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Comparison of 99mTc-HMPAO-labeled leukocyte scintigraphy findings with systemic inflammatory markers

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ABSTRACT

Aims: Technetium-99m-hexamethylpropylene amine oxime (99mTc-HMPAO) labeled leukocyte scintigraphy is frequently used for infection imaging. The systemic immune-inflammation index is a new marker. In this study, we aim to investigate the relationship between 99mTc-HMPAO-labeled leukocyte scintigraphy findings and systemic inflammatory markers such as Neutrophil/lymphocyte ratios (NLR) and Platelet lymphocyte ratio (PLR) and systemic immune-inflammation index (SII).

Methods: Patients who underwent 99mTc-HMPAO-labeled leukocyte scintigraphy between 2014 and 2020 due to suspected infection such as diabetic foot infection or prosthesis infection vs. in any part of the body were included in our study. In addition, a negative control group consisting of 19 normal subjects who had no leukocyte scintigraphy and had hemogram examination was added to the study. Cases with findings consistent with infection in labeled leukocyte scintigraphy and infectious symptoms in this area of involvement in the clinical examination were considered as the positive group. The data were evaluated with the SPSS 23.0 program.

Results: Our study included 36 patients (28 males,8 females, mean age: 59.7). The mean SII was 1526±787 x109 cells/L in patients with positive findings in leukocyte scintigraphy that might be compatible with infection, while it was 1025 ± 370 x109 cells/L in patients who did not (p=0.017). The mean PLR was 183.95±68.30 in patients with positive findings in leukocyte scintigraphy that might be compatible with infection, while it was 145.81±58.30 in patients who did not (p=0.102). The mean NLR was 4.82±1.91 in patients with positive findings on leukocyte scintigraphy that might be compatible with infection, while it was 4.15±1.40 in patients who did not (p=0.181). While the negative control group and the patients who were considered positive in leukocyte scintigraphy were compared; a statistically significant difference was found between SII, NLR and PLR values. When the relationship between SII was evaluated, the mean SII was 1526±787 x109 cells/L in patients with involvement that may be compatible with infection in leukocyte scintigraphy, while it was 762±224 x109 cells/L in the negative control group (p<0.05). While the relationship between PLR was evaluated, the mean PLR was 183.95±68.30 in patients with involvement that might be compatible with infection in leukocyte scintigraphy, while it was 100.67±26.18 in the negative control group (p<0.05). When the relationship between NLR was evaluated, the mean NLR was 4.82±1.91 in patients with involvement that might be compatible with infection in leukocyte scintigraphy, while it was 3.11±0.85 in the negative control group (p<0.05).

Conclusion: When labeled leukocyte scintigraphy and systemic inflammatory markers were compared, there was a statistically significant relationship between the presence of infection in scintigraphy and SII, but the relationship with NLR and PLR were not statistically significant. When the negative control group and the patients who were considered positive in leukocyte scintigraphy were compared; a statistically significant difference was found between SII, NLR and PLR values. For this reason, we think that SII, NLR and PLR may be useful markers for diagnosis confirmation in centers that can't perform radiolabeled infection imaging.

Keywords: Leukocyte scintigraphy, Infection, SII, NLR, PLR, systemic immune-inflammation index

This study was presented as an oral presentation at the 33rd National Nuclear Medicine Congress held online on 28-29 May 2021 in Turkey.

INTRODUCTION

Blood consists of plasma and cells. Plasma contains protein, amino acids, enzymes, antibodies, lipids, salts, carbohydrates, hormones and gases. Blood cells are divided into three erythrocytes, leukocytes and platelets. Leukocytes are major cellular components of the inflammatory and immune response that play a protective role against infections and neoplasia and also help repair damaged tissue. 55-65% of peripheral leukocytes are neutrophils, 3% are eosinophils, 0.5% are basophils, 25-35% are lymphocytes, and 3-7% are monocytes. In normal times, only 2-3% of leukocytes are found in the circulating blood. The remainder of the leukocytes, attached to the vascular endothelial tissue, are found in the bone marrow, liver, lung, spleen, gastrointestinal tract, and oropharynx. In the presence of an acute inflammatory condition, these cells accumulate in this region by performing chemotaxis and diapedesis. In the chronic phase, lymphocytes migrate to the inflammatory region.[1]

Radiolabeled leukocyte scintigraphy, which is based on the detection of areas where leukocytes accumulate by labeling them with radioactive substances that

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emit gamma radiation, is frequently used for infection imaging. One of the radiopharmaceuticals used for this purpose is 99mTc HMPAO. 99mTc-HMPAO, a cerebral perfusion agent, enters the cell by passive diffusion. Hexamethylpropyleneamine oxime is labeled with 99mTc and is used in brain perfusion imaging and labeled leukocyte scintigraphy. It has a lipophilic structure, but it reacts with glutathione in the cell and turns into a hydrophilic structure and binds to the nucleus and mitochondria. Once injected i.v. to the patient, radiolabeled leukocyte migrates rapidly to the lungs and, if not damaged, proceeds to the liver, spleen and the reticuloendothelial system, including bone marrow. Approximately 1 hour after injection, labeled cells further migrate to bone marrow and, in case of an infection, to the infected tissue due to chemotactic attraction caused by biofilm and its soluble products.[2] The sensitivity, specificity and accuracy values of leukocyte scintigraphy show different results within the infection groups. There are different values for prosthetic infections and osteomyelitis. In the study by Love et al.[3] they investigated the diagnostic accuracy of labeled lymphocyte scintigraphy in 59 patients with painful, failed, lower extremity joint prostheses, In this study 40 hip and 19 knees who underwent (18)F-FDG, labeled leukocyte, and bone marrow imaging, and had histopathologic and microbiologic confirmation of the final diagnosis, the sensitivity, specificity, and accuracy of labeled leukocyte/marrow imaging were 100%, 91%, and 95%, respectively. With the addition of F-18 FDG PET/CT examination to the marked leukocyte scintigraphy for the diagnosis of osteomyelitis, the sensitivity increases to 90%.[4] Autologous labeled leukocytes are very specific as they accumulate after adhering to the vascular endothelium by active migration across the basement membrane into infected tissue.[5] HMPAO, a lipophilic chelator, has high efficacy in labeling leukocytes with Tc-99m.[6] The neutrophil/lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are used to evaluate systemic inflammation. However, these two inflammatory markers allow an evaluation based on neutrophil and lymphocyte counts. Abnormal increases in inflammatory blood cell parameters including neutrophil count, the neutrophil-to-lymphocyte ratio[7], [8], the monocyte-to-lymphocyte ratio[9], and the platelet-to-lymphocyte ratio[10,11] serve as simple markers of inflammation. But these biomarkers involve only two types of immune-inflammatory cells and might not accurately reflect the inflammation status. The marker called systemic immune-inflammation index is a new prognostic marker that allows an evaluation based on neutrophil, platelet and lymphocyte counts.[12,13] All three parameters in this marker can be easily calculated from routine complete blood counts in peripheral blood.

In this study, we aimed to investigate the relationship between 99mTc-HMPAO-labeled leukocyte scintigraphy findings and systemic inflammatory markers such as NLR, PLR and SII.

METHODS

Ethical Approval

This study was approved by the Sancaktepe Şehit Prof. Dr. İlhan Varank Training And Research Hospital Non-interventional Clinical Researches Ethics Committee of (Date: 2023-03-08, No: 37). Medical records, scintigraphy findings and other data of the patients were evaluated retrospectively. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population

Patients who underwent 99mTc-HMPAO-labeled leukocyte scintigraphy between 2014 and 2020 due to suspected infection such as diabetic foot infection or prosthesis infection vs. in any part of the body were included in our study. Patients under antibiotic treatment and patients who do not have a recent hemogram were not included in our study. Cases with findings consistent with infection in labeled leukocyte scintigraphy and infectious symptoms in this area of involvement in the clinical examination were considered as the positive group. However, clinical follow-up was not performed for patients. In addition, a negative control group consisting of 20 normal subjects who had no leukocyte scintigraphy and had hemogram examination was added to the study and included in the statistical evaluations.

Radiolabeling of Leukocytes and Scintigraphic Imaging

Labeling of leukocytes in the blood with 99mTc-HMPAO is a complex process consisting of several steps. To have sufficient leukocytes in the labeling, 30-50 cc of blood from the patient is taken into a tube containing Anticoagulant Citrate Dextrose (ACD, consisting of 0.73 g of anhydrous citric acid, 2.2 g of sodium citrate dihydrate and 2.45 g of dextrose monohydrate in 100 ml of water for injection), which has anticoagulant properties. By adding 6% hetastarch to this tube, erythrocytes are precipitated. The red blood cells remain in the pelleted part by forming a precipitate with the starch solution. The supernatant contains white blood cells. This part is taken with the help of a butterfly needle. Platelets and proteins are removed from the blood and centrifuged for 5 minutes at 300-350 g centrifuge speed. White blood cells accumulate at the bottom of the tube. The plasma is separated and purified by centrifugation, and leukocyte isolation is completed. Isotonic NaCl solution is added to the white blood cells and incubated with 99mTc-HMPAO for 10 min at room temperature.

99mTc-HMPAO enters into leukocytes and is labeled by passive diffusion. The purification process is done by centrifugation at 150 g for 5 min of 99mTc-HMPAO-leukocyte suspension, to remove 99mTc-HMPAO that is not labeled with leukocytes and free 99mTc in the medium. The obtained radiopharmaceutical is injected into the patient through the peripheral vein.

After the injection, whole-body scintigraphic imaging was performed at the 1st hour, and static scintigraphic imaging was performed from the relevant regions at the 4th and 24th hours. All data acquisition was performed with a double-head SPECT system (DDD-Quantum Cam, Denmark) equipped with a low-energy, high-resolution collimator and a 140 keV energy photopeak. Visual and semiquantitative interpretations were based on the current guidelines of the European Association of Nuclear Medicine and performed by nuclear medicine physicians without knowing the results of the corresponding hemogram results. Patients without significant pathological accumulation of increased activity during labeled leukocyte scintigraphy were considered to be negative for leukocyte scintigraphy (**Figure 1**). Visual interpretation defined a case as positive for infection when there was a clear increase of radiotracer uptake (in terms of intensity or size) in the late images compared with the early images (**Figure 2A**, **2B**, **2C**).

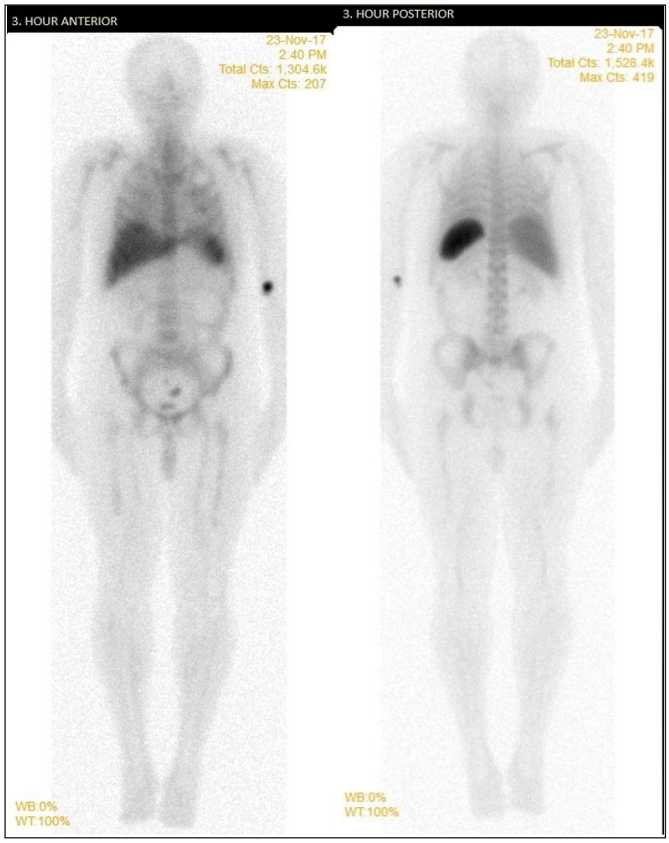

Figure 1: Tc-99m HMPAO labeled leukocyte scintigraphy images of the patient who did not have pathological findings compatible with infection (SII value was 544, leukocyte count was 5660, NLR value was 3.16, and PLR value was 96).

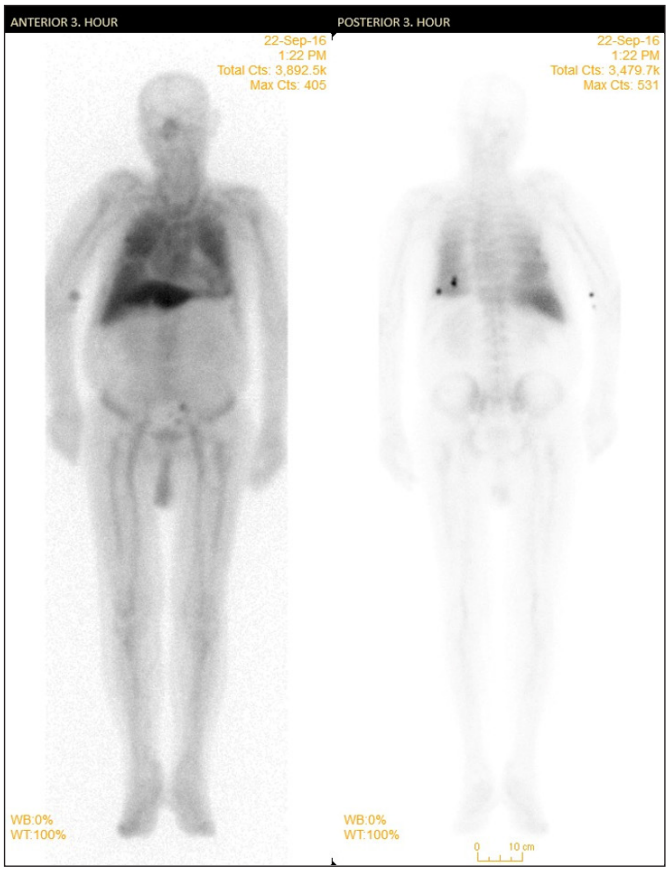

Figure 2A: Whole body images of the Tc-99m HMPAO labeled leukocyte scintigraphy taken 3 hours after the radiopharmaceutical injection of the patient referred for suspected diabetic foot infection (SII value was 1658, leukocyte count was 9310, NLR value was 9.70, and PLR value was 178).

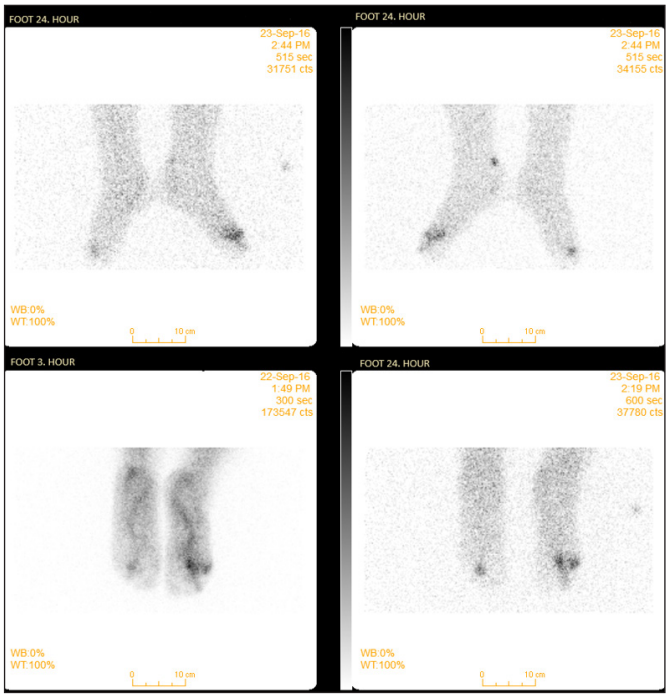

Figure 2B: Static spot foot images of the Tc-99m HMPAO labeled leukocyte scintigraphy taken 4 hours and 24 hours after the radiopharmaceutical injection of the patient referred for suspected diabetic foot infection (SII value was 1658, leukocyte count was 9310, NLR value was 9.70, and PLR value was 178).

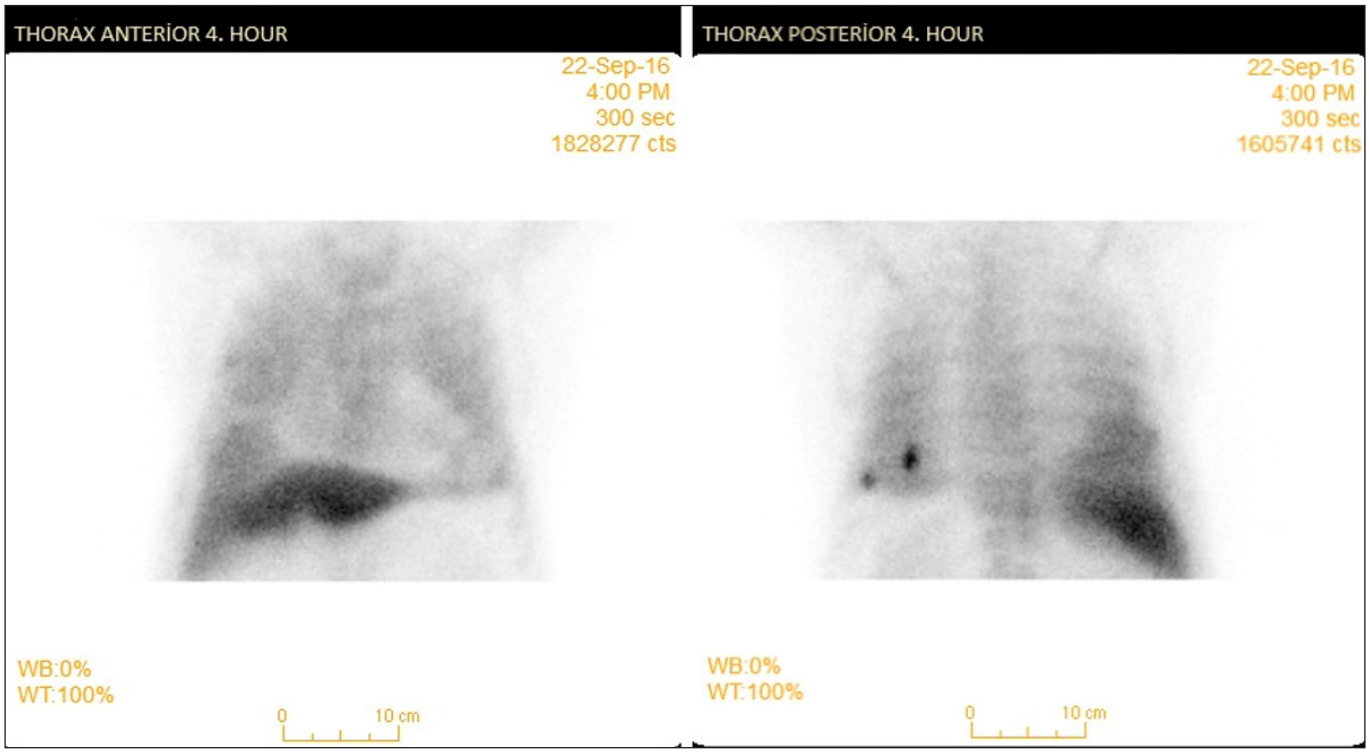

Figure 2C: Static spot thorax images of the Tc-99m HMPAO labeled leukocyte scintigraphy taken 4 hours after the radiopharmaceutical injection of the patient referred for suspected diabetic foot infection (SII value was 1658, leukocyte count was 9310, NLR value was 9.70, and PLR value was 178).

Blood Count

Complete blood count analysis was performed using an autoanalyzer (Sysmex XN1000, Japan). C-reactive protein (CRP) measurements were performed using the turbidimetric method (Roche Cobas c702, Mannheim, Germany). The normal CRP values in our laboratory are <5 mg/L. Platelet count was measured using an automatic blood counter. The SII value was obtained by multiplying the absolute platelet count in the hemogram with the absolute neutrophil count and dividing this value by the absolute lymphocyte value (SII = (platelet count × neutrophil count) / lymphocyte count). NLR was calculated by dividing the absolute neutrophil count by the absolute number of lymphocytes, and PLR was calculated by dividing the absolute platelet count by the absolute number of lymphocytes. The data were evaluated with the SPSS 23.0 program.

Statistical Analysis

Analysis was performed by using the SPSS Statistical Software program (SPSS version 23.0, SPSS Inc., Chicago). A p-value of <0.05 was considered statistically significant during the tests. During the comparison of categorical and numerical data, Independent Student's t-Test was used for normally distributed data, and Mann Whitney U test was used for the analysis of non-normally distributed data. All the continuous variables of the study were described by descriptive statistics such as mean, median, and standard deviation (SD). Categorical variables were described by frequency and percentages.

RESULTS

In our study, there are 36 patients who had labeled leukocyte scintigraphy for infection imaging. Of the patients included in the study, 8 (22.2%) were female and 28 (77.8%) were male (age range: 19-88; mean: 59.7). There were 19 people in the negative control group. Of the people included in the negative control group, 8 (42%) were female and 11 (58%) were male. There was an average of 4 days between scintigraphic imaging and hemogram examinations (range 0-10 days). The mean 99mTc-HMPAO radiopharmaceutical dose given to the patients was 10.03±4.06 mCi.

When the patients who were reported as positive and negative for leukocyte scintigraphy were evaluated among themselves; there was a statistically significant relationship between the presence/absence of findings compatible with infection in leukocyte scintigraphy and platelet count, hemoglobin level, SII and erythrocyte sedimentation rate, no significant relationship was found between WBC, NLR, lymphocyte count, PLR and CRP. When the relationship between presence/absence of findings consistent with infection in leukocyte scintigraphy and SII was evaluated, the mean SII was 1526±787 $\times 10^9$ cells/L in patients with involvement that may be compatible with infection in scintigraphy, while it was 1025±370 $\times 10^9$ cells/L in patients without (p=0.017). When the relationship between presence/absence of findings consistent with infection in leukocyte scintigraphy and PLR was evaluated, the mean PLR was

183.95±68.30 in patients with involvement that might be compatible with infection in scintigraphy, while it was 145.81±58.30 in patients without (p=0.102). When the relationship between presence/absence of findings consistent with infection in leukocyte scintigraphy and NLR was evaluated, the mean NLR was 4.82±1.91 in patients with involvement that might be compatible with infection in scintigraphy, while it was 4.15±1.40 in patients without (p=0.181). When the relationship between presence/absence of findings consistent with infection in leukocyte scintigraphy and WBC was evaluated, the mean WBC was 8.43±2.69 $\times 10^9$/L in patients with involvement that may be compatible with infection in scintigraphy, while it was 7.31±2.07 $\times 10^9$/L in patients without (p=0.170). When the relationship between presence/absence of findings consistent with infection in leukocyte scintigraphy and the platelet count was evaluated, the mean platelet count was 321±98 $\times 10^9$/L in the patients with involvement that might be compatible with the infection in the scintigraphy, while it was 251±63 $\times 10^9$/L in the patients without it (p=0.045). When the relationship between presence/absence of findings consistent with infection in leukocyte scintigraphy and hemoglobin level was evaluated, the mean hemoglobin level was 12.4±1.9 g/dL in patients with uptake in scintigraphy that might be compatible with infection, while it was 13.55±1.67 g/dL in patients without (p=0.049). When the relationship between presence/absence of findings consistent with infection in leukocyte scintigraphy and CRP level was evaluated, the mean CRP level was 48.3 mg/L in patients with uptake that might be compatible with infection in scintigraphy, while it was 31.1 mg/L in patients without (p=0.057). When the relationship between presence/absence of findings consistent with infection in leukocyte scintigraphy and erythrocyte sedimentation rate was evaluated, the mean erythrocyte sedimentation rate (ESR) was 60.8 mm/hr in patients with involvement that may be compatible with infection in scintigraphy, while it was 29.15 mm/hr in patients without (p=0.003) (**Table 1**).

Table 1. Comparison of SII, NLR and PLR values in the patients who had positive leukocyte scintigraphy and had negative leukocyte scintigraphy

	Leukocyte Scintigraphy		p
	Positive	Negative	
SII	1526±787	1025 ± 370	0.017
NLR	4.82±1.91	4.15±1.40	0,181
PLR	183.95±68.30	145.81±58.30	0,102
WBC	8.43±2.69	7.31±2.07	0.170
PLT	321±98	251±63	0.045
HGB	12.4±1.9	13.55±1.67	0.049
CRP	48.3	31.1	0.057
Erythrocyte sedimentation rate	60.8	29.15	0.003

When the negative control group and the patients who were considered positive in leukocyte scintigraphy were compared; a statistically significant difference was found between SII, NLR and PLR values. When the relationship between SII was evaluated, the mean SII was 1526±787 $\times 10^9$ cells/L in patients with involvement that may be compatible with infection in scintigraphy, while it was 762±224 $\times 10^9$ cells/L in negative control group (p<0.05). When the relationship between PLR was evaluated, the mean PLR was 183.95±68.30 in patients with involvement that might be compatible with infection in scintigraphy, while it was 100.67±26.18 in negative control group (p<0.05). When the relationship between NLR was evaluated, the mean NLR was 4.82±1.91 in patients with involvement that might be compatible with infection in scintigraphy, while it was 3.11±0.85 in negative control group (p<0.05) (**Table 2**).

Table 2. Comparison of SII, NLR and PLR values in the patients who had positive leukocyte scintigraphy and the normal negative control group who had no leukocyte scintigraphy.

	Patients with positive leukocyte Scintigraphy	Negative Control Group	p
SII	1526±787	762±224	<0.05
NLR	4.82±1.91	3,11±0,85	<0.05
PLR	183.95±68.30	100.67±26,18	<0.05
WBC	8.43±2.69	7.66±1.74	>0.05
PLT	321±98	249±60	<0.05
HGB	12.4±1.9	13.9±1.2	<0.05

DISCUSSION

99mTc-HMPAO-labeled leukocyte scintigraphy is a noninvasive imaging method with high diagnostic accuracy and is highly preferred in infection imaging due to its high specificity and sensitivity. In their studies, Govaert et al.[14] obtained 0.79 sensitivity, 0.97 specificity in fracture-related infections, Granados et al.[15] obtained 0.72 sensitivity, 0.95 specificity in periprosthetic infections. It is based on the principle that the blood taken from the patient is injected into the patient by separating the white blood cells (leukocytes, WBC) and marking them with 99mTc-HMPAO and imaging on gamma cameras. The main laboratory tests for the diagnosis of infection are erythrocyte sedimentation rate, CRP and leukocyte count. These tests are non-specific indicators of inflammation. In recent studies, NLR, PLR and SII, which are novel inflammatory markers, have been considered useful indicators for the diagnosis and prognosis of various infectious diseases. In our study, there was a significant relationship between ESR and the presence of infection.

In the study by Şener et al.[16], it was investigated whether the systemic immune-inflammation index is a reliable parameter that can be used in the diagnosis of acute

appendicitis and they stated that systemic immune-inflammation index may be used to promote the diagnosis of acute appendicitis and may reduce the need for radiation exposure and diagnostic imaging tests such as contrast-enhanced abdominal computed tomography. And also they claimed that it can also be used to differentiate between complicated and non-complicated acute appendicitis cases.

The study by Ozer et al.[17] aimed to investigate the clinical and diagnostic significance of inflammatory markers, including the systemic immune-inflammation index (SII) and erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and procalcitonin (PCT) to differentiate osteomyelitis and cellulitis. In conclusion, given that the patients with osteomyelitis had much higher ESR, CRP, PCT, and SII levels combined with the fact that SII is a low-cost and easy-to-measure index, suggests that the same may serve as an effective and novel marker alternative to other inflammatory markers for predicting diabetic foot osteomyelitis. A significant portion of the patients in our study group consisted of labeled leukocyte scintigraphy performed due to diabetic foot infection. Also, in our study when presence/absence of findings consistent with infection in leukocyte scintigraphy and SII was evaluated, the mean SII was higher in patients with involvement that may be compatible with infection in scintigraphy.

The study by Wang et al.[18] aimed to compare the predictive value of the NLR, SII, SIRI and PLR for stroke-associated pneumonia in patients with intracerebral hemorrhage to determine their application potential in the early identification of the severity of pneumonia. Among the four indexes, the NLR was the best predictor for stroke-associated pneumonia occurrence and a poor outcome at discharge in intracerebral hemorrhage patients. It can therefore be used for the early identification of severe stroke-associated pneumonia and to predict ICU admission. Although it was not statistically significant in our study, when the relationship between presence/absence of findings consistent with infection in leukocyte scintigraphy and NLR was evaluated, the mean NLR was higher in patients with involvement that might be compatible with infection in scintigraphy.

In the study conducted by Carpio-Orantes et al.[19], in which the usability of NLR, PLR and SII indexes were investigated to determine the severity of COVID-19, it was stated that these parameters could be used to determine the severity of COVID-19. Asik,[20] researched the usability of NLR and PLR for diagnosis in patients with urinary tract infections and during his study, he found that NLR and PLR values were higher in patients with urinary tract infections compared to the healthy volunteer control group and suggested that they can be used as inflammatory markers in patients with infection. In the study conducted by Yang et al.[21] in which he investigated the diagnostic and predictive roles of NLR and PLR in COVID-19 patients, he stated that NLR could be considered as an independent biomarker to predict poor clinical outcomes. Although it was not statistically significant in our study, when the relationship between presence/absence of findings consistent with infection in leukocyte scintigraphy and PLR was evaluated, the mean PLR was higher in patients with involvement that might be compatible with infection in scintigraphy.

CONCLUSION

99mTc-HMPAO-labeled leukocyte scintigraphy is a noninvasive method with high diagnostic accuracy used in the investigation of infection/inflammation focus. The main laboratory tests for the diagnosis of infection are erythrocyte sedimentation rate, CRP and leukocyte count. These tests are non-specific indicators of inflammation. In the first part of our study, patients who had leukocyte scintigraphy were compared. According to the first part of our study with a limited number of patients, when labeled leukocyte scintigraphy and systemic inflammatory markers were compared, there was a statistically significant relationship between the presence of infection in scintigraphy and SII, platelet count, hemoglobin level and erythrocyte sedimentation rate, while the relationship with NLR, PLR, WBC and CRP were not statistically significant. In the second part of our study, the patients who had leukocyte scintigraphy were compared with the normal negative control group who had no leukocyte scintigraphy. When the negative control group and the patients who were considered positive in leukocyte scintigraphy were compared; a statistically significant difference was found between SII, NLR and PLR values. For this reason, we think that SII, NLR and PLR may be useful markers for diagnosis confirmation in centers that cannot perform radiolabeled infection imaging.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Non-interventional Clinical Researches Ethics Committee (Date: 08.03.2023, Decision No: 37)

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.

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