarının Öngörülmesinde Stir Sekanslardaki Radyomik Özelliklerin Performansı

ABSTRACT

Objective

Histopathological features of breast cancer are critical in determining treatment and prognosis. The aim of this study is to investigate the performance of radiomic features in short tau inversion recovery (STIR) sequences in predicting histopathological outcomes of invasive breast cancer.

Methods

Pre-treatment (Magnetic resonance imaging) MRI examinations of women diagnosed with invasive breast cancer were evaluated retrospectively. Histologic grade, estrogen receptor (ER), progesterone receptor (PR), Her-2, Ki-67 expressions, and molecular subtypes were noted. Lesions were manually segmented from STIR sequences using the 3D Slicer software, and volumes of interest was obtained. Machine learning (ML) analysis was performed using Python 3.11, Pycaret library. The performance of ML algorithms was evaluated with area under curve (AUC), accuracy, recall, precision and F1 score.

Results

A total of 197 patients with a mean age of 50.72±11 (range 28-82) years were included in the study. The mean lesion size was 23.71±14.86 (5-120) mm. The best performance was obtained in ER+/- discrimination and luminal A+B prediction. The CatBoost classifier was the most successful ML algorithm with AUC, accuracy, recall, precision and F1 values were 0.75, 80%, 0.96, 0.81, 0.88 respectively for ER+/- .In predicting luminal A+B tumors, AUC, accuracy, recall, precision and F1 values were 0.72, 79%, 0.79, 0.64, 0.70, respectively.

Conclusion

Radiomic features obtained from STIR sequences have potential utility in predicting ER receptor status and luminal tumors.

Key Words

Breast neoplasms, Magnetic resonance imaging, Artificial Intelligence, Histology, Machine learning

ÖZ

Amaç

Meme kanserinin histopatolojik özellikleri tedavi ve prognozun belirlenmesinde kritik öneme sahiptir. Bu çalışmanın amacı, short tau inversion recovery (STIR) sekanslarındaki radyomik özelliklerin, invazif meme kanserinin histopatolojik sonuçlarının tahmin edilmesindeki performansını araştırmaktır.

Gereç ve Yöntemler

İnvazif meme kanseri tanısı alan kadınların tedavi öncesi Manyetik rezonans görüntüleme (MRG) incelemeleri retrospektif olarak değerlendirildi. Histolojik grade, östrojen reseptörü (ER), progesteron reseptörü (PR), Her-2, Ki-67 ekspresyonları ve moleküler alt tipler not edildi. Lezyonlar, 3D Slicer programında STIR sekanslarından manuel olarak segmente edildi ve ilgilenilen hacim elde edildi. Makine öğrenimi (MÖ) analizi Python 3.11, Pycaret kütüphane programı kullanılarak yapıldı. MÖ algoritmalarının başarısı eğri altındaki alan (AUC), doğruluk, geri hatırlama, kesinlik ve F1 puanı ile değerlendirildi.

Bulgular

Çalışmaya yaş ortalaması 50,72±46 (dağılım 28-82) yıl olan toplam 197 hasta dahil edildi. Ortalama lezyon boyutu 23,71±14,86 (5-120) mm idi. En iyi performans ER+/- ayırımında ve luminal A+B tahmininde elde edildi. CatBoost sınıflandırıcısı en başarılı MÖ algoritması olup, AUC, doğruluk, geri hatırlama, kesinlik ve F1 değerleri ER+/- için sırasıyla 0,75, %80, 0,96, 0,81, 0,88 olarak bulunmuştur. Luminal A+B tümörlerini öngörmede AUC, doğruluk, hatırlama, kesinlik ve F1 değerleri sırasıyla 0,72, %79, 0,79, 0,64, 0,70 olarak belirlendi.

Sonuç

STIR sekanslardan elde edilen radyomik özellikler, ER reseptör durumunu ve luminal tümörleri tahmin etme potansiyeline sahiptir.

Anahtar Kelimeler

Meme neoplazmi, Manyetik rezonans görüntüleme, Yapay Zeka, Histoloji, Makine öğrenimi

INTRODUCTION

Breast cancer is the most common cancer among women and one of the leading causes of cancer-related deaths (1). It is a heterogeneous disease with varying clinical presentations, treatment responses and survival outcomes (2).

Tumor size, histological grade and type, receptor status, and multifocality have been reported as prognostic and predictive factors of breast cancer (3). Estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER-2) status plays an important role in determining the subtypes and treatment. Overall survival and relapse rates vary according to treatment across these subtypes (4-7).

Four molecular subtypes have been described based on ER, PR, Her-2 and Ki-67 expression. These types are luminal A, luminal B, Her-2 positive, and triple negative (TN) breast cancer (8).

Radiomics provides quantitative information about the internal structure of tissues through a large number of numerical features obtained from medical images. Radiomics, which has attracted considerable attention in the field of oncology, provides data on the tumor shape, size, volume, density and heterogeneity. Studies have shown that it is successful in tumor diagnosis and classification, evaluation of treatment response. Radiomics is also associated with the clinical and laboratory data of patients (9).

In most studies conducted with different modalities, radiomics has demonstrated promising results in the field of breast cancer. Many studies involving magnetic resonance imaging (MRI) based models have achieved successful performance in differentiating benign and malignant breast tumors, determining the histological grade, receptor status and molecular subtypes of tumors, and evaluating the response to neoadjuvant chemotherapy (10).

The aim of this study is to investigate the performance of radiomic features obtained from short tau inversion recovery (STIR) images in predicting the histopathological outcomes of breast cancer.

MATERIALS and METHODS

Ethics

Permission was obtained from the Ethics Committee of Kartal Doctor Lütfi Kırdar City Hospital for this retrospective study. (approval date: 28.08.2023, approval number: 202351425620). Due to the retrospective design of the study, the requirement for informed consent was waived by the institutional review board. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Study Population

Data of female patients diagnosed with invasive breast cancer between 2017 and March 2023 were evaluated retrospectively. Patients were excluded based on the following criteria: lack of pre-treatment MRI, prior administration of neoadjuvant chemotherapy before MRI, missing pathological data, and MRI examinations compromised by artifacts.

Immunohistochemical Examination

US-guided core biopsies were performed by a radiologist with 8 years of experience in breast imaging. Specimens were fixed in 10% neutral buffered formalin. Histological grade was determined using the modified Bloom-Richardson method. Expression of ER, PR, Her-2 and Ki-67 was determined by immunohistochemical analysis. The receptor status was divided into two groups as positive and negative. Those with Ki-67 expression greater than or equal to 20%

were considered high, and those below it were considered low. Her-2 expression score of 1 was considered negative, and score of 3 was considered positive. The final results of the cases with score 2 were determined by fluorescence in situ hybridization (FISH). The patients were divided into three groups according to their molecular subtypes: luminal A (ER and/or PR +, Her-2 -, Ki-67 < 20 %) + luminal B (ER and/or PR +, Her-2 -, Ki-67 $\geq$ 20 % and ER and/or PR +, Her-2 +, Ki-67 $\geq$ 20 %), Her-2 enriched (ER -, PR-, Her-2 +) and TN (ER -, PR-, Her-2-).

MRI Examination Protocol

MRI examinations were obtained using a 16-channel breast coil on a 1.5 Tesla device (Philips Ingenia, Philips Healthcare, Best, The Netherlands). The acquisition parameters of STIR sequences were FOV: 341x341 mm, matrix: 263x223, FA: 90 deg, TR: 4040 ms, TE: 65 ms, slice thickness: 3 mm, slice gap: 3 mm.

Feature Extraction and Machine Learning Analysis

The 3D Slicer software (version 4.10.2; <https://www.slicer.org>) was used to extract radiomic features. Lesions were segmented on all slices from resampled images (size: 1x1x1 mm). Segmentation was performed by two radiologists (with 8 and 10 years of breast imaging experience) blinded to the histopathologic outcomes. In cases of multifocal

and multicentric disease, the largest lesion was selected for segmentation. The lesion, including necrotic areas, was manually segmented on all axial STIR sections and volume of interest was obtained. 851 radiomic features were extracted, consisting of first-order, shape features, texture and wavelet-based texture features. One month later, measurements were repeated in 30 randomly selected patients. Interobserver agreement was evaluated using intraclass correlation coefficient (ICC). Six hundred sixty-seven radiomic features with aICC value over 0.7 were included in the machine learning (ML) process.

Data processing and ML analysis were performed using the Python 3.11 (Pycaret Library). 15 ML algorithms were used (CatBoost Classifier, Quadratic Discriminant Analysis, Naive Bayes, Dummy Classifier, Extra Trees Classifier, Random Forest Classifier, Light Gradient Boosting Machine, K Neighbors Classifier, Extreme Gradient Boosting, Gradient Boosting Classifier, Logistic Regression, Decision Tree Classifier, Ridge Classifier, Ada Boost Classifier, SVM - Linear Kernel, Linear Discriminant Analysis). Five-fold cross validation was used to avoid data overfitting. The features with the highest correlation were selected by ML algorithms. Binary classification was used to classify groups of two (ER, PR, Her-2, Ki-67), and multiclass classification was used to classify groups of three (histologic grade, luminal A+luminal B/Her-2 enriched/TN). The Radiomics and ML workflow is summarized in Figure 1.

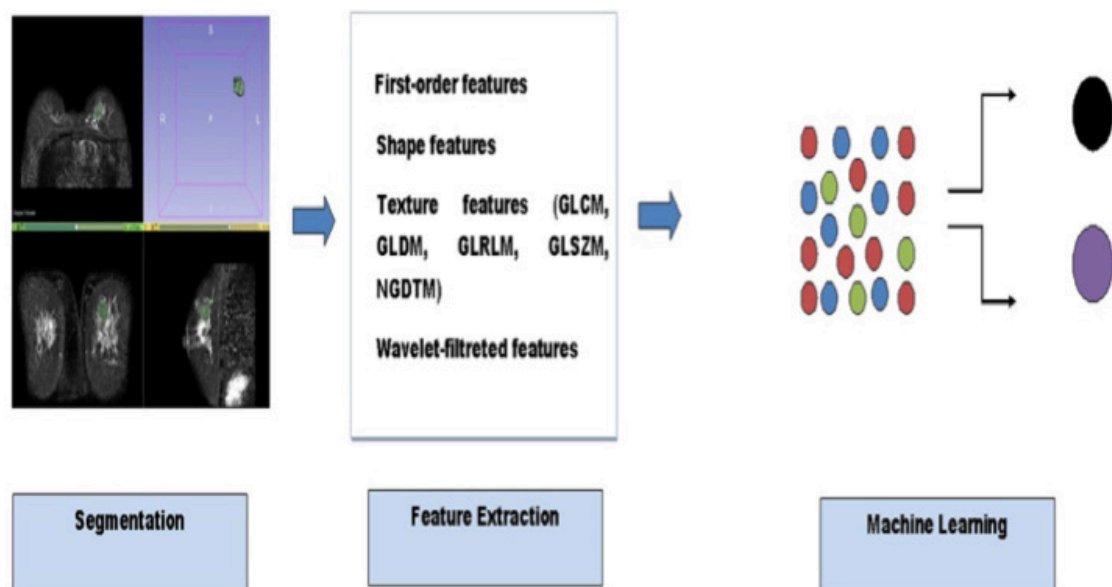


Figure 1. The tumor was manually segmented in all sections from STIR sequences. Radiomic features were extracted from the segmented areas. The predictive potential of the groups was determined by machine learning method using radiomic features.

The performance of 15 different ML algorithms was evaluated using AUC, accuracy, precision, recall and F1 scores. The ML model with the best performance was re-evaluated on the test dataset. And subsequently optimized.

Statistical Analysis

Statistical Package for Social Sciences (SPSS) version 25 software was used for statistical analysis. Descriptive results were given as percentage, mean and standard deviation. The distribution of the data was examined with the Kolmogorov–Smirnov test. Interobserver agreement was evaluated with ICC values.

RESULTS

Data from a total of 432 patients were evaluated. Of these 166 patients who did not have MRI before treatment, 56 patients who received neoadjuvant chemotherapy before MRI, 17 patients who underwent pathological examination at an external center, and 46 patients with suboptimal im-

age quality were excluded from the study. Ultimately, 197 patients (mean age 50.72 ± 11 , range 28-82 years) who met the inclusion criteria were included in the study. The mean lesion size was 23.71 ± 14.86 (5-120) mm. The histopathological outcomes of the patients are presented in Table I.

Table I. Histopathological features of the patients

Groups	Patient number (n, %)
ER positive/ER negative	156 /41 (79.2%/20.8%)
PR positive/PR negative	126 /71 (63.9%/36.1%)
Her-2 positive/Her-2 negative	58/139 (29.4%/70.6%)
Histological Grade 1/2/3	43/ 104/ 50 (21.8%/52.8%/25.4%)
Ki-67 high/Ki-67 low	136/61 (69.1%/30.9%)
Luminal A/LuminalB/Her-2 enriched/TN BC	57/99/17/24(28.9%/50.3%/8.6%/12.2%)

Patients were randomly divided into training set (n=137) and test set (n=60). The selected features for each group are shown in Table II. AUC values for distinguishing ER+/-, PR+/-, Her-2+/-, Ki-67 low/high tumors were 0.75, 0.66, 0.57, 0.66, respectively. Grade 1 tumors could be distinguished from grade 2 and 3 tumors with an AUC of 0.63. Luminal A+B tumors were differentiated from Her-2 en-

riched and TN BC tumors with an AUC of 0.72. The Her-2 positive and TN group could not be distinguished from the other groups. The performance of the models is shown in detail in the classification report and confusion matrix in Figure 2. AUC, accuracy, recall, precision and F1 values of all groups in the test set are presented in Table III.

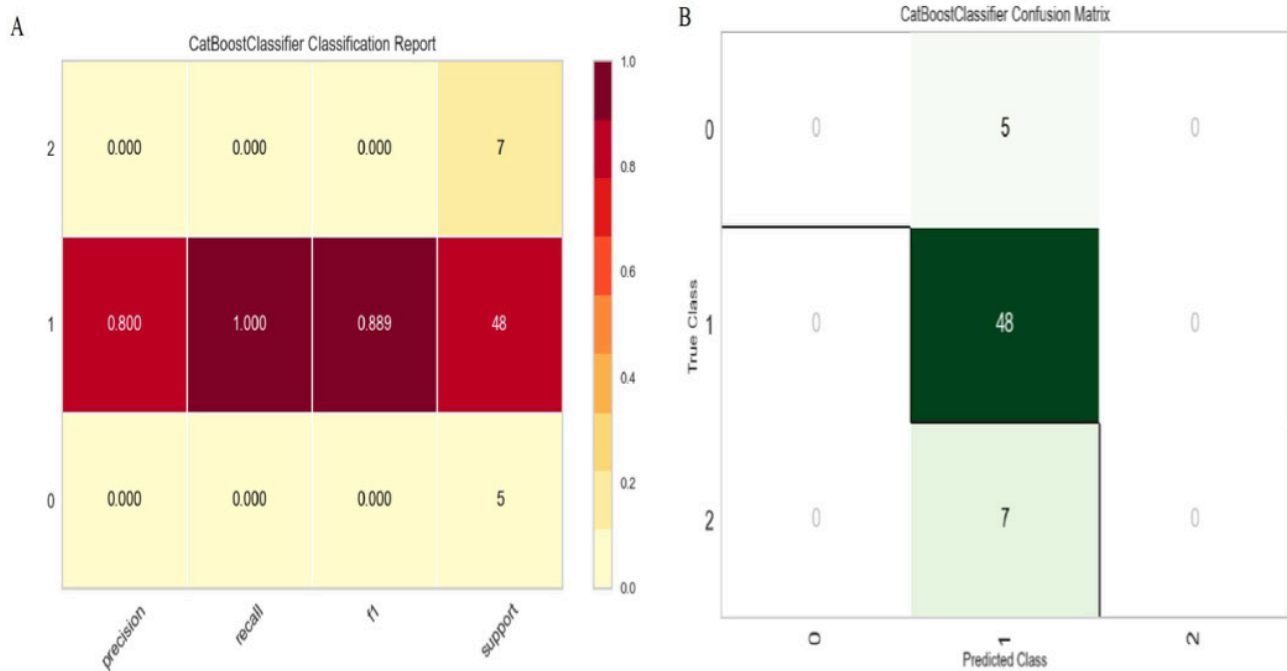
Table II. Features selected in the analysis of groups

Molecular Subtype	ER positive/negative	PR positive/negative	Her-2 positive/negative	Grade	Ki-67 low/high
*GLRM-RV	*Minimum	GLCM-CS	Elongation	*Skewness	*Skewness
*Minimum	*Kurtosis	*GLCM-DE	*Skewness	*Range	Maximum
*GLCM-MCC	*GLDM-DNN	GLSZM-SZNN	Maximum2D	*GLRLM-LGLE	GLDM-LDHGLE
*GLDM-SDHGLE	*Kurtosis	*GLSZM-LAHGLE	*GLSZM-ZV	*GLRLM-SRE	*GLCM-MCC
*GLCM-Imc1	*Range	*GLCM-CP	MAL	*GLCM-SS	*Median
*Skewness	*GLSZM-SDHGLE	*GLSZM-ZP	*GLSZM-LAE	*GLSZM-GLNN	*GLSZM-SAE
*MAD	GLSZM-SAE	*GLSZM-SZN	*GLDM-DV	*Maximum	*GLCM-JA
*GLCM-IV	*Maximum	*GLSZM-SZN	*GLDM-GLE	*GLSZM-SALGLE	*GLCM-Imc1
*Minimum	*GLCM-DV	*GLSZM-ZP	Sphericity	GLCM-DE	*GLDM-LDHGLE
*GLCM-Correlation	*GLCM-DA	*Minimum	Maximum2D	*Minimum	*GLCM-CS

Abbreviations: GLRM, Gray-Level Run Length Matrix; GLCM, gray-level co-occurrence matrix; GLDM, gray-level dependence matrix; GLSZM, gray-level size zone matrix; GLRLM, gray-level run length matrix; Asterisk (*), Wavelet; RV, Run variance; SDHGLE, Small Dependence High Gray Level Emphasis; MAD Mean Absolute Deviation; IV Inverse Variance; DNN Dependence Non Uniformity-Normalized; SDHGLE Small Dependence High Gray Level Emphasis; SAE Small Area Emphasis; DV Difference Variance; DA, Difference Average; CS Cluster Shade; DE Difference Entropy; SZNN Size Zone Non Uniformity Normalized; LAHGLE Large Area High Gray Level Emphasis; CP Cluster Prominence; ZP Zone Percentage; SZN Size Zone Non Uniformity; ZV Zone Variance; MAL Major Axis Length; LAE Large Area Emphasis; DV Difference Variance; GLE Gray Level Emphasis; LGLE Low Gray Level Run Emphasis; SRE Short Run Emphasis; SS Sum Squares; GLNN Gray Level Non Uniformity Normalized; SALGLE Small Area Low Gray Level Emphasis; LDHGLE Large Dependence High Gray Level Emphasis; SAE Small Area Emphasis; JA Joint Average; LDHGLE Large Dependence High Gray Level Emphasis

Table III. The most successful ML algorithm and AUC, accuracy, recall, precision, F1 values in the test set.

Groups	Best Model	AUC	Accuracy	Recall	Precision	F1
ER positive/ER negative	CatBoost Classifier	0.75	80 %	96 %	81 %	88 %
PR positive/PR negative	Extreme Gradient Boosting	0.66	66 %	94 %	67 %	78 %
Her-2 positive/Her-2 negative	Extra Trees Classifier	0.57	70 %	15 %	54 %	23 %
Histological Grade 1/2/3	Extra Trees Classifier	0.63	57 %	57 %	60 %	53 %
Ki-67 high/low	CatBoost Classifier	0.66	72 %	92 %	74 %	82 %
Luminal A+B/Her-2 enriched/TN BC	CatBoost Classifier	0.72	80 %	79 %	64 %	70 %
Luminal A/Luminal B/Her-2 enriched/TN BC	Extra Trees Classifier	0.64	52 %	52 %	47 %	47 %

**Figure 2.** Classification report (A) showing the precision, recall, F1 score in predicting molecular subtypes of the catBoost classifier, which is the most successful among the algorithms, and the confusion matrix (B) showing the prediction rates of the groups.

DISCUSSION

In this study, we investigated the performance of radiomics features obtained from STIR sequences of invasive breast cancer lesions in predicting the histopathological outcomes and molecular subtypes using ML algorithms. We were able to distinguish ER + and ER – lesions with an AUC of 0.75. Furthermore, luminal A+luminal B tumors were predicted with an accuracy of 80% and an AUC of 0.72.

In previous studies, MRI has been shown to be successful in predicting histopathological results using radiomic features extracted from MRI (11). In studies conducted with DCE-MRI, ER status could be predicted with radiomic features, with AUC ranging between 0.65-0.73. The predictability of PR status ranged between 0.62-0.69 AUC (12-14). In our study, ER and PR were within a similar range, with AUCs of 0.75 and 0.66, respectively. Using radiomics derived from DCE-MRI and MRI, Her-2 status was estimated with an AUC of 0.68-0.87 (15, 16). In contrast, our study yielded an AUC of 0.57 suggesting that radiomics obtained from STIR sequences may be less successful in predicting Her-2 status. Szep et al. predicted ER and PR status in the validation set using an ADC-based radiomics model with an AUC of 0.93 (17). Estimation of Ki-67 ratios with DCE-MRI-based radiomics resulted in an AUC of 0.71-0.80 (15, 18). In our study, with an AUC of 0.66, STIR-based radiomics demonstrated lower performance in predicting Ki-67 compared with DCE-MRI approaches. In a study by Sheng et al., using patient age, menstrual status, and tumor type and MRI radiomics, luminal tumors could be distinguished from other groups with 0.82 AUC, 0.75 sensitivity, 0.65 specificity, 0.69 accuracy, and 0.60 F1-Score (19).

Unlike this study, clinical parameters were not incorporated into our model. Although our AUC was slightly lower, our model demonstrated higher recall and accuracy values, suggesting potential advantages in classification sensitivity. In previous studies conducted with DCE MRI, skewness, related to tumor heterogeneity, was found to be one of the features that showed a high correlation in molecular subtype prediction (10). Similarly, in our study, skewness was an important feature in predicting molecular subtypes. Skewness also correlated with grade, Her-2 and Ki-67. The entropy feature, associated with tumor heterogeneity, correlated with PR receptor status. Minimal signal feature showed a high correlation with ER status and hormone-positive tumors.

Luminal A and B tumors are hormone-positive tumors and respond well to hormone therapy, but their response to chemotherapy is limited. Survival rates in these subtypes are better than other types and relapse rates are lower than oth-

er types (3, 4). Accurate differentiation of these subtypes is therefore critical for optimal treatment planning. In our study, luminal A and B tumors were successfully distinguished from HER-2 positive and TN types. Radiomics features obtained from STIR sequences represent a noninvasive approach with potential in predicting luminal tumors. The relatively small sample size and retrospective design are the limitations of our study. In patients with more than one lesion, only the largest lesion was analyzed which may limit the generalizability of the findings. Additionally, the lack of external validation constitutes another important limitation.

CONCLUSION

In conclusion, radiomic features obtained from STIR sequences may be useful in predicting the histopathological outcomes of breast cancer. The advantages of this method are that it is noninvasive, can be used in routine breast MRI examinations, and does not require contrast material. Thus, radiomic features may serve as a supportive tool in treatment planning of breast cancer. The results of our study should be validated in larger, prospective cohorts.

Ethical Approval

This retrospective study was approved by the Clinical Research Ethics Committee of Kartal Doctor Lütfi Kırdar City Hospital . (approval date: 28.08.2023, approval number: 202351425620). The study was conducted in accordance with relevant ethical guidelines and the principles of the Declaration of Helsinki Due to the retrospective design of the study, the requirement for informed consent was waived.

Conflict of Interest

The authors have no conflict of interest to declare.

Author Contributions

Concept – G.R.; Design- G.R., M.A., ; Supervision – G.R., M.A. Ş.K.; Resources – G.R.,M.A., Ö.A.K.; Materials – G.R., M.A., Ş.K.; Data Collection and/or Processing – G.R., M.A., Ö.A.K, Ş.K.; Analysis and/ or Interpretation – G.R., T.A.S.; Literature Search – G.R., M.A., Ö.A.K.; Writing Manuscript G.R., M.A.; Critical Review – G.R., M.A, T.A.S.

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Declaration of AI and AI-assisted technologies in the writing process: This study was written without the assistance of artificial intelligence technologies.

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