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Effect of glucose lymphocyte ratio on prognosis in patients operated with the diagnosis of pancreatic adenocarcinoma

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ABSTRACT

Aims: Pancreatic adenocarcinoma is one of the most aggressive cancers, and predicting prognosis and survival clinically is challenging. Prognostic markers, easily accessible and routinely evaluated in diagnostic tests, are frequently seen in the literature for survival prediction. So far, the glucose lymphocyte ratio (GLR) has emerged as an indicator that can assess both metabolic dysregulation and immune response. In this study, the aim was to assess the impact of GLR on prognosis and survival by following patients diagnosed with pancreatic adenocarcinoma who underwent surgery.

Methods: Between January 1, 2016, and April 31, 2021, a totalof 58 patients who underwent Whipple procedure due to pancreatic adenocarcinoma at the Department of General Surgery, Hitit University, were included in the study. Demographic characteristics, tumor features, laboratory results, and survival durations of the patients were collected. GLR was determined as a mortality predictor, and estimated survival times associated with GLR were determined using Kaplan-Meier Survival analysis. The optimal GLR value was determined through ROC analysis.

Results: During the postoperative period, the average follow-up time for patients was 11.39 months, with the longest follow-up time being 48 months. During this period, 43 patients (74.14%) were deceased, while 15 patients (25.86%) survived. The mean age and ASA scores of deceased patients were significantly higher compared to survivors ($p < 0.001$ and $p < 0.001$, respectively). Glucose levels were significantly higher in the mortality group compared to the survival group ($p=0.008$). GLR was notably higher in the mortality group ($p=0.170$; $p=0.703$; $p=0.429$; and $p=0.031$). The GLR value that best distinguished the two groups was found to be 94.6387 with 93.3% specificity and 95.8% positive predictive value. Crossing this threshold increased the mortality risk approximately 4.27 times within one year and increased the overall mortality risk by approximately 15 times ($p=0.014$ and $p=0.002$). The estimated life expectancy for patients below the threshold value was calculated to be an average of 20.996 months, whereas for patients above the threshold value, this expectation was calculated to be an average of 4.427 months ($p < 0.001$).

Conclusion: We believe that GLR may be helpful in predicting one-year survival and determining overall survival duration in patients undergoing surgery for pancreatic adenocarcinoma.

Keywords: Pancreatic adenocarsinoma, glucose lymphocyte ratio, prognosis, survival

INTRODUCTION

Pancreatic cancer ranks 12th in incidence according to 2022 WHO data, yet it ranks 6th in mortality.[1] This signifies its highly aggressive nature. The 5-year survival rate is reported at 9%, with a 20-year survival rate of only 5%.[2,3] It is projected that the incidence of pancreatic cancer will rapidly increase.[4] While surgical resection is the most effective treatment, in this disease, which typically progresses silently and is often diagnosed in advanced stages, efforts are made to maximize benefits through neoadjuvant or adjuvant chemotherapy, radiotherapy, and immunotherapy. Knowing the prognosis is crucial for treatment planning, as it's necessary to understand how much benefit a patient will derive from treatment. Therefore, numerous studies have been conducted on the prognosis of pancreatic adenocarcinoma, identifying various prognostic factors and formulas.[3,5-9] Glucose lymphocyte ratio (GLR) has been identified as a prognostic marker in many cancers such as gastric cancer, hematoma, colorectal cancer, breast cancer, and esophageal cancer. However, there is limited research on the use of GLR as a prognostic marker in pancreatic cancer.[10-13] This study aimed to investigate

the impact of GLR on prognosis and survival in patients undergoing surgery for pancreatic adenocarcinoma.

METHODS

The study was carried out with the permission of Hitit University Non-interventional Studies Ethics Committee (Date: 03.06.2021, Decision No: 2021-69). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Between January 1, 2016, and April 31, 2021, a retrospective analysis was conducted on 103 patients aged 18 to 90 who underwent Whipple procedure at the Department of General Surgery, Hitit University. Exclusion criteria included pathologies other than pancreatic adenocarcinoma, hematologic diseases, medication use affecting hematologic and biochemical parameters, inflammatory or infectious diseases. A total of 58 patients were included in the study. Demographic characteristics, tumor features, laboratory results, and survival durations were collected. Statistically significant prognostic markers, including GLR, were identified.

Statistical Analysis

This study was prospectively designed. IBM SPSS Statistics for Windows software (version 26; IBM Corp., Armonk, N.Y., USA) was utilized for all statistical analyses. Descriptive statistics were employed to present categorical variables as counts and percentages, and numerical variables were expressed as mean±standard deviation for normally distributed variables or median (minimum-maximum value) for non-normally distributed variables. The normality of the distribution of data was evaluated using the Shapiro-Wilks test. Pearson and Spearman correlation coefficients were employed to assess correlations between variables, depending on the data distribution. To compare numerical measurements between independent groups, such as WBC, neutrophil count, platelet count, clucose, CRP, GLR, NLR, PLR, and overall survival duration the Mann-Whitney U test was utilized for comparisons among two groups, considering the distribution of the data. Student t-test analysis was conducted to assess age and lymphocyte count, in accordance with the distribution of the data. Categorical variables such as gender, ASA scores, localization, differentiation and 1 year survival rate were evaluated for ratio comparisons between research groups using the Chi-square test. Receiver operating characteristic (ROC) curves were utilized to demonstrate the discriminative ability of statistically significant variables. Cut-off values for these markers were determined using the area under the curve and the Youden index. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy values were calculated based on these cut-off values. Odds ratio values were computed for these cut-off points. Kaplan-Meier survival analyses for disease-free survival were performed, and statistical significance between the two groups was assessed through the Log-Rank test. A linearity diagram illustrating GLR and overall total survival duration was generated. A significance level of $p<0.05$ was deemed statistically significant.

RESULTS

During the postoperative period, the average follow-up time for patients was 11.39 months, with the longest follow-up time being 48 months. During this period, 43 patients (74.14%) passed away, while 15 patients (25.86%) survived. A total of 27 patients (62.7%) died within 0-3 months postoperatively due to early complications. The causes of death were as follows: 4 (9.3%) due to COVID-19, 7 (16.2%) due to cardiac disease, 6 (13.9%) due to pulmonary disease, and 10 (23.2%) due to anastomotic leakage-sepsis. Additionally, 16 patients (37.3%) were lost during follow-up after discharge due to underlying diseases.

The mean age of deceased patients was 72±8 years, whereas the mean age of surviving patients was 62±11 years, showing a statistically significant difference ($p <0.001$). The 58 patients were divided into two groups: 15 survivors and 43 deceased. When comparing groups based on gender, tumor localization, tumor differentiation, neutrophil, lymphocyte, and platelet count, CRP level, NLR, and PLR, no statistically significant differences were observed.

Of the 58 patients, 23 (39.66%) were classified as ASA3, and 35 (60.34%) were classified as ASA4. Among the surviving patients, 12 (80%) were ASA3, and 3 (20%) were ASA4; among the deceased patients, 11 (25.58%) were ASA3, and 32 (74.42%) were ASA4, showing a significant statistical difference ($p<0.001$). The median glucose level for all patients was 116 (70-360) mg/dl, while among survivors it was 97 (70-193) mg/dl, and among deceased patients it was 118 (79-360) mg/dl, with a statistically significant higher level observed among deceased patients ($p=0.008$). The median glucose lymphocyte ratio for all patients was 83.85 (23.74-280.95), among survivors it was 76.52 (30.3-177.06), and among deceased patients it was 98.29 (23.74-280.95), with a statistically significant higher level observed among deceased patients ($p=0.031$). The median survival time for all patients was 3 (0-48) months, 27 (3-48) months for survivors, and 1 (0-40) month for deceased patients, with a statistically significant difference observed ($p <0.001$). When examining one-year survival durations, it was observed that 23 out of 58 patients (39.66%) survived beyond one year, while all patients in the surviving group (15 patients, 100%) lived longer than one year. In contrast, only 8 out of 43 deceased patients (18.6%) survived one year, showing a statistically significant difference between the two groups ($p <0.001$) (Table 1).

The significant difference in GLR values between the alive and mortality groups prompted an assessment of the optimal cut-off value for distinguishing between the two using ROC analysis, resulting in an AUC of 0.668 (95% CI=0.544-0.833, $p=0.031$) (Figure 1). The optimal GLR value identified for mortality prediction was 94.6387, with 93.3% specificity, 53.5% sensitivity, 95.8% positive predictive value, 41.2% negative predictive value, and 63.79% test accuracy (OR 16.1, 95% CI 1.941-133.516, $p=0.002$) (Table 2). GLR above 94.6387 was associated with approximately a 4.27-fold increase in the risk of mortality within one year and an approximately 15-fold increase in the overall mortality risk ($p=0.014$ and $p=0.002$). Additionally, a negative correlation was observed between GLR and overall total survival duration ($r=-0.282$, $p=0.032$) (Figure 2).

Furthermore, comparing the overall survival times of patients stratified by their GLR values revealed a significant difference in median survival time between those with GLR values below and above 94.6387. The median survival time for patients with GLR values below this threshold was 8.8 months, while for those above the threshold, it was 1 month. Kaplan-Meier Survival Analysis also showed a significant difference in estimated overall survival time between the two groups, with patients having GLR <94.6387 showing a longer estimated survival time (20.996 months) compared to those with GLR ≥94.6387 (4.427 months, $p <0.001$) (Table 3 and Figure 3).

Table 1. Assessment of all patients and statistical comparison results between alive and deceased patients

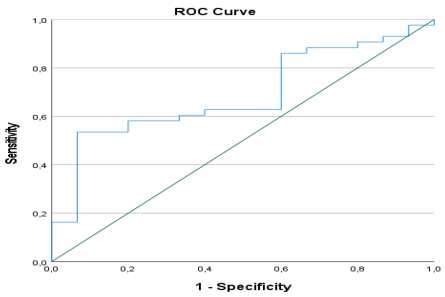
Variables		All patients (n=58)	Alive (n=15; 25.86%)	Deceased (n=43; 74.14%)	Statistical significance
Age		70±10	62±11	72±8	<0.001
Gender	Male	35 (60.34%)	9 (60%)	26 (60.47%)	0.975
	Female	23 (39.66%)	6 (40%)	17 (39.53%)	
ASA	ASA 3	23 (39.66%)	12 (80%)	11 (25.58%)	<0.001
	ASA 4	35 (60.34%)	3 (20%)	32 (74.42%)	
Localization	Ampulla	14 (24.14%)	5 (33.33%)	9 (20.93%)	0.484
	Head	44 (75.86%)	10 (66.67%)	34 (79.07%)	
Differentiation	Well-differentiated	9 (15.52%)	1 (6.67%)	8 (18.6%)	0.354
	Moderately-differentiated	42 (72.41%)	11 (73.33%)	31 (72.09%)	
	Poorly-differentiated	7 (12.07%)	3 (20%)	4 (9.3%)	
WBC		6.88 (3.61-16.13)	6.49 (4.68-12.51)	7.04 (3.61-16.13)	0.908
Neutrophil count		4.57 (1.28-15)	4.19 (2.57-9.2)	4.7 (1.28-15)	0.894
Lymphocyte count		1.58±0.63	1.59±0.47	1.57±0.68	0.907
Platelet count		252 (108-737)	256 (108-345)	250 (117-737)	0.993
Glucose		116 (70-360)	97 (70-193)	118 (79-360)	0.008
CRP		11.5 (3-150)	7 (3-90)	14 (3-150)	0.170
GLR		83.85 (23.74-280.95)	76.52 (30.3-177.06)	98.29 (23.74-280.95)	0.031
NLR		3.08 (0.64-35.71)	2.76 (1.34-7.28)	3.39 (0.64-35.71)	0.703
PLR		172.52 (38.58-619.51)	173.45 (56.25-289.92)	171.58 (38.58-619.51)	0.429
1-year Survival	Deceased	35 (60.34%)	0 (0%)	35 (81.4%)	<0.001
	Survived (1 year)	23 (39.66%)	15 (100%)	8 (18.6%)	
Overall total survival duration		3 (0-48)	27 (3-48)	1 (0-40)	<0.001

ASA: American Society of Anesthesiologists, WBC: White blood count, CRP: C-reactive protein, GLR: Glucose lymphocyte ratio, NLR: Neutrophil lymphocyte ratio, PLR: Platelet/lymphocyte ratio

Table 2. Diagnostic value of GLR in the prediction of mortality

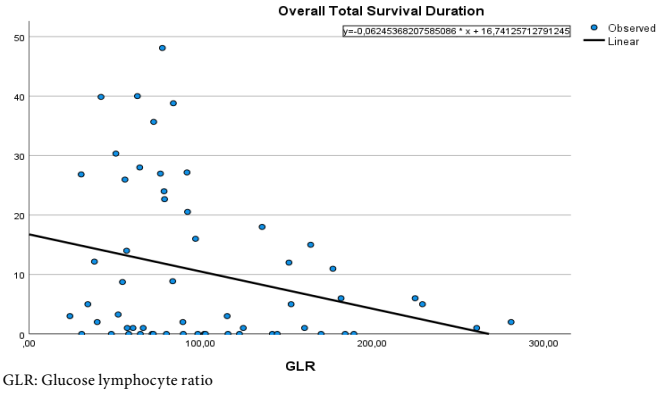
Variables	Cut-off value	Diagnostic parameters					ROC analysis			Odds ratio		
		Sensitivity	Specificity	PPV	NPV	Accuracy	AUC (SE)	95% CI	p	Odds Ratio	95% CI	p
GLR	94.6387	53.50%	93.30%	95.80%	41.20%	63.79%	0.668 (0.074)	0.544-0.833	0.031	16.100	1.941-133.516	0.002

GLR: Glucose lymphocyte ratio, ROC: Receiver operating characteristic, PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under the curve, CI: Confidence interval



GLR: Glucose lymphocyte ratio

Figure 1. Receiver operating curve of GLR in the distinction of alive and mortality patient groups



GLR: Glucose lymphocyte ratio

Figure 2. Linear graph of overall total survival duration and GLR

Table 3. Kaplan-Meier survival analysis-estimated overall total survival duration according to patient groups

Group	Estimated Mean	95% CI	Log-Rankp
Negative (<94.6387)	20.996 (3.69)	13.763-28.229	<0.001
Positive (>94.6387)	4.427 (1.249)	1.979-6.875	
Overall	14.182 (2.5)	9.281-19.083	

CI: Confidence interval

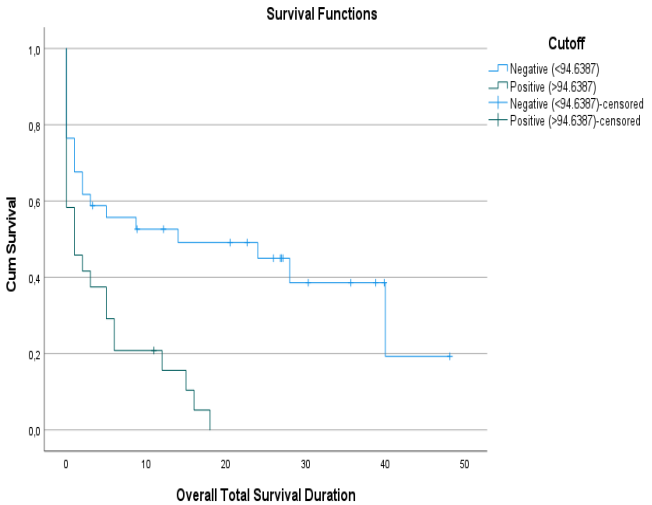


Figure 3. Kaplan-Meier survival analysis-cumulative survival to overall total survival duration graph according to patient groups

When evaluating only the one-year period, patients with GLR <94.6387 had a longer estimated life expectancy (7.043 months) compared to those with GLR ≥94.6387 (3.75 months, p=0.016). Additionally, approximately 80% of patients with GLR ≥94.6387 died within the first year, while this rate was approximately 45% in patients with GLR <94.6387 (Table 4 and Figure 4).

Table 4. Kaplan-Meier survival analysis-estimated 1-year period survival duration table according to patient groups

Group	Estimated mean	95% CI	Log-Rank p
Negative (<94.6387)	7.043 (0.941)	5.198 (8.889)	0.016
Positive (>94.6387)	3.75 (0.951)	1.887 (5.613)	
Overall	5.667 (0.71)	4.275 (7.06)	

CI: Confidence interval

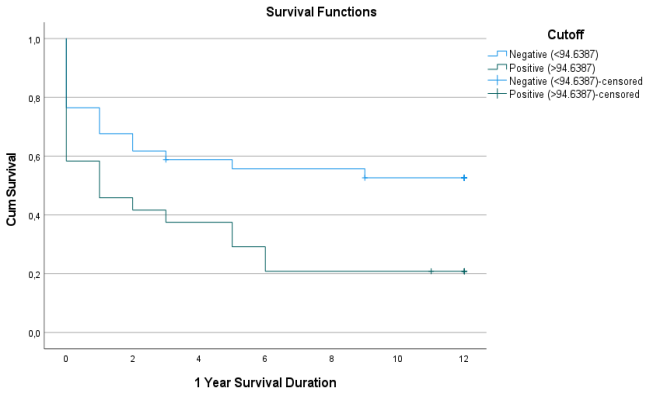


Figure 4. Kaplan-Meier survival analysis-cumulative survival to 1-year survival period graph according to patient groups

DISCUSSION

Periampullary tumors are characterized by their insidious clinical presentation, often resulting in delayed diagnosis, and typically being diagnosed in advanced stages, which contribute to their aggressive course and poor prognosis. According to the WHO's 2022 data, the incidence of these tumors is 510,992, with a mortality rate of 467,409 patients.[1] Despite ranking 12th in incidence, they rank 6th in mortality. Given their relatively common occurrence and poor prognosis, research efforts have been and continue to be focused on finding the most effective treatments for these tumors.

Knowing the prognosis of the disease is crucial for determining the appropriate treatment. Studies have focused on various factors including demographic information such as age, comorbidities, ASA score, and gender; easily detectable inflammatory markers such as neutrophil count, lymphocyte count, platelet count, hemoglobin level, CEA level, Ca 19-9 level, CRP level, glucose, and HbA1c levels, AST/ALT level; tumor-related information such as tumor location, differentiation, perineural or lymphovascular invasion status, lymph node metastasis, stage, proliferation index; as well as biomarkers such as IL-15, GM-CSF, and genetic analyses related to various genes such as FZD, GSTM4, ICOSLG.

Zhang et al.[2] categorized the pathogenesis of pancreatic cancer into inflammation, desmoplastic stroma, immunosuppressive tumor microenvironment, epithelial-mesenchymal transition, angiogenesis, cancer stem cells, and gut microbiota. Inflammation has been proposed to play a significant role in the initiation and progression of pancreatic cancer.[14] It has been understood that inflammatory cells such as monocytes, lymphocytes, neutrophils, and cytokines released by these cells interact with cancer cells and are effective in the tumor microenvironment.[14]

Lymphocytes are an essential component of the immune system working to eliminate tumor cells. A decrease in lymphocyte count can result in both a reduction in lymphocyte cytotoxic effects and a weakening of immunity due to decreased cytokine levels. Glucose also plays a crucial role in metabolism, and its regulation is vital. Impaired glucose regulation in diabetic patients is associated with chronic inflammation. Studies have reported that high glucose levels are associated with poor prognosis in both pancreatic cancer and other cancer patients[15,16]. Additionally, diabetes mellitus (DM) has been shown to have an impact on the development, perioperative complications, and prognosis of pancreatic cancer.[17]

While some of the prognostic factors mentioned and unspecified can be evaluated in secondary and tertiary care hospitals, certain markers such as genetic analyses are complex, expensive, and time-consuming tests primarily available in specialized centers. Therefore, as evident from the literature review, research has predominantly focused on developing formulas and scoring systems based on easily accessible and cost-effective inflammatory markers and simple laboratory results, which provide objective outcomes.

The Gustave Roussy Immun Score (GRIm-Score), initially defined by Bgot and al.[18] in 2017, is calculated based on serum lactate dehydrogenase (LDH), serum albumin, and neutrophil-lymphocyte ratio (NLR). Önder et al.[19] and Başoğlu et al.[7] have demonstrated that GRIm-Score is a readily applicable prognostic marker in colorectal cancers and pancreatic adenocarcinomas, respectively.

The modified Glasgow Prognostic Score (mGPS) is a prognostic indicator easily accessible, determined by C-reactive protein (CRP) and albumin levels. There are numerous studies and differing opinions regarding mGPS. Petrelli et al.[20] have shown it to be a weak prognostic marker for colorectal cancers. Conversely, Imakoa et al.[21] have argued it to be a robust prognostic marker for pancreatic cancer.

The Memorial Sloan Kettering Prognostic Score (MPS), an alternative scoring system to the Glasgow Prognostic Score, is based on albumin and neutrophil-lymphocyte ratios. In a study by Lebenthal et al.[22] MPS was found to be an independent tool predicting survival in metastatic pancreatic cancers.

The Globulin-lymphocyte ratio (GLR) has been associated with poor prognosis in various cancer types including lung, breast, stomach, liver, esophageal, kidney, colorectal cancers, and melanoma, as evidenced by a study encompassing 2172 patients.[10] Similarly, Hannarici et al.[13] for metastatic stomach cancer and Yang et al.[12] for colorectal cancers have shown GLR to be an independent prognostic marker.

In this study, age, ASA score, glucose, and GLR were identified as prognostic factors. ROC analysis was employed to determine the optimal cut-off value for GLR, resulting in 94.6387. While the specificity and positive predictive value were high, sensitivity and negative predictive value were found to be low. It was demonstrated that having a GLR value above the cut-off posed a 15-fold risk for overall survival and a 4.27-fold risk for 1-year survival. Survival analysis conducted by dividing patients into two groups based on GLR

cut-off revealed an estimated survival time of 20.996 months for those with low GLR and 4.427 months for those with high GLR. When examining the 1-year survival, it was estimated that 80% of those with high GLR and 45% of those with low GLR would die within a year. Furthermore, although NLR and TLR ratios, which have shown significance in other studies, did not demonstrate statistical significance in our study.

Zhong et al.[23] conducted a study with 360 pancreatic adenocarcinoma patients, investigating the role of NLR, TLR, GLR, and LMR in predicting the prognosis of pancreatic cancer based on pre-treatment laboratory parameters. They found GLR to be significant with 66.4% sensitivity and 77.6% specificity in ROC analysis. Similarly, PLR, LMR, and NLR were also found to be significant. However, when subjected to multivariate analysis, only GLR and CA19-9 were identified as independent factors for survival, with GLR being superior to CA19-9.

Zhang et al.[24] examined 259 patients with pancreatic adenocarcinoma. In their study, they applied ROC analysis to inflammatory markers including NLR, PLR, CLR, LMR, and CA19-9, comparing them with each other. Only PLR had a higher AUC value than GLR. In univariate analyses, T and N stage, tumor differentiation, neural invasion, and GLR were identified as prognostic factors for survival. In multivariate analysis, N stage and GLR were independent prognostic factors, although GLR was not found to be prognostic for OS. Subsequently, they divided these patients into a subgroup and reanalyzed, revealing prognostic significance in young male patients with pancreatic body-tail, N1 lymph node involvement, and CA19-9>200 U/ml.

Limitations

Some limitations of our study can be identified as follows. Firstly, due to being conducted in a single center and within a limited period, our sample size remained at 58. Conducting the study in a larger patient cohort could provide more reliable results. While our study addressed some prognostic factors mentioned in the literature, expanding the number of factors and conducting the study with more detailed data could be beneficial. Independent factors can be identified through multivariate analyses. There have been numerous studies on inflammatory markers, and different results have been obtained among them. While markers such as NLR, TLR, GLR, and LMR have been found to be prognostic in some studies, they have not been found to be so in others. We believe this may be related to other events triggering inflammation. Although conditions triggering inflammation have been excluded from the studies, the retrospective nature of the conducted studies reduces their reliability.

CONCLUSION

We believe that GLR may be helpful in predicting one-year survival and determining overall survival duration in patients undergoing surgery for pancreatic adenocarcinoma. We believe that prospective studies with pre-defined exclusion criteria would be more meaningful and reliable.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Hitit University Non-interventional Studies Ethics Committee (Date: 03.06.2021, Decision No: 2021-69).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Data availability statement

Data and materials in this study can be requested upon reasonable request directly from the corresponding author.

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