The role of neutrophil to lymphocyte ratio in predicting lung metastasis in giant cell tumor of the extremities

M.P. JOHAN[1], I.A. PATURUSI[1], H. YURIANTO[1], M.A. USMAN[1], J. ARIFIN[1], M.A. ABIDIN[2], M.A. KAWILARANG[1], D. KENNEDY[1]

[1]Department of Orthopedics and Traumatology, Faculty of Medicine, Hasanuddin University, Dr. Wahidin Sudirohusodo General Hospital, Makassar, Indonesia
[2]Medical Faculty, Muhammadiyah University, Makassar, Indonesia

Abstract. – OBJECTIVE: Inflammation has a vital role in tumor development and metastasis. Changes in blood count parameters have been associated with tumor prognosis. We aimed to evaluate the prognostic significance of neutrophil to lymphocyte ratio (NLR) in predicting lung metastasis of giant cell tumors of the bone (GCTB) of the extremities.

PATIENTS AND METHODS: 34 GCTB patients (22 males and 12 females) were included in the study. Patients were divided into two groups. The metastasis group (n = 7) included GCTB patients with lung metastasis, while the non-metastasis group (n = 27) included those without lung metastasis. Descriptive statistics and frequency distribution were calculated [age, white blood cell (WBC), neutrophil, lymphocyte, platelets, neutrophil to lymphocyte ratio (NLR), and platelets to lymphocytes ratio (PLR)]. Continuous normal variables were expressed as mean ± standard deviation and compared using Student's *t*-tests. The receiver operating characteristic (ROC) curve analysis was used to evaluate the ability of NLR and PLR to predict lung metastasis. The factors were considered to be statistically significant at $p < 0.05$.

RESULTS: There were no significant differences between the lymphocyte count (1.81 *vs.* 2.23 $10^3/mm^3$), platelet count (436 *vs.* 364 $10^3/mm^3$), and PLR values (247 *vs.* 190) of the two groups ($p > 0.05$). The WBC count (11.8 *vs.* 8.95 103/mm3), neutrophil count (8.78 *vs.* 5.69 103/mm3), and NLR levels (5.45 *vs.* 2.81) ($p < 0.05$) were significantly higher in the metastasis group. The presence of an NLR cut-off value of 3.7 significantly predicted the existence of lung metastasis (AUC = 0.857 [95%CI = 0.714-1], $p = 0.004$) with a sensitivity of 85% and specificity of 82%.

CONCLUSIONS: NLR may serve as a promising prognostic marker for predicting lung metastasis in GCTB patients.

Key Words:
Neutrophil to lymphocyte ratio, NLR, Lung metastasis, Giant cell tumor of the bone.

Introduction

Giant cell tumor of the bone (GCTB) is a rare, invasive, and benign bone tumor consisting of a large number of osteoclast-like giant cells between which mononuclear stromal cells are embedded[1,2]. Metastasis in GCTB occurs most commonly in the lung, with a reported number ranging from 1-9%[3-10]. Accurate prediction of the prognosis of GCTB remains difficult due to the scarcity of prospective studies. Many researchers suggested that some criteria, including grading and surgical margin, affect the progression of GCT[11-14]. However, the prognosis of this condition varied significantly even with the same grade and surgical approach. Therefore, a better understanding of the pathogenesis of GCTB and finding alternative prognostic markers would greatly improve its clinical treatment.

According to growing data, inflammation appears to have an important role in the development and progression of various cancers. Impairment of adaptive immune response may stimulate the initiation of tumor growth and angiogenesis[15-19]. Inflammation may favor tumorigenesis phases, including initiation, promotion, and metastasis progression[20]. Various cytokines are secreted during tumor growth, such as vascular endothelial growth factor (VEGF), interleukins (ILs), and tumor necrosis factor (TNF), which trigger the production of platelets and granulocytes[15,21-23].

Corresponding Author: Muhammad Phetrus Johan, MD, Ph.D; e-mail: muhpjo@gmail.com

Some cytokines, such as interleukin (IL)-8, could contribute to the metastatic potential of tumor cells *via* the chemoattraction of neutrophils, which release enzymes that may enhance metastasis. These series of enzymes facilitate the remodeling of the extracellular matrix, which favors tumor angiogenesis and permits neutrophil migration. These enzymes also activate proteases and weaken cell-cell interactions, thereby allowing the detachment of tumor cells from the primary tumor mass[24-26]. It has been shown that activated platelets enhance tumor development by secreting cytokines and growth factors such as interleukin 6, granulocyte colony-stimulating factor, VEGF, and fibroblast growth factor. Furthermore, they promote metastatic development by causing tumor cell aggregation in the circulatory system[27-34]. Previous research[35] has demonstrated that the adaptive and innate immune system lymphocytes prevent tumor development. A specific cytotoxic immune response against a tumor needs a complex interaction between the adaptive and innate immune systems as the main immune cells of the human body. Activated neutrophils can induce T-cell death and suppress the proliferation of activated T-cells *via* an H_2O_2 dependent pathway, thereby allowing tumor immune tolerance, which contributes to uncontrolled tumor growth[36]. Therefore, inflammation forms the basis of tumor development, including metastasis.

A complete blood count is the most common examination performed clinically. Neutrophils, platelets, and lymphocytes may indicate the immune response and are important value for tumor prognosis prediction. The predictive value of the ratio of neutrophils to lymphocytes (NLR) and platelets to lymphocytes (PLR) have been assessed in many tumors, including lung, colorectal, breast, thyroid, and gastric cancer[37-42]. Based on previous studies, NLR and PLR can potentially become predictive factors in tumor prognosis and metastasis. As an element of complete blood count, NLR and PLR are cost-effective and simple markers for evaluating inflammation. However, the potential of NLR and PLR as predictive indicators for lung metastasis in GCTB has not been systematically investigated. In this retrospective study, we evaluated the diagnostic efficacy of NLR and PLR for assessing lung metastasis in GCTB.

Patients and Methods

We retrospectively reviewed the clinical data of patients diagnosed with GCTB of the extremities at Wahidin Sudirohusodo General Hospital, affiliated with the Faculty of Medicine of Hasanuddin University, between January 2019 – June 2022. The inclusion criteria comprised the following: (1) Patients with histopathological diagnosis of giant cell tumor of the bone at the extremities; (2) Pre-treatment inflammatory markers were measured; (3) No infection, hematological disease, blood transfusion or fever; (4) No concurrent malignancies; (5) No chronic disease such as diabetes and chronic obstructive pulmonary disease; (6) Radiologic findings of chest computed tomography (CT) were assessed. There were nine patients diagnosed with GCTB but not included in the study. A total of 34 patients with GCTB who met the inclusion criteria were finally included in the study. Hospital records of age, gender, tumor stage, tumor location, white blood cell count, absolute neutrophil count, absolute lymphocyte count, absolute platelet count, and chest CT evaluation were collected for each patient. White blood cell count, absolute neutrophil, platelets, and lymphocyte count were measured within three days before operative intervention as part of routine preoperative laboratory assessments. Hematological parameters were analyzed by using a hematology analyzer (The Sysmex XP300 Hematology Analyzer, 2015 Sysmex America Inc, USA) immediately after blood samples were taken. NLR and PLR were calculated separately as the absolute count of neutrophils and platelets divided by the absolute lymphocyte count. Pulmonary metastasis was established when abnormal lesions were found as single or multiple pulmonary nodules and well-defined opacities on chest CT. Due to the COVID-19 outbreak in Indonesia since March 2020, all patients scheduled for surgery underwent a preoperative COVID-19 test. This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of Hasanuddin University (245/UN.4.6.4.531/PP36/2022).

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics v.23 for Windows (Statistical Package for Social Science, IBM Corp., Armonk, NY, USA). The data distribution was analyzed in terms of normality using the Kolmogorov-Smirnov test. Depending on the normality of the distribution, continuous normal variables were expressed as mean ± standard deviation and compared using Student's *t*-tests. In contrast, non-normal continuous variates were presented as median and interquartile range and compared with the log-rank test. The count data were presented as frequency or rate. The receiver operating characteristic (ROC) curve analysis was used to evaluate the ability of NLR and PLR factors to predict lung metastasis. Sensitivity and specificity ratios of significant threshold values were calculated according to the ROC curve analysis results. The factors were considered to be statistically significant at $p < 0.05$. All confidence intervals (CI) were expressed as a 95% confidence level. Critical appraisal for this journal was analyzed using STROBE table (**Supplementary Table I**)[43].

Results

A cross-sectional study involving patients with giant cell tumors of bone (GCTB) was conducted in Dr. Wahidin Sudirohusodo Central General Hospital, Makassar. After selecting patients according to the inclusion and exclusion criteria, there were 34 sample patients to be included in the data analysis.

Among the 34 patients with GCTB of the extremities, 22 were males (64.7%), and 12 were females (35.3%). The mean age of patients was 34.73 ± 13.57. At the time of diagnosis, all patients were stratified according to Campanacci classification, with 0 (0%) grade I, 4 (12.8%) grade II cases, and 30 (87.2%) grade III cases. The most common tumor location was the femur (n=10) while the least common location (n=1) was the ulna and ilium. 7 (20.6%) out of 34 patients developed pulmonary metastasis (Table I). Bilateral metastasis occurred in 7 cases, and they had multiple metastasis lesions. The representative pulmonary metastasis of GCTB is shown in Figure 1. Two of seven patients had lung metastasis within ≤ 3 months of the initial diagnosis of GCTB (synchronous disease), and five patients had lung metastasis during follow-up of > 3-31 months (metachronous disease) (Table II). There were 18 patients with Giant Cell Tumors of Bone scheduled for surgery since the outbreak of COVID-19. SARS-Cov-2 (COVID-19- testing was performed before definitive surgery based on reverse transcriptase polymerase chain reaction (RT-PCR). Two GCTB patients (11%) were infected by COVID-19, presenting with asymp-

Table I. Baseline characteristic of giant cell bone tumor patients.

	Results (n = 34)
Age, years	34.73 ± 13.57
Gender, male (%)	22 (64.7)
Campanacci staging (%)	
Stage I	0
Stage II	4 (12.8)
Stage III	30 (87.2)
Tumor location (%)	
Humerus	4 (11.8)
Radius	7 (20.6)
Ulna	1 (2.9)
Hand	3 (8.9)
Ilium	1 (2.9)
Femur	10 (29.4)
Tibia	8 (23.5)
Lung metastasis (%)	
Yes	7 (20.6)
No	27 (79.4)

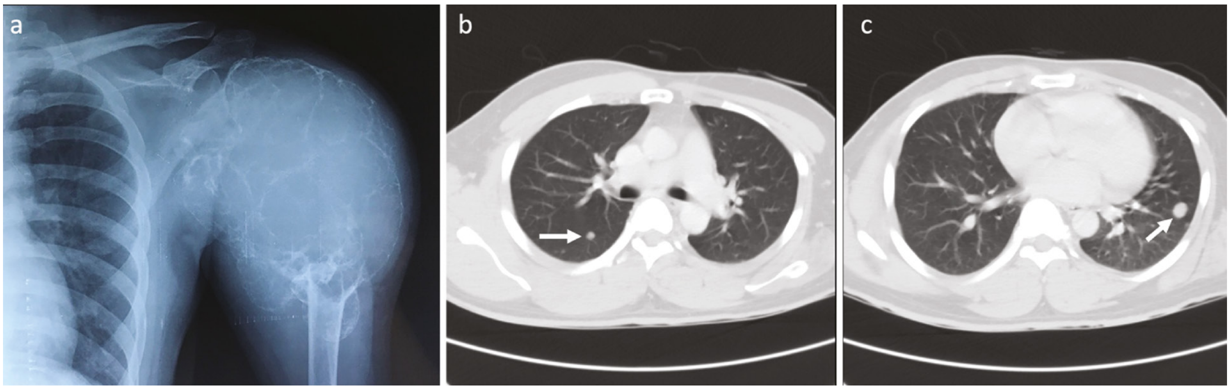

Figure 1. Representative case of giant cell tumor of bone at the proximal humerus. The radiograph showed osteolytic lesions with cortical thinning, expansile remodeling, and cortical breakthrough (**a**). Chest CT showed lung metastasis in the right lung (**b**) and left lung (**c**) 10 months after the initial operation.

Table II. Clinical detailed information of 34 patients with GCTB.

No	Age	Gender	Location of tumor	Campanacci	Previous surgery	Surgery for primary tumor	Local recurrence	Lung metastasis
1	35	M	Femur	III	No	Resection	No	No
2	46	M	Femur	II	No	Curretage	No	No
3	34	F	Femur	III	No	Curretage	No	No
4	47	F	Femur	II	No	Curretage	No	No
5	51	M	Metacarpal	III	Yes	Resection	No	Synchronous
6	19	M	Radius	III	No	Resection	Yes	Metachronous
7	26	M	Radius	III	No	Resection	No	No
8	21	M	Tibia	III	No	Resection	No	Metachronous
9	40	M	Tibia	III	No	Curretage	No	No
10	27	F	Tibia	II	No	Curretage	No	No
11	42	M	Tibia	III	No	Resection	No	No
12	60	F	Ulna	II	No	Resection	No	No
13	26	F	Femur	III	No	Curretage	No	No
14	28	M	Femur	III	No	Resection	No	No
15	47	M	Femur	III	No	Resection	No	No
16	23	M	Femur	III	No	Resection	No	No
17	24	M	Femur	III	No	Curretage	Yes	Metachronous
18	22	M	Femur	III	No	Curretage	No	No
19	35	M	Humerus	III	No	Resection	No	Metachronous
20	43	M	Humerus	III	No	Resection	No	No
21	35	F	Humerus	III	No	Curretage	No	No
22	39	M	Humerus	III	No	Resection	No	No
23	41	M	Ilium	III	No	Curretage	No	Synchronous
24	25	F	Phalanx of hand	III	Yes	Resection	No	No
25	62	F	Phalanx of hand	III	No	Curretage	No	No
26	27	M	Radius	III	No	Resection	No	No
27	42	F	Radius	III	No	Curretage	No	No
28	19	M	Radius	III	No	Resection	No	No
29	19	M	Radius	III	No	Resection	No	No
30	28	F	Radius	III	No	Resection	No	No
31	39	F	Tibia	III	No	Resection	No	Metachronous
32	16	M	Tibia	III	No	Curretage	No	No
33	72	M	Tibia	III	No	Resection	No	No
34	21	F	Tibia	III	No	Curretage	No	No

tomatic symptoms. Elective surgical procedures were delayed until the patients were no longer infectious and had demonstrated negative results from RT-PCR COVID-19 tests. Until the last follow-up, neither lung metastasis nor complications had been found in the patients.

Routine preoperative laboratory assessments, including white blood cell count, absolute neutrophil count, absolute lymphocyte count, and platelet count, were compared between metastasis and non-metastasis groups. There was a significant difference in the WBC count and absolute lymphocyte count parameters. WBC counts were significantly higher in the metastasis group [11.8 ± 3.19 $10^3/mm^3$] compared to the non-metastasis group [8.95 ± 2.27 $10^3/mm^3$] (p=0.009). Neutrophil counts were significantly higher in the metastasis group [8.78 ± 2.69 $10^3/mm^3$] compared to the non-metastasis group [5.69 ± 1.58 $10^3/mm^3$] (p=0.022). Lymphocyte counts were 1.81 ± 0.7 $10^3/mm^3$ in the metastasis group and 2.23 ± 0.78 $10^3/mm^3$ in the non-metastasis group (p=0.208). Platelet counts were 436 ± 164 $10^3/mm^3$ in the metastasis group and 364 ± 106 $10^3/mm^3$ in the non-metastasis group (p=0.305) (Table III). Neutrophil to lymphocyte ratio was significantly higher in the metastasis group [5.45 ± 2.29] compared to the non-metastasis group [2.81 ± 1.37] (p=0.022) (Figure 2). Platelet to lymphocyte ratio was higher in the metastasis group [247.41 ± 39.8] compared to the non-metastasis group [190.08 ± 98.17]; however, the difference is not statistically significant (p=0.144) (Figure 3).

The value of NLR level in predicting the presence of advanced stages of metastasis was evaluated by ROC analysis. It was found that the NLR cut-off value of 3.7 was significant in predicting the presence of metastasis (AUC = 0.857 [95% CI=0.714-1], p=0.004) with a sensitivity of 85% and specificity of 82% (Figure 4).

Table III. Comparison of inflammation indicators between metastasis group and non-metastasis group.

	Non-metastasis group	Metastasis group	*p*-value
White blood cell count, $10^3/mm^3$	8.95 ± 2.27	11.8 ± 3.19	0.009
Absolute neutrophil count, $10^3/mm^3$	5.69 ± 1.58	8.78 ± 2.69	0.022
Absolute Lymphocyte Count, $10^3/mm^3$	2.23 ± 0.78	1.81 ± 0.70	0.208
Platelet count, $10^3/mm^3$	364 ± 106	436 ± 164	0.305
Neutrophil-lymphocyte ratio	2.81 ± 1.37	5.45 ± 2.29	0.022
Platelet-lymphocyte ratio	190.08 ± 98.17	247.41 ± 39.8	0.144

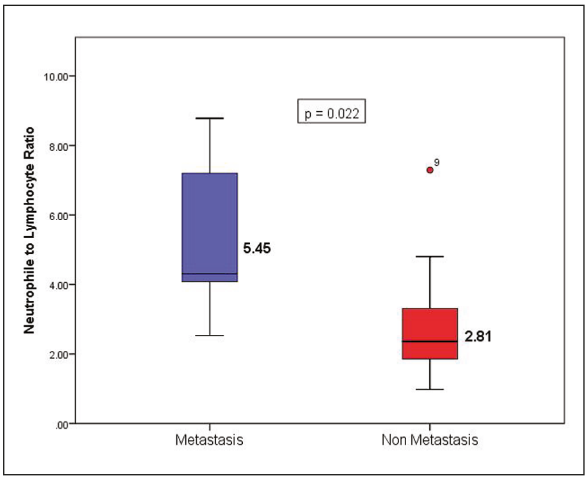

Figure 2. Comparison NLR values of metastasis and non-metastasis group.

Discussion

Despite seemingly simple, the relationship between inflammatory markers and outcomes in tumor patients may involve a complex interaction that is yet little understood. Continuous cell renewal and proliferation cause the persistent inflammatory environment linked with tumors. The inflammatory tumor microenvironment ultimately encourages angiogenesis, tumor proliferation and metastasis through interactions between malignant and non-malignant cells[44]. On the other hand, inflammation inhibits anti-tumor immune responses, which aids tumors in evading host immunosurveillance[45].

Neutrophil infiltration of the tumor environment also reflects changes in circulating neutrophils. This shows us that the number of circulating neutrophils in tumor patients may indicate the presence of tumor metastases[46]. In fact, by inhibiting peripheral leukocyte activation, circulating tumor-associated neutrophils in patients with advanced cancer help the circulating tumor cell survive. As a tumor grows, circulating neutrophils rise gradually and change into tumorigenic tumor-associated neutrophils, distinguished from naive neutrophils by upregulation of CCL12, CXCL2, and Arg1[47]. To facilitate tumor metastasis, neutrophils can surround circulating tumor cells in a protective layer. These findings may describe how neutrophils function in predicting tu-

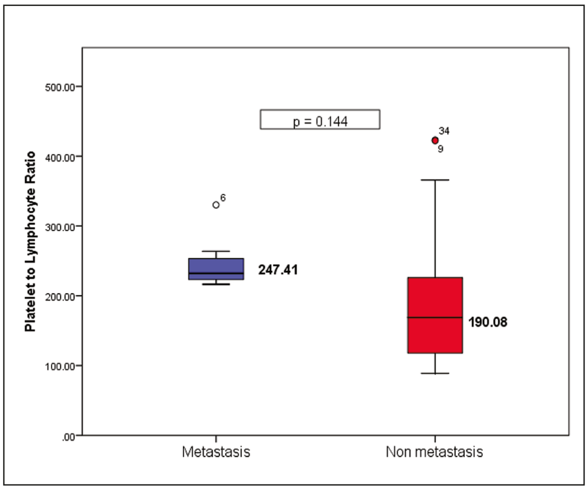

Figure 3. Comparison PLR values of metastasis and non-metastasis group.

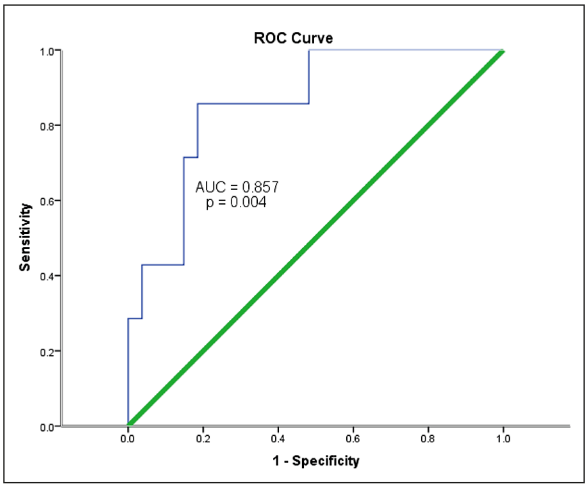

Figure 4. Receiver operating characteristic (ROC) curve of NLR in predicting lung metastasis in GCTB patients.

mor metastasis and therapy[48]. Cancer-associated neutrophilia has been demonstrated to facilitate extracellular matrix remodeling, which triggers the release of basic fibroblast growth factors, migration of endothelial cells, and dissociation of tumor cells. Additionally, neutrophil-derived reactive oxygen species are known to inhibit lymphocyte cytotoxicity, reduce the extracellular matrix's ability to promote adhesion and suppress cancer cell apoptosis in the tumor microenvironment[25,49,50].

The predictive effect on cancer prognosis may be strengthened when combined with lymphopenia, which also appears to be associated with a poor prognosis in cancer patients. The substantial correlation between high densities of tumor-infiltrating lymphocytes and improved responses to both cytotoxic therapies and outcomes in patients with breast cancer illustrates of the involvement of lymphocytes in cancer control[51-55]. Lymphocytes are a crucial component of cell-mediated immunity and the host's defenses against malignancy. Numerous malignancies have been linked to impaired lymphocyte function and decreased lymphocyte counts[56]. High recurrence in GCTB is linked to perioperative lymphopenia[57]. More studies have shown that tumor growth correlates with absolute lymphocyte counts (ALC) in peripheral blood and tumor-infiltrating lymphocytes (TIL). Poor prognosis in esophageal squamous cell carcinoma is associated with low TIL. Furthermore, there is a positive correlation between TIL and ALC in peripheral blood[58]. GCT is a locally aggressive tumor composed of mesenchymal stromal cells (mononuclear myeloid cells) characterized by osteoclast-like, multinucleated giant cells. It was reported that individuals with myeloproliferative neoplasms with the same stromal cell group as GCT had increased levels of NLR[59,60].

The platelet count is another indicator of a systemic inflammatory response and possible micro-vessel thrombosis, which may impair tissue blood flow and impede wound healing[61-63]. Aggregated platelets can accelerate the growth of tumors by releasing pro-angiogenic mediators into the tumor's microvasculature[64]. To promote tumor cell growth and metastasis, platelets facilitate tumor cell adherence and dissemination across the extracellular matrix[65]. Therefore, thrombocytosis is a poor prognostic indicator in various malignancies[66-68]. The PLR, a biomarker that combines platelet and lymphocyte counts, may reflect the information provided by thrombocytosis and lymphocytopenia and predict the prognosis of GCTB patients. Additionally, PLR's value could be obtained at minimal cost through routine laboratory testing, which offers clinical consequences.

To the best of our knowledge, this is the first study to describe that NLR may serve as a predictive factor for metastasis to the lung in the GCTB of extremities. The current study found that white blood cell (WBC) counts, and absolute neutrophil counts increased significantly in the metastasis patient group. These high levels of WBC and neutrophil counts were associated with the invasive behavior of tumor cells. Absolute lymphocyte count decreased in the metastasis patient's group, although it was not statistically significant. The predictive and prognostic significance of NLR in tumors has received substantial research since tumor patients frequently have elevated neutrophils and decreased lymphocytes[69]. The majority of earlier studies either emphasized high NLR as an effective indicator of cancer patients' long-term survival or investigated the function of NLR in the evaluation of lymph node metastases[70-74]. The predictive role of NLR in assessing distant metastases has received less attention. Although the association of NLR and PLR with postoperative recurrence of GCTB has been reported, researchers did not evaluate its role in predicting lung metastasis[57,75]. Elevated NLR has been linked to an increased risk of metastasis in thyroid cancer patients[59]. Our current study tested a simple prognostic index of NLR for predicting lung metastasis in GCTB. We found a significantly higher NLR level in metastasis groups than in non-metastasis groups. NLR, at a cut-off level of 3.7, predicted lung metastasis of GCTB with a sensitivity of 85% and specificity of 82%. On the other hand, there was no significant difference in the PLR levels of the two groups. Our results are consistent with the previous study by He et al[76] which describes that initial NLR is superior to PLR as a prognostic and predictive factor in patients with metastasis colorectal cancer. Another literature reveals that myeloid-derived suppressor cells, which are actively immunosuppressive by sustaining pathological angiogenesis and suppressing cytotoxic lymphocyte, were directly correlated with NLR as opposed to PLR, which may also account for the benefit of NLR[77,78].

Limitations

This study has several limitations. Firstly, metastatic lesions were diagnosed according to chest CT evaluation, and it required histological confirmation. However, the majority of patients are healthy and young, and lung abnormalities are uncommon; therefore, these lung lesions found on imaging examinations of GCTB patients most likely represented GCTB lung metastasis. Secondly, this was a retrospective study, and it was possible that several cases or information may have been lost during follow-up. Thirdly, there was a risk of statistical error due to the small sample size. If a large number of cases is gathered in the future, significant differences regarding the other variables in this study may emerge.

Conclusions

The prognosis of neoplastic disorders is determined by various factors, and NLR might be one of them. Our findings show that NLR may serve as a promising prognostic marker for predicting lung metastasis in GCTB patients. Future prospective multicentre studies with larger-scale randomized trials are required to corroborate our findings and clarify the relationship between NLR and lung metastasis in GCTB patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Funding

This research received no external funding.

Authors' Contribution

Conceptualization and design of the study: M. P. Johan, I. A. Paturusi, H. Yurianto, M. A. Usman, J. Arifin, and M. A. Kawilarang; acquisition of data: M. P. Johan, M. A. Abidin, M. A. Kawilarang, D. Kennedy; analysis and interpretation of data: M. P. Johan, I. A. Paturusi, H. Yurianto, M. A. Usman, J. Arifin, M. A. Abidin, M. A. Kawilarang; drafting the article or making critical revisions related to relevant intellectual content of the manuscript: M. P. Johan, I. A. Paturusi, H. Yurianto, M. A. Usman, J. Arifin.l, M. A. Abidin, M. A. Kawilarang, D. Kennedy; supervision: M. P. Johan, I. A. Paturusi, H. Yurianto, M. A. Usman, J. Arifin; validation: M. P. Johan, I. A. Paturusi, H. Yurianto, M. A. Usman, J. Arifin, M. A. Abidin, M. A. Kawilarang, D. Kennedy; final approval of the version of the article to be published: M. P. Johan, I. A. Paturusi, H. Yurianto, M. A. Usman, J. Arifin, M. A. Abidin, M. A. Kawilarang, D. Kennedy. All authors have read and agreed to the published version of the manuscript.

ORCID ID

Muhammad Phetrus Johan: 0000-0002-5567-4710; Henry Yurianto: 0000-0001-8937-4663; Muhammad Andry Usman: 0000-0002-0287-1737; Dave Kennedy: 0000-0003-0131-9163.

Data Availability

The datasets generated during and/or analyzed during the current study are not publicly available due privacy of patient data but are available from the corresponding author on reasonable request.

Informed Consent

Written informed consent has been obtained from the patients to publish this paper.

Ethics Approval

This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Hasanuddin University (245/UN.4.6.4.531/PP36/2022).

References

1) Salerno M, Avnet S, Alberghini M, Giunti A, Baldini N. Histogenetic characterization of giant cell tumor of bone. Clin Orthop Relat Res 2008; 466: 2081-2091.
2) Campanacci M, Baldini N, Boriani S, Sudanese A. Giant-cell tumor of bone. J Bone Joint Surg Am 1987; 69: 106-114.
3) Kito M, Matusmoto S, Ae K, Tanizawa T, Gokita T, Kobayashi H, Hayakawa K, Funauchi Y. Pulmonary metastasis from giant cell tumor of bone: clinical outcome prior to the introduction of molecular target therapy. Jpn J Clin Oncol 2017; 47: 529-534.
4) Wang B, Chen W, Xie X, Tu J, Huang G, Zou C, Yin J, Wen L, Shen J. Development and validation of a prognostic index to predict pulmonary metastasis of giant cell tumor of bone. Oncotarget 2017; 8: 108054-108063.
5) Rosario M, Kim HS, Yun JY, Han I. Surveillance for lung metastasis from giant cell tumor of bone. J Surg Oncol 2017; 116: 907-913.
6) Yang Y, Huang Z, Niu X, Xu H, Li Y, Liu W. Clinical characteristics and risk factors analysis of lung metastasis from benign giant cell tumor of bone. J Bone Oncol 2017; 7: 23-28.
7) Chan CM, Adler Z, Reith JD, Gibbs CP. Risk factors for pulmonary metastases from giant cell tumor of bone. J Bone Joint Surg Am 2015; 97: 420-428.
8) Dominkus M, Ruggieri P, Bertoni F, Briccoli A, Picci P, Rocca M, Mercuri M. Histologically veri-

fied lung metastases in benign giant cell tumours - 14 cases from a single institution. Int Orthop 2006; 30: 499-504.

9) Viswanathan S, Jambhekar NA. Metastatic giant cell tumor of bone: are there associated factors and best treatment modalities? Clin Orthop Relat Res 2010; 468: 827-833.

10) Bertoni F, Bacchini P, Staals EL. Malignancy in giant cell tumor of bone. Cancer 2003; 97: 2520-2529.

11) Malek F, Krueger P, Hatmi ZN, Malayeri AA, Faezipour H, O'Donnell RJ. Local control of long bone giant cell tumour using curettage, burring and bone grafting without adjuvant therapy. Int Orthop 2006; 30: 495-498.

12) Klenke FM, Wenger DE, Inwards CY, Rose PS, Sim FH. Giant cell tumor of bone: risk factors for recurrence. Clin Orthop Relat Res 2011; 469: 591-599.

13) Turcotte RE, Wunder JS, Isler MH, Bell RS, Schachar N, Masri BA, Moreau G, Davis AM. Giant cell tumor of long bone: a Canadian Sarcoma Group study. Clin Orthop Relat Res 2002: 248-258.

14) Raskin KA, Schwab JH, Mankin HJ, Springfield DS, Hornicek FJ. Giant cell tumor of bone. J Am Acad Orthop Surg 2013; 21: 118-126.

15) Elinav E, Nowarski R, Thaiss CA, Hu B, Jin C, Flavell RA. Inflammation-induced cancer: crosstalk between tumours, immune cells and microorganisms. Nat Rev Cancer 2013; 13: 759-771.

16) Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell 2010; 140: 883-899.

17) O'Callaghan DS, O'Donnell D, O'Connell F, O'Byrne KJ. The role of inflammation in the pathogenesis of non-small cell lung cancer. J Thorac Oncol 2010; 5: 2024-2036.

18) Galizia G, Orditura M, Romano C, Lieto E, Castellano P, Pelosio L, Imperatore V, Catalano G, Pignatelli C, De Vita F. Prognostic significance of circulating IL-10 and IL-6 serum levels in colon cancer patients undergoing surgery. Clin Immunol 2002; 102: 169-178.

19) Mei Z, Liu Y, Liu C, Cui A, Liang Z, Wang G, Peng H, Cui L, Li C. Tumour-infiltrating inflammation and prognosis in colorectal cancer: systematic review and meta-analysis. Br J Cancer 2014; 110: 1595-1605.

20) Singh R, Mishra MK, Aggarwal H. Inflammation, immunity, and cancer. Mediators Inflamm 2017; 2017: 6027305.

21) Stotz M, Pichler M, Absenger G, Szkandera J, Arminger F, Schaberl-Moser R, Samonigg H, Stojakovic T, Gerger A. The preoperative lymphocyte to monocyte ratio predicts clinical outcome in patients with stage III colon cancer. Br J Cancer 2014; 110: 435-440.

22) Jenne CN, Kubes P. Platelets in inflammation and infection. Platelets 2015; 26: 286-292.

23) Li J, Xu H, Sun Z, Hou Q, Kwok LY, Laga W, Wang Y, Ma H, Yu Z, Menghe B, Zhang H. Effect of dietary interventions on the intestinal microbiota of Mongolian hosts. Chin Sci Bull 2016; 20: 1605-1614.

24) Shamamian P, Schwartz JD, Pocock BJ, Monea S, Whiting D, Marcus SG, Mignatti P. Activation of progelatinase A (MMP-2) by neutrophil elastase, cathepsin G, and proteinase-3: a role for inflammatory cells in tumor invasion and angiogenesis. J Cell Physiol 2001; 189: 197-206.

25) De Larco JE, Wuertz BRK, Furcht LT. The potential role of neutrophils in promoting the metastatic phenotype of tumors releasing interleukin-8. Clin Cancer Res 2004; 10: 4895-4900.

26) Folkman J. Tumor angiogenesis: therapeutic implications. N Engl J Med 1971; 285: 1182-1186.

27) Gasic GJ, Gasic TB, Stewart CC. Antimetastatic effects associated with platelet reduction. Proc Natl Acad Sci U S A 1968; 61: 46-52.

28) Sousou T, Khorana AA. New insights into cancer-associated thrombosis. Arterioscler Thromb Vasc Biol 2009; 29: 316-320.

29) Khorana AA, Francis CW, Menzies KE, Wang JG, Hyrien O, Hathcock J, Mackman N, Taubman MB. Plasma tissue factor may be predictive of venous thromboembolism in pancreatic cancer. J Thromb Haemost 2008; 6: 1983-1985.

30) van Doormaal F, Kleinjan A, Berckmans RJ, Mackman N, Manly D, Kamphuisen PW, Richel DJ, Büller HR, Sturk A, Nieuwland R. Coagulation activation and microparticle-associated coagulant activity in cancer patients. An exploratory prospective study. Thromb Haemost 2012; 108: 160-165.

31) Enomoto T, Oda T, Aoyagi Y, Sugiura S, Nakajima M, Satake M, Noguchi M, Ohkochi N. Consistent liver metastases in a rat model by portal injection of microencapsulated cancer cells. Cancer Res 2006; 66: 11131-11139.

32) Goubran HA, Burnouf T, Radosevic M, El-Ekiaby M. The platelet-cancer loop. Eur J Intern Med 2013; 24: 393-400.

33) Nash GF, Turner LF, Scully MF, Kakkar AK. Platelets and cancer. Lancet Oncol 2002; 3: 425-430.

34) Chen Y, Wang YR, Deng GC, Dai GH. CA19-9 decrease and survival according to platelet level in patients with advanced pancreatic cancer. BMC Cancer 2019; 19: 860.

35) Dunn GP, Old LJ, Schreiber RD. The immunobiology of cancer immunosurveillance and immunoediting. Immunity 2004; 21: 137-148.

36) Hock BD, Taylor KG, Cross NB, Kettle AJ, Hampton MB, McKenzie JL. Effect of activated human polymorphonuclear leucocytes on T lymphocyte proliferation and viability. Immunology 2012; 137: 249-258.

37) Kim H, Ro SM, Yang JH, Jeong JW, Lee JE, Roh SY, Kim IH. The neutrophil-to-lymphocyte ratio prechemotherapy and postchemotherapy as a prognostic marker in metastatic gastric cancer. Korean J Intern Med 2018; 33: 990-999.

38) Li Y, Wang C, Xu M, Kong C, Qu A, Zhang M, Zheng Z, Zhang G. Preoperative NLR for predicting survival rate after radical resection combined with adjuvant immunotherapy with CIK and postoperative chemotherapy in gastric cancer. J Cancer Res Clin Oncol 2017; 143: 861-871.

39) Yang HJ, Guo Z, Yang YT, Jiang JH, Qi YP, Li JJ, Li LQ, Xiang BD. Blood neutrophil-lymphocyte ratio predicts survival after hepatectomy for hepatocellular carcinoma: A propensity score-based analysis. World J Gastroenterol 2016; 22: 5088-5095.

40) Templeton AJ, Ace O, McNamara MG, Al-Mubarak M, Vera-Badillo FE, Hermanns T, Seruga B, Ocaña A, Tannock IF, Amir E. Prognostic role of platelet to lymphocyte ratio in solid tumors: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 2014; 23: 1204-1212.

41) Yildirim MA, Seckin KD, Togrul C, Baser E, Karsli MF, Gungor T, Gulerman HC. Roles of neutrophil/lymphocyte and platelet/lymphocyte ratios in the early diagnosis of malignant ovarian masses. Asian Pac J Cancer Prev 2014; 15: 6881-6885.

42) Zhang X, Wang X, Li W, Sun T, Diao D, Dang C. Predictive value of neutrophil-to-lymphocyte ratio for distant metastasis in gastric cancer patients. Sci Rep 2022; 12: 10269.

43) Cuschieri S. The STROBE guidelines. Saudi J Anaesth 2019; 13: S31-S34.

44) Schäfer M, Werner S. Cancer as an overhealing wound: an old hypothesis revisited. Nat Rev Mol Cell Biol 2008; 9: 628-638.

45) Greten FR, Grivennikov SI. Inflammation and cancer: triggers, mechanisms, and consequences. Immunity 2019; 51: 27-41.

46) Rosales C. Neutrophil: a cell with many roles in inflammation or several cell types? Front Physiol 2018; 9: 113.

47) Zhang J, Qiao X, Shi H, Han X, Liu W, Tian X, Zeng X. Circulating tumor-associated neutrophils (cTAN) contribute to circulating tumor cell survival by suppressing peripheral leukocyte activation. Tumour Biol 2016; 37: 5397-5404.

48) Tao L, Zhang L, Peng Y, Tao M, Li L, Xiu D, Yuan C, Ma Z, Jiang B. Neutrophils assist the metastasis of circulating tumor cells in pancreatic ductal adenocarcinoma: A new hypothesis and a new predictor for distant metastasis. Medicine (Baltimore) 2016; 95: e4932.

49) Rodriguez PC, Ernstoff MS, Hernandez C, Atkins M, Zabaleta J, Sierra R, Ochoa AC. Arginase I-producing myeloid-derived suppressor cells in renal cell carcinoma are a subpopulation of activated granulocytes. Cancer Res 2009; 69: 1553-1560.

50) Müller I, Munder M, Kropf P, Hänsch GM. Polymorphonuclear neutrophils and T lymphocytes: strange bedfellows or brothers in arms? Trends Immunol 2009; 30: 522-530.

51) Loi S, Sirtaine N, Piette F, Salgado R, Viale G, Van Eenoo F, Rouas G, Francis P, Crown JPA, Hitre E, de Azambuja E, Quinaux E, Di Leo A, Michiels S, Piccart MJ, Sotiriou C. Prognostic and predictive value of tumor-infiltrating lymphocytes in a phase III randomized adjuvant breast cancer trial in node-positive breast cancer comparing the addition of docetaxel to doxorubicin with doxorubicin-based chemotherapy: BIG 02-98. J Clin Oncol 2013; 31: 860-867.

52) Gooden MJM, de Bock GH, Leffers N, Daemen T, Nijman HW. The prognostic influence of tumour-infiltrating lymphocytes in cancer: a systematic review with meta-analysis. Br J Cancer 2011; 105: 93-103.

53) Denkert C, Loibl S, Noske A, Roller M, Müller BM, Komor M, Budczies J, Darb-Esfahani S, Kronenwett R, Hanusch C, von Törne C, Weichert W, Engels K, Solbach C, Schrader I, Dietel M, von Minckwitz G. Tumor-associated lymphocytes as an independent predictor of response to neoadjuvant chemotherapy in breast cancer. J Clin Oncol 2010; 28: 105-113.

54) Mahmoud SM, Paish EC, Powe DG, Macmillan RD, Grainge MJ, Lee AHS, Ellis IO, Green AR. Tumor-infiltrating CD8+ lymphocytes predict clinical outcome in breast cancer. J Clin Oncol 2011; 29: 1949-1955.

55) West N, Milne K, Truong P, Macpherson N, Nelson B, Watson P. West NR, Milne K, Truong PT, Macpherson N, Nelson BH, Watson PH. Tumor-infiltrating lymphocytes predict response to anthracycline-based chemotherapy in estrogen receptor-negative breast cancer. Breast Cancer Res 2011; 13: R126.

56) Matsuzaki J, Gnjatic S, Mhawech-Fauceglia P, Beck A, Miller A, Tsuji T, Eppolito C, Qian F, Lele S, Shrikant P, Old LJ, Odunsi K. Tumor-infiltrating NY-ESO-1-specific CD8+ T cells are negatively regulated by LAG-3 and PD-1 in human ovarian cancer. Proc Natl Acad Sci U S A 2010; 107: 7875-7880.

57) Yapar A, Atalay İB, Tokgöz MA, Ulucaköy C, Güngör BŞ. Prognostic significance of the preoperative neutrophil-to-lymphocyte ratio patients with giant cell tumor of bone. Afr Health Sci 2021; 21: 1250-1258.

58) Zhu Y, Li M, Bo C, Liu X, Zhang J, Li Z, Zhao F, Kong L, Yu J. Prognostic significance of the lymphocyte-to-monocyte ratio and the tumor-infiltrating lymphocyte to tumor-associated macrophage ratio in patients with stage T3N0M0 esophageal squamous cell carcinoma. Cancer Immunol Immunother 2017; 66: 343-354.

59) Xu N, Jian Y, Wang Y, Tian W. Evaluation of neutrophil-to-lymphocyte ratio and calcitonin concentration for predicting lymph node metastasis and distant metastasis in patients with medullary thyroid cancer. Mol Clin Oncol 2018; 9: 629-634.

60) Lucijanic M, Cicic D, Stoos-Veic T, Pejsa V, Lucijanic J, Fazlic Dzankic A, Vlasac Glasnovic J, Soric E, Skelin M, Kusec R. Elevated neutrophil-to-lymphocyte-ratio and platelet-to-lympho-

cyte ratio in myelofibrosis: inflammatory biomarkers or representatives of myeloproliferation itself? Anticancer Res 2018; 38: 3157-3163.

61) Kim EY, Lee JW, Yoo HM, Park CH, Song KY. The platelet-to-lymphocyte ratio versus neutrophil-to-lymphocyte ratio: which is better as a prognostic factor in gastric cancer? Ann Surg Oncol 2015; 22: 4363-4370.

62) Zhou X, Du Y, Huang Z, Xu J, Qiu T, Wang J, Wang T, Zhu W, Liu P. Prognostic value of PLR in various cancers: a meta-analysis. PLoS One 2014; 9: e101119.

63) Neal CP, Mann CD, Garcea G, Briggs CD, Dennison AR, Berry DP. Preoperative systemic inflammation and infectious complications after resection of colorectal liver metastases. Arch Surg 2011; 146: 471-478.

64) Sierko E, Wojtukiewicz MZ. Platelets and angiogenesis in malignancy. Semin Thromb Hemost 2004; 30: 95-108.

65) Honn KV, Tang DG, Crissman JD. Platelets and cancer metastasis: a causal relationship? Cancer Metastasis Rev 1992; 11: 325-351.

66) Hutterer GC, Krieger D, Mrsic E, Pohlmann K, Bezan A, Stojakovic T, Pummer K, Zigeuner R, Pichler M. Preoperative leucocytosis, thrombocytosis and anemia as potential prognostic factors in non-metastatic renal cell carcinoma. Anticancer Res 2015; 35: 3463-3469.

67) Josa V, Krzystanek M, Eklund AC, Salamon F, Zarand A, Szallasi Z, Baranyai Z. Relationship of postoperative thrombocytosis and survival of patients with colorectal cancer. Int J Surg 2015; 18: 1-6.

68) Buergy D, Wenz F, Groden C, Brockmann MA. Tumor-platelet interaction in solid tumors. Int J Cancer 2012; 130: 2747-2760.

69) Cupp MA, Cariolou M, Tzoulaki I, Aune D, Evangelou E, Berlanga-Taylor AJ. Neutrophil to lymphocyte ratio and cancer prognosis: an umbrella review of systematic reviews and meta-analyses of observational studies. BMC Med 2020; 18: 360.

70) Aoyama T, Takano M, Miyamoto M, Yoshikawa T, Kato K, Sakamoto T, Takasaki K, Matsuura H, Soyama H, Hirata J, Suzuki A, Sasa H, Tsuda H, Furuya K. Pretreatment neutrophil-to-lymphocyte ratio was a predictor of lymph node metastasis in endometrial cancer patients. Oncology 2019; 96: 259-267.

71) Xia X, Li K, Wu R, Lv Q, Deng X, Fei Z, Zou C, Yang X. Predictive value of neuron-specific enolase, neutrophil-to-lymphocyte-ratio and lymph node metastasis for distant metastasis in small cell lung cancer. Clin Respir J 2020; 14: 1060-1066.

72) Yang JJ, Hu ZG, Shi WX, Deng T, He SQ, Yuan SG. Prognostic significance of neutrophil to lymphocyte ratio in pancreatic cancer: a meta-analysis. World J Gastroenterol 2015; 21: 2807-2815.

73) Moon G, Noh H, Cho IJ, Lee JI, Han A. Prediction of late recurrence in patients with breast cancer: elevated neutrophil to lymphocyte ratio (NLR) at 5 years after diagnosis and late recurrence. Breast Cancer 2020; 27: 54-61.

74) Wang Y, Zhai J, Zhang T, Han S, Zhang Y, Yao X, Shen L. Tumor-associated neutrophils can predict lymph node metastasis in early gastric cancer. Front Oncol 2020; 10.

75) Chen Z, Zhao G, Chen F, Xia J, Jiang L. The prognostic significance of the neutrophil-to-lymphocyte ratio and the platelet-to-lymphocyte ratio in giant cell tumor of the extremities. BMC Cancer 2019; 19: 329.

76) Azab B, Shah N, Radbel J, Tan P, Bhatt V, Vonfrolio S, Habeshy A, Picon A, Bloom S. Pretreatment neutrophil/lymphocyte ratio is superior to platelet/lymphocyte ratio as a predictor of long-term mortality in breast cancer patients. Med Oncol 2013; 30: 432.

77) Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011; 144: 646-674.

78) Angell TE, Lechner MG, Smith AM, Martin SE, Groshen SG, Maceri DR, Singer PA, Epstein AL. Circulating myeloid-derived suppressor cells predict differentiated thyroid cancer diagnosis and extent. Thyroid 2016; 26: 381-389.