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Fragmented QRS and Neutrophil-to-Lymphocyte Ratio as Noninvasive Biomarkers of Lymphovascular Space Invasion in Endometrial Cancer: A Retrospective Cohort Study

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Abstract

Objective

To evaluate the prognostic significance of fragmented QRS (fQRS) on electrocardiography and the neutrophil-to-lymphocyte ratio (NLR) as noninvasive biomarkers in endometrial cancer, with particular focus on their association with lymphovascular space invasion (LVSI).

Material and Method

In this retrospective cohort study, 198 patients who underwent surgery for endometrial cancer were included. All cases were staged according to the 2023 FIGO classification. Preoperative complete blood counts and electrocardiograms were assessed to determine NLR and the presence of fQRS. Clinicopathological variables, including LVSI status, were recorded and statistically analyzed.

Results

The median NLR was significantly higher in patients with fragmented QRS compared with those without fragmented QRS (2.45 [1.46–12.42] vs. 2.04 [0.66–7.72], p = 0.013). LVSI positivity was observed more frequently among patients with fQRS (30% vs. 11.3%, p = 0.007). ROC curve analysis identified an optimal NLR cut-off value of 2.4 for predicting substantial LVSI (AUC = 0.62, 95 % CI: 0.55–0.69, p = 0.013), with a sensitivity of 64.3% and specificity of 58.2%. Multivariable logistic regression analysis demonstrated that higher BMI (OR: 1.07, 95% CI: 1.01–1.14, p = 0.031), smoking (OR: 2.84, 95% CI: 1.18–6.84, p = 0.020), hypertension (OR: 0.38, 95% CI: 0.15–0.96, p = 0.041), and LVSI positivity (OR: 3.21, 95% CI: 1.24–8.31, p = 0.016) were independently associated with the presence of fragmented QRS.

Conclusion

Both fQRS and NLR were associated with LVSI in patients with endometrial cancer and may reflect adverse pathological features related to tumor aggressiveness. However, these findings should be considered exploratory, and further prospective studies are required before clinical implementation can be recommended.

Keywords: Endometrial cancer; Fragmented QRS; Lymphovascular space invasion; Neutrophil-to-lymphocyte ratio; Prognostic biomarker

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Introduction

Endometrial cancer (EC) is the most common gynecologic malignancy, and its incidence has been steadily increasing worldwide, particularly in developed countries, with over 417,000 new cases and 97,000 deaths reported in 2020 according to GLOBOCAN estimates (1). Prognostic factors for EC include advanced stage, type II subtype, deep myometrial invasion, lymphovascular space invasion (LVSI) and lymph node metastasis.

Among these, LVSI is considered one of the most powerful predictors of recurrence and survival, with large database analyses showing that LVSI-positive patients have nearly double the risk of death compared with LVSI-negative cases (2). In the updated FIGO 2023 EC staging system (3), LVSI has gained increased prognostic significance, with extensive LVSI leading to stage migration. Although MRI provides valuable preoperative information, its ability to accurately detect LVSI is limited. Noninvasive markers such as ultrasound and CA-125 are commonly used, but CA-125 lacks specificity, as its levels may rise in benign gynecologic and systemic conditions. Recent studies suggest peripheral blood markers may offer better predictive value than CA-125 for EC (4).

The neutrophil-to-lymphocyte ratio (NLR), a readily available and cost-effective inflammatory marker derived from a routine complete blood count, has shown prognostic relevance in multiple solid tumors, including ovarian, cervical, and endometrial cancers (5–9). Fragmented QRS (fQRS), defined as the presence of additional R′ waves or notching within the QRS complex in two or more contiguous ECG leads, reflects abnormalities in ventricular depolarization (10). fQRS has been associated with arrhythmias, sudden cardiac death, and poorer outcomes in various cardiomyopathies, and emerging evidence suggests its prevalence may increase in patients with cancer or those receiving chemotherapy or radiotherapy (11). However, the prognostic significance of fQRS in gynecologic malignancies has not been previously explored.

Therefore, identifying patients with LVSI preoperatively is essential for accurate risk stratification and individualized management, as its presence can directly influence the need for adjuvant therapy and modify treatment decisions even in patients with similar surgical staging. This study aims to evaluate whether NLR and fQRS are associated with LVSI in endometrial cancer, thereby determining their potential value as noninvasive preoperative biomarkers.

Material and Method

This retrospective cohort study included 198 consecutive patients who underwent surgery for endometrial cancer at our gynecologic oncology clinic. All patients were staged according to the FIGO 2023 classification system. This study was approved by Ankara Etlik Integrated Health Institutional Ethics Committee (AESHBADEK2, Approval No: 2025-414). Because of the retrospective study design, the requirement for informed consent was waived by the ethics committee.

The standard surgical procedure consisted of total hysterectomy with bilateral salpingo-oophorectomy (TH + BSO). Intermediate- and high-risk patients additionally underwent pelvic and para-aortic lymphadenectomy with or without omentectomy, while low-risk patients typically received TH + BSO combined with sentinel lymph node mapping in line with current guidelines. Histopathological diagnoses were independently reviewed by two gynecologic oncology pathologists, and discrepancies were resolved by consensus in accordance with NCCN guidelines (12). Adjuvant treatment decisions, including radiotherapy and/or chemotherapy, followed the ESMO–ESGO–ESTRO Consensus Conference recommendations (13).

Lymphovascular space invasion (LVSI) was defined as the presence of tumor cells in five or more lymphovascular spaces, corresponding to substantial LVSI, whereas involvement of fewer than five spaces was classified as LVSI-negative, consistent with previously published criteria (13).

Clinical variables collected included age, body mass index (BMI), tumor diameter, preoperative CA-125 levels, number of lymph nodes removed, FIGO grade, histologic subtype, LVSI status, depth of myometrial invasion, adjuvant treatment administration, and surgical procedure type.

Preoperative complete blood count (CBC) values, including absolute neutrophil and lymphocyte counts, were recorded. The neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. The optimal NLR cut-off for predicting LVSI was determined using receiver operating characteristic (ROC) curve analysis.

For high-risk patients, adjuvant chemotherapy and/or radiotherapy were administered for systemic or locoregional control in accordance with ESMO guidelines. Overall, 97 patients (49.0%) received adjuvant treatment, while 101 (51.0%) did not.

All patients underwent preoperative 12-lead ECG examination. Fragmented QRS (fQRS) was defined according to standard criteria, characterized by additional R′ waves (notching) separated by at least 40 ms or by various RSR′ patterns in two contiguous leads (Fig 1). Two experienced cardiologists, blinded to all clinical and pathological data, independently evaluated the ECGs. Blinding encompassed all histopathological findings, including LVSI status, tumour grade, and FIGO stage. Interobserver agreement was high (κ = 0.86), and discrepancies were resolved through consensus review.

Patients were categorized into two groups based on the absence (Group 1) or presence (Group 2) of fQRS. The anatomical localization of fQRS (anterior, inferior, or lateral) was also recorded, as suggested by prior studies (10,11), although subgroup analysis by localization was not performed due to the limited number of fQRS-positive cases.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics, version 31.0.2 (IBM Corp., Armonk, NY, USA). Continuous variables were assessed for normality using the Shapiro–Wilk test and are presented as median (minimum–maximum), as the majority did not conform to a normal distribution. Categorical variables are expressed as frequency and percentage. Between-group comparisons of continuous variables were performed using the Mann–Whitney U test. Categorical variables were compared using the Pearson chi-square test or Fisher's exact test, as appropriate, particularly in cases where expected cell counts were fewer than five. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cut-off value of NLR for predicting lymphovascular space invasion (LVSI), and the area under the curve (AUC) with 95% confidence interval (CI) was reported. Binary logistic regression analysis was performed using variables that were clinically relevant or statistically significant in univariable analyses ($p < 0.05$) as covariates, including BMI, smoking status, hypertension, and LVSI. Results of the multivariable model are reported as odds ratio (OR) with 95% CI and p value. A sample size calculation was performed using G*Power version 3.1 based on the study by Aoyama et al. (5), in which a high preoperative NLR was observed in 92.0% of patients with lymph node metastasis and 56.4% of patients without lymph node metastasis or without nodal assessment in endometrial cancer. Using a two-sided alpha level of 0.05, 80% statistical power, and an allocation ratio derived from the reference study, the minimum required sample size was calculated as 94 patients. The final cohort of the present study included 198 patients, exceeding the required sample size. A two-tailed p value of less than 0.05 was considered statistically significant for all analyses.

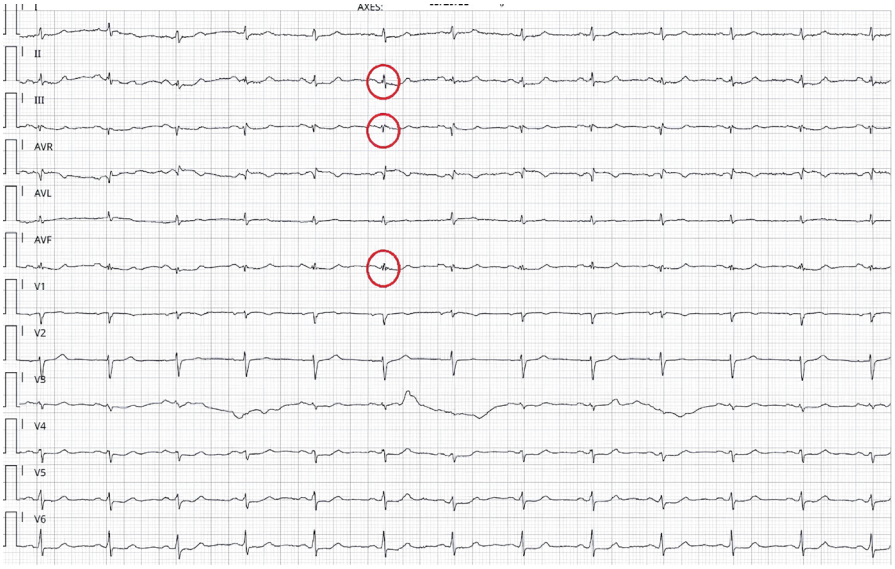


Figure 1

Representative 12-lead electrocardiogram demonstrating fragmented QRS (fQRS). Fragmented QRS was defined as the presence of an additional R′ wave, notching in the nadir of the R or S wave, or more than one R′ deflection in at least two contiguous leads in accordance with established diagnostic criteria. Red circles indicate representative fragmented QRS complexes.

Results

The median age of the patients was 60 years (range, 35–82), with no significant difference observed between the fQRS-positive and fQRS-negative groups (p = 0.885). The median BMI of the cohort was 32 kg/m² (range, 21–58). Fragmented QRS was identified in 15.1% of patients (30/198), while the remaining 84.9% (168/198) did not exhibit fQRS.

When clinical and biochemical parameters were compared between the groups, patients with fQRS had a significantly higher BMI [36.5 (23–53) vs. 32 (21–58), p = 0.024] and were more frequently smokers (p = 0.001). Hypertension was less common among individuals with fQRS (26.7% vs. 49.4%, p = 0.021). Furthermore, both neutrophil count [5.34 (3.17–14.71) vs. 4.45 (2.13–11.04), p = 0.018] and NLR [2.45 (1.46–12.42) vs. 2.04 (0.66–7.72), p = 0.013] were significantly higher in the fQRS-positive group (Table 1).

The median preoperative CA-125 level was 20 U/mL (range, 5–200), with no significant difference between patients with and without fQRS (p = 0.642), consistent with previous reports underscoring its limited prognostic utility compared with inflammatory markers (4).

Histopathological evaluation revealed that LVSI was significantly more frequent in patients with fQRS (30% vs. 11.3%, p = 0.007). No significant differences were observed between the groups regarding tumor diameter, histologic subtype, depth of myometrial invasion, or FIGO stage (Table 2). Tumor grade demonstrated a borderline difference, with grade 2 disease occurring more frequently in the fQRS-positive group (p = 0.053).

ROC curve analysis for the NLR cut-off of 2.4 in predicting LVSI demonstrated an AUC of 0.62 (95% CI: 0.55–0.69, p = 0.013), with a sensitivity of 64.3% and specificity of 58.2% (Fig 2).

Binary logistic regression analysis was performed to identify factors independently associated with the presence of fragmented QRS (fQRS). Variables included in the multivariable model were selected based on clinical relevance and univariable analysis results. Multivariable analysis demonstrated that BMI (OR: 1.07, 95% CI: 1.01–1.14, p = 0.031), smoking (OR: 2.84, 95% CI: 1.18–6.84, p = 0.020), hypertension (OR: 0.38, 95% CI: 0.15–0.96, p = 0.041), and LVSI positivity (OR: 3.21, 95% CI: 1.24–8.31, p = 0.016) were independently associated with fQRS presence (Table 3).

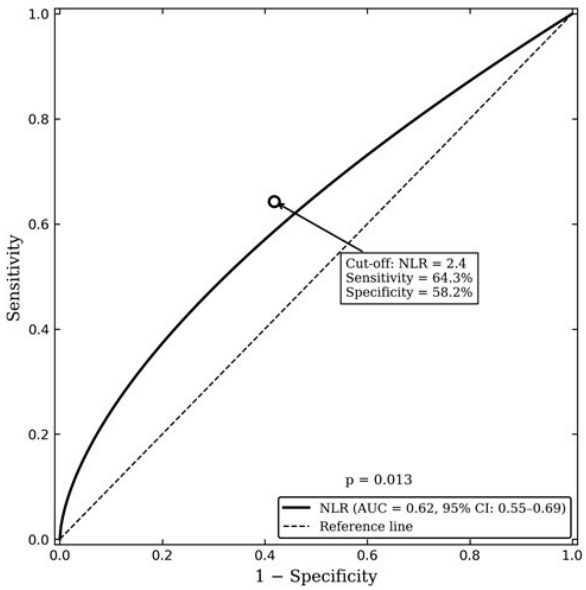


Figure 2

Receiver operating characteristic (ROC) curve analysis demonstrating the discriminatory performance of neutrophil-to-lymphocyte ratio (NLR) for substantial lymphovascular space invasion (LVSI) in endometrial cancer. AUC = 0.62 (95% CI: 0.55–0.69, p = 0.013). The optimal NLR cut-off value was 2.4, with a sensitivity of 64.3% and specificity of 58.2%.

AUC: Area Under the Curve; CI: Confidence Interval; LVSI: Lymphovascular Space Invasion; NLR: Neutrophil-to-Lymphocyte Ratio.

Table 1 Comparison Of Clinical And Biochemical Parameters Between Groups.

	Group 1 (n=168) Without fQRS	**Group 2 (n=30) With fQRS**	**p**
Age (Years), median (min-max)	60 (35-82)	60 (46-79)	0.885
BMI (kg/m²), median (min-max)	32 (21-58)	36.5 (23-53)	**0.024**
Smoking n, (%)			
Yes	36 (21.4)	15 (50)	**0.001**
No	132 (78.6)	15 (50)	
Additional disease			
Hypertension n, (%)			
Yes	83 (49.4)	8 (26.7)	**0.021**
No	85 (50.6)	22 (73.3)	
Diabetes Mellitus n, (%)			
Yes	58 (34.5)	9 (30)	0.630
No	110 (65.5)	21 (70)	
HPL n, (%)			0.115
Yes	13 (7.7)	0	
No	155 (92.3)	30 (100)	
Neutrophil	4.45 (2.13-11.04)	5.34 (3.17-14.71)	**0.018**
Lymphocyte	2.18 (0.53-4.75)	1.98 (0.62-5.48)	0.092
NLR	2.04 (0.66-7.72)	2.45 (1.46-12.42)	**0.013**
Surgery Type n, (%)			0.543
Laparoscopic	64 (38.1)	13 (43.3)	
Laparotomic	76 (45.2)	15 (50)	
Robotic	24 (14.3)	2 (6.7)	
Vaginal	4 (2.4)	0	
Adjuvant Therapy n, (%)			0.782
Yes	83 (49.4)	14 (46.7)	
No	85 (50.6)	16 (53.3)	

Data are expressed as median, minimum, maximum, and number (%).
$p \leq 0.05$ significant difference, comparison of groups Fisher's Exact Test was applied for HPL and Vaginal surgery subgroups due to zero observed cell counts in Group 2.
BMI: Body Mass Index. HPL: Hyperlipidemia NLR: Neutrophil Lymphocyte Ratio.

Table 2 Comparison of Histopathological Findings Between Groups.

	Group 1 (n=168) (without fQRS)	Group 2 (n=30) (with fQRS)	p
Histological Subtype n, (%)			
Endometrioid	147 (87.5)	27 (90)	0.960
Clear Cell	1 (0.6)	0	
Serous	9 (5.4)	2 (6.7)	
Mixed	7 (4.3)	1 (3.3)	
Undifferentiated	4 (2.4)	0	
PTD (mm) median (min-max)	33 (2-140)	34 (2-150)	0.910
Grade n, (%)			
1	107 (63.7)	16 (53.4)	0.053
2	37 (22)	12 (40)	
3	22 (13.1)	1 (3.3)	
NR	2 (1.2)	1 (3.3)	
LVSI n, (%)			
Negative	149 (88.7)	21 (70)	**0.007**
Positive	19 (11.3)	9 (30)	
MMI n, (%)			
Non-invasive	22 (13.1)	6 (20)	0.68
<1/2	85 (50.6)	15 (50)	
≥1/2	61 (36.3)	8 (26.7)	
Serous invasion	0	1 (3.3)	
FIGO 2023 Stage n, (%)			
Ia1	18 (10.7)	4 (13.4)	0.229
Ia2	62 (36.9)	13 (43.4)	
Ia3	1 (0.6)	0	
Ib	33 (19.6)	2 (6.7)	
Ic	2 (1.2)	1 (3.3)	
IIa	2 (1.2)	1 (3.3)	
IIb	8 (4.8)	6 (20)	
IIc	19 (11.3)	1 (3.3)	
IIIa1	4 (2.4)	0	
IIIa2	2 (1.2)	0	
IIIb1	1 (0.6)	0	
IIIc1	3 (1.8)	1 (3.3)	
IIIc2	5 (2.9)	1 (3.3)	
IVb	7 (4.2)	0	
IVc	1 (0.6)	0	

Fisher's Exact Test was applied for Histological Subtype, MMI (Serous invasion subgroup), and FIGO 2023 Stage comparisons due to expected cell counts below five in multiple subgroups.
PTD: Primary Tumor Diameter. LVSI: Lymphovascular Space Invasion. MMI: Myometrial invasion

Table 3 Multivariable Logistic Regression Analysis: Factors Independently Associated with Fragmented QRS Presence

Variable	OR	95% CI	p value
BMI (kg/m²)	1.07	1.01–1.14	0.031
Smoking	2.84	1.18–6.84	0.020
Hypertension	0.38	0.15–0.96	0.041
LVSI positivity	3.21	1.24–8.31	0.016

OR: Odds Ratio. CI: Confidence Interval. LVSI: Lymphovascular Space Invasion. BMI: Body Mass Index.
* $p < 0.05$. Dependent variable: presence of fragmented QRS (fQRS).

Discussion

The present study investigated the association between fragmented QRS (fQRS), neutrophil-to-lymphocyte ratio (NLR), and lymphovascular space invasion (LVSI) in endometrial cancer. Consistent with prior evidence, NLR, an established marker of systemic inflammation, was significantly associated with adverse clinicopathological features, including higher histologic grade, deeper myometrial invasion, and lymph node involvement (5-9). Our findings further support the role of systemic inflammation in tumor aggressiveness, as patients with substantial LVSI demonstrated higher NLR values.

In contrast, the prognostic significance of fQRS in gynecologic malignancies has not previously been explored. In this study, patients exhibiting fQRS had significantly higher NLR values and a nearly threefold greater likelihood of substantial LVSI compared with those without fQRS. Although these findings suggest a potential relationship between ventricular conduction abnormalities and aggressive tumor characteristics, the mechanistic basis of this association remains unclear. fQRS reflects electrical fragmentation due to myocardial scarring or conduction delay rather than tumor-specific processes, and there is no established biological pathway linking fQRS directly to LVSI or tumor invasion. Therefore, the association observed in this study should be interpreted cautiously and considered hypothesis-generating rather than indicative of a causal relationship. Supporting this interpretation, prior cardiovascular studies have demonstrated that fragmented QRS is independently associated with systemic inflammatory activity; in patients with acute coronary syndromes, fQRS correlated strongly with elevated inflammatory markers (14). These observations suggest that fQRS may be more closely related to systemic inflammatory burden than to a tumor-specific process.

LVSI is a well-recognized prognostic factor in endometrial cancer, and large population-based cohorts have noted LVSI in nearly one-third of surgically staged cases (2). Because our definition required involvement of five or more lymphovascular spaces, the findings of this study are specifically applicable to substantial LVSI, which carries markedly higher recurrence risk compared with focal LVSI (13). The predictive relevance of NLR or fQRS for minimal LVSI cannot be determined from these data and should be addressed in future studies.

Another important consideration is the absence of molecular subtype data. Contemporary risk stratification increasingly incorporates genomic categories, POLE-mutated, MMR-deficient, p53-abnormal, and NSMP, each associated with distinct biological behavior and prognosis. Because POLE sequencing and complete p53 immunohistochemistry were not routinely available during the study period, molecular classification was not feasible. Residual confounding related to unmeasured molecular profiles, particularly the aggressive p53-abnormal subtype, may therefore influence the associations observed. Integrating molecular subtype information into future biomarker studies will be essential to determine whether relationships between fQRS, NLR, and LVSI persist across genomic subgroups.

Previous studies have noted that fQRS may increase following anthracycline chemotherapy (15), suggesting a potential interaction between systemic inflammatory or metabolic disturbances and myocardial conduction. However, none of the patients in the present cohort had received chemotherapy or radio-

therapy at the time of evaluation, limiting comparability with prior reports. The presence of fQRS in other systemic conditions such as HIV infection (16) further supports the likelihood that fQRS reflects broad physiological alterations rather than cancer-specific processes.

The multivariable logistic regression analysis was performed to identify preoperative clinical characteristics independently associated with the presence of fQRS, with fQRS included as the dependent variable. This approach was intended to explore whether adverse tumour features, such as LVSI, are associated with this electrocardiographic finding, rather than to establish fQRS as a predictive biomarker for LVSI. Accordingly, the study should be regarded as hypothesis-generating, and the regression findings should be interpreted within this exploratory context.

NLR showed only modest discriminatory ability for identifying LVSI (AUC = 0.62), which is below the level generally considered sufficient for clinical utility (AUC ≥ 0.70). Therefore, neither NLR nor the association between fQRS and LVSI should be considered clinically applicable at present. Instead, these findings should be viewed as hypothesis-generating and confirmed in larger prospective studies before clinical implementation.

Although exploratory multivariable adjustment was performed, the relatively small number of patients with fQRS (n = 30) limited the statistical power of the model and may have left residual confounding. In particular, baseline differences in BMI, smoking status, and hypertension-factors known to influence both systemic inflammation and ventricular conduction-may have contributed to the observed associations. Therefore, these findings should be interpreted as exploratory and should not be considered evidence of an independent predictive relationship.

In conclusion, our findings suggest that fragmented QRS (fQRS) and an elevated neutrophil-to-lymphocyte ratio (NLR) may reflect systemic inflammatory or metabolic alterations associated with more aggressive tumor behavior, including substantial lymphovascular space invasion in endometrial cancer. At present, these markers should be considered exploratory indicators of adverse pathological features rather than definitive predictive tools.

The findings of this study should be interpreted with caution due to several important limitations, including the retrospective single-center design, limited adjustment for potential confounding variables, lack of molecular classification, modest biomarker performance, and the relatively small number of patients with fQRS. Larger prospective studies with external validation and integrated molecular profiling are needed to better clarify the potential clinical utility of fQRS and NLR in preoperative risk assessment and individualized treatment planning.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Ethical Approval
The study protocol was approved by Ankara Etlik Integrated Health Institutional Ethics Committee (AESH-BADEK2) (Approval No: 2025-414).

Consent to Participate and Publish
Because of the retrospective study design, the requirement for informed consent was waived by the ethics committee.

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Availability of Data and Materials
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Artificial Intelligence Statement
During the preparation of this manuscript, ChatGPT (OpenAI) was used solely for language editing and stylistic improvement. No part of the scientific content, data analysis, or interpretation was generated by artificial intelligence. All scientific content was created and verified by the authors.

Authors Contributions
C.H: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing–original draft.

H.N.Ö: Investigation; Validation; Writing–original draft.

N.Ç: Data curation; Formal analysis; Writing–review & editing.

Ç.S: Methodology; Supervision; Writing–review & editing.

V.K: Supervision; Project administration; Writing–review & editing.

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