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LOW-ENERGY VERTEBRAL COMPRESSION FRACTURES: DIFFERENTIAL DIAGNOSIS BETWEEN OSTEOPOROTIC AND MALIGNANT FRACTURES BY INFLAMMATORY BIOMARKERS

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ABSTRACT

Objective: Spontaneous or low-energy vertebral compression fractures are encountered in clinical practice and pose a diagnostic challenge. This study aimed to determine the role of systemic inflammatory markers in the differential diagnosis of malignant and osteoporotic vertebral fractures (MVF and OVF).

Materials and Methods: Patients who underwent surgical treatment for OVF and MVF at our center were retrospectively analyzed. Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic inflammatory index (SII) values were calculated using complete blood count data obtained before treatment. Optimal cut-off values were determined for the differentiation of OVF and MVF. The results were correlated with the histopathological and surgical findings.

Results: The study was conducted with 72 patients, 73.6% (n=53) of whom were women and 26.4% (n=19) were men. Of the patients participating in the study, 63.9% (n=46) had OVF and 36.1% (n=26) had MVF. The mean age of the OVF group (69.93±15.52) was significantly higher than that of the MVF group (56.38±19.76) (p=0.001; p<0.01). Furthermore, the ratio of women in the OVF group (84.8%) was significantly higher than that in the MVF group (53.8%) (p=0.006; p<0.01). The lymphocyte measurements of the MVF group were significantly lower than those of the OVF group (p=0.029; p<0.05). The PLR (p=0.026; p<0.05), NLR (p=0.009; p<0.01), and SII (p=0.007; p<0.01) measurements were significantly higher in the MVF group than in the OVF group.

Conclusion: Our study found significantly elevated levels of inflammatory markers (NLR, PLR, SII) in MVF compared with OVF. These findings suggest that NLR, PLR, and SII hold promise as concise and effective tools for the differential diagnosis of low-energy vertebral compression fractures.

Keywords: Vertebral fractures, Neutrophil-to-Lymphocyte ratio, Platelet-to-Lymphocyte ratio, Metastasis, inflammatory markers

INTRODUCTION

Vertebral compression fractures occur because of various reasons, such as trauma, osteoporosis, infection, and tumor. While these fractures can occur with high energy, such as in trauma, they can also occur with low energy in the presence of osteoporosis, infection, and malignancy. In low-energy vertebral compression fractures, it is necessary to determine whether the underlying cause is malignancy or a benign cause, such as osteoporosis or infection.

Identifying whether a vertebral fracture is due to a benign or malignant cause is important for approaching the patient because the clinical course, prognosis, and treatment strategies vary greatly. Moreover, early detection of malignancy can profoundly improve the success of the treatment and increase the overall survival[1]. The differential diagnosis is usually based on anamnesis, physical examination, clinical findings, localization, and radiological imaging findings. Magnetic resonance imaging (MRI) plays an important role in the differential diagnosis of such lesions. However, primary malignant tumors, metastatic malignancies, acute benign and malignant vertebral fractures (MVF), and infectious conditions present with similar signal changes on routine MRI[2]. A definitive diagnosis can be made in this case using pathological examination via biopsy. However, it is an invasive procedure.

In addition to the clinical and radiological approach, laboratory tests that can be used in the diagnosis of malignancy have long been the subject of research. So far, researchers have explored various sources of blood-based biomarkers in their quest to identify the most suitable biomarker for early-stage cancer detection[3]. Although there has been no consensus on a definitive and reliable parameter so far, the presence and role

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of inflammatory biomarkers in tumor physiopathology have been widely studied in recent years.

The importance of chronic inflammation in the pathogenesis and progression of various cancers has been demonstrated in many studies[4-6]. Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic inflammatory index (SII) are known markers of the systemic inflammatory response and have been used to determine the diagnosis and prognosis of several musculoskeletal tumors[7-11], as well as being associated with spinal tumoral pathologies[12]. Similarly, there are studies on biomarkers for early diagnosis of osteoporosis[13-17]. However, the importance of inflammatory markers in differentiating MVF from osteoporotic vertebral fracture (OVF) has not been evaluated. Therefore, this study aimed to differentiate MVF from OVF of the spine using inflammatory biomarkers.

MATERIALS AND METHODS

Ethics committee approval of Atlas University Non-interventional Scientific Research (approval number: E-22686390-050.99-28169/14.06.2023) was obtained, and the study was conducted according to the principles of the Declaration of Helsinki.

Inclusion criteria: Low energy or spontaneous OVFs and MVFs were included in the study. The exclusion criteria are as follows: Vertebral fractures due to infection and other benign causes, leukocytosis and elevated C-reactive protein levels, absence of pathological data, rheumatologic, hematologic, or inflammatory diseases, steroid and anti-inflammatory drug use, non-vertebral invasion or metastasis, and previous diagnosis and treatment of malignancy.

A total of 123 low-energy or spontaneous vertebral fractures diagnosed and surgically treated in our hospital between 2011 and 2022 were retrospectively analyzed. Accordingly, 51 patients who did not meet the inclusion criteria were excluded from the study. A total of 72 patients with fracture were included in the study and evaluated.

Age, sex, pathological diagnosis, cause of fracture, and blood parameters before treatment were analyzed. Clinical and demographic data of the patients were obtained from hospital records.

Neutrophil, lymphocyte, and platelet counts obtained from a complete blood count taken before the treatment were evaluated. NLR was obtained by dividing the neutrophil count by the lymphocyte count, and PLR was obtained by dividing the platelet count by the lymphocyte count. SII was obtained by multiplying the neutrophil count and platelet count and dividing this value by the lymphocyte count. The patients were categorized into two groups, i.e., OVF and MVF. Results were correlated with histopathological and surgical findings.

Statistical Analysis

While evaluating the findings obtained in the study, Statistical Package for the Social Sciences, Version 26, program was used for statistical analysis. For descriptive statistics, quantitative variables were represented as mean, standard deviation, median, and minimum and maximum values. On the contrary, qualitative variables were represented as frequency and percentage. Shapiro-Wilk test and box plot graphs were used to evaluate the conformity of the data to normal distribution. Student's t-test was used to evaluate quantitative data with normal distribution between two groups. Mann-Whitney U test was used to evaluate non-normally distributed variables between two groups. Receiver operating characteristic curve (ROCC) analysis was used to predict malignancy. Chi-square test was used to compare qualitative data. Results were evaluated at a 95% confidence interval, and $p<0.05$ was accepted as statistically significant in all analyses.

RESULTS

This study was conducted at the Atlas University Medicine Hospital between 2012 and 2022 with a total of 72 patients, 73.6% (n=53) of whom were women and 26.4% (n=19) were men. The age of the patients ranged between 17 years and 98 years, with a mean of 62.48±17.65 years. When the diagnoses of the patients who participated in the study were analyzed, 63.9% (n=46) were OVF and 36.1% (n= 26) were MVF (Table 1). The OVF group had a significantly higher age ($p=0.001$; $p<0.01$) and a significantly higher female: male ratio ($p=0.006$; $p<0.01$) (Table 1).

Of the patients with MVF, 4 (12.5%) were cervical, 15 (46.8%) were thoracic, and 17 (53.1%) were lumbar. Four patients had involvement of multiple vertebrae. Of the patients with OVF, 27 (50.0%) were thoracic and 30 (55.5%) were lumbar. Seven patients had multiple fractures.

In the MVF group, the cause of fractures was determined to be metastasis in 19 patients, primary bone tumor in 4 patients, and multiple myeloma in 3 patients. In the OVF group, 5 patients underwent instrumented fusion and 41 patients underwent

Table 1. Comparison of descriptive characteristics by diagnosis

		Total (n=72)	OVF (n=46)	MVF (n=26)	p-value
Sex	**Women**	53 (73.6)	39 (84.8)	14 (53.8)	[a]**0.006****
	Men	19 (26.4)	7 (15.2)	12 (46.2)	
Age (years)	Mean ± SD	62.48±17.65	69.93±15.52	56.38±19.76	[b]**0.026**
	Median (min.-max.)	64.5 (17-98)	67.5 (19-98)	58 (17-87)	

[a]Pearson chi-square test, [b]Student's t-test, **p<0.01, SD: Standard deviation, OVF: Osteoporotic vertebral fracture, MVF: Malignant vertebral fracture, min.: Minimum, max.: Maximum

vertebroplasty. In the MVF group, 20 patients underwent instrumented fusion and 6 patients underwent vertebroplasty.

The lymphocyte measurements of the MVF group were statistically significantly lower than those of the OVF group (p=0.029; p<0.05). PLR (p=0.026; p<0.05), NLR (p=0.009; p<0.01), and SII (p=0.007; p<0.01) values were statistically significantly higher in the MVF group than those in the OVF group. According to the diagnoses, platelet and neutrophil counts of the patients did not show a statistically significant difference (p>0.05) (Table 2).

For predicting malignancy, a cut-off value of 1.76 for lymphocyte count had a sensitivity of 76.92%, specificity of 67.39%, positive predictive value of 57.10%, and negative predictive value of 83.80%. In the receiver operating characteristic ROOC obtained, the underlying area was 68.1% with a standard error of 6.7%. There was a statistically significant correlation between lymphocyte count with a cut-off value of 1.76 and malignancy (p=0.011; p<0.05). However, there was no statistically significant correlation between PLR value and malignancy (p=0.053; p>0.05).

For predicting malignancy, a cut-off value of 2.42 for NLR had a sensitivity of 53.85%, specificity of 78.26%, positive predictive value of 58.30%, and negative predictive value of 75%. In the ROCC obtained, the underlying area was 67.1% with a standard error of 6.8%. There was a statistically significant correlation between NLR level with a cut-off value of 2.42 and malignancy (p=0.017; p<0.05).

For predicting malignancy, a cut-off value of 483.52 for SII had a sensitivity of 69.23%, specificity of 60.87%, positive predictive value of 50%, and negative predictive value of 77.80%. In the ROCC obtained, the underlying area was 65.1% with a standard error of 7.2%. There was a statistically significant correlation between SII with a cut-off value of 483.52 and malignancy (p=0.035; p<0.05) (Table 3) (Figure 1).

DISCUSSION

In this study, the role of inflammatory markers in the differential diagnosis between MVF and OVF was investigated. The results showed that systemic inflammatory biomarkers measured in peripheral blood samples collected before treatment had an important diagnostic value in this differentiation.

When malignancy develops, the immune system components, including neutrophils, platelets, and lymphocytes, can be impacted[18]. Tumors induce an inflammatory response, triggering increased neutrophil production and release into the bloodstream, potentially contributing to neutrophilia in cancer patients[19,20]. In our series, the neutrophil count was higher in the MVF group compared to the OVF group, although not statistically significant. Platelets play a crucial role in malignancy by influencing tumor angiogenesis, growth, and metastasis. The intricate interaction between platelets and

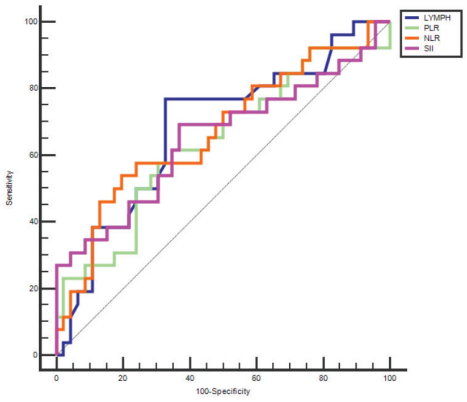

Figure 1. ROCC for predicting malignancy

LYMPH: Lymphocyte, PLR: Platelet-to-lymphocyte ratio, NLR: Neutrophil-to-lymphocyte ratio, SII: Systemic inflammatory index, ROCC: Receiver operating characteristic curve

Table 2. Comparison of measurement values according to diagnoses

		Total	OVF (n=46)	MVF (n=26)	p-value
PLT	Mean ± SD	233.45±74.24	239.63±78.37	222.53±66.35	[a]0.351
	Median (min.-max.)	214 (85-458)	223.5 (85-458)	208 (107-370)	
LYMPH	Mean ± SD	1.87±0.71	2.01±0.71	1.63±0.66	[a]0.029*
	Median (min.-max.)	1.8 (0.5-3.6)	1.9 (0,5-3.6)	1.6 (0.6-2.9)	
NEUT	Mean ± SD	3.66±1.57	3.48±1.42	3.99±1.78	[a]0.183
	Median (min.-max.)	3.5 (0.3-7.5)	3.4 (0.3-6.4)	4.2 (1.2-7.5)	
PLR	Mean ± SD	137.65±54.15	127.04±39.13	156.42±70.69	[a]0.026*
	Median (min.-max.)	122.5 (43.2-368.3)	119 (71.2-220.6)	149.1 (43.2-368.3)	
NLR	Mean ± SD	2.30±1.55	1.95±1.07	2.93±2.02	[b]0.009**
	Median (min.-max.)	2 (0.2-9.4)	1.7 (0.2-5.6)	2.6 (0.4-9.4)	
SII	Mean ± SD	522.35±336.65	442.97±204.69	662.80±462.97	[a]0.007**
	Median (min.-max.)	483.1 (32.7-1987.5)	464.9 (32.7-754.1)	590.3 (51.9-1987.5)	

[a]Student's t-test, *p<0.05, **p<0.01, SD: Standard deviation, OVF: Osteoporotic vertebral fracture, MVF: Malignant vertebral fracture, PLT: Platelet, LYMPH: Lymphocyte, NEUT: Neutrophil, PLR: Platelet-to-lymphocyte ratio, NLR: Neutrophil-to-lymphocyte ratio, SII: Systemic inflammatory index, min.: Minimum, max.: Maximum

malignant diseases leads to altered platelet function and properties, contributing to an accelerated progression of cancer[21,22]. Lymphocytes, essential for antitumor immunity, engage in attacking and eliminating tumor cells within the microenvironment. Prolonged exposure to this environment may lead to lymphocyte depletion, impacting their effectiveness and correlating with poor prognostic outcomes in cancer, although some inconsistencies exist in pre-treatment lymphocyte counts' predictive value[21].

In the light of this information, markers such as NLR, PLR, and SII are expected to vary in inflammation-related events, including malignancy. Indeed, NLR and other values have been reported to be high in many studies on malignancy. However, some studies have reported that the reason for the increase in NLR in these multicomponent ratios is the decrease in lymphocytes rather than neutrophils[23,24]. Similarly, in the present study, lymphocyte ratios were found to be significantly lower in the MVF group.

Studies have shown that inflammatory biomarkers can be used in the diagnosis and prognosis of malignancy[9,10,25,26]. In a study evaluating all spinal tumors, including bone and soft tissue tumors, in 503 patients, NLR and PLR were found to be valuable markers for preoperative diagnosis and differentiation of primary and secondary tumors. Cut-off values for NLR (>3.19) and PLR (>141) were also reported to be associated with a high risk of malignancy[12]. In their study, Caliskan and Korkmaz[7] analyzed patients for whom scintigraphy was recommended for suspected bone metastasis and compared the results with NLR values. Accordingly, NLR was found to be higher in the group with bone metastasis. In this group, the median neutrophil count was 4.9 (range: 3.1-10.8), median lymphocyte count was 1.6, and NLR was 2.5[7]. In our series, the median neutrophil count was 4.2 (1.2-7.5), median lymphocyte count was 1.6 (0.6-2.9), and median NLR was 2.6 (0.4-9.4).

In addition to malignancies, different biomarkers have been investigated for the early detection of osteoporosis[27]. The pathogenesis of postmenopausal osteoporosis (PMO) has long been recognized to be closely related to immune system dysfunction and systemic inflammation, with T cells, neutrophils, and platelets playing a role in the mechanism of the relationship between osteoporosis and immunity[28-30]. Several publications have reported that NLR levels are elevated in elderly people with osteoporosis[16,17,31-33]. T cells, notably Th17 cells promoting osteoclast formation and Treg cells inhibiting bone loss, play a crucial role in the regulation of bone resorption[34,35]. These findings indicate that an imbalance in the immune system contributes to bone loss by fostering osteoclast formation[36]. There is literature evidence that platelets are active in osteoporosis. Elevated inflammatory stimuli initiate platelet activation[37], and activated platelets influence osteoclast formation via receptor activation, which affects prostaglandin and RANKL signaling[38]. Furthermore, thromboxanes and other mediators secreted by activated platelets can increase inflammation as a result of this process[37].

The literature encompasses numerous studies investigating the association between osteoporosis and various biomarkers. Yolaçan and Guler[39] assessed 148 Turkish women with PMO and observed an inverse correlation between NLR, PLR, MLR, and SII values and alterations in bone mineral density (BMD), suggesting their potential role in early diagnosis. While some authors reported a correlation, others did not detect any significant association[13-17,32,33,39]. Koseoglu[15], categorizing postmenopausal patients into normal and low BMD groups, found an inverse relationship between PLR and BMD. However, no statistically significant relationship was observed between NLR and BMD[15]. In our present study, the mean PLR was 119 (range: 71.2-220.6) in the OVF group and 149.1 (range: 43.2-368.3) in the MVF group. Additionally, the mean NLR was 1.95±1.07 in the OVF group and 2.93±2.02 in the MVF group.

A review of the literature showed that NLR, PLR, and SII are increased in both malignancy and osteoporosis. In Tables 4 and 5, our results in osteoporosis and malignancy groups are compared with similar studies in the literature[40-45]. Of the studies in the literature investigating the relationship between several biomarkers and osteoporosis and bone malignancies, a considerable number of studies have reported that certain biomarkers are not associated with osteoporosis and malignancy[14,17]. In the present study, the primary comparison was not based on normal values but rather on the distinction in biomarker ratios resulting from the two pathologies. In other words, we compared the NLR, PLR, and SII values between OVF and MVF. The findings revealed statistically significant elevations in NLR, PLR, and SII in MVF compared to OVF. In

Table 3. Diagnostic screening tests and ROCC results for lymphocyte, PLR, NLR, and SII in predicting malignancy

	Diagnostic scan					ROCC		
	Cut-off	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area	95% confidence interval	p-value
LYMPH	⩽1.76	76.92	67.39	57.10	83.80	0.681	0.550-0.812	0.011*
PLR	⩾137.98	57.69	67.39	50.00	73.80	0.638	0.500-0.776	0.053
NLR	⩾2.42	53.85	78.26	58.30	75.00	0.671	0.536-0.805	0.017*
SII	⩾483.52	69.23	60.87	50.00	77.80	0.651	0.509-0.792	0.035*

*p<0.05, LYMPH: Lymphocyte, PLR: Platelet-to-lymphocyte ratio, NLR: Neutrophil-to-lymphocyte ratio, SII: Systemic inflammatory index, ROCC: Receiver operating characteristic curve

Table 4. Comparison of malignant cases in our sample with similar studies in the literature. Measurements are shown in the table as mean ± SD, median (min.-max.), and median (Q1-Q3)

Author of the article	Disease	Number of patients	NLR	PLR	SII
Caliskan and Korkmaz[7] median (min.-max.)	Various malignancies with bone metastases	25	2.83 (1.56-31.8)		
Li et al.[12]	Malignant spine tumors	262	3.31 (0.41, 18.82)	150.31 (16.84, 548.00)	
Chen et al.[40]	Hepatocellular carcinoma bone metastases	239	4.73 (IQR, 2.38-6.00)	163.56 (IQR, 95.12-196.67)	705.05 (IQR, 298.28-783.23)
Xia et al.[41] median (min.-max.)	Osteosarcoma	359	3.19 (0.79-74.49)	142 (5.4-3111)	
Thio et al.[8]	Various malignancies with bone metastases	1012	6.4 (IQR 3.6-11.8)	283 (IQR, 174-452)	
Wang et al.[42] Mean ± SD	Bone metastasis in patients with prostate cancer	67	2.83±0.55	127.89±29.28	
Yapar et al.[9] median (min.-max.)	Enchondroma and low-grade chondrosarcoma	101	2.54 (1.12-7.46)		
This study mean ± SD median (min.-max.)	Various malignancies, pathological vertebral fracture	26	2.93±2.02 2.6 (0.4-9.4)	156.42±70.69 149.1 (43.2-368.3)	662.80±462.97 590.3 (51.9-1987.5)

SD: Standard deviation, PLR: Platelet-to-lymphocyte ratio, NLR: Neutrophil-to-lymphocyte ratio, SII: Systemic inflammatory index, IQR: Interquartile range, min.: Minimum, max.: Maximum

Table 5. Comparison of osteoporosis cases in our sample with similar studies in the literature. Measurements are shown in the table as mean ± SD, median (min-max), and median (Q1-Q3)

Author of the article	Disease	Number of cases	NLR	PLR	SII
Eroglu and Karatas[13]	PMO	48	1.71 (0.81-8.9)	134 (52.89-385)	
Yolaçan and Guler[39]	PMO	148	2.3±0.81	149.9±54.9	641.2±362.7
Kale[43]	PMO	48	1.91±0.74	132.83±29.4	
Al Salmani et al.[44]	PMO	221	1.19 (0.20-4.43)	131.47 (39.74-256.92)	
Onalan and Gokalp[45]	Osteoporosis	169	3.5±4.2	179.2±130.7	
Qin et al.[31]	Osteoporosis	29	2.11±0.73		
Huang and Li[14]	PMO	122	2.74±1.06		
Koseoglu[15]	PMO	179	1.9±0.7	136.3±50.4	
This study mean ± SD median (min.-max.)	Osteoporosis	46	1.95±1.07 1.7 (0.2-5.6)	127.04±39.13 119 (71.2-220.6)	442.97±204.69 464.9 (32.7-754.1)

SD: Standard deviation, PLR: Platelet-to-lymphocyte ratio, NLR: Neutrophil-to-lymphocyte ratio, SII: Systemic inflammatory index, PMO: Postmenopausal osteoporosis, min.: Minimum, max.: Maximum

general, when examining NLR, PLR, and SII values in literature series, it is evident that NLR, PLR, and SII values of patients with malignancy are higher than those of patients with osteoporosis. This observation supports the conclusions reached in the present study.

This study has important strengths. To the best of our knowledge, this is the first study to examine the association of inflammatory markers with spontaneous low-energy vertebral fractures. Furthermore, the association between osteoporotic and pathological fractures and inflammatory markers was also evaluated. Lastly, the study examined the role of inflammatory markers in differentiating osteoporosis from malignancy in the etiology of this type of vertebral fractures.

Study Limitations

The number of patients with MVF evaluated in this study was relatively low, which is due to the rarity of such cases. Furthermore, we could not create more similar groups in terms of age, sex, and comorbidity. Working with a larger dataset and

selecting groups with similar characteristics are necessary for the results to be more reliable and meaningful.

Furthermore, although statistically significant, the sensitivity and specificity of inflammatory biomarkers are low. Systemic inflammatory biomarkers are non-specific predictors of MVF and OVF, which is one of their main disadvantages. Lastly, the study was retrospective and conducted in a single center. Multicenter prospective studies are required.

CONCLUSION

This study showed that MVF has a higher level of increased inflammation than OVF. The main aim of this study was to investigate the usefulness of such a relationship in distinguishing between MVF and OVF. Our results support that such an approach can be used for the differential diagnosis of MVF and OVF. In conclusion, systemic inflammatory biomarkers have diagnostic value in differentiating MVF from OVF. Although these markers are not reliable on their own, when used in combination with other medical tests, they can make an important contribution to pretreatment assessment. Moreover, they have practical and cost advantages, making them preferred markers.

When faced with a low-energy vertebral fracture, it is important to examine parameters such as NLR, PLR, and SI, which can be easily measured in any medical center. If these values are high, the probability of an underlying malignancy increases.

Ethics

Ethics Committee Approval: Ethics committee approval of Atlas University Non-interventional Scientific Research (approval number: E-22686390-050.99-28169/14.06.2023) was obtained, and the study was conducted according to the principles of the Declaration of Helsinki.

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: H.D., A.O.M., D.A., N.D., H.A., Concept: H.D., Design: H.D., D.A., Data Collection or Processing: N.D., Analysis or Interpretation: H.A., Literature Search: H.D., A.O.M., Writing: H.D., A.O.M.

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