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The relationship between severity of periapical periodontitis and next-generation systemic inflammatory biomarkers in children with early childhood caries

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Abstract

Introduction Early childhood caries (ECC) is closely associated with poor oral hygiene and cariogenic diet. Untreated ECC results in recurrent odontogenic infections and local and systemic consequences. In this study, our goal is to assess the relationship between the intensity of odontogenic infection-associated periapical periodontitis and new generation of systemic inflammatory markers (SII, NLR, PLR) in ECC-affected children.

Material and method 95 healthy patients in early childhood and demonstrating periapical periodontitis who underwent dental treatment under general anesthesia (GA) in the last two years were included in the present study. Their periapical statuses were dichotomized as mild and severe. Periapical Index (PAI) scores of 2 and 3 were regarded as "mild" whereas 4 and 5 as "severe". Of the complete blood test (CBC) parameters, systemic inflammatory index (SII), neutrophil-to-lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), neutrophilic granulocyte (NEUT), lymphocyte (LYMPH) and platelet (PLT) were recorded. The relationship between the degree of periapical pathology and the evaluated markers was assessed using Receiver Operating Characteristic (ROC) analysis.

Results Results of the present study revealed that mean NLR, SII and NEUT index scores of the patients having severe periapical periodontitis were statistically higher than those of the ones with mild pathology ($p < 0.05$). A positive, statistically significant interrelationship was found between the number of teeth demonstrating a PAI score of severe periapical periodontitis with the signs of exacerbation (PAI 5) and NLR and SII values ($p < 0.05$). Area under the ROC curve (AUC) values for NLR and SII were determined as 66.8% and 66.6% respectively, indicating that classification performance was sufficient and statistically significant ($p < 0.05$).

Conclusion Postponing the management of odontogenic infections will induce some complications such as, infective endocarditis and cause the systemic inflammatory process to continue by aggravating the systemic effects of local lesions. Thus, underlying mechanism should be eliminated and oral hygiene should be maintained, also novel biomarkers may be recommended to be used for the decision-making process for the teeth with persistent periapical lesions unresponsive to treatment.

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Keywords Early childhood caries, Systemic inflammatory markers, Complete blood test parameters

Introduction

Early childhood caries (ECC) is defined as the presence of one or more decayed, missing or filled teeth in the children less than 72 months old [1]. ECC, which is known as the most common chronical disease in the early childhood has been reported to be associated with poor oral hygiene and cariogenic diet [2] .

Early childhood caries (ECC), known to be the most widespread chronic disease impacting the children early in life is associated with poor oral hygiene and karyogenic nutrition. Frequently recurrent odontogenic infections and pain upon mastication, growth retardation, reduced sleep quality, poor school performance, problematic social relationships, agitation and irritability, and low self-confidence may be observed in the children with untreated ECC [3–6]. Cariogenic microorganisms may penetrate into the pulpal tissue and lead to periapical periodontitis, which may subsequently spread to adjacent bone and soft tissues and even deeper systems in the children who did not receive dental treatment. An elevated systemic inflammation may be seen in untreated chronic odontogenic infections [7]. In literature, there are limited number of studies of the relationship between the untreated ECC and consequently developed systemic inflammations. Thus, in our study, it is of utmost importance to research the relationship between the local inflammations caused by odontogenic infections and systemic inflammatory markers in the children with untreated ECC.

In recent years, laboratory parameters of systemic inflammation became essential in disease activity assessment and in the evaluation of the prognosis of many disorders. A number of previous studies explored systemic inflammation in some serious complications such as, infective endocarditis, which can be particularly linked with dental lesions [8, 9]. Next-gen biomarkers like systemic inflammatory index (SII), neutrophil-to-lymphocyte ratio (NLR) and platelet–lymphocyte ratio (PLR) have been used to evaluate the systemic inflammation [9–12]. These inflammatory biomarkers have been investigated in several systemic diseases but not yet in the children with untreated ECC.

X-ray imaging are commonly used for assessing the influence of chronical odontogenic infection on the apical periodontium. Changes in bone density and presence or progress of periapical inflammation can be monitored via radiography [13]. Periapical index (PAI) is a 5-score guide with grades ranging from healthy periodontal tissue to severe periodontitis with the signs of exacerbation, used for measuring the status of periapical health through periapical or panoramic radiographs [14]. PAI is based on reference radiographic images with standard histological diagnosis, which were originally introduced by Brynolf et al. in 1967 [13]. We also used PAI for assessing the periapical pathologies of the children experiencing ECC in the present study, which is the first to evaluate PAI and SII together in the ECC-impacted children.

Our goal was to assess the relationship between the degree of periapical periodontitis, associated with odontogenic infections in the children suffering from ECC and SII, NLR, NEUT, LYMPH, PLT, and PLR markers. The null hypothesis of our study states that "In the children with ECC, there is no relationship between the severity of the odontogenic infection associated-periapical lesion and SII, NLR, NEUT, LYMPH, PLT, and PLR markers.

Materıal and method

This cross-sectional, descriptive and relational study has been carried out with the approval of Ataturk University's clinical research ethics committee dated as 20-03-24/session#2/Decision 09.

Patient selection

Our study consisted of 3–8 years of old children who were diagnosed with ECC based on the initial oral examinations at the time of their first admissions and with untreated ECC. At the baseline, 269 child patients with untreated ECC and with periapical periodontitis who were treated under general anesthesia (GA) between 1-1-22 and 9-2-24 were examined. However, 126 of them were excluded due to their systemic disorders and disabilities. Additionally, 36 children having no pre-study periapical radiographs and 12 patients with radiographic image artifacts were also excluded from the study. Consequently, a total of 95 children with no systemic disease and disability, indicating periapical periodontitis in one or more X-ray images and having complete blood count (CBC) test parameters were involved in. Using pre-op periapical x-ray images of these patients, we evaluated 305 primary teeth from 89 children and 19 permanent teeth from 6 children.

Exclusion criteria

Children with any previous systemic disorder, syndrome, and congenital abnormality, history of trauma at the related sites and having no periapical X-ray and/or OPG images were excluded.

Sample size

In order to calculate the study sample size, we reviewed some similar researches and chose the size providing the highest size. In our study, standardized effect size was

estimated as 0.9753 at a 95% confidence interval and a significance level at 5% (α = 0.05) by a previous similar study's results [15] and a minimum sample size of 58 was obtained with 0.95 theoretical power using G. Power-3.1.9.2 [16]. Thus, all eligible patients were included in the study reaching a sample size of 95.

Data collection

Complete blood count analysis

In this retrospective study, we used archive data of the healthy children whose dental treatments were previously performed under GA. Gender and age parameters of each patient were recorded. CBC analysis was routinely made for all participants for pre-operative evaluation. Of these parameters, PLT, NEUT and LYMPH counts were noted for each patient. NLR, PLR and SII index calculations, below formulas were used;

SII = (PLT count x NEUT count)$$\:\:÷$$ LYMPH count

NLR = NEUT count$$\:\:÷$$ LYMPH count

PLR = PLT count ÷ LYMPH count

Radiographic recordings

Intraoral periapical radiographs were taken in parallel technique using a dental X-ray film positioner holder. Plates were subsequently exposed at a typical posterior periapical setting by using a Belmont PHOT-xIIs Intraoral X-Ray unit (Takara Belmont, Somerset, MA) with exposure parameters of 70 kVp, 6.0 mA, 0.22 s exposure time.

Periapical assessment

For pre-op patient evaluation, archived preapical X-ray images of the participants were used. Periapical statuses of the patients were assessed via PAI, a scoring system, which is based on the evaluation of periapical radiographs introduced by Ørstavik et al. [14]. PAI is based on reference dental X-ray images with accepted histological diagnosis and composed of five categories;

Score 1 Normal periapical structure (Fig. 1. A).

Score 2 Minor changes in bone shape (Fig. 1. B).

Score 3 Bone structural changes with minimum mineral loss (Fig. 1. C).

Score 4 Periodontitis with obvious radiolucency (Fig. 1. D).

Score 5 Severe periodontitis with symptoms of exacerbation (Fig. 1. E).

We evaluated multi-rooted teeth in our study and accepted the highest score measured among all individual roots as the PAI score [14].

In order for better revealing the relationship between periapical pathologies and systemic inflammatory markers, PAI score was divided into two groups; PAI 4, PAI 5 in which clinical and periapical pathologies were more clearly observed and PAI 2, PAI 3 in which these findings were less observed [17].

Group 1 Mild periapical periodontitis (PAI score of 2 and/or 3).

Group 2 Severe periapical periodontitis (PAI score of 4 and/or 5).

Calibration and decision procedures

Periapical lesions were evaluated independently by two researchers to minimize measurement bias during PAI scoring. To assess inter-rater reliability, Kappa statistics were employed to determine the consistency of categorical data between the two observers. The Kappa

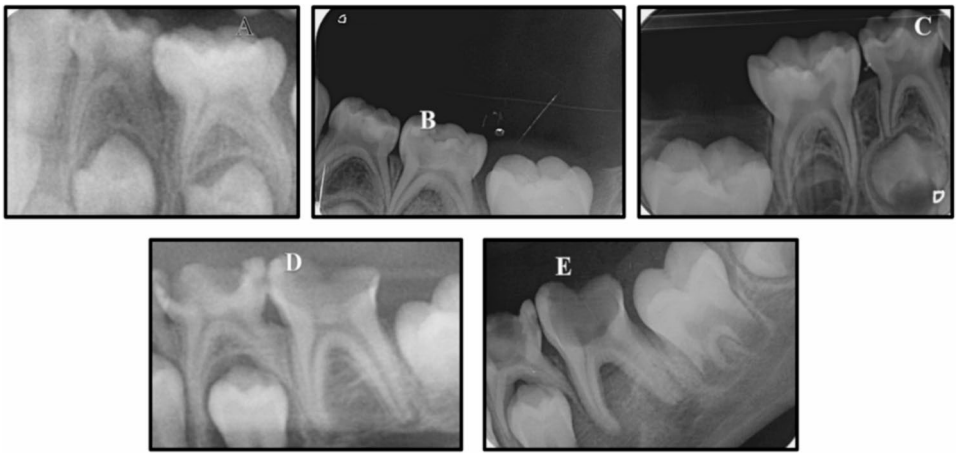

Fig. 1 Radiographs showing the PAI scoring used

Table 1 Relationship between PAI and CBC-based inflammatory biomarker index scores of the patients

	Group I ($n=27$)		Group II ($n=68$)		
	Min.-Max.	Mean ± S.D. (Median)	Min.-Max.	Mean ± S.D. (Median)	*p*
PLR	53.7-135.9	89.9 ± 22.9(86.1)	44.2-216.3	98.0 ± 3.1(91.8)	0.391
NLR	0.37–1.4	0.7 ± 0.2(0.7)	0.2–10.2	1.2 ± 1.2(0.9)	0.010*
SII	125.3-500.1	282.7 ± 94.8(263.7)	73.4-3181.5	449.7 ± 413.1(371.7)	0.010*
NEUT	1.5-8.0	3.2 ± 1.2(3.0)	0.9–51.7	4.7 ± 6.1(3.6)	0.031*
LYMPH	2.1–7.4	4.3 ± 1.3(4.3)	1.9–7.8	4.0 ± 1.13(3.9)	0.221
PLT	217–704	375.3 ± 97.2(360)	192–611	373.6 ± 83.2(363.5)	0.804

*$p<0.05$, S.D.: Standard deviation

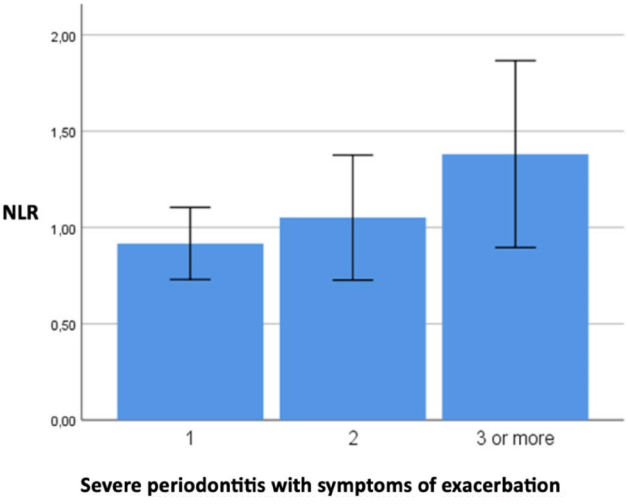

Fig. 2 Distribution of mean NLR in the number of severe periodontitis with symptoms of exacerbation (PAI 5)

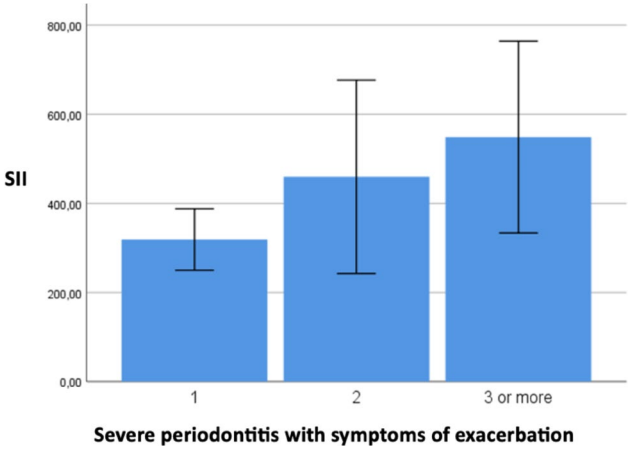

Fig. 3 Distribution of mean SII in the number of severe periodontitis with symptoms of exacerbation (PAI 5)

coefficient was found to be 0.951, indicating a significantly high level of inter-rater reliability ($p<0.05$).

Statistical analysis

In the present study, descriptive statistics were expressed as count, mean, standard deviation, minimum and maximum. Shapiro-Wilk test was used for assessing the assumption of normality. Differences between the means of independent variables in the groups without normal distribution was compared with Mann Whitney U test whereas Kruskal Wallis test was performed for comparing the means of three or more independent groups without normal distribution. Relationship between two categorical variables was analyzed with Pearson's Chi-Square test when estimated sample size (expected value > 5) has been met. The correlation between categorical and continuous variables was measured using Kendall's Tau test. Thresholds were determined with ROC (Receiver Operating Characteristic) curve analysis. All data were analyzed with IBM SPSS 25.

Results

The present study included 95 patients (44 girls and 51 boys) with a mean age of 5.5±1.5. Mean age score of Group II (5.82±1.68) was higher than Group I (4.74±0.98) ($p<0.05$).

Relationship between PAI and CBC- based inflammatory biomarker index scores of the participants is given in Table 1. Mean NLR, SII and NEUT scores of the patients experiencing severe periapical periodontitis were observed to be statistically higher than those of patients with mild pathologies. (p_{NLR} =0.01, p_{SII} =0.01, p_{NEUT}=0.031)

There was a statistically significant positive relation between the number of the teeth having periapical PAI score of severe periodontitis with signs of exacerbation (PAI5) and NLR, and SII indices (correlation coefficients of 0.263 and 0.292 respectively) ($p<0.05$, $p<0.05$). NLR and SII scores elevated as the number of the teeth with PAI5 increased. (Figures 2 and 3)

Area under the ROC curve (AUC) values for NLR and SII were determined as 66.8% and 66.6% respectively, manifesting that classification performance was sufficient and statistically significant ($p<0.05$).

Optimal threshold value providing the best sensitivity and specificity of for NLR was obtained as 0.8553. Sensitivity of prediction for the patients in Group 2 was

Table 2 ROC analysis of inflammatory markers in the prediction of PAI scores

	AUC	S.D.	95% Level of confidence		*p*	Sensitivity	1-Specificity	Threshold value
			Lower	Upper				
PLR	0.559	0.065	0.432	0.686	0.373	-	-	-
NLR	0.668	0.057	0.557	0.780	0.011*	0.612	0.370	0.8553
SII	0.666	0.055	0.557	0.775	0.012*	0.657	0.259	312.869

*$p<0.05$, AUC: Area under the ROC curve, S.D.: Standard deviation

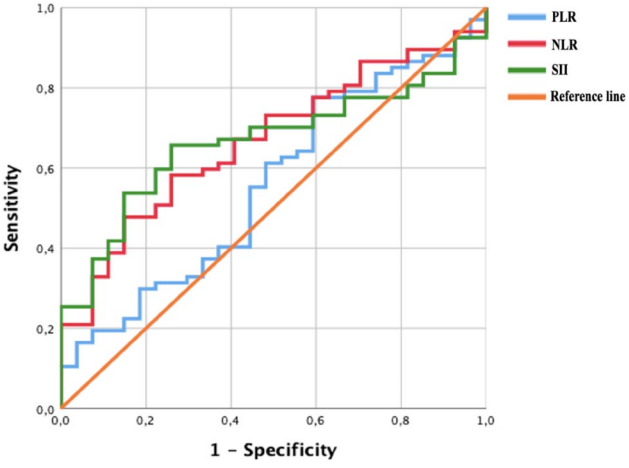

Fig. 4 ROC curve plot for clinical measurements

determined as 61.2% whereas specificity was 37%. 63% sensitivity of prediction was observed in the Group 1 patients.

The optimum threshold for SII using the best sensitivity and specificity was 312.869. For this optimum threshold value, sensitivity of Group1 prediction was determined as 65.7% and specificity was obtained as 25.97%. Sensitivity of Group 1 prediction was 74.1%. (Table 2; Fig. 4)

Discussion

ECC is one of the most significant among the chronic infectious diseases seen in children. ECC cases involve multiple decayed teeth, which pose a difficulty in management due to the younger age of the children and the accompanying necessity for long-term treatments, both of which can result in late dental interventions [18]. This increases the risk of systemic effects caused by chronic odontogenic infections [19]. Several scientific articles [18–21] have previously reported the impact of ECC on children; however, the scarcity of studies for the systemic effects of ECC fostered the idea of researching this subject. The present study assessed the systemic effects of ECC by comparing PAI that is used for determining the severity of caries-associated periapical lesions and systemic inflammatory indices (SII, NLR, NEUT, LYMPH, PLT and PLR). In the present study, although there was a strong relationship between the severity of odontogenic infection-associated periapical lesions, no significant difference was observed between periapical lesions and LYMPH, PLT, and PLR. Since the results of this research revealed a strong relationship between the groups regarding SII, NLR, NEUT scores, the null hypothesis was partly rejected. It was partly accepted due to no significant relationship between the LYMPH, PLT and PLR values of each group.

Inflammatory response is the physiological reaction of the human body against infections. Neutrophils, which form the first line of defense towards bacterial infections constitute an important part of the innate immune system [22, 23]. Platelet count differs with age, infectious agents, and type of treatment and may increase secondarily in response to infection or inflammation in some infectious diseases. The number of platelets may not change dynamically in every infectious disease since platelets do not act as the main inflammatory response agents in blood [24, 25]. However, viral infections may substantially change the number and localization of T and B lymphocytes in the human body [26, 27].

In the pathogenesis of odontogenic infections, anti-inflammatory responses may develop at different levels of severity in accordance with the intensity of the infection, and the synergy between aerobic and anaerobic bacteria [28]. Dental caries is a chronic infectious disease and cariogenic microbes consequently induce inflammatory reactions in the dental pulp [29]. Thus, the organism actuates chronic inflammatory response unless the caries are treated.

Recently, some convenient and cost-effective indices that can be calculated with neutrophil, platelet and lymphocyte counts (NLR, PLR, and SII) have become standard for evaluating the systemic effects of the chronic inflammatory responses in different diseases [30–32]. These indices were also used to assess the systemic inflammatory effects of chronic odontogenic infections in children with untreated ECC in the current study, which is pioneering the investigation of the relationship between systemic inflammatory indicators and severity of periapical lesions in ECC-impacted children. In the current study, 89 of the total participants were children under 72 months of age. Additionally, 6 children with a history of ECC from the clinic's archives, who had untreated cavities and early periapical lesions in both primary and permanent dentition, were also included. Although this research emphasized ECC, children older than 72 months were not excluded as their ages were

synchronous with the study group and their permanent first molars were affected by untreated ECC. Indeed, it has been reported that children with ECC are highly likely to experience cavities in their permanent teeth as they transition to the permanent dentition phase [2].

The present study investigated the relationship between the hematologic markers and periapical pathologies that are regarded as source of focal infections. Accordingly, using the neutrophil, platelet, and lymphocyte counts of the children with CBCs and NLR, SII and PLR scores were calculated. The present study demonstrated that the number of neutrophils were higher in the group with severe pathologies; however, platelet and lymphocyte counts as well as PLR did not differ between the groups, which might be explained by the bacterial pathogenesis of the odontogenic infection.

In the present study, the increase in neutrophils triggered by bacterial pathogenesis in individuals with chronic infections, while not affecting platelet and lymphocyte counts, can be explained by the activation of different cellular response mechanisms. Indeed, neutrophils are the first line of defense against bacterial infections. They migrate rapidly to the site of infection and neutralize pathogens through phagocytosis. The increase in neutrophil count during this process is a natural response of the organism to acute bacterial infection [33]. In contrast, platelets and lymphocytes play different roles. Platelets are primarily associated with hemostasis and wound healing, and therefore, do not exhibit a dramatic increase like neutrophils during the initial phase of bacterial infections [34]. Lymphocytes, on the other hand, are generally associated with chronic inflammatory responses and adaptive immune responses. During an acute bacterial infection, a significant increase in lymphocyte count is not expected; instead, lymphocytes play a more prominent role in combating viruses and developing long-term immunity [35]. Therefore, the increase in neutrophils triggered by bacterial pathogenesis reflects a rapid innate response to infection, while the lack of significant changes in platelet and lymphocyte counts may be due to these cells playing a lesser role in the acute phase of the infection [36]. This distinction highlights the organism's different cellular responses to bacterial infections and demonstrates the specificity and timing of immunological reactions.

SII is a calculated index that combines neutrophil, lymphocyte, and platelet counts and is considered a powerful biomarker reflecting the severity of systemic inflammatory conditions [37]. The present study determined a significant relationship between SII and PAI scores. This can be explained by the increase in the number of severe periapical lesions leading to an increased infection burden. The increased infection burden may result in enhanced mobilization of neutrophils to strengthen the body's immune response, leading to elevated inflammatory indices such as NLR and SII [38]. These results suggest that severe periapical pathologies increase the systemic inflammatory burden and that indices such as NLR and SII may reflect the severity and extent of these infections. These findings also indicate that periapical lesions may have not only local but also systemic effects.

The present study also analyzed the correlation between the number of teeth having a periapical PAI score of severe periodontitis with signs of exacerbation (PAI5) and NLR, and SII indices. A significant increase in both SII and NLR scores was observed when the number of the teeth with severe periapical lesions was three and more. These findings are consistent with previous our findings which demonstrated a relationship between SII, NLR, and periapical pathology. The increase in the number of teeth with higher PAI scores within the same individual may have led to an increased infection burden, consequently resulting in elevated SII and NLR indices.

The current study also determined that the group with more severe periapical pathologies had higher SII and NLR scores. ROC analysis, a statistical method used for distinguishing ill and healthy individuals in clinical studies to determine the predictive power of severity of the periapical pathologies, was utilized. In accordance with the study's results, it was concluded that the predictive accuracy of NLR and SII values was statistically significant and sufficient ($p<0.05$). SII was reported to be used to predict the prognosis of many diseases in some recently conducted research [39–42]. The present study also determined that the significant relationship between SII and severe periapical periodontitis might be beneficial in assessing the prognosis of persistent and treatment-resistant periapical lesions. Thus, when planning treatment approaches for dental infections with poor prognosis, by considering systemic effects, a decision may be made for more radical methods such as tooth extraction.

Indices such as NLR and SII can be used together to assess the systemic spread and severity of infection [43]. The increase in these indices, in conjunction with the rise in the number of severe periapical lesions, suggests the potential use of these parameters as prognostic biomarkers. The findings from this current study indicate that NLR and SII indices could be valuable tools in evaluating the prognosis of severe periapical pathologies. Specifically, the increase in these indices in the presence of three or more severe lesions suggests that controlling the infection may become more challenging, potentially necessitating more aggressive treatment approaches such as antibiotic therapy and tooth extraction. The clinical use of SII could be valuable in determining dental treatment strategies for managing persistent dental infections. These findings highlight the importance of future

research which integrates SII into dental clinical practice. Further investigation into this index could lead to the development of new strategies in the treatment of periapical lesions and its incorporation into routine clinical practice.

Despite the well-documented relationship between NLR and SII indices and chronic inflammatory conditions in the literature, studies exploring the relationship between these indices and severe periapical lesions are limited. The present study addresses this gap, contributing to a better understanding of the impact of severe periapical infections on systemic inflammation and emphasizing the importance of not underestimating dental infections. In the younger age group of children, dental phobia and its management is one of the most commonly encountered challenges in ECC, which is characterized by extensive dental decays. Unfortunately, some patients present uncooperative behavior during clinical dental treatment and often go about their daily lives with odontogenic infection-associated inflammations for long periods of time. Delayed treatment of odontogenic infections may magnify the systemic effects of local infections in children. And consequently, may cause the systemic inflammatory process to continue, making these children potential future candidates to develop one or more systemic diseases at early ages. Therefore, precautions should be taken globally to prevent and manage ECC in order to maintain a healthier population.

The results from this current study suggest that the NLR and SII indices could be useful tools in the clinical evaluation of periapical lesions. The routine use of these indices in clinical practice may be beneficial for the early detection of severe infections and the optimization of treatment strategies.

The primary limitation of this retrospective, single-center study is the relatively small sample size. However, this study is the first to investigate the relationship between systemic inflammatory markers and periapical periodontitis. As such, while the findings are pioneering in this area of research, they underscore the need for further comprehensive and prospective studies to validate and expand upon these results.

Conclusion

The results of the present study revealed a strong relationship between the severity of odontogenic infection-associated periapical lesions and NEUT count, NLR, and SII. No significant difference was observed between the study groups regarding scores of LYMPH, PLT, and PLR. Study data also demonstrated the potential presence of the bacterial pathogenesis and systemic effects of local odontogenic infections.

Author contributions
Author Contributions: Conceptualization, F.S. and S.Ş.D; methodology, F.S. and S.Ş.D.; software, P.Ç.; validation, F.S. and S.Ş.D.; formal analysis, S.Ö. and F.E.; investigation, P.Ç., F.S.; resources, T.A. and S.Ö; data curation, P.Ç., T.A; writing—original draft preparation, F.S., S.Ş.D. supervision, S.Ş.D.; funding acquisition, F.S., S.Ö, P.Ç., F.E, T.A. and S.Ş.D. All authors have read and agreed to the published version of the manuscript.

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Data availability
All data generated or analysed during this study are included in this published article.

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the guidelines of the Helsinki Declaration. Ataturk University Faculty of Medicine Ethics Committee approval, (date:29.03.2024/ session#02/ Decision 09) was obtained and the need for the consents of participating children' parents/guardians was waived by the Ethical Committee for Noninvasive clinical Trials", Ataturk University Faculty of Medicine.

Consent for publication
Not applicable.

Informed consent
As the study was conducted retrospectively and designed as an archive review of the files of all patients, it was neither necessary nor possible to acquire informed consent from the patients.

Competing interests
The authors declare no competing interests.

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