Lymphocyte to Monocyte Ratio as a Dependent Indicator in Spine Metastasis

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Abstract

Introduction

The majority of cancer morbidity and mortality is caused by metastatic events, where metastasis accounts for 90% of the mortality rate. The most common predilection of metastatic spine disease was thoracic (70%), lumbar (20%), and cervical (10%). One of the markers in cancer is pro-inflammatory cytokines and chemokines that present around the tumor environment. Several studies showed a strong correlation between neutrophil/lymphocytes ratio (NLR), platelet/lymphocytes ratio (PLR), and lymphocytes/monocytes ratio (LMR) and prognostic of the tumor.

Methods

This consecutive retrospective study was carried out from January 2014 to December 2019. Patient eligibility criteria were as follows: 1) metastatic spine disease patient; 2) history of cancer. The patients with 1) history of trauma; 2) metastatic spine disease with infection; 3) history of tuberculous spondylitis were excluded from the study. The outcome of this study is to assess the eligibility of LMR in predicting the survival rate of metastatic spine disease and to look for the cut-off value of the LMR.

Results

The ROC analysis was carried out between the LMR and the survival time of the patients. The sensitivity and specificity of the LMR was 0.857 and 0.879, respectively. The Youden index was performed to obtain the LMR cut-off value shown in Figure 2. The cut-off value of the LMR was 2.5250. Hence, the LMR ratio of more than 2.5250 was classified into a high LMR and vice versa.

Conclusions

In this study, the cut-off value for serum levels of the LMR was 2,5250 with a sensitivity value of 85,7% and specificity of 87,9%. There is a significant association between LMR and survival rate as a prognostic marker for spinal metastases.

Keyword: Leukocyte, Monocyte, Spine, Metastasis

1. Introduction

Cancer is a significant public health burden in both developed and developing countries. Based on the GLOBOCAN research, in 2012, there were about 14.1 million new cases and 8.2 million deaths caused by cancer.(Torre et al., 2015) The majority of cancer morbidity and mortality is caused by metastatic events, where metastasis accounts for 90% of the mortality rate.(Guan, 2015)

Cancer treatment has developed rapidly. Hence, it increases the survival rate in patients with advanced cancer. However, bone metastasis remains a problem. Lung, liver, and bone are the common predilection for cancer metastasis. A study showed that bone was the most common location for cancer metastasis.(Araujo et al., 2013; Quraishi et al., 2010)

The new incidence of metastatic spine disease reaches 10-30% per year.(Dunning, 2012) Spine is the most common bone metastasis among all bones where the incidence of terminal cancer reaches up to 30-90%.(Araujo et al., 2013) The most common predilection of metastatic spine disease was thoracic (70%), lumbar (20%), and cervical (10%).(Liu et al., 2016)

Spine metastasis may produce several clinical problems, such as pathologic fracture, spinal cord paralysis, and deterioration of quality of life.(Kimura, 2018; Switlyk et al., 2015) The most severe complication of spine metastasis is spinal cord compression, which occurs in 20% of metastatic patients. Untreated spinal cord compression will progress into paraplegia, tetraplegia, and incontinent sphincter.(Hirabayashi et al., 2003) The management of spine metastases consists of surgery, radiotherapy, medication, and palliative care. Estimation of survival rate before surgery plays a pivotal role in determining whether a patient is suitable for invasive treatment.(Lim et al., 2016)

One of the markers in cancer is pro-inflammatory cytokines and chemokines that present around the tumor environment.(Mantovani et al., 2008) Several studies showed a strong correlation between neutrophil/lymphocytes ratio (NLR), platelet/lymphocytes ratio (PLR), and lymphocytes/monocytes ratio (LMR) and prognostic of the tumor. Several studies demonstrated that NLR and PLR were independently correlated with the cancer patients' survival rate.(Al Murri et al., 2007; Cho et al., 2014; Forrest et al., 2005; Halazun et al., 2008; Zhang et al., 2015) However, the correlation between PLR and bone metastasis was not yet known. This study aims to evaluate the LMR as a prognostic factor in spinal bone metastasis. This study aims the evaluate

2. Methods

This consecutive retrospective study was carried out from January 2014 to December 2019. Patient eligibility criteria were as follows: 1) metastatic spine disease patient; 2) history of cancer. The patients with 1) history of trauma; 2) metastatic spine disease with infection; 3) history of tuberculous spondylitis were excluded from the study.

2.1. Definitions

Lymphocyte/monocyte ratio was defined as measured lymphocyte was divided by monocyte pre-operatively. The survival rate of metastatic spine disease patients was defined as the survival time of the patients in months.

2.2. Outcomes

The outcome of this study is to assess the eligibility of LMR in predicting the survival rate of metastatic spine disease and to look for the cut-off value of the LMR.

2.3. Statistical analysis

Patients matched according to the inclusion and exclusion criteria were included in this study. The nominal and numeric data were reported using mean and median, respectively. Data distribution was assessed using the Shapiro-Wilk test or Kolmogorov-Smirnov test. The patient's survival time was recorded as nominal data as follows 3-6 months, 6-12 months, and more than 12 months. Sensitivity and specificity between the LMR and survival time were assessed using ROC analysis. Youden indexes were used to obtain a cut-off value of the LMR. Chi-square or Fischer exact was used to assess the lower and upper cut-off value of the LMR based on the Youden index and survival time. This study considered $p<0.05$ as statistically significant.

3. Result

3.1. Baseline characteristics of patients

According to the inclusion and exclusion criteria, a total of 54 patients were included in this study. The characteristics of the included patient are shown in Table 1.

Table 1. Characteristics of the included patients

Variables	Frequencies (n)	Percentages (%)
Age (yo)		
- Adult (20-60)	49	90,7
- Elderly (>60)	5	9,3
Gender		
- Male	29	53,7
- Female	25	46,3

Table 2. Characteristic of age, lymphocytes count, and monocytes count

Variable	Mean	Mode	Minimum – Maximum
Age	50,15	55	30 - 79
Lymphocytes count	15,97	-	2,90 - 62,30
Monocytes count	6,96	-	1,30 - 12,50

3.2. Association between the LMR and Related Outcome

The ROC analysis was carried out between the LMR and the survival time of the patients, and the result showed in Figure 1. The sensitivity and specificity of the LMR was 0.857 and 0.879, respectively.

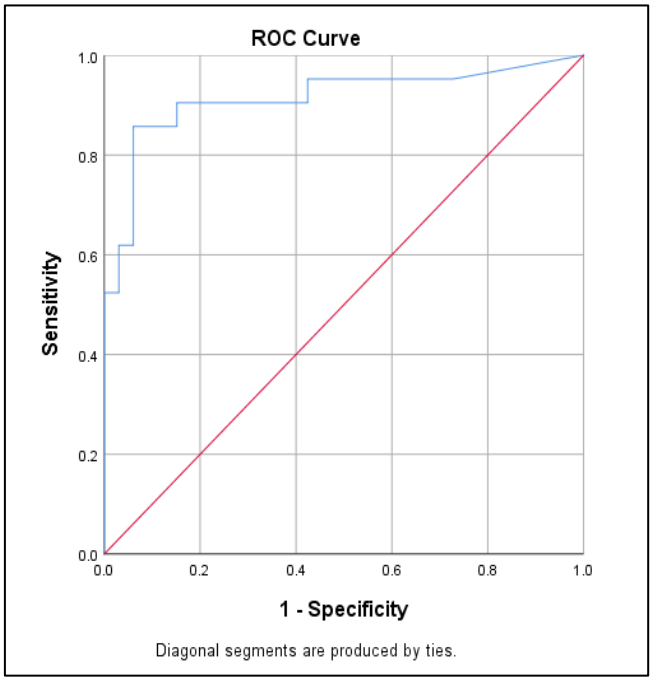

Figure 1. ROC Curve in LMR

The Youden index was performed to obtain the LMR cut-off value shown in Figure 2. The cut-off value of the LMR was 2.5250. Hence, the LMR ratio of more than 2.5250 was classified into a high LMR and vice versa.

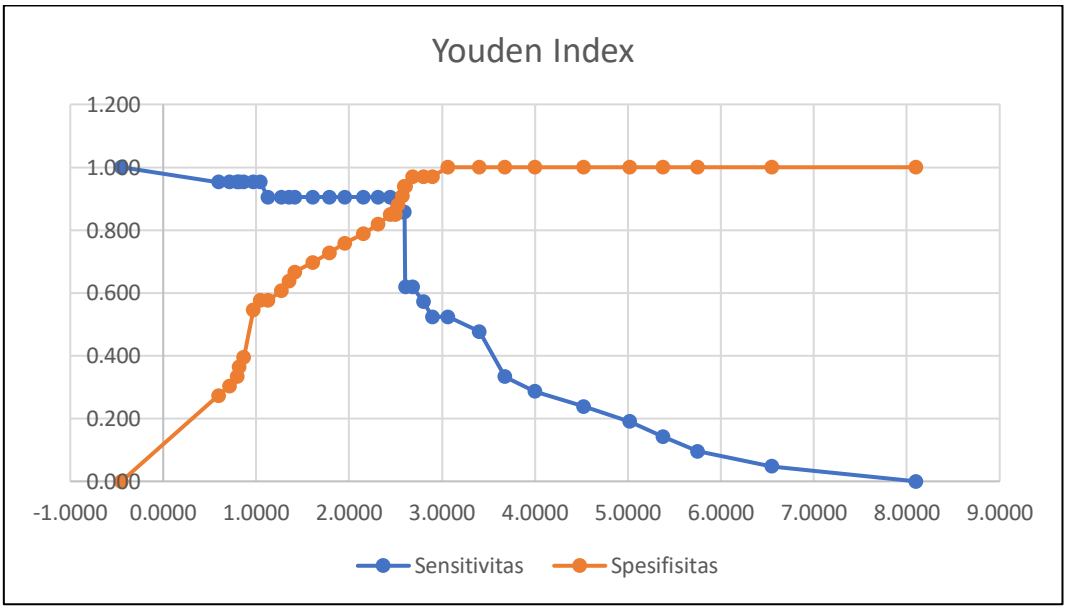

Figure 2. Youden index graphic in LMR

Further analysis was carried out to assess the association between high and low LMR values to the survival time of the patients [Table 3]. An analysis was carried out to association LMR and Tokuhashi scores [Table 4] and Tomita Score [Table 5]. LMR value was not associated with Tokuhashi (p=0.945) and Tomita score (p=0.393).

Table 3. Association between LMR cut-off value and survival time.

LMR Value	Survival time (mo)			Total	p-value
	3-6	6-12	>12		

Low	25	6	1	32	0,001
High	0	11	11	22	
Total	25	17	12	54	

Table 4. Association between LMR value and Tokushashi score

LMR value	Tokuhashi score		Total	p-value
	< 6 month	6-11 month		
Low	23	9	32	0,945
High	16	6	22	
Total	39	15	54	

Table 5. Association between LMR value and Tomita Score

LMR value	Tomita Score				Total	p-value*
	< 6 mo	6-12 mo	1-2 years	≥2 years		
Low	3	12	16	1	32	0,393
High	2	4	14	2	22	
Total	5	16	30	3	54	

*Fischer exact test was used in this analysis

4. Discussion

A total of 54 patients were included in this study. The characteristic of the included patients was similar to the previous study that spine metastasis disease was more affected in males between 40 to 70 years. The reason was associated with prostate cancer that metastasis to the bone.(Bhat et al., 2016; Wang et al., 2019) In this study, the mean and mode of the age were 50 and 55, respectively. The youngest age was 30 years and the oldest age was 79 years. Li et al.(Li et al., 2019) study showed that the characteristic patient's age of spine metastasis was 60.5 (range 21-84 years).

The decrease in lymphocytes was thought to be an incapable immunologic reaction to the tumor and caused tumor progression and metastasis.(Goto et al., 2018; Hu et al., 2018) Monocytes can infiltrate the tumor and differentiate into macrophages of the associated tumor, such as osteoclast in bone cancer, that is involved in tumor proliferation, invasion, metastasis, neovascularization, and recurrency.(Hu et al., 2018) The secondary lymphocytopenia has several etiology, such as malnutrition, infection, corticosteroid used, radiotherapy, chemotherapy, and spine metastasis.(Anzuatégui et al., 2019) A study showed that among 185 patients with spine metastasis, a total of 44.8% had lymphocytes ≤20%, and 55.2% had lymphocytes >20%. The monocytes count was less than 8% in 53.8% and more than 8% in 46.2%. (He et al., 2020)

This study found that the cut-off LMR was 2.525. Hence, the LMR below the cut-off value was categorized into low LMR and vice versa. The sensitivity and 1-specificity of LMR were 0.857 and 0,879, respectively. A study that observed spine metastasis from breast cancer showed that the LMR value was higher than 1.95 in 107 patients and lower than 1.95 in 37 patients.(Zhao et al., 2020)

This study showed an association between the LMR value and survival time with p=0.001. The LMR value was also associated with survival time lower and higher than one year with p=0.001. These findings were similar to the previous study, which showed a relationship between the LMR value and the prognostic factor of the spine disease [HR: 0.172 (0.093- 0.318), P<0.001].(Zhao et al., 2020) The low LMR value was associated with poor prognosis in spine metastasis.(Zhao et al., 2020) The LMR was considered as a prognostic factor in several tumors. Liu et al.(Liu et al., 2016) reported that a low LMR was associated with a poor prognosis in patients with osteosarcoma. Goto et al.(Goto et al., 2018) reported that patients with low LMR had a significantly worse disease-free survival rate (p = 0.005) in patients with breast carcinoma. Elevated monocyte levels reflect a high tumor burden in patients with cancer. With this understanding, LMR is believed to reflect the immune status of the host and the extent of tumor progression. Given that low lymphocyte counts, and high monocyte counts reflect anti-tumor immune insufficiency and an increased tumor burden, a low LMR is associated with a poorer prognosis.(Goto et al., 2018)

Preoperative prognostic prediction in patients with spinal metastatic lesions plays an important role in surgical decision making. Ahmed et al.(Ahmed et al., 2018) reviewed 176 patients and compared nine scoring systems, and found that the revised Tokuhashi Score was better prognostic than the modified Tomita Score and Bauer Score. A study conducted by Pollner et al.(Pollner et al., 2018) showed that the modified Tomita Score and Bauer Score separated the classes of patients with good and moderate prognosis, and patients with poor condition were easily identified by the revised Tokuhashi Score.

In this study showed that there was no association between serum levels of LMR to survival rates as a prognostic marker for spinal metastases in the Tokuhashi category data analysis test results with p-value=0,945. The results also showed that there was no association between serum levels of LMR to survival rates as a prognostic marker for spinal with p-value=0,393.

The Tomita and Tokuhashi systems have always been considered the two most representative scoring categories for predicting overall survival. However, much external validation has been performed to assess the predictive ability and consistency of these two systems, pointing to a confusing inconsistency between the predicted and actual survival rates. A study conducted by He et al.(He et al., 2020) compared various predictive tools for predicting survival in spinal metastases patients. It was reported that when compared to the specific survival times provided by traditional prediction tables such as Tokuhashi and Tomita systems, survival rates predicted by nomograms such as LMR could make more sense to guide treatment decisions.(He et al., 2020)

In future study, it is recommended to conduct a prospective study. In order to further ensure external validity, it is best to assess the prognostic predictive capacity using samples collected from several different hospitals or health centers, or even from several different countries.

5. Conclusion

In this study, the cut-off value for serum levels of the LMR was 2,5250 with a sensitivity value of 85,7% and specificity of 87,9%. There is a significant association between LMR and survival rate as a prognostic marker for spinal metastases.

References

Ahmed, A. K., Goodwin, C. R., Heravi, A., Kim, R., Abu-Bonsrah, N., Sankey, E., Kerekes, D., De la Garza Ramos, R., Schwab, J., & Sciubba, D. M. (2018). Predicting survival for metastatic spine disease: a comparison of nine scoring systems. *The Spine Journal : Official Journal of the North American Spine* Society, 18(10), 1804–1814. https://doi.org/10.1016/j.spinee.2018.03.011

Al Murri, A. M., Wilson, C., Lannigan, A., Doughty, J. C., Angerson, W. J., McArdle, C. S., & McMillan, D. C. (2007). Evaluation of the relationship between the systemic inflammatory response and cancer-specific survival in patients with primary operable breast cancer. British Journal of Cancer, 96(6), 891–895. https://doi.org/10.1038/sj.bjc.6603682

Anzuatégui, P. R., Cunha, L. A. M. da, Mello, G. J. P., Stieven Filho, E., & Graells, X. S. (2019). Cirurgia em metástase vertebral: Proposta de modelo preditivo de morbimortalidade. Revista Brasileira de Ortopedia, 54(06), 665–672. https://doi.org/10.1055/s-0039-1697018

Araujo, J. L. V., Veiga, J. C. E., Figueiredo, E. G., Barboza, V. R., Daniel, J. W., & Panagopoulos, A. T. (2013). Manejo das neoplasias metastáticas da coluna vertebral - uma atualização. Revista Do Colégio Brasileiro de Cirurgiões, 40(6), 508–514. https://doi.org/10.1590/S0100-69912013000600015

Bhat, A. R., Kirmani, A. R., Wani, M. A., & Bhat, M. H. (2016). Incidence, histopathology, and surgical outcome of tumors of spinal cord, nerve roots, meninges, and vertebral column-Data based on single institutional (Sher-i-Kashmir Institute of Medical Sciences) experience. Journal of Neurosciences in Rural Practice, 07(03), 381–391. https://doi.org/10.4103/0976-3147.181489

Cho, I. R., Park, J. C., Park, C. H., Jo, J. H., Lee, H. J., Kim, S., Shim, C. N., Lee, H., Shin, S. K., Lee, S. K., & Lee, Y. C. (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. https://doi.org/10.1007/s10120-013-0330-2

Dunning, E. C. (2012). Complications in the management of metastatic spinal disease. World Journal of Orthopedics, 3(8), 114. https://doi.org/10.5312/wjo.v3.i8.114

Forrest, L. M., McMillan, D. C., McArdle, C. S., Angerson, W. J., Dagg, K., & 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. British Journal of Cancer, 92(10), 1834–1836. https://doi.org/10.1038/sj.bjc.6602591

Goto, W., Kashiwagi, S., Asano, Y., Takada, K., Takahashi, K., Hatano, T., Takashima, T., Tomita, S., Motomura, H., Hirakawa, K., & Ohira, M. (2018). Predictive value of lymphocyte-to-monocyte ratio in the preoperative setting for progression of patients with breast cancer. BMC Cancer, 18(1), 1137. https://doi.org/10.1186/s12885-018-5051-9

Guan, X. (2015). Cancer metastases: challenges and opportunities. Acta Pharmaceutica Sinica B, 5(5), 402–418. https://doi.org/10.1016/j.apsb.2015.07.005

Halazun, K. J., Aldoori, A., Malik, H. Z., Al-Mukhtar, A., Prasad, K. R., Toogood, G. J., & Lodge, J. P. A. (2008). Elevated preoperative neutrophil to lymphocyte ratio predicts survival following hepatic resection for colorectal liver metastases. European Journal of Surgical Oncology (EJSO), 34(1), 55–60. https://doi.org/10.1016/j.ejso.2007.02.014

He, X., Jiao, Y., Yang, X., & Hu, Y. (2020). A Novel Prediction Tool for Overall Survival of Patients Living with Spinal Metastatic Disease. World Neurosurgery, 144, e824–e836. https://doi.org/10.1016/j.wneu.2020.09.081

Hirabayashi, H., Ebara, S., Kinoshita, T., Yuzawa, Y., Nakamura, I., Takahashi, J., Kamimura, M., Ohtsuka, K., & Takaoka, K. (2003). Clinical outcome and survival after palliative surgery for spinal metastases. Cancer, 97(2), 476–484. https://doi.org/10.1002/cncr.11039

Hu, R., Liu, Q., Ma, J., Zhou, J., & Liu, G. (2018). Preoperative lymphocyte-to-monocyte ratio predicts breast cancer outcome: A meta-analysis. Clinica Chimica Acta, 484, 1–6. https://doi.org/10.1016/j.cca.2018.05.031

Kimura, T. (2018). Multidisciplinary Approach for Bone Metastasis: A Review. Cancers, 10(6), 156. https://doi.org/10.3390/cancers10060156

Li, Y., Wang, B., Zhou, S., Jiang, L., Yang, S., Liu, X., Wei, F., Zhang, H., Wang, Y., & Liu, Z. (2019). Do routine blood test results help in the diagnosis of spine tumors? A retrospective study of the significance of pretreatment neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios from 503 spine tumor patients. Medicine, 98(15), e14902. https://doi.org/10.1097/MD.0000000000014902

Lim, S. M., Kim, Y. N., Park, K. H., Kang, B., Chon, H. J., Kim, C., Kim, J. H., & Rha, S. Y. (2016). Bone alkaline phosphatase as a surrogate marker of bone metastasis in gastric cancer patients. BMC Cancer, 16(1), 385. https://doi.org/10.1186/s12885-016-2415-x

Liu, B., Huang, Y., Sun, Y., Zhang, J., Yao, Y., Shen, Z., Xiang, D., & He, A. (2016). Prognostic value of inflammation-based scores in patients with osteosarcoma. Scientific Reports, 6(1), 39862. https://doi.org/10.1038/srep39862

Mantovani, A., Allavena, P., Sica, A., & Balkwill, F. (2008). Cancer-related inflammation. Nature, 454(7203), 436–444. https://doi.org/10.1038/nature07205

Pollner, P., Horváth, A., Mezei, T., Banczerowski, P., & Czigléczki, G. (2018). Analysis of Four Scoring Systems for the Prognosis of Patients with Metastasis of the Vertebral Column. World Neurosurgery, 112, e675–e682. https://doi.org/10.1016/j.wneu.2018.01.124

Quraishi, N. A., Gokaslan, Z. L., & Boriani, S. (2010). The surgical management of metastatic epidural compression of the spinal cord. The Journal of Bone and Joint Surgery. British Volume, 92-B(8), 1054–1060. https://doi.org/10.1302/0301-620X.92B8.22296

Switlyk, M. D., Kongsgaard, U., Skjeldal, S., Hald, J. K., Hole, K. H., Knutstad, K., & Zaikova, O. (2015). Prognostic Factors in Patients with Symptomatic Spinal Metastases and Normal Neurological Function. Clinical Oncology, 27(4), 213–221. https://doi.org/10.1016/j.clon.2015.01.002

Torre, L. A., Bray, F., Siegel, R. L., Ferlay, J., Lortet-Tieulent, J., & Jemal, A. (2015). Global cancer statistics,

2012. CA: A Cancer Journal for Clinicians, 65(2), 87–108. https://doi.org/10.3322/caac.21262

Wang, F., Zhang, H., Yang, L., Yang, X., Zhang, H., Li, J., Qiao, R., & Hu, Y. (2019). Epidemiological Characteristics of 1196 Patients with Spinal Metastases: A Retrospective Study. Orthopaedic Surgery, 11(6), 1048–1053. https://doi.org/10.1111/os.12552

Zhang, S., Zhang, F., Sheng, X., & Chen, L. (2015). Decreased pretreatment lymphocyte/monocyte ratio is associated with poor prognosis in stage Ib1–IIa cervical cancer patients who undergo radical surgery. OncoTargets and Therapy, 1355. https://doi.org/10.2147/OTT.S82174

Zhao, C., Wang, Y., Cai, X., Xu, W., Wang, D., Wang, T., Jia, Q., Gong, H., Sun, H., Wu, Z., & Xiao, J. (2020). Prognostic Significance of a Novel Score Model Based on Preoperative Indicators in Patients with Breast Cancer Spine Metastases (BCSM). Cancer Management and Research, Volume 12, 11501–11513. https://doi.org/10.2147/CMAR.S273785