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Significance of preoperative peripheral blood neutrophil-lymphocyte ratio in predicting postoperative survival in patients with multiple myeloma bone disease

Xu ZY *et al*. NLR in MMBD patients.

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Abstract

BACKGROUND

The neutrophil-lymphocyte ratio (NLR) is often used to predict a poor prognosis in patients with tumors. This study investigated the preoperative peripheral blood NLR in predicting postoperative survival (POS) in patients with multiple myeloma bone disease (MMBD).

AIM

To evaluate whether NLR can be used to predict the prognosis of MMBD patients after surgery.

METHODS

The clinical data of 82 MMBD patients who underwent surgical treatments in Beijing Chao-yang Hospital were collected. The NLR was obtained from the absolute number of neutrophils, and lymphocytes, calculated by the number of neutrophils divided by the number of lymphocytes. The peripheral blood lymphocyte percentage was used as the major marker to analyze the change in characteristics of the immune statuses of multiple myeloma patients.

RESULTS

The NLR cut-off values of NLR ≥ 3 patients and NLR ≥ 4 patients were significantly correlated with POS. The 3- and 5-year cumulative survival rates of the high NLR group (NLR ≥ 3 patients) were 19.1% and 0.0%, respectively, which were lower than those of

the low NLR group (NLR < 3 patients) (67.2% and 48.3%) (*P* = 0.000). In the high NLR group, POS (14.86 ± 14.28) was significantly shorter than that in the low NLR group (32.68 ± 21.76). Univariate analysis showed that the lymphocyte percentage 1 wk after the operation (19.33 ± 9.08) was significantly lower than that before the operation (25.72 ± 11.02). Survival analysis showed that postoperative chemotherapy, preoperative performance status and preoperative peripheral blood NLR ≥ 3 were independent risk factors for POS.

CONCLUSION
The preoperative peripheral blood NLR can predict POS in MMBD patients. MMBD patients with a high preoperative NLR (NLR ≥ 3) showed poor prognosis.

Key Words: Multiple myeloma bone disease; Neutrophil-lymphocyte ratio; Lymphocyte percentage; Postoperative survival

Core Tip: The clinical data of 82 MMBD patients who underwent operations in our hospital were collected. By observing the change characteristics of NLR at different stages after operation, to make a preliminary analysis of the effect of operation on the immune status of MM patients and study the prognostic value of peripheral blood NLR in predicting the treatment of multiple myeloma bone disease (MMBD). Data showed that NLR was significant for the prediction of the postoperative survival (POS) of MMBD patients treated with operation, and MMBD patients with high preoperative NLR (NLR ≥ 3) had a poorer prognosis and shorter POS.

INTRODUCTION

Multiple myeloma (MM) is a malignant proliferative disease of plasma cells, with the second highest incidence among blood tumor diseases. Due to the growth of the aging population, the incidence of MM has increased, and there are many studies on prognosis, especially on prognostic factors and relevant stratification data. Such studies are based on the characteristics of patients, tumor load, and cytogenetics[1], and mainly target the selection of chemotherapy regimens and other medical treatments. However, to date, only a few studies have reported MM surgical treatment prognosis stratification[2-4].

As a marker of systematic inflammation, the neutrophil-lymphocyte ratio (NLR) has been used to diagnose infectious diseases. The NLR has also been used as an immune status evaluation indicator to assess the prognosis of solid tumors, such as hepatocellular carcinoma, gastric cancer, renal cell carcinoma, colorectal cancer, ovarian cancer, and prostate cancer. These studies suggested that a high NLR may predict a poor prognosis[5-7]. Although some retrospective studies have initially explored the influence of NLR on the prognosis of MM in recent years, these studies have been inadequate due to a small number of cases included in the study and shorter follow-up times[8,9]. These studies did not report on whether there was any change in the immune status of MM patients before and after the operation. Can NLR be used for the prognostic evaluation of surgically treated MM bone disease (MMBD)? Thus, the effect of the NLR on the prognosis of MM patients remains to be studied further.

This study reviewed the general conditions, indicators, surgical information, and follow-up of MMBD patients from 2007 to 2017 to analyze the value of the preoperative peripheral blood NLR in predicting the prognosis of patients and its impact on postoperative survival (POS). According to the changes in the absolute neutrophil count, absolute lymphocyte count, and lymphocyte percentage at different time points before and after the surgical treatments, the effect of the surgical treatments on the immune status of patients was discussed.

MATERIALS AND METHODS

General data

The institutional review board of our hospital approved this retrospective study. A total of 82 MMBD patients from the Beijing Chao-Yang Hospital were enrolled between 2007 and 2017. The sites and number of their lesions were determined according to computed tomography and magnetic resonance imaging findings. General information of patients, including age, sex, Durie/Salmon (DS) stage, international staging system (ISS) stage, isotype, iesion site, preoperative/postoperative treatment, chemotherapy regimens, radiotherapy, operation scheme, and stem cell transplantation therapy, were collected.

The general physical condition of patients before surgical treatments, including nutrition status, body mass index (BMI), performance status and MM activity, were collected. The classification criteria of nutrition status are as follows: (1) "Well", the mucous membrane is ruddy, the skin is shiny and elastic, the subcutaneous fat is plump and elastic, the skinfold thickness is normal or enlarged, the muscle is strong, the nails and hair are moist, the intercostal space and supraclavicular fossa are moderate, and the scapular and abdominal muscles are plump. Body weight and body mass index are in the normal range or slightly above normal; (2) "Poorly", the skin and mucous membrane is dry, the elasticity is reduced, the subcutaneous fat is thin, the skinfold thickness is lower than normal, the muscle is loose and weak, the nails are rough, the hair is sparse and dull, the intercostal space and supraclavicular fossa are sunken, and the shoulder, ribs and iliac bones are prominent. Body weight and body mass index were significantly lower than normal; (3) "Fairly", between the above two classification criteria.

The evaluation of the patient's performance status is based on the Zubrod-ECOG-WHO score (ZPS score, 5-point method), as follows: Grade 0 normal activity, Grade 1 symptoms but nearly ambulatory, Grade 2 some bed time but needs to be in bed less than 50% of the normal daytime, Grade 3 needs to be in bed more than 50% of the normal daytime, Grade 4 unable to get out of bed, Grade 5 death.

According to routine blood examination, the NLR was obtained using the absolute number of neutrophils and lymphocytes, calculated by the number of neutrophils divided by the number of lymphocytes. According to their NLR values, patients were grouped into a high NLR group (NLR ≥ 3 patients) and a low NLR group (NLR < 3 patients). Moreover, their cumulative survival rates were calculated according to their survival 1 year, 3 years, and 5 years after the operation.

Statistical analysis

Patient clinical data were analyzed by the chi-square test and independent sample *t*-test. The risk factors that may affect the POS in patients were analyzed by Cox model analysis. The survival time was assessed by the Kaplan-Meier method and examined by the log-rank test. The chi-square test was used to analyze the 1-year, 3-year, and 5-year cumulative survival rates of patients with different preoperative peripheral blood NLRs to calculate the cut-off value and select the NLR cut-off value with the most significant difference for grouping. Peripheral blood lymphocyte percentage was used as the evaluation indicator to preliminarily assess the immune status of 82 MMBD patients before and after the operation and to perform a univariate analysis on the lymphocyte percentages of the 82 postoperative patients at different stages and preliminarily assess the effect of operations on the immune status of MMBD patients. One-way ANOVA and the Mann-Whitney *U* test for further comparisons between specific group pairs were used. All data were analyzed by SPSS 19.0 statistical software (IBM SPSS Statistics 19.0). The measurement data are expressed as the mean ± standard deviation, and $P < 0.05$ was considered as a significant difference.

RESULTS

Among the 82 MMBD patients with an average age of 60.33 ± 9.62 years, 44 patients were male (53.7%) and 38 patients were female (46.3%). The spine was involved in 56 patients (68.3%), long bone of the limb in 19 (23.2%) patients, and the soft tissue in 7 (8.5%) patients. The average time from diagnosis to treatment of 82 patients was 19.48

mo (19.48 ± 26.69). Nine patients (11%) underwent complete excision, 72 (87.8%) underwent partial excision/intra-lesion curettage, and 1 patient (1.2%) underwent tissue biopsy. Twenty patients (24.4%) received autologous stem cell transplantation, while sixty-two patients (75.6%) did not. The average follow-up period of 82 patients was 27.03 ± 21.31 mo (range, 0.25-84 mo) (Table 1).

General physical condition before surgical treatment
The results showed that the preoperative BMI of 82 patients was 23.14 ± 3.36. The preoperative nutrition status classification showed "Well" in 68 patients, "Fairly" in 6 patients and "Poorly" in 8 patients. The results of the preoperative performance status of 82 patients showed that 16 patients (19.5%) were grade 0-2, and 66 patients (80.5%) were grade 3-4. The data on MM activity at the time of surgery of 82 patients showed that there were 2 cases (2.4%) of partial remission, 8 cases (9.8%) of stable disease and 72 cases (87.8%) of progressive disease (Table 2).

Effect of preoperative peripheral blood NLR on the POS of MMBD patients
After statistically analyzing the correlation between the preoperative peripheral blood NLR and POS, it was observed that the NLR cut-off values of the preoperative peripheral blood NLR ≥ 3 and NLR ≥ 4 were significantly correlated with the postoperative cumulative survival rate (Table 3). In particular, when the NLR cut-off value was set to 3, the difference was most significant. The POS of NLR ≥ 3 patients (n = 26)(14.86 ± 14.28 mo) was significantly lower than that of NLR < 3 patients (n = 56)(32.68 ± 21.76 mo) (P = 0.000) (Table 4, Figure 1). Among the 82 patients, 48 patients have received chemotherapy before surgical treatments. There were 11 (22.9%) patients in the immunomodulator-based treatment group, 20 (41.7%) patients in the proteasome inhibitor-based treatment group and 17 (35.4%) patients in the immunomodulator and proteasome inhibitor treatment groups. Seventy-one patients have received chemotherapy after surgical treatments (Table 4).

Univariate analysis showed that the preoperative BMI in the high NLR group was significantly lower than that in the low NLR group (21.74 ± 3.13 *vs* 23.79 ± 3.29, *P* = 0.009). There was no significant difference in preoperative chemotherapy regimens (*P* = 0.216), the time from diagnosis of MM to surgery (*P* = 0.321), the performance status (*P* = 0.066), MM activity at the time of surgery (*P* = 0.590) and postoperative chemotherapy regimens (*P* = 0.159) between the high NLR group and the low NLR group (Table 4).

The general condition of patients on preoperative peripheral blood NLR
Univariate analysis showed that the number of lesions affected NLR to some extent (*P* = 0.033), while sex, ISS stage, lesion sites, chemotherapy, and autologous stem cell transplantation did not affect the NLR (Table 4). Differences in preoperative Hb and aspartate aminotransferase (AST) were found between the high NLR group and the low NLR group (*P* = 0.047, *P* = 0.007), while no difference was found for PLT and pre/postoperative C-reactive protein (CRP) (Table 5).

Changes in peripheral blood absolute lymphocyte count and absolute neutrophil count before and after the operation
The absolute neutrophil count 1 wk after the operation significantly increased (4.78 ± 2.37 × 109/L). One month after the operation (3.72 ± 1.96 × 109/L), the levels returned to those before the operation (Table 6, Figure 2). The peripheral blood NLR after the operation significantly increased (2.78 ± 1.97 *vs* 4.56 ± 2.33, *P* = 0.002) and then declined 1 mo after the operation (3.14 ± 2.19). The levels increased again at the last follow-up visit (5.03 ± 6.73) (Table 6, Figure 3).

When preliminarily analyzing the immune status of the 82 MMBD patients before and after the operation with the peripheral lymphocyte percentage as the evaluation indicator, the results showed that the peripheral lymphocyte percentage of MMBD patients before operation (25.09% ± 9.96%) was at a normal (low) level; 1 wk after operation, it (18.19% ± 7.19%) significantly declined; 1 mo after operation, it (26.66% ±

10.70%) returned to that before operation; at the last follow-up visit, it (22.83% ± 12.68%) returned to a low level again (Table 6, Figure 4).

Factors affecting the POS of MMBD patients

Kaplan-Meier analysis showed that the number of lesions, site of lesion, postoperative chemotherapy, preoperative performance status and preoperative peripheral blood NLR ≥ 3 were risk factors affecting POS (Table 7). Multivariate survival analysis showed that postoperative chemotherapy (P = 0.000), preoperative performance status (P = 0.002), and preoperative peripheral blood NLR ≥ 3 (P = 0.000) were independent risk factors affecting POS (Table 8).

DISCUSSION

Clinical value of peripheral blood NLR in predicting the prognosis of MMBD patients treated with an operation. Multiple myeloma is a malignant proliferative disease of plasma cells, where its occurrence and development are strongly dependent on the microenvironment. The interaction between MM cells and the microenvironment has a crucial role in the pathogenesis of MM[10-12]. The MM microenvironment is mainly composed of inflammatory cells (including macrophages, dendritic cells, mast cells, and myeloid-derived suppressor cells). Tnflammatory cells are the main source of MM-infiltrating bone marrow cytokines and also mediate immune suppression of MM[13-16]. Inflammation is one of the characteristics of malignant tumors, and tumor-related inflammation has an important role in promoting tumorigenesis by inducing tumor cell growth, angiogenesis, and genomic instability[17]. As a marker of systematic inflammation, NLR has also been used as an immune status indicator for the prognosis of solid tumors[18].

Our study showed that compared with MMBD patients in the low NLR group, those in the high NLR group had a different number of lesions, preoperative hemoglobin levels, preoperative glutamate transaminase, and preoperative absolute lymphocyte count. Multivariate survival analysis showed that postoperative chemotherapy and

preoperative peripheral blood NLR were independent risk factors affecting the POS of MMBD patients.

Some studies have also reported on NLR prognosis prediction in patients with hematologic tumors[19-23]. Zhou *et al*[24] found that an elevated NLR is associated with decreased overall survival in MM patients receiving bortezomib induction therapy. Wongrakpanich *et al*[25] reported that an elevated NLR and a decreased platelet-lymphocyte ratio are independent prognostic factors for progression-free survival in MM patients. Shi *et al*[26] indicated that an elevated NLR, a decreased monocyte-lymphocyte ratio and a decreased platelet-lymphocyte ratio predict adverse clinical outcomes in MM patients and may serve as cost-effective and readily available prognostic biomarkers. Lee *et al*[27] analyzed 179 MM patients treated with the VMP regimen and found that a high NLR was an independent poor prognostic factor. Solmaz *et al*[28] reviewed 150 MM patients who underwent autologous stem cell transplantation (ASCT), and found that a high NLR on the 100th day posttransplantation was associated with inferior overall survival (OS) and Progression-free survival (PFS). Romano *et al*[29] showed that the median PFS was significantly shorter for MM patients with NLR ≥ 2 when considering the clinical outcomes of ASCT. In summary, MM patients have shortened OS with a high NLR.

To date, there are no reports on the prognostic value of NLR in MM patients who undergo an operation. We think that elevated NLR may be used as a prognostic biomarker for the prediction of survival and help predict clinical outcome in patients with MMBD. Before it can be used in clinical practice, the time to detect NLR and the cut-off value should be further standardized.

Change laws of peripheral blood NLR before and after the operation

Due to the great range of tumor tissue removal during surgery, the tumor load significantly decreased, and the stimulating effect of tumor cells on the immune and inflammatory reaction was reduced, resulting in great changes in the NLR before and after the operation. A previous study found that the NLR of a nonsmall cell lung cancer

patient at 1 mo after operation increased by over 0.27, and the DFS and OS of the same patient were significantly shorter than those whose NLR declined or increased by less than 0.27, thus suggesting that NLR changes before and after the operation could be used for the early evaluation of the effectiveness of tumor therapy[30].

In this study, we found that MM patients had a high NLR before the operation, which significantly increased 1 wk after the operation. In the second week after the operation, the absolute neutrophil count significantly increased while the absolute lymphocyte count declined; in the second month, the NLR declined while the absolute neutrophil count and absolute lymphocyte count returned to levels before the operation. At the last follow-up visit, the NLR returned to a high level while the absolute neutrophil count significantly increased and the absolute lymphocyte count significantly declined. This change indicates that a high preoperative NLR, which may be the result of the imbalance of inflammatory reactions between antitumor and protumor effects, may be used to predict poor prognosis in MM patients[26]. An elevated NLR indicates that the neutrophils in an MM patient's blood increased while the lymphocytes decreased, resulting in an imbalance between the antitumor effect of lymphocytes and the protumor effect of neutrophils, thus affecting the prognosis of tumor patients.

Changes in the immune status of MMBD patients before and after the operation and their effect on prognosis

Cellular immunity and humoral immunity play a key role in the occurrence and progression of tumors. The function and status of cellular immunity largely reflect the progression of tumors and the prognosis of patients. At present, antitumor cell immunotherapy based on the correlation between cellular immunologic function and status and tumors is commonly applied in clinical practice.

In this study, we found normal levels of neutrophils in MM patients before surgery. These levels significantly increased 1 wk after the operation and then returned to normal levels 1 mo after the operation; at the last follow-up visit, the levels were lower

than before the operation. We believe that 1 wk after the operation, patients were in the postoperative inflammatory reaction stage, so their neutrophils were high. However, with time, the immune status recovered, which led to a decrease in neutrophils. This may be a normal body reaction; however, whether such a reaction affects tumors needs to be further explored. At the last follow-up visit, the tumor status of patients was improved, and the level of their neutrophils declined over that before operation due to the application of treatment measures such as operations and chemotherapy. Peripheral blood NLR before and 1 mo after operation may reflect the immune status of patients from one side and can be used as one of the indicators for predicting operative prognoses.

Correct judgment and evaluation of the cellular immunologic function of patients with malignant tumors have an important role in evaluating disease development and guiding clinical treatment. Multiple myeloma is characterized by immunologic dysfunction. MM immune injury has been considered as another tool to predict prognosis[30]. Long-term survival in MM patients may result from unique immunologic characteristics[31]. Lymphocytes are an important part of the immune system. They contain subsets of different functions, which can be roughly divided into T cells, B cells, and NK cells. Domestic and foreign studies have found various defects in the immune system of MM patients, including abnormal quantities and functional defects in B cells, T cells, NK cells, and DC cells, as well as abnormal regulatory Tregs[32,33]. Bernal et al[34] found that the number of NK cells in the peripheral blood of MM patients was increased, while their activity declined. Furthermore, Jurisic et al[35] proved that the decline in NK cell activity in patients was related to disease progression and the degree of plasma cell infiltration.

T cells have a major role in the antitumor immune reaction of tumor patients and regulate the immune reaction and maintain immune stability. T cell subset expression anomalies have an important role in the pathogenesis of MM. Koike et al[36] and Oken et al[37] have found a decrease in CD4(+) T/CD8(+) T cells in MM patients, which disrupts the immune balance of MM patients and weakens their existing antitumor functions.

Tregs are a subset of T cells that control autoimmunity and have a negative immunoregulatory function, which maintains the immune system stability of the body together with Th1 and Th2 cells. It is related to the immune tolerance and tumor immune escape mechanisms[38,39]. Recent studies have found a lower proportion of Th1 and Th2 cells in MM patients that in healthy controls, suggesting that both humoral and cellular immunity of MM patients are impaired to varying degrees[40]. Therefore, lymphocyte subsets and Th cells are of great significance in the prognostic evaluation of MM patients. Lymphocytes have a key role in cell-mediated antitumor immune reactions, and their amount reflects the degree of reaction of the host immune system.

Whether operations affect the immune status of MM patients has not yet been clarified. Our data showed that the lymphocyte percentage of MM patients was within normal (low) levels before the operation. These levels declined 1 mo after surgery and returned to normal levels later on (at the last follow-up visit), which suggests that operations affect the immune status of patients with MM. After the operation, the immune balance of MM patients is disrupted, which in turn affects the immune status. However, with time, immune status is recovered. Therefore, for MM patients who undergo surgery, adjuvant therapy to enhance their immunity may be given when necessary to allow patients to build up their immune status, which may be helpful for the overall treatment of MM patients. The correlation between such results and the timing of chemotherapy after surgery needs further study.

Neutrophils have a multivariate role in tumor diseases. However, their role in cancer is not been fully understood[41]. Neutrophils reflect the inflammatory state of tumor patients and have different roles in different stages of tumor diseases[42]. Neutrophils release reactive nitrogen species, reactive oxygen species, and proteases that promote the occurrence of tumors[43]. Nitric oxide synthase or arginase 1 released by neutrophils can inhibit the antitumor reaction of CD8(+) T lymphocytes[44] by weakening the immune system, promoting tumor proliferation, and invasion and stimulating TGF-β[45]. Moreover, some researchers believe that an increase in neutrophil count is one of the adverse prognostic factors of head and neck cancer progression[46].

Nonetheless, this study had some limitations. Due to the length of diagnosis and treatment and numerous follow-up visits, the lymphocyte subset information at different time points was not available for some patient. Second, due to different treatment regimens of patients during the treatment period, the detection of peripheral blood-related cells alone cannot fully reflect the body's immune status.

Related risk factors in MMBD patients

The lesion site, number of lesions, postoperative chemotherapy, preoperative peripheral blood NLR and preoperative performance status are the risk factors affecting POS in MMBD patients. Postoperative chemotherapy, preoperative peripheral blood NLR and preoperative performance status are independent risk factors.

Performance status, as a score to evaluate the physical activity status of patients, can reveal their general health status and tolerance to treatment based on their physical strength. For patients with poor general health before surgery, their tolerance to surgery is worse, recovery time is slower, and postoperative complications are more likely to occur, and the survival time is often shorter. However, as a subjective scoring system, some results do not fully respond to the true condition of patients. Comprehensive evaluation of other indicators such as BMI, muscle fat ratio, and bone density, is required to determine this.

Chemotherapy is another independent risk factor affecting the POS of patients with MMBD. Chemotherapy is the most important treatment method for multiple myeloma, and helps to control tumors and extend the survival period. However, there is often a large disparity in treatment tolerance that affects the statistical analysis. If some patients are insensitive to chemotherapy or change chemotherapy regimens frequently, this may affect the accuracy of the statistical results. To a certain extent, NLR is an indicator of systemic inflammatory reactions, which can reflect the balance between inflammation and immunity in tumor patients. We can obtain relevant values directly from the peripheral blood. However, NLR easily interferes with other factors. For patients with other infectious diseases or those who are using certain drugs, the values from the

peripheral blood are not completely accurate. If the numerical difference is found in the measurement, it should be rerecorded in time.

CONCLUSION

MMBD patients with a high preoperative NLR had a poorer prognosis and shorter POS. The immune status of MMBD patients was at a normal low level and then significantly declined after surgical treatments. The NLR can predict the prognosis of MM patients undergoing surgical treatments.

ARTICLE HIGHLIGHTS

Research background

This study investigated the preoperative peripheral blood neutrophil-lymphocyte ratio (NLR) in predicting postoperative survival (POS) in patients with multiple myeloma bone disease (MMBD).

Research motivation

As a marker of systematic inflammation, NLR has been used to diagnose infectious diseases. Although some retrospective studies have initially explored the influence of NLR on the prognosis of MM in recent years, these studies didn't report on whether there is any change in the immune status of MM patients before and after the operation.

Research objectives

To analyze the effect of preoperative peripheral blood NLR on the prognosis of MMBD patients and evaluate the immune status of MMBD patients in different time periods.

Research methods

The clinical data of 82 MMBD patients who underwent surgical treatments in Beijing Chaoyang hospital were collected.

Research results

Data showed that the NLR cut-off values of the NLR ≥ 3 group and NLR ≥ 4 group were significantly correlated with POS. The POS of NLR ≥ 3 patients (14.86 ± 14.28) was significantly shorter than that of NLR < 3 patients (32.68 ± 21.76). The lymphocyte percentage 1 wk after operation (19.329 ± 9.083) was significantly lower than that before operation (25.723 ± 11.016). Survival analysis showed that postoperative chemotherapy and preoperative peripheral blood NLR were independent risk factors for POS.

Research conclusions

MMBD patients with high preoperative NLR had a poorer prognosis and shorter POS. NLR can predict the prognosis of MM patients undergoing surgical treatments.

Research perspectives

Preoperative peripheral blood NLR can predict POS in MMBD patients. The immune status of MMBD patients was at a normal low level and then it significantly declined after surgical treatments.
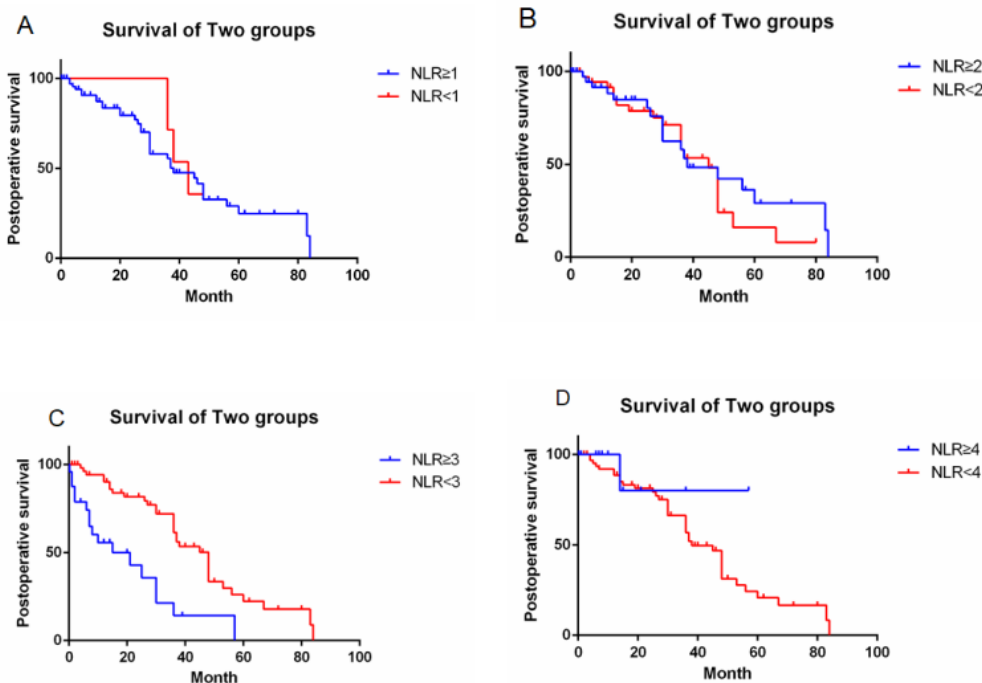
Figure 1 title. A: Comparison of postoperative survival (POS) in patients within the neutrophil-lymphocyte ratio (NLR ≥ 1) group and NLR < 1 group, among which the POS of patients in the NLR ≥ 1 group and the NLR < 1 group showed no significant difference ($P > 0.05$); B: The POS of patients in the preoperative peripheral blood NLR ≥ 2 group and the NLR < 2 group showed no significant difference ($P > 0.05$); C: The POS of patients in the preoperative peripheral blood NLR < 3 group was significantly longer than that in the NLR ≥ 3 group ($P < 0.05$); D: The POS of patients in the preoperative peripheral blood NLR < 4 group was significantly longer than that in the NLR ≥ 4 group ($P < 0.05$). NLR: Neutrophil-lymphocyte ratio.
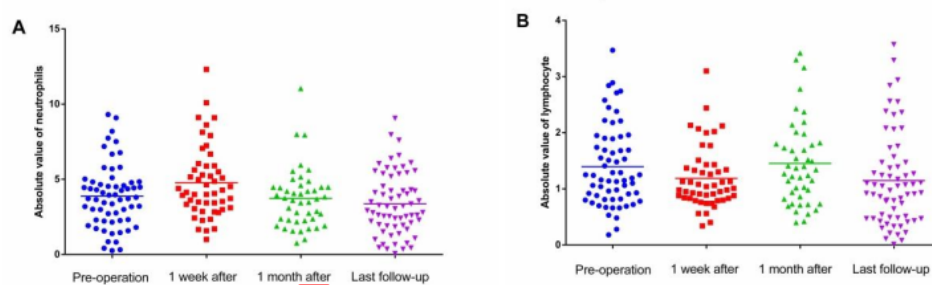
Figure 2 Comparison of absolute neutrophil count and lymphocyte count between preoperation, 1 week after the operation, 1 month after the operation and the last follow-up visit in multiple myeloma bone disease patients. A: The absolute neutrophil count increased significantly 1 wk after the operation and returned to that before the operation 1 mo after the operation; B: The peripheral blood absolute lymphocyte count declined after the operation, returned to that before the operation 1 mo after the operation, and returned to a low level at the last follow-up visit.

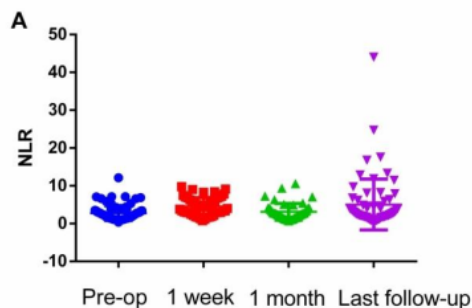**Figure 3 Comparison of peripheral blood neutrophil-lymphocyte ratio between preoperation, 1 week after the operation, 1 month after the operation and the last follow-up visit in multiple myeloma bone disease patients.**
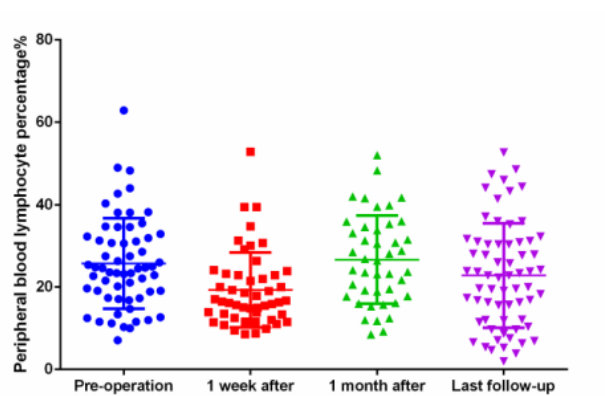
Figure 4 Comparison of lymphocyte percentage between preoperation, 1 week after the operation, 1 month after the operation and the last follow-up visit in multiple myeloma bone disease patients.

Table 1 General information of the 82 multiple myeloma bone disease patients who underwent surgical treatments

Characteristic	Value *n* (%) or *n* [SD]
Age (yr)	60.33 [9.620]
Gender	
Male	44 (53.7)
Female	38 (46.3)
ISS stage	
ISS-I	15 (18.3)
ISS-II	37 (45.1)
ISS-III	30 (36.6)
Number of lesions	
1	53 (64.6)
2	18 (22.0)
≥ 3	11 (13.4)
Site of lesion	
Spine	56 (68.3)
Long bone of limb	19 (23.2)
Soft tissue	7 (8.5)
Isotype	
IgA	23 (28)
IgD	3 (3.7)
IgG	45 (54.9)
Light chain κ/λ	11 (13.4)
Preoperative chemotherapy	
Yes	48 (58.5)
No	34 (41.5)
Postoperative chemotherapy	
Yes	71 (86.6)
No	11 (13.4)
Preoperative radiotherapy	

Yes	6 (7.3)
No	76 (92.7)
Time from a diagnosis to surgery (mo)	19.48 [26.69]
Operation scheme	
Complete excision[1]	9 (11)
Partial excision/intramedullary curettage[2]	72 (87.8)
Tissue biopsy[3]	1 (1.2)
Autologous stem cell transplantation	
Yes	20 (24.4)
No	62 (75.6)
POS (mo)	27.03 [21.31]
Total survival (mo)	46.63 [31.04]

[1]The soft-tissue mass extended resection or partial rib resection.

[2]Intralesional resection and filling with polymethylmethacrylate bone cement in long bone of limb metastases or incomplete metastasectomy in spinal metastases.

[3]Percutaneous biopsy.

SD: Standard Deviation; ISS: International staging system; POS: Postoperative survival.

Table 2 General physical condition of 82 multiple myeloma bone disease patients before surgical treatments

Characteristic	Value n (%) or n [SD]
Preoperative nutrition	
Well	68 (82.9)
Fairly	6 (7.3)
Poorly	8 (9.8)
Preoperative BMI (kg/m^2)	23.14 [3.36]
Preoperative performance status	
Grade 0-2	16 (19.5)

Grade 3-4	66 (80.5)
Preoperative MM activity	
Partical remission	2 (2.4)
Stable disease	8 (9.8)
Progression disease	72 (87.8)

BMI: Body mass index; MM: Multiple myeloma.

Table 3 Comparison of 1-year, 3-year and 5-year cumulative survival rates between the high and the low neutrophil-lymphocyte ratio group

Cutoff value of NLR	1-yr CSR[a]	3-yr CSR[a]	5-yr CSR[a]	Chi-square	P value
NLR ≥ 4	41.7% vs 82.5%	10.4% vs 60.9%	0.0% vs 41.7%	15.969	0.000[a]
NLR ≥ 3 (n = 26)	52.0% vs 87.3%	19.1% vs 67.2%	0.0% vs 48.3%	22.192	0.000[a]
NLR ≥ 2	65.8% vs 88.9%	46.5% vs 61.1%	31.0% vs 34.0%	2.015	0.156
NLR ≥ 1	75.3% vs 85.7%	52.6% vs-	30.6% vs-	0.459	0.498

[a]$P < 0.05$.

NLR: Neutrophil-lymphocyte ratio; CSR:

Table 4 Univariate analysis of the general information of patients in the high and the low neutrophil-lymphocyte ratio group

Characteristic	NLR < 3 (n = 56)	NLR ≥ 3 (n = 26)	P Value
Age (Yr)	60.93 ± 9.88	59.04 ± 9.10	0.411
Gender			0.981
Male	30 (53.6%)	14 (53.8%)	
Female	26 (46.4%)	12 (46.2%)	
ISS stage			0.693
ISS-I	10 (17.9%)	5 (19.2%)	
ISS-II	27 (48.2%)	10 (38.5%)	

ISS-III	19 (33.9%)	11 (42.3%)	
Number of lesions			0.033a
1	41 (73.2%)	12 (46.2%)	
2	8 (14.3%)	10 (38.5%)	
≥ 3	7 (12.5%)	4 (15.4%)	
Site of lesion			0.982
Spine	38 (67.9%)	18 (69.2%)	
Long bone of limb	13 (23.2%)	6 (23.1%)	
Soft tissue	5 (8.9%)	2 (7.7%)	
Time from a diagnosis to surgery (mo)	21.18 ± 29.75	15.81 ± 18.44	0.321
Preoperative nutrition			0.071
Well	50 (89.3%)	18 (69.2%)	
Fairly	3 (5.4%)	3 (11.5%)	
Poorly	3 (5.4%)	5 (19.2%)	
Preoperative BMI (kg/m^2)	23.80 ± 3.29	21.74 ± 3.13	0.009a
Preoperative performance status			0.066
Grade 0-2	14 (25.0%)	2 (7.7%)	
Grade 3-4	42 (75.0%)	24 (92.3%)	
MM activity at the time of surgery			0.590
Partical response	2 (3.6%)	0 (0.0%)	
Stable disease	5 (8.9%)	3 (11.5%)	
Progressive disease	49 (87.5%)	23 (88.5%)	
Preoperative chemotherapy			0.707
Yes	32 (57.1%)	16 (61.5%)	
No	24 (42.9%)	10 (38.5%)	
Preoperative chemotherapy regimens ($n = 48$)			0.216
Immunomodulator-based	6 (37.5%)	5 (15.6%)	
Proteasome inhibitor-based	6 (37.5%)	14 (43.8%)	
Both immunomodulator and proteasome inhibitor	4 (25.0%)	13 (40.6%)	

Postoperative chemotherapy			0.080
Yes	51 (91.1%)	20 (76.9%)	
No	5 (8.9%)	6 (23.1%)	
Postoperative chemotherapy regimens ($n = 71$)			0.159
Immunomodulator-based	3 (6.0%)	4 (19.0%)	
Proteasome inhibitor-based	17 (34.0%)	4 (19.0%)	
Both immunomodulator and proteasome inhibitor	30 (60.0%)	13 (61.9%)	
Autologous stem cell transplantation			0.458
Yes	15 (26.8%)	5 (19.2%)	
No	41 (73.2%)	21 (80.8%)	
POS (mo)	32.68 ± 21.76	14.86 ± 14.28	0.001

[a]$P < 0.05$.

NLR: Neutrophil-lymphocyte ratio; POS: Postoperative survival; ISS: International staging system; BMI: Body mass index; MM: Multiple myeloma.

Table 5 Univariate analysis of the preoperative laboratory examination of patients in the high and the low neutrophil-lymphocyte ratio group

Preoperative laboratory examination	NLR < 3 (*n* = 56)	NLR ≥ 3 (*n* = 26)	P value
Hb (g/L)	112.66 ± 24.88	100.58 ± 25.91	0.047[a]
PLT ([a]10⁹/L)	208.38 ± 77.39	196.89 ± 103.64	0.577
ALb (g/L)	32.88 ± 6.02	31.16 ± 6.29	0.237
AST (U/L)	22.89 ± 8.39	33.96 ± 18.79	0.007[a]
ALT (U/L)	19.89 ± 10.28	28.46 ± 24.17	0.093
Γ-GT (U/L)	34.11 ± 27.52	47.58 ± 38.19	0.073
Blood β2-MG (mg/L)	5.43 ± 9.08	4.10 ± 2.85	0.475
Cr (umol/L)	84.54 ± 73.73	89.38 ± 85.84	0.794
Preoperative CRP (mg/L)	2.60 ± 3.84	3.67 ± 3.93	0.411
Post-operative CRP (mg/L)	1.98 ± 2.79	1.83 ± 2.06	0.877

[a]$P < 0.05$.

NLR: Neutrophil-lymphocyte ratio; CPR: C-reactive protein; AST: Aspartate aminotransferase; Hb: Alb: ALT: Γ-GT: Cr:

Table 6 One-way ANOVA results of peripheral blood absolute lymphocyte counts, absolute neutrophil counts and neutrophil-lymphocyte ratio of the 82 multiple myeloma bone disease patients at different time points (Mean ± SD)

Characteristic	Before operation	1 wk after operation	1 mo after operation	Last follow-up visit	F	P value
Absolute blood lymphocyte counts	1.34 ± 0.75	1.19 ± 0.55	1.45 ± 0.76	1.15 ± 0.82ab	2.382	0.070
Absolute neutrophil counts	3.87 ± 2.07	4.79 ± 2.37cde	3.72 ± 1.96	3.36 ± 2.04	4.376	0.005
NLR	2.78 ± 1.97fg	4.56 ± 2.33	3.14 ± 2.19h	5.03 ± 6.73	4.998	0.002
Lymphocyte percentages (%)	25.09 ± 9.96	18.19 ± 7.19cd	26.66 ± 10.70	22.83 ± 12.68	5.770	0.001

NLR: Neutrophil-lymphocyte ratio.

Table 7 Kaplan–Meier analysis of postoperative survival of patients with multiple myeloma bone disease (univariate survival analysis)

Characteristic	Chi-Square	*P* value
Gender	1.703	0.192
ISS stage	1.966	0.374
Number of lesions	7.055	0.029[a]
Site of lesion	8.160	0.017[a]
Isotype	1.526	0.676
Preoperative chemotherapy	0.387	0.534
Postoperative chemotherapy	35.837	0.000[a]
Preoperative radiotherapy	0.908	0.341
Time from a diagnosis to surgery	1.841	0.606
Operation scheme	3.583	0.167
Stem cell transplantation	2.836	0.092
Preoperative peripheral blood NLR ≥ 3	22.192	0.000[a]
Preoperative nutrition	0.782	0.676
Preoperative performance status	20.775	0.000[a]
Preoperative MM activity	1.634	0.652

[a]*P* < 0.05.

NLR: Neutrophil-lymphocyte ratio; ISS: International staging system; MM: Multiple myeloma.

Table 8 Multivariate Cox regression analysis of postoperative survival of patients with multiple myeloma bone disease

Characteristic	*P* value	HR	95% CI
Site of lesion	0.185	-	-
Number of lesions	0.462	-	-
Postoperative chemotherapy	0.000[a]	0.142	0.057-0.357

Preoperative peripheral blood NLR ≥ 3	0.000[a]	3.503	1.815-6760
Preoperative performance status	0.002[a]	0.041	0.005-0.318

[a]$P < 0.05$

NLR: Neutrophil-lymphocyte ratio.

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