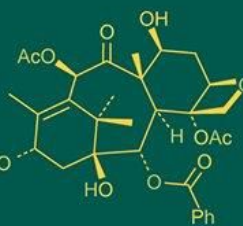
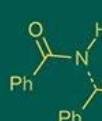


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Immune response to possible suppressive or stimulatory effects of ionizing radiation on the immune system

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Abstract

Aim: The aim of this study is to investigate the effects of ionizing radiation on immune response and to evaluate its potential suppressive or stimulatory effects on the immune system. In this context, the impact of radiation exposure on complete blood parameters was examined, with a focus on the Systemic Immune-Inflammation Index (SII) and Pan-Immune-Inflammation Value (PIV).

Material and method: This cross-sectional study evaluated healthcare workers exposed (n=60) and not exposed (n=39) to ionizing radiation. Inclusion criteria were ages 18–65, ≥1 year of experience, and no chronic diseases. Blood samples were analyzed for Systemic Immune-Inflammation Index (SII) and Pan-Immune-Inflammation Value (PIV) using a Sysmex XN 1000 analyzer.

Result: The case group had a significantly lower neutrophil-to-lymphocyte ratio (NLR) (1.68 ± 0.77 vs. 2.16 ± 0.87 , $p=0.027$) and systemic immune-inflammation index (SII) (426.07 ± 187.17 vs. 553.41 ± 207.24 , $p=0.015$) compared to the control group. No significant differences were found between the groups for neutrophil count, lymphocyte count, monocyte count, platelet count, monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), and pan-immune-inflammation value (PIV) ($p > 0.05$ for all).

Conclusion: The study revealed that healthcare workers exposed to radiation had lower NLR and SII levels than the control group, indicating potential effects on inflammation and immunity. No significant differences in other blood parameters suggest that these impacts may target specific systems. The results highlight the need for regular medical screenings and monitoring of long-term immune effects in these workers. Further research with larger samples and extended follow-ups is essential to validate these findings and establish protective measures against radiation exposure.

Keywords: Ionizing Radiation, Immune Response, Systemic Immune-Inflammation Index (SII), Pan-Immune-Inflammation Value (PIV), neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR)

Introduction

In recent years, ionizing radiation has become increasingly prevalent worldwide due to its diverse and beneficial applications [1]. The medical field, in particular, has witnessed a rising demand for radiological imaging procedures used in both diagnosis and treatment, as approximately 30-50% of medical diagnoses rely on X-ray imaging reports [2]. Consequently, exposure to ionizing radiation has become an unavoidable aspect of medical practice for both patients and radiation workers [3]. The utilization of radiation to improve public health inherently subjects patients and healthcare professionals to the potential risks associated with ionizing radiation [4]. Ionizing radiation exposure is recognized for its significant impact on various bodily systems, including the hematopoietic, immune, reproductive, circulatory, respiratory, musculoskeletal, endocrine, nervous, digestive, and urinary systems. Additionally, it is associated with adverse outcomes such as cataracts, skin burns, leukemia, and a range of other cancer types [5]. Both high doses of radiation and prolonged exposure to low doses are known to pose risks of mutagenic and carcinogenic effects [6]. Medical radiation workers, who utilize radiation in diagnostic and therapeutic procedures, are classified as individuals exposed to low, chronic doses and face potential risks of unintended radiation exposure. Annually, approximately 7 million healthcare workers worldwide are exposed to occupational radiation doses [7]. Thus, the use of ionizing radiation represents a double-edged sword: while it offers significant benefits to patients, improper or unskilled

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application of radiation technologies can result in health risks for both patients and radiation workers. Consequently, greater efforts are required to reduce unnecessary radiation exposure for both occupational workers and the general public [3].

The pan-immune-inflammation value (PIV), derived from comprehensive blood count data, shows potential as a biomarker for forecasting the progression of illnesses in children associated with immune disorders and different tumor types. Additionally, it acts as an important biomarker to differentiate patients from healthy individuals and to identify periods of remission versus active phases in rheumatoid arthritis, a chronic autoimmune condition that leads to systemic inflammation [8]. Additionally, a study examining two decades of data indicated that PIV serves as a measure for assessing inflammation and immune response. It found that both inflammation and immunity influence the outcomes for individuals with hypertension, and that elevated PIV levels are associated with cardiovascular death as well as a rise in overall mortality among those with high blood pressure [9]. Conversely, the systemic immune inflammation index (SII), which is derived from counts of platelets, lymphocytes, and neutrophils, is regarded as an effective measure of systemic inflammation and the local immune response [10]. Additionally, research analyzing data from a group of 40,937 people indicated that SII is a recent metric employed to assess a person's systemic inflammatory response. The study found a notable correlation between SII and both the occurrence and death rates associated with chronic kidney disease, which are connected to immune system activity and inflammation [11].

This study aims to evaluate the immunological and inflammatory effects of radiation by comparing the Systemic Immune-Inflammation Index (SII) and Pan-Immune-Inflammation Value (PIV) levels in healthcare workers exposed to ionizing radiation and those not exposed.

Materials and Methods

This cross-sectional study was conducted in a tertiary healthcare facility to evaluate healthcare workers exposed and not exposed to ionizing radiation. Participants were divided into two groups: First the exposed group, consisting of workers regularly exposed to ionizing radiation (e.g., radiology technicians, interventional radiologists), and second the non-exposed group, comprising workers not exposed to ionizing radiation (e.g., administrative staff, nurses in non-radiology departments). The study included 60 healthcare workers exposed to ionizing radiation as the case group, of whom 25 were female. Additionally, 39 healthcare workers not exposed to ionizing radiation were enrolled as the control group, with 15 being female. Inclusion criteria were being 18–65 years old, having at least one year of professional experience, and no history of chronic inflammatory, autoimmune, or hematological diseases. Exclusion criteria included recent infections, use of anti-inflammatory or immunosuppressive medications, and recent radiation therapy. Data collection involved demographic and clinical data (age, gender, duration of occupational exposure, and medical history) and venous blood samples taken after 8–12 hours of fasting. Laboratory analyses included calculating the Systemic Immune-Inflammation Index (SII) using the formula: platelet count $\times$ neutrophil count / lymphocyte count, and the Pan-Immune-

Inflammation Value (PIV) using the formula: neutrophil count $\times$ platelet count $\times$ monocyte count / lymphocyte count. Hematological tests were performed using the Sysmex XN 1000 analyzer (Sysmex Turkey Diagnostic Systems Limited Company, Sariyer, Istanbul, Turkey), which is a high-precision automated hematology analyzer widely used for comprehensive evaluation of whole blood parameters. Our study was carried out following the ethics committee decision of Health Sciences University Erzurum Faculty of Medicine numbered BAEK 2024/04-95 (date: 03.04.2024).

Statistical Analysis

The data were analyzed using SPSS version 25.0, with the normality of continuous variables assessed via the Kolmogorov-Smirnov test. Variables with a normal distribution were expressed as mean $\pm$ standard deviation (SD) and analyzed using the Independent Samples t-Test, while non-normally distributed variables were presented as median (minimum-maximum) and compared using the Mann-Whitney U test. Categorical variables were analyzed using the Chi-square test, and a p-value of <0.05 was considered statistically significant. The results were interpreted for both statistical significance and clinical relevance.

Results

The study included 60 healthcare workers exposed to ionizing radiation as the case group, of whom 25 were female. The control group consisted of 39 healthcare workers not exposed to ionizing radiation, with 15 being female. The mean age of the case group was 42.83 ± 9.31 years, while the control group had a mean age of 40.62 ± 10.44 years. No significant differences were observed between the two groups in terms of mean age or gender distribution ($p > 0.05$). Hematological parameters for both groups are presented in Table 1.

Table 1: Hematological Parameters for Control and Case Groups

Parameter	Control group (n=39)	Case group (n=60)	P
Neutrophil ($\times 10^9/L$)	4.73 ± 1.31	4.15 ± 1.14	>0.05
Lymphocyte ($\times 10^9/L$)	2.38 ± 0.67	2.73 ± 0.96	>0.05
Monocyte ($\times 10^9/L$)	0.59 ± 0.15	0.65 ± 0.37	>0.05
Platelet ($\times 10^9/L$)	262.46 ± 59.7	257.53 ± 54.66	>0.05
NLR	2.16 ± 0.87	1.68 ± 0.77	0.027
MLR	0.27 ± 0.11	0.27 ± 0.23	>0.05
PLR	115.94 ± 30.72	104.11 ± 36.38	>0.05
SII	553.41 ± 207.24	426.07 ± 187.17	0.015
PIV	331.04 ± 161.15	288.11 ± 264.74	>0.05

Abbreviations: NLR: neutrophil/lymphocyte ratio, MLR: monocyte/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, SII: Systemic Immune Inflammation Index, PIV: Pan-immune-inflammation value

The neutrophil-to-lymphocyte ratio (NLR) was significantly lower in the case group compared to the control group (1.68 ± 0.77 vs. 2.16 ± 0.87 , $p = 0.027$). Similarly, the systemic immune-inflammation index (SII) was significantly lower in the case group than in the control group (426.07 ± 187.17 vs. 553.41 ± 207.24 , $p = 0.015$). No statistically significant differences were observed between the two groups for other parameters, including neutrophil count, lymphocyte count, monocyte count, platelet count, monocyte-to-lymphocyte

ratio (MLR), platelet-to-lymphocyte ratio (PLR), and pan-immune-inflammation value (PIV) ($p > 0.05$ for all).

Discussion

This study aimed to investigate the effects of ionizing radiation on systemic inflammation and immune response by evaluating differences in the Systemic Immune-Inflammation Index (SII) and Pan-Immune-Inflammation Value (PIV) between healthcare workers exposed and not exposed to radiation. The findings revealed that SII levels were significantly lower in the radiation-exposed group, while no significant differences were observed in PIV levels. These results provide valuable insights into the specific effects of ionizing radiation on inflammatory markers.

SII, calculated using the formula $\text{platelet count} \times \text{neutrophil count} / \text{lymphocyte count}$, is a biomarker that reflects systemic inflammation and immune activation. Elevated SII levels are typically associated with chronic inflammatory conditions, malignancies, and cardiovascular diseases [12]. In our study, the lower SII levels observed in healthcare workers exposed to radiation may indicate immune suppression or alterations in the regulation of inflammatory responses. Lymphocytes are known to be among the most radiation-sensitive blood cells [13]. This may explain how a relative increase in lymphocyte count, combined with a decrease in neutrophil count, contributes to the reduction in SII levels.

Previous studies have reported that low-dose ionizing radiation can modulate the immune system and induce changes in inflammatory markers. For instance, Hayashi *et al.* suggested that low-dose radiation suppresses the production of certain inflammatory cytokines and exerts an inhibitory effect on immune cells [14]. Our findings support the notion that long-term exposure to ionizing radiation leads to alterations in inflammatory processes.

PIV, calculated using the formula $\text{neutrophil count} \times \text{platelet count} \times \text{monocyte count} / \text{lymphocyte count}$, is a comprehensive inflammatory parameter [15-17]. This marker provides a more holistic reflection of systemic inflammation by assessing all immune cell subtypes collectively. In our study, the lack of a significant difference in PIV levels between the two groups suggests that PIV may be less sensitive to the effects of low and chronic doses of radiation. Additionally, the impact of radiation might manifest in more long-term inflammatory changes, or the sample size of this study may have been insufficient to detect significant differences in PIV levels.

Our study contributes to the literature evaluating the effects of ionizing radiation on immune response. It is thought that changes caused by radiation may suppress the immune system, thereby reducing the risk of chronic inflammation, or alternatively, may increase susceptibility to infections due to immune suppression [18]. The decrease in SII levels supports the hypothesis that radiation exerts cytotoxic effects on lymphocytes, suppressing the inflammatory response. However, broader markers such as PIV need to be examined through further studies to evaluate the long-term effects of radiation.

Conclusion

Our study has several limitations. First, radiation exposure doses were not measured, which makes it challenging to accurately assess the effects of exposure. Additionally, due

to the cross-sectional design, establishing a cause-and-effect relationship is not possible. To enhance the generalizability of the study results, larger sample sizes and prospective, multicenter studies are needed.

This study holds a unique position as it is the first research in the literature to evaluate the effects of ionizing radiation on immune response. No comprehensive assessment on this topic has been conducted previously, and the findings fill a significant gap in the literature, providing guidance for future studies.

This study demonstrated that NLR and SII levels were lower in healthcare workers exposed to radiation compared to the control group. This finding highlights the potential effects of radiation exposure on inflammatory response and its impact on the immune system. The absence of significant differences in other hematological parameters between the groups suggests that these effects may be mediated through more specific systems. The study's findings emphasize the importance of regular medical screenings for healthcare workers exposed to radiation and the need to closely monitor the long-term effects on their immune systems. Future research involving larger sample sizes and long-term follow-ups would help validate these findings and contribute to the development of protective measures against radiation exposure.

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