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Differential Diagnosis of Septic and Aseptic Bone Lesions of the Foot in Patients With Diabetic Foot Syndrome: the Potential of Using a Standardized Uptake Value with Osteotropic Radiopharmaceuticals

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ABSTRACT

Aim. The study was conducted to calculate standardized uptake values (SUVs) for foot bones, determine the optimal SUV type in patients with degenerative changes, and assess the potential of quantitative single-photon emission computed tomography (SPECT/CT) in patients with diabetic foot syndrome (DFS) complicated by osteomyelitis.

Materials and methods. The study design was prospective. Patients with a documented clinical diagnosis of diabetic foot and confirmed or suspected osteomyelitis underwent SPECT/CT scanning after intravenous injection of the radiopharmaceutical (^{99m}Tc – Pyrophosphate). The calculation of standardized uptake values – mean SUV (SUVmean), maximum SUV (SUVmax), and peak SUV (SUVpeak) – was performed using the SyngoVia software. To calculate the threshold standardized uptake value, receiver operating characteristic analysis (ROC) was conducted, followed by the calculation of the area under the ROC curve (AUC).

Results. Forty-eight patients were examined: 28 people with septic foot lesions and 20 individuals with aseptic foot lesions. Calculations revealed no statistically significant differences between the SUV values (max, mean, and peak) for septic and aseptic lesions. However, the standardized uptake value normalized by lean body mass (SUVlbm (max)) demonstrated the largest ROC AUC. A threshold value for differentiating between pathological and healthy bone tissues was 1.64, with sensitivity of 93.5% and specificity of 95.6%.

The threshold value for distinguishing between septic and aseptic inflammations in patients with diabetic foot syndrome was 4.35, with sensitivity of 82.4% and specificity of 80.3%.

Conclusion. The study confirmed that the use of SUVlbm (max) threshold value of 4.35 (Se = 82.4%; Sp = 80.3%; AUC = 0.883) is possible for the differential diagnosis of osteomyelitis and Charcot foot in patients with diabetic foot syndrome. Additionally, to confirm inflammation, a SUVlbm (max) threshold value of 1.64 (Se = 93.5%; Sp = 95.6%; AUC = 0.983) is applicable.

Keywords: Charcot foot, inflammation, osteomyelitis, radionuclide diagnosis

Conflict of interest. The authors declare the absence of obvious or potential conflicts of interest related to the publication of this article.

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Conformity with the principles of ethics. All patients signed a voluntary informed consent to participate in the study. The study was approved by the local Ethics Committee at SibSMU (Minutes No. 9418 dated March 27, 2023).

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Дифференциальная диагностика септического и асептического поражений костных структур стоп у пациентов с синдромом диабетической стопы: возможности применения стандартизированного уровня захвата остеотропного радиофармпрепарата

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РЕЗЮМЕ

Цель. Провести исследование с целью расчета показателей стандартизированных уровней захвата (SUV) для костей стоп и определения оптимального типа SUV у пациентов с дегенеративными изменениями и определить возможности количественной оценки однофотонной эмиссионной компьютерной томографии (ОФЭКТ/КТ) у пациентов с синдромом диабетической стопы осложненным остеомиелитом.

Материалы и методы. Дизайн исследования – проспективное. Пациентам с документально подтвержденным клиническим диагнозом диабетической стопы и наличием остеомиелита или подозрением на его наличие было проведено ОФЭКТ/КТ сканирование после внутривенного ведения радиофармпрепарата (^{99m}Tc – пирфотех). Расчет показателей стандартизированных уровней захвата: среднего SUV (mean), максимального SUV (max) и пикового SUV (peak) производился при помощи программного обеспечения SyngoVia. Для вычисления порогового значения стандартизированного уровня захвата выполнялся ROC-анализ с последующим расчетом площади под ROC-кривой.

Результаты. Обследованы 48 пациентов (28 с септическим поражением и 20 с асептическим поражением стоп). Расчеты показали, что статистически значимых отличий между значениями SUV (max, mean, peak) септического и асептического поражения не выявлено, при этом наибольшей площадью под ROC-кривой обладает стандартизированный уровень захвата, нормированный по безжировой массе тела (SUVlbm (max)). Определено пороговое значение для разграничения патологического очага от здоровой костной ткани, равное 1,64, с чувствительностью 93,5% и специфичностью 95,6%. Пороговое значение для разграничения септических и асептических воспалительных процессов у пациентов с синдромом диабетической стопы равно 4,35 с чувствительностью 82,4% и специфичностью 80,3%.

Заключение. Для дифференциальной диагностики остеомиелита и стопы Шарко у пациентов с синдромом диабетической стопы возможно применение порогового значения SUVlbm (max), равного 4,35 (Se = 82,4%; Sp = 80,3%; AUC = 0,883), а для установления факта воспалительного процесса – порогового значения SUVlbm (max), равного 1,64 (Se = 93,5%; Sp = 95,6%; AUC = 0,983).

Ключевые слова: стопа Шарко, остеомиелит, радионуклидная диагностика, воспаление

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

Соответствие принципам этики. Все пациенты подписали информированное согласие на участие в исследовании. Исследование одобрено локальным этическим комитетом СибГМУ (протокол № 9418 от 27.03.2023).

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INTRODUCTION

Diabetes mellitus is an endocrine disease characterized by relative or absolute deficiency of insulin due to dysfunction or destruction of β-cells. It is one of the fastest growing global health concerns in the 21st century [1]. The primary pathogenetic mechanisms involve impaired insulin secretion and insulin resistance. Chronic hyperglycemia in diabetes mellitus leads to damage, dysfunction, and insufficiency of various organs, particularly the eyes, kidneys, nerves, heart, and blood vessels [2].

Diabetic foot syndrome (DFS) is one of the most dangerous and severe complications of diabetes mellitus. According to the World Health Organization, approximately 422 million people worldwide suffer from diabetes mellitus, with 15–25% developing diabetic foot ulcers [3]. Despite advancements in complex surgical interventions, a significant percentage of patients (25–30%) still require above-the-knee amputations. One-year mortality rate following major lower limb amputation reaches 50% [4]. This results in patient disability and a significant reduction in the patient's quality of life.

A gold standard for evaluating diabetic foot pathology is three-phase bone scintigraphy. However, the specific pattern of radiotracer accumulation in the region of interest often results in low specificity for this diagnostic technique. The specificity of radionuclide imaging for inflammation can be improved using labeled leukocyte scintigraphy, typically performed with single-photon emission computed tomography (SPECT) [5]. Additionally, there is a method using radiolabeled antimicrobial peptides. These peptides can selectively bind to pathogenic microorganisms and can be successfully used for differential diagnosis of osteomyelitis. Due to its high cost, this method is not widely available in routine clinical practice. Positron emission tomography / computed tomography (PET/CT) with 18F-fluorodeoxyglucose (18F-FDG) has gained importance in diagnosing infections and inflammations regardless of their etiology or location. PET/CT provides precise anatomical localization and allows to assess spread of infection to soft tissues or bone. However, 18F-FDG PET/CT imaging has limitations, particularly in the evaluation of Charcot foot due to the intense uptake of 18F-FDG in this condition.

In recent years, the role of quantitative analysis of PET results using standardized uptake values (SUVs) has been explored in patients with diabetic foot. Studies have shown higher SUV values in patients with osteomyelitis compared to those with Charcot foot, suggesting that SUV is a valuable parameter for differentiating these conditions [6]. Currently, this parameter is widely used in diagnosis of oncological diseases, for example, in the differential diagnosis of lung neoplasms. SUV is a crucial parameter and is broadly applicable in clinical practice [7].

There are new methods for quantitative assessment of hybrid SPECT/CT images using SUVs. One of these methods is xSPECT Quant, which has demonstrated accuracy and reproducibility with an error margin of up to 3% for standardized quantitative analysis of radionuclide images. The xSPECT Quant is applicable to Technetium-99m (99mTc) imaging and allows for clinical quantitative SPECT/CT assessment for more precise disease detection and improved therapeutic management [8].

Currently, there are no universally accepted interpreting criteria for differential diagnosis of inflammation, osteomyelitis, and Charcot foot. Quantitative analysis of hybrid SPECT/CT images holds promise for significantly improving the diagnosis of septic and aseptic lesions of the diabetic foot. This study is aimed at demonstrating that utilizing standardized uptake values can enhance diagnosis of complicated diabetic foot progression.

MATERIALS AND METHODS

The study design was prospective, non-randomized, and controlled. The study included 48 patients with DFS: 147 regions of radiopharmaceutical uptake were analyzed in 28 patients with septic lesions, 113 regions – in 20 patients with aseptic lesions, and 160 regions exhibiting normal bone metabolism. All patients were examined and treated at the clinics of Siberian State Medical University.

The study was conducted using a SPECT scanner (Siemens Symbia Intevo Bold), with an intravenous injection of the radiopharmaceutical (^{99m}Tc – pyrophosphate). The intensity of radiopharmaceutical uptake was evaluated using the SUV. The following types of SUV were distinguished: SUV Body Weight (SUVbw) – normalized by body weight; SUV Body Surface Area (SUVbsa) – normalized by body surface area; and SUV Lean Body Mass (SUVlbm) – normalized by lean body mass [9]. The analysis included maximum, mean, and peak SUV values.

Statistical data processing was performed using the Medcalc software (version 22.023). Descriptive statistics for quantitative variables not following normal

distribution were presented as the median and the interquartile range $Me\,[Q_1; Q_3]$. Intergroup comparisons were conducted using the non-parametric Mann – Whitney *U*-test, with a significance level set at $p < 0.05$. The ROC analysis was performed to evaluate the prognostic value of SPECT/CT parameters.

RESULTS

At the first stage of the study, SUVs across all three groups (areas of septic and aseptic inflammation, as well as regions with normal bone metabolism) were analyzed using the Kolmogorov – Smirnov test to assess the normality of distribution. The test results indicated that the distribution of the studied parameters was statistically significantly not normal. Consequently, the data were described using medians and interquartile ranges $Me\,[Q_1; Q_3]$ (Table 1–3), while non-parametric tests were employed for intergroup comparisons. Even though the data did not follow a normal distribution, the ROC analysis was used to evaluate diagnostic performance of the quantitative variables, since the ROC analysis itself does not require any specific data distribution.

Subsequently, SUVs of lesions (regardless of aseptic or septic origin) were compared with healthy bone tissues using the ROC analysis (Fig. 1–3).

Table 1

Standardized Uptake Values in Regions with Normal Bone Metabolism, $Me\,[Q_1; Q_3]$

Parameter	SUV bw	SUV lbm	SUV lbm janma	SUV bsa
Max	1.45 [1.01; 2.18]	1.00 [0.72; 1.43]	0.96 [0.67; 1.37]	0.34 [0.24; 0.50]
Mean	1.12 [0.69; 1.69]	0.81 [0.52; 1.14]	0.74 [0.48; 1.06]	0.27 [0.18; 0.39]
Peak	1.28 [0.91; 1.94]	0.92 [0.68; 1.29]	0.87 [0.64; 1.22]	0.32 [0.23; 0.47]

Table 2

Standardized Uptake Values in Areas with Septic Lesions, $Me\,[Q_1; Q_3]$

Parameter	SUV bw	SUV lbm	SUV lbm janma	SUV bsa
Max	11.17 [7.91; 17.32]	8.11 [5.48; 11.24]	7.27 [5.32; 10.89]	2.82 [1.99; 3.99]
Mean	9.18 [6.68; 13.69]	6.53 [4.51; 9.50]	6.21 [4.39; 9.32]	2.34 [1.63; 3.16]
Peak	9.73 [6.76; 14.91]	6.93 [4.50; 9.91]	6.41 [4.35; 9.74]	2.35 [1.61; 3.55]

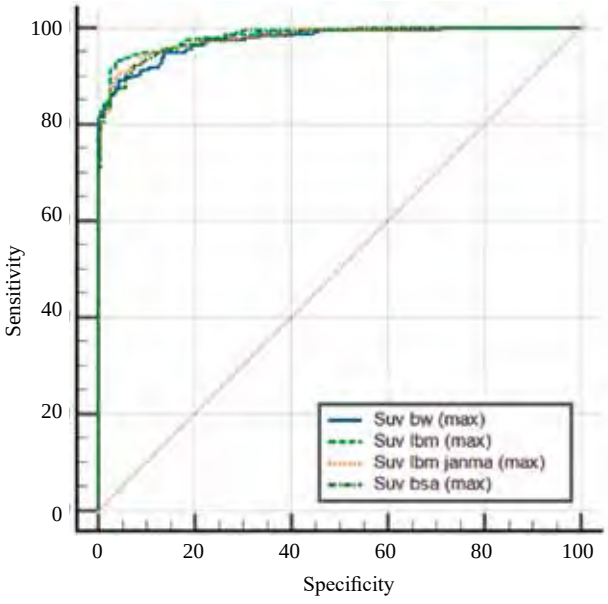


Fig. 1. Graph comparing ROC curves for maximum radiopharmaceutical SUVs: comparison of pathological areas with septic and aseptic inflammation with zones with normal bone metabolism – SUVmax. Here and in Fig. 2–5: X-axis – Specificity, Y-axis – Sensitivity

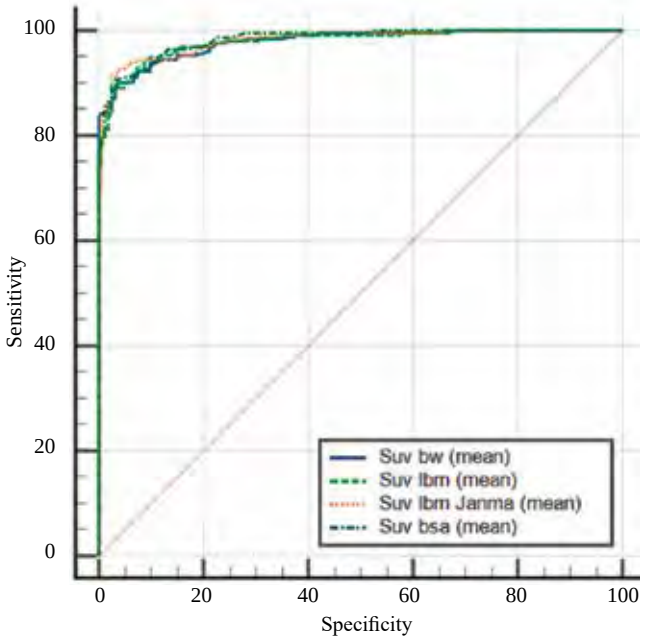


Fig. 2. Graph comparing ROC curves for mean radiopharmaceutical SUVs: comparison of pathological areas with septic and aseptic inflammation with zones with normal bone metabolism – SUVmean

Table 3

Standardized Uptake Values in Areas with Aseptic Lesions, *Me* [Q_1; Q_3]				
Parameter	SUV bw	SUV lbm	SUV lbm janma	SUV bsa
Max	5.84 [3.83; 7.84]	3.69 [2.78; 5.10]	3.59 [2.64; 4.90]	1.35 [0.88; 1.83]
Mean	4.80 [3.12; 6.24]	3.07 [2.09; 4.00]	2.94 [2.07; 3.89]	1.10 [0.71; 1.43]
Peak	4.91 [3.30; 6.80]	3.10 [2.22; 4.49]	3.13 [2.21; 4.31]	1.12 [0.77; 1.58]

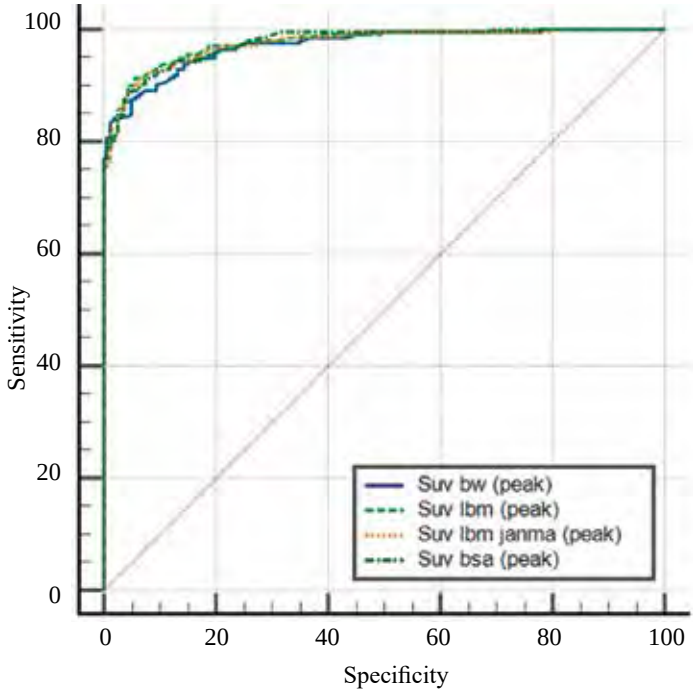


Fig. 3. Graph comparing ROC curves for peak radiopharmaceutical SUVs: comparison of pathological areas with septic and aseptic inflammation with zones with normal bone metabolism – SUVpeak.

Calculations revealed no statistically significant differences among the SUV parameters (Table 4). However, SUVlbm (max) demonstrated the largest area under the ROC curve (ROC AUC) and is suitable for establishing reference values.

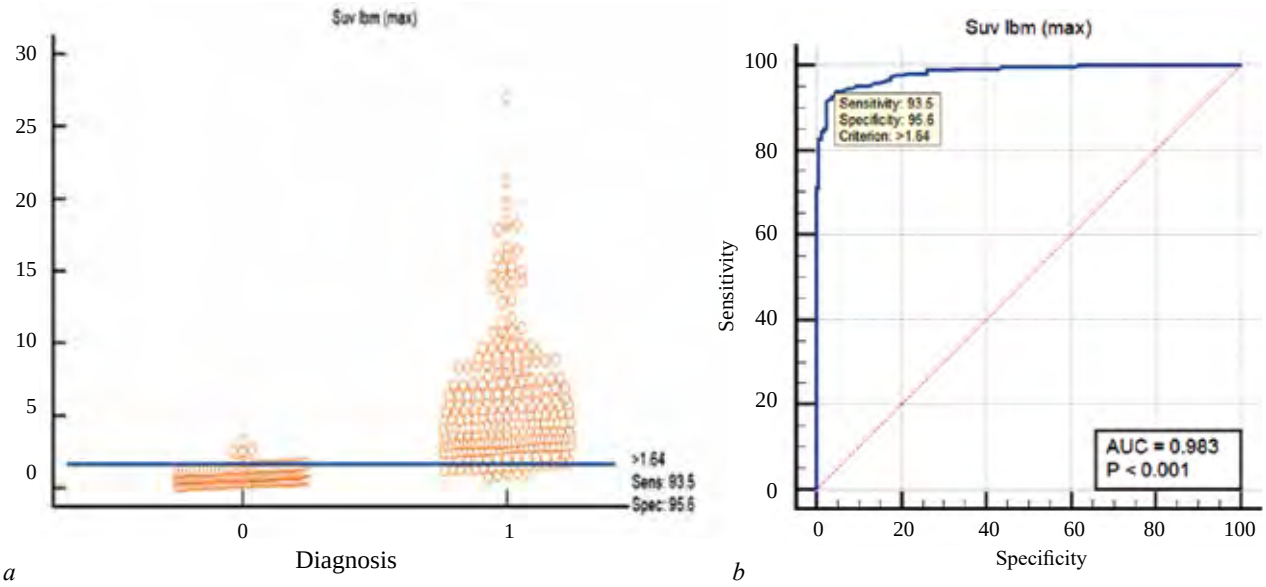
In the second stage of the study, the Mann – Whitney test revealed a statistically significant difference ($p < 0.05$) in SUVlbm (max) values in the pathological regions between patients with inflammation (septic/aseptic) and those with normal bone metabolism. Using the ROC analysis, a threshold value for SUVlbm (max) = 1.64 was established to differentiate inflammatory areas (septic or aseptic lesions) from areas with normal bone metabolism, with sensitivity (Sens) of 93.5% and specificity (Spec) of 95.6%, indicating that an uptake level at or above this threshold suggests inflammation (Fig. 4). The next stage of the study identified a threshold value for differential diagnosis of septic and aseptic bone inflammation in patients with diabetic foot syndrome (Fig. 5).

Table 4

Areas under the ROC Curves (ROC AUC) for Radiopharmaceutical SUVs				
Parameter	SUV bw	SUV lbm	SUV lbm janma	SUV bsa
Max	0.976	0.983	0.979	0.980
Mean	0.979	0.980	0.982	0.982
Peak	0.973	0.977	0.976	0.977

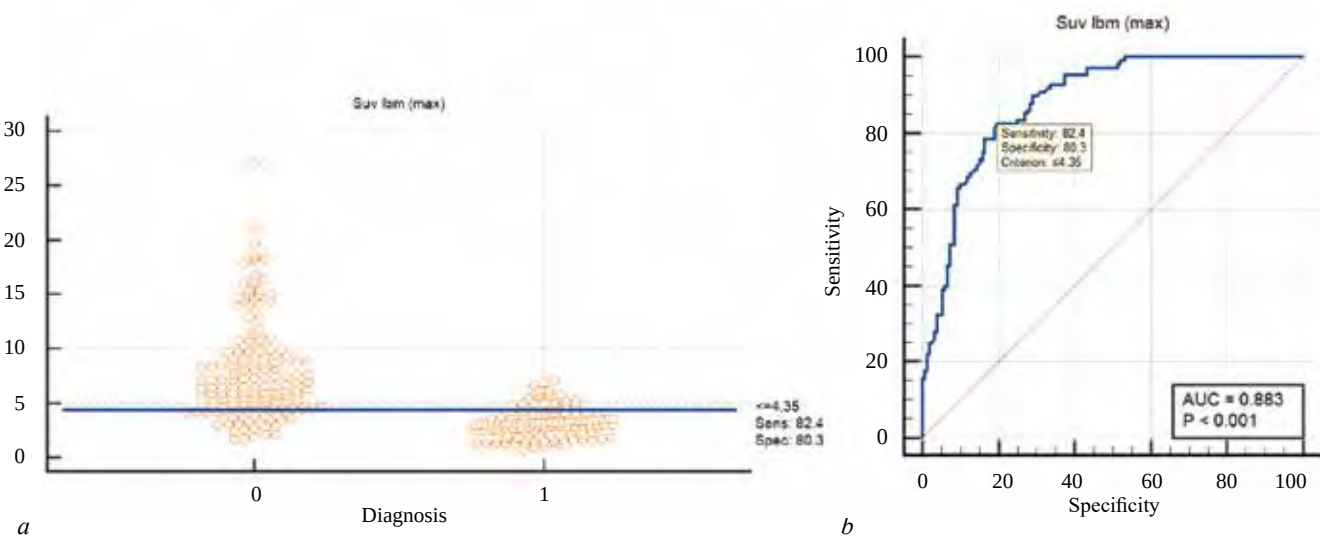
An uptake level equal to or exceeding 4.35 was associated with osteomyelitis, achieving sensitivity (Sens) of 82.4% and specificity (Spec) of 80.3%.

Below are clinical cases exemplifying septic and aseptic bone lesions in patients with type II diabetes mellitus. The cases presented similar clinical features, comparable DFS duration, and radiological evidence of destruction and disorganization of bone tissue in hindfoot (tarsal) and midfoot (metatarsal) regions. In patient N., as shown in Fig. 6, intense radiopharmaceutical hyperfixation was observed in cuneiform and metatarsal bones with SUVlbm (max) of 10.48, which exceeded the threshold of 4.35 and thereby confirmed osteomyelitis. Conversely, a clinical case of Charcot foot illustrating aseptic lesion in patients with DFS is presented in Fig. 7, where less intense radiopharmaceutical uptake (compared to septic lesions) with SUVlbm (max) = 3.87 was observed.



a *b*

Fig. 4. Results of comparing the difference in the radiopharmaceutical uptake in patients with diabetic foot syndrome (regardless of aseptic or septic lesions) and those with normal bone tissues: *a* – scatter chart showing coded areas (X-axis: 0 for normal radiopharmaceutical uptake, 1 for aseptic/septic bone lesions; Y-axis: standardized uptake value normalized by lean body mass); *b* – ROC curve illustrating differential diagnostic performance (X-axis – Specificity, Y-axis – Sensitivity)



a *b*

Fig. 5. Results of comparing the difference in radiopharmaceutical uptake in patients with diabetic foot syndrome with those with aseptic and septic lesions: *a* – scatter chart showing coded areas (0 for septic lesions, 1 for aseptic lesions; Y-axis: standardized uptake value normalized by lean body mass); *b* – ROC curve depicting differential diagnostic performance (X-axis – Specificity, Y-axis – Sensitivity)

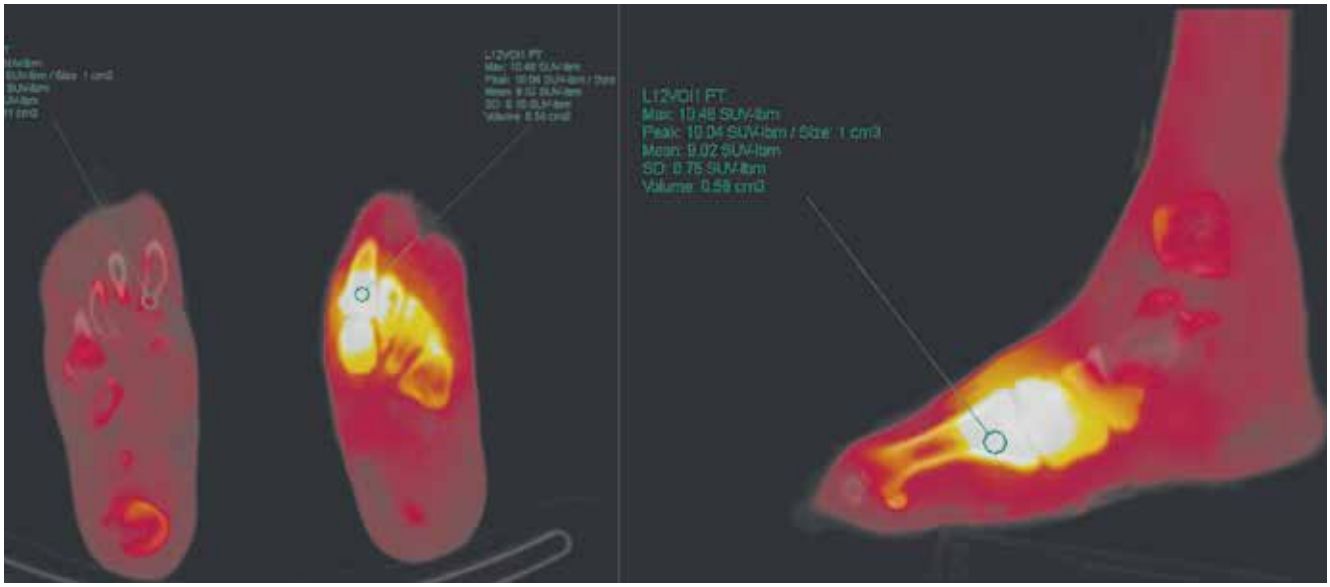


Fig. 6. Patient N., type II diabetes mellitus – osteomyelitis case: SPECT/CT images in axial and sagittal planes demonstrating intense radiopharmaceutical hyperfixation (SUVlbm (max) = 10.48) in medial cuneiform, base of first metatarsal, intermediate cuneiform, base of second metatarsal, stumps of third and fourth metatarsals, and base of fifth metatarsal – with signs consistent with marginal lytic lesion (septic lesion)

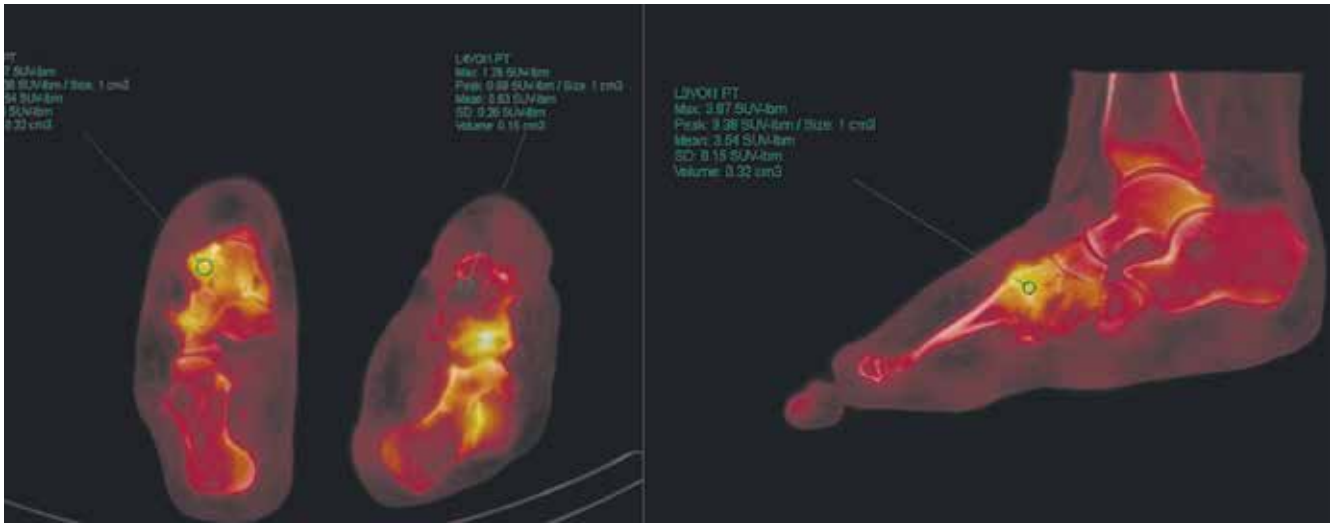


Fig. 7. Patient N. – Charcot foot case: SPECT/CT images in axial and sagittal planes showing intense radiopharmaceutical hyperfixation (SUVlbm (max) = 3.87) in ankle joint, Lisfranc and Chopart joints on the left foot. Similar, but less intense radiopharmaceutical hyperfixation is seen in Lisfranc and Chopart joints on the right foot indicating aseptic inflammation

DISCUSSION

The study evaluated the potential application of SUV in SPECT/CT imaging. It was established that SUV could assist in the differential diagnosis of septic and aseptic lesions of foot bones in patients with DFS.

The results of the study by M. Yoshiyuki [10] demonstrated high efficacy of SPECT/CT imaging using SUVs for the differential assessment of chronic osteomyelitis, osteoradionecrosis, and medication-related osteonecrosis of the jaw. K Kazuhiro et al. [11] investigated the use of osteoscintigraphy for dynamic evaluation of a treatment response in a patient with mandibular osteomyelitis, showing that quantitative SPECT/CT-derived parameters, such as SUV, can be useful for assessing inflammatory activity during therapy.

The clinical significance of these findings lies in the fact that utilizing the SUV in SPECT/CT imaging can serve as a diagnostic tool for osteomyelitis in patients with diabetic foot. This approach has the potential to reduce diagnostic and treatment times in this patient group.

CONCLUSION

This study analyzed the potential application of the standardized uptake value in SPECT/CT imaging for the differential diagnosis of septic and aseptic lesions of foot bones in patients with diabetic foot syndrome. The analysis demonstrated that standardized uptake values allow for the differentiation between inflammatory and non-inflammatory bone tissue lesions. SUVlbm (max) values exceeding 5 are associated with septic inflammation, supporting the clinical utility of this parameter. The data obtained indicate that the standardized uptake value in SPECT/CT imaging possesses high information value for diagnosing osteomyelitis in diabetic foot, which may facilitate more accurate choice of a treatment strategy and reduce the number of invasive procedures.

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Author Contribution

Balabenko A.O. – examination of patients, analysis and statistical processing of the data, drafting of the manuscript. Udodov V.D. – conception and design, examination of patients, editing of the manuscript. Zamyshevskaya M.A., Zorkaltsev M.A. – conception and design. Zavadovskaya V.D. – final approval of the manuscript for publication.

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