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Neutrophil-lymphocyte ratio (NLR) e *platelet-lymphocyte ratio* (PLR) podem ser indicadores de prognóstico para complicações operatórias e sobrevida em metástases ósseas?

Can neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) be prognostic indicators for operative complications and survival in bone metastases?

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ABSTRACT

Introduction: In general, inflammation stimulates the production and release of neutrophils and, at the same time, decreases the production of lymphocytes. Lymphopenia reflects that cell-mediated immunity is impaired, while neutrophilia represents a response to systemic inflammation in these cancers.

Objective: To review the incidence of complications and postoperative survival rates in patients with bone metastases in long bones, correlating them with markers NLR and PLR.

Method: Narrative review carried out collecting information published on virtual platforms in Portuguese and English, initially carried out by searching for descriptors related to the topic, which were: "lower extremity, surgery, metastasis, epidemiology, postoperative complications, neutrophils, lymphocytes, platelets". The extension incorporated AND or OR, by title and/or summary, and full reading of the texts most related to the topic.

Result: 23 articles were included.

Conclusion: The higher both the NLR and PLR are associated with lower survival in patients with bone metastases when undergoing surgical treatment, especially after 3 months postoperatively. However, there is still no confirmation that they signal any outcome, favorable or not, in relation to postoperative complications.

KEYWORDS: Lower extremity. Surgery. Metastasis. Epidemiology. Survival. Complications. Neutrophils. Lymphocytes. Blood Platelet.

Central Message

Life expectancy in metastatic bone disease varies according to the primary cancer, and different types have specific survival rates. Thus, reviewing the incidence of complications and postoperative survival in patients with bone metastasis in long bones, correlating them with the prognostic markers NLR and PLR, is still under discussion, but it is pertinent. This is the approach of this review.

Perspective

The higher the SLN and PLR are associated with lower survival in patients with bone metastasis when undergoing surgical treatment, especially after 3 months postoperatively. However, there is still no confirmation that they signal any outcome, favorable or not, in relation to postoperative complications.

RESUMO

Introdução: De um modo geral, a inflamação estimula a produção e liberação de neutrófilos e, ao mesmo tempo, diminui a produção de linfócitos. A linfopenia reflete que a imunidade mediada por células está prejudicada, enquanto a neutrofilia representa resposta à inflamação sistêmica nesses cânceres.

Objetivo: Revisar nos pacientes com metástase óssea em ossos longos a incidência de complicações e taxas de sobrevida pós-operatória correlacionando-as com os marcadores NLR e PLR.

Método: Revisão narrativa feita colhendo informações publicadas em plataformas virtuais em português e inglês inicialmente realizada por busca dos descritores relacionados ao tema que foram: "extremidade inferior, cirurgia, metástase, epidemiologia, complicações pós-operatórias, neutrófilos, linfócitos, plaquetas" e seus equivalentes em inglês "lower extremity, surgery, metastasis, epidemiology, survival, complications, neutrophils, lymphocytes, blood platelet". A extensão incorporou AND ou OR, pelo título e/ou resumo, e leitura na íntegra dos textos mais relacionados ao tema.

Resultado: Foram incluídos 23 artigos.

Conclusão: Quanto maiores, tanto o NLR quanto o PLR estão associados à menor sobrevida em pacientes com MO quando submetidos ao tratamento cirúrgico, especialmente após 3 meses de pós-operatório. Contudo, não há ainda confirmação de que eles sinalizem algum desfecho, favorável ou não, em relação às complicações pós-operatórias.

PALAVRAS-CHAVE: Extremidade inferior. Cirurgia. Metástase. Epidemiologia; Complicações pós-operatórias. Neutrófilos. Linfócitos. Plaquetas.

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INTRODUCTION

Advances in adjuvant and neoadjuvant therapies, especially chemotherapy and hormone therapy, have improved the survival of cancer patients and increased the prevalence of bone metastases (BM). Their presence is the main cause of morbidity in those with advanced disease1 and, therefore, their control is essential for improving the patient's quality of life, pain, and maintaining independence.[2] The treatment of bone metastases is vast and multidisciplinary, including clinical and/or surgical measures. Gallaway3 observed that 13.[1%] of 1154 patients had 1 or more complications within 30 days of the operation for treatment of extremity OM.[3]

For a comprehensive assessment of the possible benefits of surgery, it is critical to understand life expectancy and weigh the benefits against the morbidity associated with the surgical procedure. Several prognostic tools have been proposed to assist in predicting life expectancy. While these tools are useful, there is scope to improve their accuracy as new factors become available.[4]

The inflammatory response plays a decisive role in different stages of tumor development, including initiation, promotion, malignant conversion, invasion, and metastasis. Recent studies show that metastasis requires close collaboration between cancer cells, immune cells, inflammatory cells, and stromal elements.[5] Generally speaking, inflammation stimulates the production and release of neutrophils and, at the same time, decreases the production of lymphocytes. Lymphopenia reflects that cell-mediated immunity is impaired, while neutrophilia represents a response to systemic inflammation. Many studies have shown that an increase in the NLR (neutrophil-to-lymphocyte ratio) is associated with lower survival in patients with various neoplasms; in turn, the PLR (platelet-to-lymphocyte ratio) has been gaining prognostic value in these cancers.[6] However, it is still necessary to understand the mechanisms of the interaction between cancer and circulating inflammatory components.[4]

Thus, the present study aimed to review clinical and surgical aspects of patients with bone metastasis in long bones, seeking to identify the incidence of complications, postoperative survival rate, and the role of NLR and PLR with complications and survival at 1 year postoperatively.

METHOD

The literature review was carried out by collecting information published on virtual platforms in Portuguese and English. The material for reading and analysis was selected from the SciELO – Scientific Electronic Library Online, Google Scholar, Pubmed and Scopus platforms. Initially, a search was carried out for descriptors related to the theme, which were identified through DeCS using the following terms: "lower extremity, surgery, metastasis, epidemiology, postoperative complications, neutrophils, lymphocytes, platelets" with AND or OR search, considering the title and/or abstract. Afterwards, separating only those that had a greater relationship with the theme, the full texts were read and finally 24 articles were included.

DISCUSSION

Metastatic bone disease is a common and challenging complication faced by cancer patients, accounting for more than 99% of malignant tumors affecting the bones and affecting about 280,000 patients annually.[7,8the] clinical courses of patients are prolonged and often accompanied by morbidity due to bone metastases. Skeletal-related events (SREs Among the sites most frequently affected by them, bones occupy the 3rd place, behind only lung and liver metastases.[1]

The most affected age group and gender are women over 40 years old.[7] They usually occur hematogenously, with preference reaching the spine in up to 87% of cases, followed by the pelvis (63%), femur and proximal humerus (53%).[1,7the] clinical courses of patients are prolonged and often accompanied by morbidity due to bone metastases. Skeletal-related events (SREs).

The incidence of BM varies among different types of cancer. Breast, prostate, and lung carcinomas are the most prevalent, accounting for about 80% of patients. The relative incidence ranges from 65-75% for breast and prostate cancer, 30-40% for lung cancer, 40% for bladder, 20-25% for renal cells, and 14-45% for melanomas.[9]

Hernadez[10] found that the incidence of OM tends to increase with the time of diagnosis of the primary tumor. About 2.9% in 30 days, 4.8% in the 1st year, 5.6% in the 2nd, 6.9% in the 5th and 8.4% in 10 years after diagnosis.

The radiological pattern of BM is inherent to the primary tumor. Osteolytic lesions, characterized by the destruction of normal bone, are frequent in patients with multiple myeloma, thyroid cancer, renal cell carcinoma, non-small cell lung cancer, melanoma, among others. On the other hand, osteoblastic lesions involve the deposition of new bone tissue and are more common in prostate cancer, Hodgkin's lymphoma, and small cell lung tumors. There are also mixed cases, in which the lesions exhibit osteolytic and osteoblastic characteristics, and are found mainly in patients with breast or gastrointestinal tract cancer.[9]

Life expectancy in metastatic bone disease varies according to the primary cancer, and different types have specific survival rates. For example, survival can be 6 months in melanoma, 6-7 months in lung cancer, 6-9 months in bladder cancer, 12 months in renal cell cancer, 12-53 months in prostate cancer, 19-25 months in breast cancer, and 48 months in thyroid cancer. Patients with breast cancer have an 85% survival rate at 5 years.[11]

The evolution of metastases from solid tumors to the bones is a complex process, which involves the formation of premetastatic niches, the spread of tumor cells through the circulation, the chemotactic attraction and the targeting of tumor cells to the

metastatic site, in addition to reciprocal interactions with local stromal cells and immune cells within the bone microenvironment. The unique environment of specialized bone cells (osteoclasts, osteoblasts and osteocytes), mineralized bone matrix and other types of cells within the bone, offers fertile soil, favoring the growth of tumor cells.[11]

The distribution of BM, preferentially in the axial skeleton and in the metaphyseal region of the long bones, suggests that the intense low-pressure blood flow in the red marrow and the presence of hematopoietic cells and growth factors may favor the attachment of metastatic tumor cells on the endosteal bone surface.[12] In addition, the destruction of the bone matrix by cancer cells results in the local release of calcium. This extracellular calcium, in turn, promotes tumor growth in the bone through the expression of extracellular calcium sensory receptors by neoplastic cells. Additionally, bone acts as a major storehouse of growth factors, such as transforming growth factor-(b TGFb), which can also promote tumor growth.[11]

The immune system and the bone microenvironment maintain an intrinsic and dynamic relationship, with inhibitory or stimulating effects between the cells of the immune system and the bone cells. For example, osteoclasts, recognized for their function of bone resorption, can differentiate into macrophages and lymphocytes. This cellular plasticity highlights fundamental interconnectedness between the immune system and bone tissue, where seemingly distinct cells share overlapping origins and functions.

The interaction between osteoblasts, osteoclasts and tumor cells plays a crucial role in bone remodeling and cancer progression. Osteoblasts deposit growth factors in the bone matrix, which are subsequently released and activated by osteoclastic bone destruction. In addition, the tumor secretes factors that amplify the activity of osteoclasts, resulting in increased osteolysis, generating additional release of growth factors, and establishing a vicious cycle that stimulates tumor growth.

In the 1990s, the first connections between inflammation and cancer emerged. In some types of tumors, inflammatory conditions exist before malignancy, while in others, tumor development induces the inflammatory response, which in turn leads to more tumor growth and proliferation. The inflammatory response plays a decisive role in different stages of tumor development, including initiation, promotion, malignant conversion, invasion, and metastasis. Studies show that metastasis requires close collaboration between cancer cells, immune cells, inflammatory cells, and stromal elements.[5]

Generally speaking, inflammation stimulates the production and release of neutrophils and, at the same time, decreases the production of lymphocytes. Lymphopenia reflects that cell-mediated immunity is impaired, while neutrophilia represents a response to systemic inflammation. The role of neutrophils is still debated. On the one hand, they play a crucial role in the immune response, by recognizing and killing invading microorganisms through cytotoxic mechanisms; on the other hand, they are thought to inhibit the immune response by suppressing cytolytic immune cells, such as lymphocytes, activated T cells, and Natural Killer cells, and promote tumor growth by releasing growth-promoting factors, such as vascular endothelial growth factor, interleukin-8, metalloproteinases, and elastases.[7] At the same time, the importance of lymphocytes has been highlighted in several studies, in which increased tumor infiltration by lymphocytes is associated with a better response to cytotoxic treatment and a better prognosis of cancer patients.

The tumor microenvironment contains innate immune cells, such as macrophages, neutrophils, mast cells, myeloid lineage-derived suppressor cells, dendritic and NK cells, and cells of the adaptive immune system, composed of T and B lymphocytes. Tumor-associated macrophages (TAMs) and T lymphocytes are the most frequent immune cells in the tumor microenvironment. While TAMs usually promote tumor growth and angiogenesis, essential factors for tumor invasion and metastasis, T cells can both suppress and promote tumor growth.

Another characteristic of the tumor microenvironment is the presence of pro-inflammatory cytokines and chemokines. In this context, platelets seem to contribute to the malignancy process with the production of inflammatory cytokines, chemiciokines, and promoting tumor angiogenesis.[6,13] the clinical courses of patients are prolonged and often accompanied by morbidity due to bone metastases. Skeletal-related events (SREs Importantly, although tumors can release cytokines and chemokines into the bloodstream, the tumor-specific environment is isolated into compartments and is not fully reflected in the overall blood circulation.[2]

NLR, defined as the neutrophil count divided by the lymphocyte count, and the PLR, defined as the platelet count divided by the lymphocyte count, have been gaining prognostic value in cancer patients.[Increases] in NLR or PLR may indicate an increase in neutrophils or platelets, a decrease in lymphocytes, or both. Although the complex mechanisms between cancer and circulating inflammatory components have yet to be unraveled, many studies have shown that increased NLR is associated with lower survival in several types of cancer.[2] Meta-analysis of 40,559 patients with malignant solid tumors found that elevated NLR above 4 was associated with poorer overall survival.[13]

From a clinical point of view, metastasis is the most critical aspect of tumorigenesis, as more than 90% of cancer mortality is caused by it.[5] The presence of OM is also the main cause of morbidity in patients with advanced disease1 and, therefore, its control is essential to improve quality of life, pain, and maintain patient independence.[2] The treatment of bone metastases is vast and multidisciplinary, encompassing clinical and/or surgical measures.

Surgery for bone metastasis is associated with morbidity, and therefore the surgical decision should take into account the location, extent of metastasis,

response to adjuvant therapies, clinical presentation, and life expectancy of the patient.[14] Complications are due to several risk factors associated with cancer: advanced age, clinical comorbidities, immunodeficiency, malnutrition, prolonged hospitalization, and local irradiation.[15] Approximately 60% of patients undergoing surgery for BM have other clinical comorbidities, especially cardiovascular, respiratory, and metabolic disorders.[15] Bindels et al.[16] found that the following factors were associated with early postoperative complications: fast-growing tumors, presence of multiple bone metastases, pathological fracture, procedures in the lower limbs, hypoalbuminemia, hyponatremia, and leukocytosis.[16,17]

In patients with short life expectancy, it is necessary to balance the benefits with the morbidity caused by the operation. Patients with a life expectancy of less than 3 months may be treated non-surgically and alternatively less invasive surgical techniques may be considered. Those with a longer life expectancy may undergo complex surgical procedures to improve the function of the affected limb.[14,18] the clinical courses of patients are prolonged and often accompanied by morbidity due to bone metastases. Skeletal-related events (SREs).

Due to the prognosis and clinical vulnerability of most patients with metastatic bone disease, it is critical to minimize postoperative complications and the long rehabilitation period during the surgical decision process. Currently, the main tools that support the surgeon in this decision-making include oncological performance status scales, anatomical classifications, survival prediction scores and algorithms, and the score that defines the risk of pathological fracture (MIRELS).[19] In this context, measurements of NLR and PLR in peripheral blood can be practical and accessible biomarkers to predict both survival and postoperative complications in patients with bone metastasis.[2]

NLR and PLR can be measured in peripheral blood and are easily accessible and cost-effective. According to British Orthopaedic Association guidelines, patients with MO should undergo a single procedure that allows for early full weight bearing and lasts the patient's anticipated life expectancy.[20] This article provides a status report on the global burden of cancer worldwide using the GLOBOCAN 2018 estimates of cancer incidence and mortality produced by the International Agency for Research on Cancer, with a focus on geographic variability across 20 world regions. There will be an estimated 18.[1] million new cancer cases (17.0 million excluding nonmelanoma skin cancer In those with short life expectancy, it is critical to balance the benefits with the morbidity caused by surgery. In a simplified way, 2 times frames - 90-day survival (intermediate) and 1 year (long-term) - were proposed for treatment decision-making in patients with long-bone metastases. Patients with a life expectancy of less than 3 months can be treated non-surgically and, alternatively, less invasive surgical techniques can be considered, such as fixation with rods, percutaneous wires, or even external fixators. Patients with longer life expectancy may undergo complex surgical procedures, such as tumor resection and long-lasting limb reconstruction with endoprostheses, in order to improve local tumor control and functionality of the affected limb.[14,18.] This article provides a status report on the global burden of cancer worldwide using the GLOBOCAN 2018 estimates of cancer incidence and mortality produced by the International Agency for Research on Cancer, with a focus on geographic variability across 20 world regions. There will be an estimated 18.[1] million new cancer cases (17.0 million excluding nonmelanoma skin cancer,21-24

The use of different cuts for the NLR and PLR are the subject of debate. The advanced stage of the disease, which implies a higher level of inflammation, may result in higher NLR or PLR, indicating that the cutoff point for distinction in the prognosis may be higher. In addition, the prognostic value of NLR and PLR, as well as their respective ideal cut-off values, may vary among different tumor types, indicating that specific analyses for each tumor type may be necessary.

According to the literature, more than 80% of OMs are located in the axial skeleton. The vertebrae, ribs, and hips are the bone sites most affected by bone-related events.[21] In relation to the appendicular skeleton, the occurrences are more frequent in the proximal part of the limbs. Metastases below the knee and elbow are rare and are often associated with lung, kidney, and thyroid neoplasms.[8]

The prognostic value of PLR has been the subject of study in recent years. However, the mechanisms underlying the association between elevated PLR and poor prognosis in cancer patients remain unknown. A meta-analysis of 12,754 patients and 20 studies on PLR in solid tumors, covering various types of cancer and stages of the disease, revealed that the cut-off values for PLR ranged from 150 to 300. A significant association was observed between high PLR and lower overall survival. In addition, this association was more pronounced in patients with metastatic disease than in those with early-stage disease.[4]

Factors such as age, gender, race, chemotherapy treatment, antibiotic use, blood transfusions, smoking, infections, and other coexisting conditions can affect neutrophil, lymphocyte, or platelet counts. However, since the precise mechanisms of the prognostic value of NLR and PLR are not yet fully elucidated, it is believed that the pre-treatment counts reflect the immune and inflammatory response of patients at that specific time, without the need to identify exactly which individual factors influenced them.

Future perspectives

Currently, surgical decisions in patients with OM are restricted to subjective clinical assessment scales, such as the Karnofsky index and the performance status (PS) score. The Mirels score evaluates the characteristics of bone lesions, indicating a prophylactic surgical approach based on the risk of pathological fracture. To date, there are no scores that help the surgeon in making decisions about which therapeutic approach to

use in metastatic patients. Future studies that correlate inflammatory biomarkers, such as NLR and PLR, with complication and survival rates, associated with PS or Karnofsky scores, may help define the most appropriate treatment for patients with bone metastases.

CONCLUSION

The higher the LTR, and PLR are associated with lower survival in patients with OM when undergoing surgical treatment, especially after 3 months postoperatively. However, there is still no confirmation that they signal any outcome, favorable or not, regarding postoperative complications.

Authors' contributions

Conceptualization: Matheus Silva Teixeira
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