FEBS Open Bio 5 (2015) 682–687

journal homepage: www.elsevier.com/locate/febsopenbio

Pre-operative lymphocyte-to-monocyte ratio as a predictor of overall survival in patients suffering from osteosarcoma

Tao Liu [a,1], Xuan-Cheng Fang [a,1], Zhen Ding [b], Ze-Gan Sun [c], Li-Ming Sun [d,*], Yi-Lian Wang [d,*]

[a] Department of Orthopaedics, The First People's Hospital of Anqing, Anhui 246000, China
[b] Department of Vascular Surgery, Anqing Municipal Hospital, Anhui 246000, China
[c] Department of Orthopaedics, Fuzhou General Hospital of Nanjing Military Command, Fujian 350025, China
[d] Department of Cardiology, The Second People's Hospital of Lianyungang, Xinpu, Jiangsu 222006, China

ARTICLE INFO

Article history:
Received 2 July 2015
Revised 31 July 2015
Accepted 3 August 2015

Keywords:
Osteosarcoma
LMR
Prognosis
Nomogram

ABSTRACT

Inflammatory markers have been proposed to predict clinical outcomes in many types of cancers. The purpose of this study was to explore the influence of the lymphocyte-to-monocyte ratio (LMR) on clinical prognosis of patients with osteosarcoma. This study collected 327 patients who underwent surgical treatment for osteosarcoma during the period 2006–2010. LMR was calculated from pre-operative peripheral blood cells counts. The optimal cut-off value of LMR was determined based on receiver operating characteristic curve analysis. Overall survival (OS) and event free survival (EFS) was plotted using the Kaplan–Meier method and evaluated by the log-rank test. A predictive model was established to predict clinical prognosis for OS, and the predictive accuracy of this model was determined by concordance index (*c*-index). Our results showed that young age, elevated alkaline phosphatase, metastasis at diagnosis, chemotherapy, lymphocyte and monocyte counts were significantly associated with LMR. Low LMR was associated with shorter OS and EFS ($P < 0.001$), and was an independent predictor of both OS and EFS (HR = 1.72, 95% CI = 1.14–2.60, $P = 0.010$; HR = 1.89, 95% CI = 1.32–2.57, $P = 0.009$). The nomogram performed well in the prediction of overall survival in patients with osteosarcoma (*c*-index 0.630). In conclusion, low pre-operative LMR is associated with a poor prognosis in patients suffering from osteosarcoma. A prospective study is warranted for further validation of our results.

1. Introduction

Osteosarcoma is the most common primary malignant tumors of bone [1]. Epidemiological data showed that there were two peaks of incidence in osteosarcoma patients, particularly among early adolescence aged 15–19 years [2]. In recent years, patients' age with osteosarcoma is increasing [3] and patients over the age of 40 years account for 13–30% of all patients with osteosarcoma [4]. According to epidemiological data, osteosarcoma is the eighth leading cancer with an incidence of 4.4 per million, mainly occurring in adolescents and adults [5]. Despite substantial progress achieved in diagnosis and treatment for osteosarcoma in the past decades, the overall 5-year survival remains unsatisfactory for local relapse or metastasis after surgical resection of primary osteosarcoma.

The poor clinical prognosis of osteosarcoma partially results from lack of a good indicator to detect tumors at an early stage. Furthermore, the ability to predict the prognosis of a patient is indispensable for selecting the optimal treatment plan and follow-up strategies. Although prognostic indicators are the Enneking surgical criteria [6] and alkaline phosphatase, heterogeneous clinical outcomes are frequently found within the same tumor stage. Therefore, it is necessary for us to further understand the underlying mechanisms and find a dependable indicator of osteosarcoma to predict clinical outcome.

Recently, the emerging evidence revealed that the systemic inflammatory response has been reported to be an independent prognostic biomarker in various types of tumor [7,8]. Published evidence has shown a significant link between inflammatory markers and poor prognosis in several types of tumors, including thrombocytosis, leukocytosis, high neutrophil-to-lymphocyte ratio (NLR) or platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-

Abbreviations: 95% CI, 95% confidence interval; AUC, areas under the curve; EFS, event free survival; HR, hazard risk; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PLR, platelet-to-lymphocyte ratio; ROC, receiver operating curve analysis

* Corresponding authors.
E-mail addresses: sunlikeday@163.com (L.-M. Sun), fangxc21@163.com (Y.-L. Wang).

[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.fob.2015.08.002
2211-5463/

monocyte ratio (LMR) [9–13]. However, the influence of LMR on the prognosis of osteosarcoma patient has been not reported. Herein, the purpose of this study was to estimate the influence of LMR on clinical prognosis in 327 osteosarcoma patients at post-operation.

2. Materials and methods

2.1. Patients

The Medical Ethics Committee of The First People's Hospital of Anqing approved this study. Written informed consents were obtained from all eligible patients. Medical records of all newly diagnosed osteosarcoma patients between 2006 and 2010 in The First People's Hospital of Anqing and The Second People's Hospital of Lianyungong were reviewed and retrospectively analyzed in the present study. The diagnosis of osteosarcoma was confirmed depended on histological evidence and classified on the basis of the Enneking surgical criteria [6]. The inclusion criteria were as follows: (1) no prior pre-operative anticancer treatment, such as chemotherapy, blood transfusion, and radiotherapy. (2) All patients with osteosarcoma underwent surgical resection. (3) No hematology disease, infection and hyperpyrexia. (4) Informed consents were obtained. Finally, 327 patients were enrolled in the present study. Clinical features of eligible patients were collected including age, sex, tumor location, pathological fracture, alkaline phosphatase (ALP), clinical stage, metastasis at diagnosis and post-operative chemotherapy.

2.2. Blood sample analysis

Blood samples were obtained for the measurement of lymphocyte and monocyte counts at pre-operation.

2.3. Definition and optimal cut-off value of LMR

LMR was defined as the lymphocyte counts divided by the monocyte counts. Using overall survival (OS), as end-point, the optimal cut-off value of LMR was obtained when the Youden index was maximal. Subsequently, patients with a LMR greater than the corresponding cut-off value were defined as high LMR (HLMR), and others were defined as low LMR (LLMR).

2.4. Patient follow-up

Each patient was followed up regularly until death or December 2014 at post-operation. Physical examination, laboratory tests and imageological diagnosis were performed at every visit. The follow-up period varied from 3 months to 5 years, with a median of 24 months. OS was calculated from the data of surgical resection to the data of death. Event free survival (EFS) was calculated from the data of surgical resection to the data of disease relapse, progression or tumor-related death. The date of last follow-up was used for drop-out patients.

2.5. Statistical analysis

To evaluate the sensitivity and specificity of the 5-year OS, the receiver operating characteristic (ROC) curve was applied and Youden index was estimated to determine the optimal LMR cut-off value. Comparison of categorical variables was conducted using a Chi-square test. Comparison of continuous variables was conducted using a Student's t test. Survival curves were plotted by the Kaplan–Meier method and the significance was assessed by the log-rank test. Significant predictors for OS and EFS determined by univariate analysis were evaluated by multivariate analysis using Cox's proportional hazards model. Nomogram for OS was performed by R 3.0.3 software using the package of *rms* (Institute for Statistics and Mathematics, Austria). A final model selection was performed by a backward step-down selection process, and Harrell's concordance index (c-index) was applied to evaluate the predictive accuracy. All results analyses were conducted by SPSS 17.0 software (IBM, USA). P values less than 0.05 were considered statistically significant.

3. Result

3.1. Clinicopathologic characteristics

Of 327 patients with osteosarcoma, 235 (71.9%) were male, and the mean age was 20 years (range 10–44 years; Table 1). The medians of lymphocyte counts and monocyte counts were 1220 and 340 per μL, respectively. 130 (39.8%) patients with initial metastasis and 58 (17.7%) patients with pathological fracture were recorded from newly diagnosed patients. According to Enneking surgical staging criteria, the number of stage I–II and III was 168 (51.4%) and 159 (48.6%), respectively. Pathological results suggested that 267 (81.7%) patients' osteosarcomas were located in the tibia or femur. During the follow-up period, 166 (50.8%) patients had experienced systemic chemotherapy. Among all enrolled patients, 184 (56.3%) patients died from cancer-related disease, and 217 (66.4%) patients experienced disease relapse, progression or tumor-related death.

3.2. The optimal cut-off value for LMR

The areas under the curve (AUC) for LMR were 0.665 ($P < 0.001$, Fig. 1), when the OS was employed as end-point for LMR. The optimal cut-off value was 3.43 for LMR. All patients were divided into two groups with the high group that $\geqslant$ the cut-off value (HLMR) and the low group less than the cut-off value (LLMR) on the basis of the optimal cut-off value.

3.3. The associations of LMR with clinicopathologic features

To explore associations of LMR with clinicopathologic features of osteosarcoma patients, comparisons between the high and low groups for LMR were carried out (Table 1). Our results indicated that young age, elevated ALP, metastasis at diagnosis, chemotherapy, lymphocyte counts and monocyte counts were significantly associated with LMR ($P < 0.05$). However, patients' sex, tumor location, pathological fracture and clinical stage were not found to be associated with LMR.

3.4. Prognostic factors for OS and EFS

The Kaplan–Meier curve showed that the 5-year OS rates of the LLMR group were significantly lower than those of the HLMR group ($P < 0.001$; Fig. 2A), and similar result was also observed in the 5-year EFS rates ($P < 0.001$; Fig. 2B). Subsequently, univariate analyses indicated that advanced clinical stage, metastasis at diagnosis, chemotherapy and LLMR were closely correlated with poor prognosis. Furthermore, multivariate analyses of OS and EFS were performed including age, sex and clinical variables with univariate log-rank $P < 0.05$: advanced clinical stage, metastasis at diagnosis, chemotherapy and LLMR. LLMR, advanced clinical stage and metastasis emerged as markers for shorter OS and EFS (Table 2),

Table 1
Association of the patients' clinical parameters with LMR.

Clinical parameters	Total $N = 327$ (%)	LMR		P
		LLMR $n = 194$ (%)	HLMR $n = 133$ (%)	
Age (year)				
≦20	217 (66.4%)	144 (74.2%)	73 (54.9%)	0.000
>20	110 (33.6%)	50 (25.8%)	60 (45.1%)	
Sex				
Male	235 (71.9%)	145 (44.3%)	90 (67.7%)	0.162
Female	92 (28.1%)	49 (55.7%)	43 (33.3%)	
Tumor location				
Tibia/ femur	267 (81.7%)	152 (78.4%)	115 (86.5%)	0.063
Elsewhere	60 (18.3%)	42 (21.6%)	18 (13.5%)	
Pathological fracture				
Yes	58 (17.7%)	32 (16.5%)	26 (19.5%)	0.478
No	269 (82.3%)	162 (83.5%)	107 (80.5%)	
ALP				
Elevated	147 (45.0%)	97 (50.0%)	50 (37.6%)	0.027
Normal	180 (55.0%)	97 (50.0%)	83 (62.4%)	
Clinical stage[a]				
I–II	168 (51.4%)	92 (47.4%)	76 (57.1%)	0.084
III	159 (48.6%)	102 (52.6%)	57 (42.9%)	
Metastasis at diagnosis				
Present	130 (39.8%)	98 (50.5%)	32 (24.1%)	0.000
Absent	197 (60.2%)	96 (49.5%)	101 (75.9%)	
Chemotherapy				
Yes	166 (50.8%)	77 (39.7%)	89 (66.9%)	0.000
No	161 (49.2%)	117 (60.3%)	44 (33.1%)	
Lymphocyte counts ($10^3/\mu L$)[b]	1.22 (0.08–4.85)	1.57 (0.60–4.83)	0.91 (0.09–4.44)	0.000
Monocyte counts ($10^3/\mu L$)[b]	0.34 (0.02–1.76)	0.34 (0.02–1.76)	0.31 (0.03–0.88)	0.000

ALP, alkaline phosphatase; LMR, lymphocyte-to-monocyte ratio; HLMR, high LMR; LLMR, low LMR.
[a] Clinical stage according to Enneking surgical stage.
[b] Median (range).

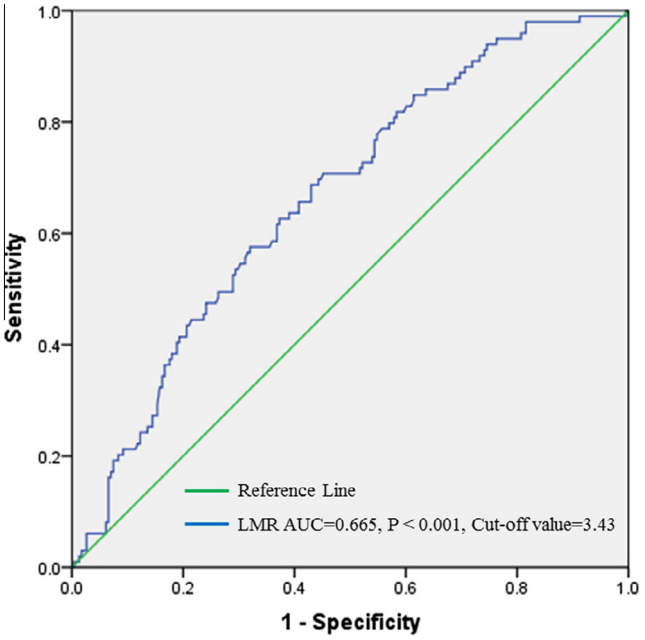

Fig. 1. ROC curves for LMR. The optimal cut-off level of LMR was determined based on the largest of sensitivity and specificity by receiver operating characteristic curve (ROC) analysis for overall survival.

and were considered as independent prognostic indicators for patients with osteosarcoma.

3.5. Prognostic nomogram for OS

To further predict the overall survival of osteosarcoma patients after surgical resection, a predictive model was constructed by Cox regression model analysis using all the significant independent risk factors for OS (Fig. 3). It can predict the probability of death of osteosarcoma within 3 or 5 years after operation, assuming the patient does not die of another cause first. The c-index for OS prediction was 0.630.

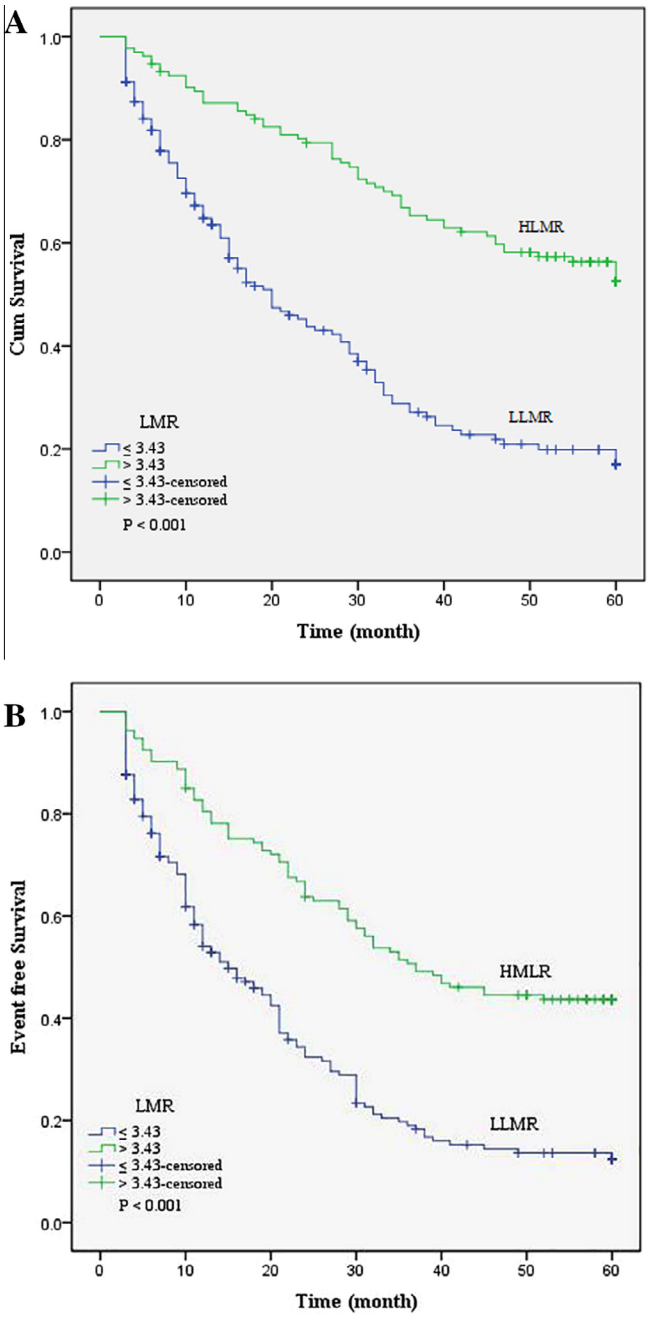

Fig. 2. Kaplan–Meier curves for survival probability according to LMR levels. (A) Patients with LMR ⩽ 3.43 had a significantly associated with worse overall survival than those with LMR > 3.43; (B) patients with LMR ⩽ 3.43 had a significantly associated with worse event free survival than those with LMR > 3.43.

Table 2
Univariate and multivariate analyses of clinical parameters for the prediction of overall survival and event free survival.

Clinical parameters	Overall survival				Event free survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*	HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Age (year)								
≦20	1		1		1		1	
>20	0.82 (0.60–1.12)	0.211	0.85 (0.62–1.16)	0.309	0.87 (0.66–1.15)	0.328	0.92 (0.69–1.23)	0.575
Sex								
Male	1		1		1		1	
Female	0.85 (0.61–1.18)	0.336	1.00 (0.71–1.40)	0.991	0.92 (0.68–1.24)	0.586	0.94 (0.69–1.27)	0.666
Tumor location								
Tibia/femur	1				1			
Elsewhere	0.83 (0.58–1.19)	0.313			0.77 (0.55–1.07)	0.113		
Pathological fracture								
Yes	1				1			
No	0.95 (0.65–1.37)	0.765			0.94 (0.66–1.32)	0.706		
ALP								
Normal	1				1			
Elevated	1.04 (0.77–1.39)	0.810			1.01 (0.78–1.32)	0.925		
Clinical stage[a]								
I–II	1		1		1		1	
III	1.59 (1.19–2.12)	**0.002**	1.44 (1.08–1.93)	**0.015**	1.46 (1.08–1.83)	**0.013**	1.21 (1.01–1.59)	**0.027**
Metastasis at diagnosis								
Absent	1		1		1		1	
Present	3.75 (2.76–5.10)	**0.000**	2.56 (1.73–3.80)	**0.000**	3.87 (3.17–4.79)	**0.000**	2.90 (2.31–3.75)	**0.001**
Chemotherapy								
Yes	1		1		1		1	
No	1.95 (1.45–2.61)	**0.000**	1.27 (0.93–1.74)	0.140	2.73 (2.32–3.27)	**0.000**	1.32 (1.00–1.76)	0.054
LMR								
HLMR	1		1		1		1	
LLMR	2.97 (2.16–4.08)	**0.000**	1.72 (1.14–2.60)	**0.010**	3.49 (2.86–4.32)	**0.000**	1.89 (1.32–2.57)	**0.009**

ALP, alkaline phosphatase; LMR, lymphocyte -to-monocyte ratio; HLMR, high LMR; LLMR, low LMR; HR, hazard ratio; CI, confidence interval.
Statistically significant results were in bold.
[a] Clinical stage according to Enneking surgical stage.

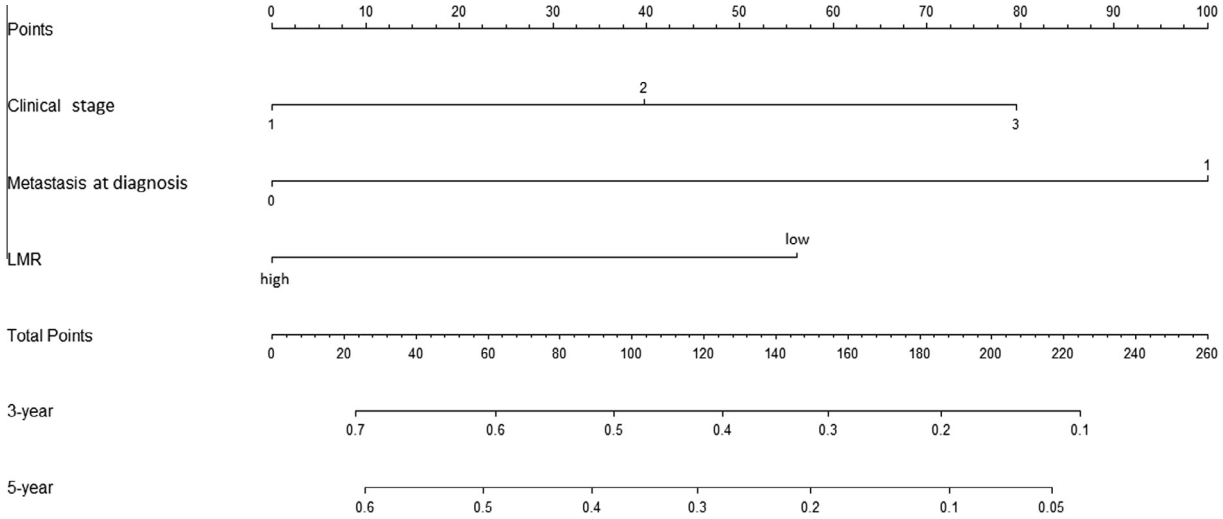

Fig. 3. Postoperative nomogram with LMR and significant clinicopathologic characteristics predicted the probability of osteosarcoma for overall survival. To use it, an individual patient's value is located on each variable axis, and a line is drawn upward to determine the number of points received for each variable parameter. The sum of these points is located on the Total Points axis, and a line is drawn downward to the survival axes to determine the probability of 3- or 5-year survival.

4. Discussion

We investigated the influence of LMR on clinical prognosis of patients with osteosarcoma which has reflected a systemic inflammatory response. The pre-operative LLMR in the peripheral blood of osteosarcoma patients was significantly associated with poor prognosis following surgery. Despite advanced progress in the understanding of the association between inflammatory biomarkers and prognosis of various cancers [7,14–16], the impact of inflammatory markers on clinical prognosis of osteosarcoma patients remains confused. Herein, this current study was the first attempt to evaluate the prognosis of patients with osteosarcoma based on LMR in the peripheral blood and establish a predictive model to improve the predictive accuracy. As the peripheral blood

cell counts test is routinely performed without need for additional effort in all patients with cancer, it is a simple, reproducible, and inexpensive parameter of the inflammatory response as well as a prognostic biomarker. Interestingly, LMR could be considered as an independent indicator for both OS and EFS by multivariate analyses.

Rudolf Virchow et al. first showed that "lymphoreticular infiltrate" could reflect the origin of tumor at the sites of chronic inflammation [17]. Over the past decades, Virchow's hypothesis was proved by the emerging studies, revealing the impact of inflammatory microenvironment on tumor. The inflammatory response, which is implicated in repair of tissue damage due to tumors, is an indispensable factor in the tumor cell microenvironment [18,19]. Hence, inflammatory cells participate in tumor proliferation, invasion, migration, angiogenesis and metastasis. Meanwhile, tumors could result from inflammatory sites, possibly by the recruitment of inflammatory cells, chemokines and cytokines. Therefore, the adaptive immune system may be converted, and this inflammatory response reactivates tumor development and progression. The inflammatory response could cause leukocytosis and lymphocytopenia [20]. The lymphocyte response plays a critical role in the suppression of tumor progression [21]. The possible mechanisms underlying neutrophilia in tumor progression and metastasis are the release of reactive oxygen species or nitric oxide and remodeling of the extracellular matrix [22]. Hence, better understanding of the links between inflammation and tumor contributes to the treatment and prevention of tumor. Various biomarkers have been reported to reflect the association of inflammation and tumor, such as interferon-gamma/interleukin-4 ratio [23] and inflammation-based prognostic score on the basis of CRP and albumin levels [24]. The systemic inflammatory marker (LMR) may be also considered as potential prognostic factors for various types of tumors. Chen et al. reported that a decreased pretreatment LMR is associated with a poor prognosis in cervical cancer patients [13]. Jiang et al. used pretreatment LMR as an independent prognostic factor in patients with metastatic nasopharyngeal carcinoma [25]. Zhang et al. found that preoperative LMR is a better prognostic factor in bladder cancer patients undergoing radical cystectomy [26].

Little evidence has shown that LMR is associated with prognosis in osteosarcoma. Our study was first attempt to evaluate the influence of LMR on prognosis of 327 osteosarcoma patients and establish a predictive model to improve the predictive accuracy for 3-year and 5-year overall survival. Similar to other results in various cancers, pre-operative LLMR was significantly associated with poor prognosis. Interestingly, a decreased preoperative LMR could be regarded as an independent prognostic factor for both OS and EFS in patients with osteosarcoma. Our constructed nomogram performed well in the prediction of overall survival (*c*-index 0.630). These data supported that the nomogram could better predict prognosis in osteosarcoma patients at post-operation.

Some limitations of our study should be acknowledged. Firstly, the study was a retrospective design, with a small population size of 327 patients, which resulted in no significant association between clinical prognosis and chemotherapy. Secondly, the peripheral blood findings were not compared with findings of peritumoral inflammation in the primary osteosarcoma tissue. Nevertheless, data in peripheral blood provided a novel horizon to understand the role of LMR in the development and progression of osteosarcoma. Finally, some heterogeneities were appeared in the treatment of osteosarcoma patients at post-operation, which resulted in different clinical prognosis. Hence, further prospective studies are necessary to illuminate the relationship between LMR and prognosis for patients with osteosarcoma.

In summary, the pre-operative LMR is associated with clinical prognosis of patients with osteosarcoma. Integrate LMR and the prognostic nomogram may be used to evaluate clinical prognosis and offer appropriate therapeutic strategy. In future, a prospective and well-designed study of LMR is warranted for further identification of our findings.

Author contributions

Conceived and designed the experiments: TL, YLW and LMS.
Performed the experiments: TL, ZD and ZGS.
Analyzed the data: TL and ZD.
Contributed reagents/materials/analysis tools: ZD and ZGS.
Wrote the manuscript: TL, YLW and XCF.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

None.

References

[1] Bielack, S., Carrle, D. and Casali, P.G. (2009) Osteosarcoma: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann. Oncol. 20 (Suppl. 4), 137–139.
[2] Damron, T.A., Ward, W.G. and Stewart, A. (2007) Osteosarcoma, chondrosarcoma, and Ewing's sarcoma: National Cancer Data Base Report. Clin. Orthop. Relat. Res. 459, 40–47.
[3] Stark, A., Kreicbergs, A., Nilsonne, U. and Silfversward, C. (1990) The age of osteosarcoma patients is increasing. An epidemiological study of osteosarcoma in Sweden 1971–1984. J. Bone Joint Surg. Br. 72 (1), 89–93.
[4] Grimer, R.J., Cannon, S.R., Taminiau, A.M., et al. (2003) Osteosarcoma over the age of forty. Eur. J. Cancer 39 (2), 157–163.
[5] Bielack, S.S., Kempf-Bielack, B., Delling, G., et al. (2002) Prognostic factors in high-grade osteosarcoma of the extremities or trunk: an analysis of 1702 patients treated on neoadjuvant cooperative osteosarcoma study group protocols. J. Clin. Oncol. 20 (3), 776–790.
[6] Enneking, W.F., Spanier, S.S. and Goodman, M.A. (1980) A system for the surgical staging of musculoskeletal sarcoma. Clin. Orthop. Relat. Res. 2003 (415), 4–18.
[7] Deng, Q., He, B., Liu, X., et al. (2015) Prognostic value of pre-operative inflammatory response biomarkers in gastric cancer patients and the construction of a predictive model. J. Transl. Med. 13, 66.
[8] Li, J., Lin, J., Luo, Y., Kuang, M. and Liu, Y. (2015) Multivariate analysis of prognostic biomarkers in surgically treated endometrial cancer. PLoS ONE 10 (6), e0130640.
[9] Forrest, L.M., McMillan, D.C., McArdle, C.S., Angerson, W.J., Dagg, K. and Scott, H.R. (2005) A prospective longitudinal study of performance status, an inflammation-based score (GPS) and survival in patients with inoperable non-small-cell lung cancer. Br. J. Cancer 92 (10), 1834–1836.
[10] Cho, I.R., Park, J.C., Park, C.H., et al. (2014) Pre-treatment neutrophil to lymphocyte ratio as a prognostic marker to predict chemotherapeutic response and survival outcomes in metastatic advanced gastric cancer. Gastric Cancer 17 (4), 703–710.
[11] Halazun, K.J., Aldoori, A., Malik, H.Z., et al. (2008) Elevated preoperative neutrophil to lymphocyte ratio predicts survival following hepatic resection for colorectal liver metastases. Eur. J. Surg. Oncol. 34 (1), 55–60.
[12] Al Murri, A.M., Wilson, C., Lannigan, A., et al. (2007) Evaluation of the relationship between the systemic inflammatory response and cancer-specific survival in patients with primary operable breast cancer. Br. J. Cancer 96 (6), 891–895.
[13] Chen, L., Zhang, F., Sheng, X.G. and Zhang, S.Q. (2015) Decreased pretreatment lymphocyte/monocyte ratio is associated with poor prognosis in stage Ib1–IIa cervical cancer patients who undergo radical surgery. Onco. Targets Ther. 8, 1355–1362.
[14] Zhang, R., Lee, S.M., Wigfield, C., Vigneswaran, W.T. and Ferguson, M.K. (2015) Lung function predicts pulmonary complications regardless of the surgical approach. Ann. Thorac. Surg. 99 (5), 1761–1767.
[15] Raffetti, E., Donato, F. and Castelli, F. (2015) The prognostic role of systemic inflammatory markers on HIV-infected patients with non-Hodgkin lymphoma, a multicenter cohort study. J. Transl. Med. 13 (1), 89.
[16] Satelli, A., Mitra, A., Cutrera, J.J., et al. (2014) Universal marker and detection tool for human sarcoma circulating tumor cells. Cancer Res. 74 (6), 1645–1650.

[17] Balkwill, F. and Mantovani, A. (2001) Inflammation and cancer: back to Virchow? Lancet 357 (9255), 539–545.
[18] Brigati, C., Noonan, D.M., Albini, A. and Benelli, R. (2002) Tumors and inflammatory infiltrates: friends or foes? Clin. Exp. Metastasis 19 (3), 247–258.
[19] Coussens, L.M. and Werb, Z. (2002) Inflammation and cancer. Nature 420 (6917), 860–867. Dec. 19–26.
[20] Ikeda, M., Furukawa, H., Imamura, H., et al. (2002) Poor prognosis associated with thrombocytosis in patients with gastric cancer. Ann. Surg. Oncol. 9 (3), 287–291.
[21] Dunn, G.P., Old, L.J. and Schreiber, R.D. (2004) The immunobiology of cancer immunosurveillance and immunoediting. Immunity 21 (2), 137–148.
[22] De Larco, J.E., Wuertz, B.R. and Furcht, L.T. (2004) The potential role of neutrophils in promoting the metastatic phenotype of tumors releasing interleukin-8. Clin. Cancer Res. 10 (15), 4895–4900.
[23] Ubukata, H., Motohashi, G., Tabuchi, T., Nagata, H. and Konishi, S. (2010) Evaluations of interferon-gamma/interleukin-4 ratio and neutrophil/lymphocyte ratio as prognostic indicators in gastric cancer patients. J. Surg. Oncol. 102 (7), 742–747.
[24] Crumley, A.B., McMillan, D.C., McKernan, M., McDonald, A.C. and Stuart, R.C. (2006) Evaluation of an inflammation-based prognostic score in patients with inoperable gastro-oesophageal cancer. Br. J. Cancer 94 (5), 637–641.
[25] Jiang, R., Cai, X.Y., Yang, Z.H., et al. (2015) Elevated peripheral blood lymphocyte-to-monocyte ratio predicts a favorable prognosis in the patients with metastatic nasopharyngeal carcinoma. Chin. J. Cancer. 34 (1), 23.
[26] G.M. Zhang, Y. Zhu, L. Luo et al., Preoperative lymphocyte-monocyte and platelet-lymphocyte ratios as predictors of overall survival in patients with bladder cancer undergoing radical cystectomy. Tumour Biol., 2015.