Int J Clin Exp Med 2016;9(9):18184-18191
www.ijcem.com /ISSN:1940-5901/IJCEM0031106

Original Article

Peripheral blood lymphocyte to monocyte ratio predicts outcome in newly-diagnosed multiple myeloma patients with extramedullary involvements

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Received April 23, 2016; Accepted July 11, 2016; Epub September 15, 2016; Published September 30, 2016

Abstract: The peripheral blood absolute lymphocyte to monocyte ratio (LMR) has been regarded as a prognostic marker of the tumor microenvironment in various cancers. The aim of this study was a retrospective analysis of the clinical features, efficacies, survival rates and prognostic factors. Also, we explored the prognostic impact of LMR in 62 newly-diagnosed MM patients with extramedullary (EM) disease (group A). Other 83 multiple myeloma MM (full name?) patients without EM (group B) were selected as the control. Compared with group B, the incidence of EM was associated with a higher level of β_2-MG, lower LMR and more extensive bone disease. The common location of EM (full name?) in order was soft tissues, intracranial, lung, pleural, skin and spinal canal. The estimated overall survival (OS) in group A was significantly shorter than those in group B (36 vs. 43 months, P=0.032). Log-rank univariate analysis showed that the number of osteolytic lesions ≥ 3 (P=0.043), β_2-microglobulin (β_2-MG) ≥5.5 mg/L (P=0.000), LMR < 2.9 (P=0.015) and hemoglobin ≤ 110 g/L (P=0.023) were poor prognostic factors in group A. Multivariate analysis with Cox model showed β_2-MG ≥ 5.5 mg/L (95% CI: 0.158-0.624) and LMR < 2.9 (95% CI: 1.312-4.774) were statistically significant. We concluded the prognosis remained poor despite intensive treatment in these newly-diagnosed MM patients with EM invasion. LMR could be an efficient prognostic factor for this cohort of disease.

Keywords: Myeloma, lymphocyte to monocyte ratio, extramedullary, prognosis

Introduction

Multiple myeloma (MM), the second most common hematological malignancies after non-Hodgkin's lymphoma, is a monoclonal malignant plasma cell disorder with an apparent homogeneity [1]. It is usually limited to the bone marrow, only in minority circumstances will move into soft tissue and form extramedullary (EM) lesion. The occurrence of EM, defined as an infiltrate of clonal plasma cells at an anatomic site distant from the bone marrow, is an uncommon manifestation of MM and can either accompany with newly diagnosed disease or develop with disease progression or relapse [2]. It develops as a result of "bone marrow escape" of MM subclone with either decreased cell adhesion or that acquires characteristics of the granulocytic lineage as observed in primary plasma cell leukemia [3].

Accumulating studies have suggested a strong link between inflammation and cancer. It has been verified that inflammation modifies the tumor biology and the quality of the immune response. Lymphocytes and monocytes are key immune cells in the inflammatory response and significantly associated with prognosis in different types of cancers [4]. Lymphocytes are crucial components of host immunity that are important in the destruction of residual tumor cells and related to micrometastases. An infiltration of lymphocytes can activate an effective antitumor cellular immune response. Moreover, monocytes are considered to represent a population of circulating hematopoietic cells that primarily arise from the bone marrow. They circulate in the peripheral blood and give rise to differentiated macrophages. Recent studies have shown that LMR is a useful predictive factor in hematologic and some solid tumors. Szerafin L

et al. [5] reported that the low absolute monocyte count was associated with increased mortality caused by infectious complications and chronic lymphocytic leukemia. The pretreatment LMR has been reported to be a prognostic factor for clinical outcomes in hematologic malignancies and the survival benefit is associated with an increased LMR in peripheral blood [6, 7]. However, the prognostic value of LMR in newly diagnosed MM patients with EM involvement has not been reported yet.

Over the last decades, encouragingly, we have witnessed booming development of novel agents and armamentarium, with which has resulted in a 50% improvement in median survival [8]. The paradigm of MM therapy has changed dramatically - from the conventional drugs to the present paradigm with high-dose glucocorticoids, cytotoxic chemotherapeutics, and novel anti-MM protocols. Meanwhile, MRI and FDG PET/CT display especially sensibility for the detection of extramedullary disease and can help detect the metabolically active lesions that often precede evidence of osseous destruction at conventional radiography [9]. However, unbalanced regulation of cytokines and chemokines in the bone marrow microenvironment leads to drug resistance or relapse of disease, which is perhaps still the major concern for this incurable disease [10]. Although published literature reports no differences in initial response to therapy in MM patients with EM involvement when treated with melphalan-based autologous stem cell transplants (ASCT), these patients appear to have a shorter progression-free survival even when treated with novel agents [11].

EM involvement, which is recognized as aggressive and associated with both early progression and short survival, has been reported in up to 15-20% of patients with myeloma at diagnosis and develops in an additional 15% during the course of the disease [12]. In our research, we noticed that newly-diagnosed MM patients with EM invasion have a poor prognosis and are difficult to treat. In such patients, late detection and delayed treatment can seriously diminish quality of life and can be life-threatening. The characters of this cohort patient, whose clinical features and outcome analyses have been seldom reported, still remain a puzzle. Although the correlation of LMR has been documented in the malignant hematonosis, previous studies did not perform a subgroup analysis in these newly-diagnosed MM patients with EM involvement(s). We hypothesized that differences in baseline LMR in patients with or without EM may be largely responsible for the observed differences. The purpose of our present study was to assess the incidence and clinicopathological features of newly-diagnosed MM patients with EM involvement(s) and assess the prognostic impact of LMR in this cohort of disease.

Patients and methods

From January 2005 to March 2015, 62 newly-diagnosed MM patients with EM involvement(s) (group A) were retrospectively reviewed from Tianjin Medical University Cancer Institute and Hospital as the experimental group. In the meantime we chose other 83 MM patients without EM involvement(s) (group B) as the control. Clinical information including sex, age, hemoglobin (HB), β_2-microglobulin (β_2-MG), the number of osteolytic lesions, the proportion of plasma cell, clinical stage, serum lactate dehydrogenase (LDH) level were obtained from the patients' medical records. ALC and AMC were obtained from routine peripheral blood of patients before any treatment. The LMR was defined as the ALC divided by AMC. Cut-off point for the entire cohort division of LMR, chosen according to the results of maximal chi-square analysis to best segregate patients, was 2.9. Relevant factors were evaluated for survival analysis by single factor and multi-factor COX regression.

Histological diagnosis of MM was based on the WHO classification system for hematologic malignancies [13]. The experimental group was screened for newly-diagnosed MM patients with EM involvement. All patients met the following criteria: Biopsy confirmation of a monoclonal plasma cell infiltration from corresponding lesion(s) is required for diagnosis (patients with the diagnosis for solitary plasmacytoma of the bone and extramedullary plasmacytoma were excluded); No previous treatment with biological therapy or chemotherapy, and no prior history of malignancy. Follow-up data was available for all included patients. And disease stage was defined using the International Staging System. The detection of osteolytic lesions was assessed and confirmed according

Table 1. Patient sociodemographic and clinical characteristics of the two groups

Initial variables	Group A	Group B	*P* value
Patients (n)	62 (42.8%)	83 (57.2%)	
Sex			0.649
Male	32 (51.16%)	46 (55.4%)	
Female	30 (48.4%)	37 (45.6%)	
Age (years)			0.792
≥ 65 (y)	16 (25.8%)	32 (38.6%)	
< 65 (y)	46 (74.2%)	51 (61.4%)	
HB (≤ 110 g /L)	28 (45.2%)	49 (59.0%)	0.098
LDH (≥ 240 U/L)	14 (22.6%)	13 (15.7%)	0.290
β_2-MG (≥ 5.5 mg /L)	32 (51.6%)	28 (33.7%)	0.031
The proportion of plasma cell ≥ 20%	25 (40.3%)	34 (41.0%)	0.938
The number of osteolytic lesions ≥ 3	36 (58.1%)	31 (37.8%)	0.016
Myeloma subtype			0.084
IgG	22 (35.5%)	39 (47.0%)	
IgA	10 (16.1%)	17 (20.5%)	
Light chain	10 (16.1%)	15 (18.1%)	
Others	20 (32.3%)	12 (14.5%)	
Abnormal Creatinine	9 (14.5%)	20 (24.1%)	0.154
Albumin (≤ 35 g /L)	20 (32.3%)	31 (37.3%)	0.525
Stage			0.164
ISS I/II	49 (79.0%)	57 (68.7%)	
ISS III	13 (21.0%)	26 (31.3%)	
LMR			0.037
LMR ≥ 2.9	37 (59.7%)	63 (75.9%)	
LMR < 2.9	25 (40.3%)	20 (24.1%)	

Note: Group A refers to those newly-diagnosed MM patients with EM; Group B refers to those newly-diagnosed MM patients without EM.

to imaging techniques which has been published by the International Myeloma Working Group (IMWG) [14]. Positron emission tomography (PET)/computed tomography (CT) imaging may be very useful and a PET/CT should be performed in all patients in whom extramedullary involvement is suspected [15]. All the patients' pathological specimens were examined independently by two pathologists of our research group. The IMWG criteria were carried to discriminate different therapeutic efficiency among patients, including CR, PR, MR, NC, and PD [16].

For the statistical tests, SPSS Statistics 17.0 software package were performed, using two-tailed *p* values. And a *p* value of < 0.05 was considered statistically significant. The overall survival (OS) time was measured in months and calculated from the time of diagnosis to the last follow-up date or date of death. Progression-free survival (PFS) was calculated from the date of diagnosis to the date of treatment failure, relapse, evidence of disease progression, or death due to any cause or last follow-up. Clinical characteristics that affect survival were analyzed according to Fisher's exact test and chi-square (χ^2) test. Survival analysis was performed by Kaplan-Meier method, and the COX proportional hazard model was used to perform multivariate analysis.

Results

Clinical and laboratory features

From 2005 to 2015, there were 62 consecutively admitted patients with EM involvement in Tianjin Medical University Cancer Institute and Hospital. The distribution of additional baseline characteristics for the 2 groups of patients is presented in **Table 1**. The median age of group A was 59 years (range, 19-82) while the median age of group B was 62 years (range, 38-84) years. The male/female ratio in group A was 1.07, the ratio was 1.24 in group B. According to the age subgroup, there was 16 in group A while 32 in group B of the patients whose age ≥ 65. There was no obvious difference about the age and sex indexes. Clinical manifestation and lab findings showed that no significant difference was observed in the two groups on the HB, LDH, the proportion of plasma cell, myeloma subtype, abnormal creatinine, Albumin, clinical stage. Significantly, compared with the two groups, our study showed that there were statistically significant associated with the number of osteolytic lesions ≥ 3 (P=0.016), β_2-MG ≥ 5.5 mg/L (P= 0.031) and LMR < 2.9 (P=0.037).

Treatment and response

The main therapeutic approaches included radiotherapy, surgery, chemotherapy, and comprehensive therapeutic strategies. The com-

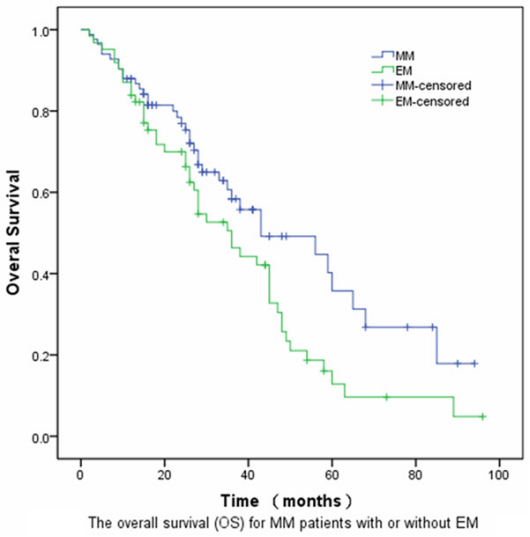

Figure 1. Patient's survival of the two groups is shown in the above figure. The estimated overall survival (OS) of the patients with EM was significantly shorter than those without EM (36 vs. 43 months, P=0.032).

monly used chemotherapy regimens were mainly including MP (melphalan 8 mg/m^2, days 1-4; prednisone 60 mg/m^2, days 1-4), VBMCP (carmustine 20 mg/m^2, day 1; cyclophosphamide 400 mg/m^2, day 1; vincristine 1.2 mg/m^2, day 1; melphalan 8 mg/m^2, days 1-4; prednisone 80 mg/m^2, days 1-7), BD (bortezomib 1.3 mg/m^2, days 1, 4, 8, 11; dexamethasone 20 mg/d, days 1~4, 8~11, 17~20) and VAD (vincristine 0.4 mg/day, days 1-4; epirubicin 9 mg/m^2, days 1-4; examethasone 40 mg/day, days 1-4, 9-12, 17-20). As published literature has proven that new drug containing regimens is widely accepted as the frontline induction treatment followed by ASCT [17], this remains the standard treatment for the EM involvement disease in MM in our hospital. During and following therapy, we regularly assessed the local control through repeated skeletal survey and bone marrow examination and M-protein levels were periodically monitored.

Among all the patients, 26 cases received chemotherapy combined radiation therapy in our radiotherapy department of Tianjin Medical University Cancer Institute and Hospital (14 cases of group A and 12 cases of group B; 25-65 Gy). Some patients accepted the chemotherapy containing the administration of Bortezomib (7 cases of group A and 15 cases of group B); 25 cases accepted autologous hemopoietic stem cell transplantation (8 cases of group A and 17 cases of group B). There was no statistical significance about the treatment comparing two groups (P>0.05). The latest follow-up for all patients was in March 2015. At that time, the median follow-up of the total 145 patients had been 27 months (range, 2 to 96). The estimated overall survival (OS) of the patients with EM was significantly shorter than those without EM (36 vs. 43 months, P=0.032) (see **Figure 1**).

In the panel of 62 patients, 47 had extranodal involvement at one site and 15 at multiple sites (2 or higher). The most commonly primarily extranodal sites were soft tissue (46 cases), followed by the intracranial (9 cases), lung (6 cases), pleural (5 cases), skin (4 cases) and spinal canal (5 cases), other less common parts, including the ocular adnexal (3 cases), mediastinum (2 cases), breast (2 cases) and skeletal muscle (2 cases). Also, we found the injured part of pancreas, parotid gland and dacryocyst account for each site, respectively. After careful analysis, we found among the 46 cases with soft tissue involvement, 22 cases occurred in chest wall. Along with the mass, patients usually developed with a palpable boundary, but without pain, when they received physical examination. CT showed prominent chest wall tumor, PET-CT shows local metabolism activity increased.

In our study cohort of group A, the total number of PR and CR arrived 35, while the counterpart in group B is 63. And the total effective rates of groups A and B were 56.5% (35/62) and 75.9% (63/83), respectively. The difference was statistically significant (P < 0.05). Among group A, 14 accepted radiotherapy with a median radiotherapy dose of 45 Gy. Radiotherapy did not show statistically significant influence on overall survival (P=0.126). Meanwhile, 9 patients received bortezomib-containing regimens (5 CR, 3 PR, and 1 die of myelosuppression of bortezomib). 7 patients received ASCT-based regimens (4CR, 1PR, and 2 die of relapse of MM). Obviously, efficiency has been obviously improved. To sum up, we thought new drugs such as bortezomib-contained regimens as the induction therapy or ASCT as the consolidation therapy may be the best choice for this cohort of disease.

Survival and prognostic analysis

Log-rank univariate analysis showed that the number of osteolytic lesions ≥ 3 (P=0.043),

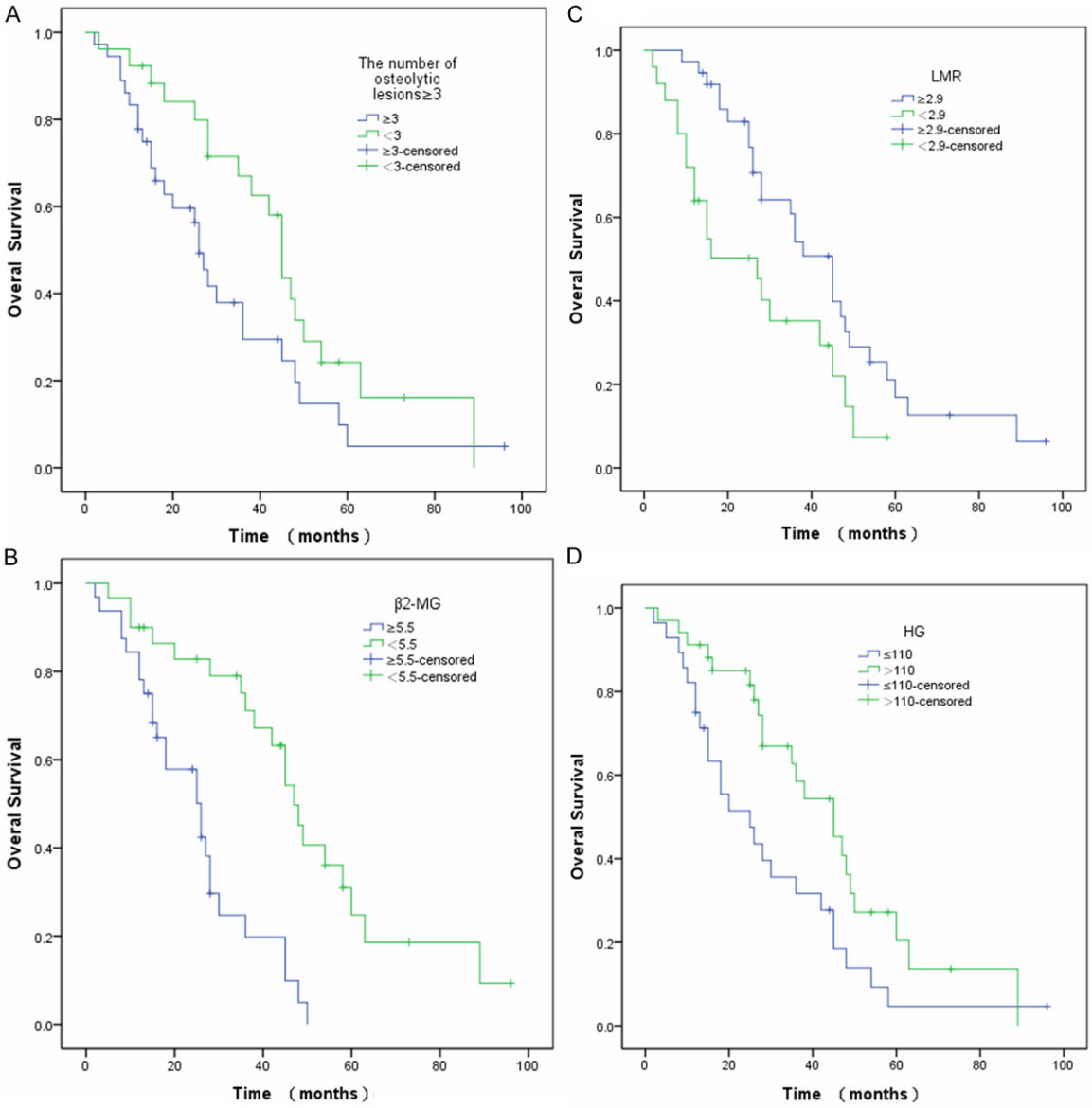

Figure 2. A-D: Log-rank univariate analysis for the two groups, there exist statistical significance in the index of osteolytic lesions ≥ 3 (P=0.043), β_2-MG ≥ 5.5 mg/L (P=0.000), LMR < 2.9 (P=0.015) and hemoglobin ≤ 110 g/L (P=0.023).

β_2-MG ≥ 5.5 mg/L (P=0.000), LMR < 2.9 (P= 0.015) and hemoglobin ≤ 110 g /L (P=0.023) were poor prognostic factors in MM patients with EM (see **Figure 2A-D**). However, there is no statistical significance of the index of LMR < 2.9 in group B (P=0.081). Multivariate analysis with Cox model showed β_2-MG ≥ 5.5 mg/L (95% CI: 0.158-0.624) and LMR < 2.9 (95% CI: 1.312-4.774) were statistically significant. The characters of sex, age, LDH, the proportion of plasma cell, myeloma subtype, abnormal creatinine, Albumin, clinical stage did not show statistically significant influence of patients in the OS of group A. Taken together, we concluded the response to conventional chemotherapy is poor and the prognosis is unfavorable for the newly-diagnosed MM with EM, especially for those with a higher level of β_2-MG, LMR < 2.9, the number of osteolytic lesions ≥ 3 or hemoglobin ≤ 110 g/L.

Discussion

The occurrence of EM disease in MM patients is an uncommon event and more attention was directed toward the feature of these patients

due to its aggressiveness and shorter survival. In this study, we performed a retrospective cohort study on the features of 62 newly-diagnosed MM patients with a median age of 59 years having EM involvements. Our results confirmed previous findings that the increased number of osteolytic lesions and level of β_2-MG, lower LMR and hemoglobin were associated with a positive prognosis for the cohort of newly-diagnosed MM patients with EM involvements. More importantly, we found that an elevated LMR was significantly associated with better OS in this kind of disease which is in accordance with the discovery from Korea [18]. Zhang et al. [19] reported that most of the MM patients with EM invasion of the spinal canal in their study had IgG MM (41.6%) or light chain MM (41.6%). What's different to them, our study showed the type of IgG MM accounts for 35.5%, while the type of IgA and light chain accounts for only a small proportion of 16.1%, respectively.

Few physicians are familiar with newly-diagnosed MM patients with EM involvements, and information about this rare disease is scanty and unavailable. It has been pointed that the incidence of EM disease has increased, which might be related to the availability of more sensitive imaging techniques and the prolongation of patients' survival [11]. The mechanisms of EM in MM are poorly understood. A study from Spain showed that 18% of MM patients had EM involvement and the proportion of patients with high-risk cytogenetics was similar in patients with and without EM involvement (24% *vs.* 21%, respectively) [20]. The conclusion is consistent with the opinion from Blade J and his colleagues that bone marrow genetic abnormalities might not associated with EM and that microenvironmental interactions might key element [21]. However, what's different to them, Qu X et al. demonstrated that patients with EM manifestation bore high incidence of poor cytogenetic aberration and novel agents resistance. The overall survival of patients with EM manifestations in their study was 30 months, in comparison to 104 months for patients without EM involvement (P=0.002) [22]. Similarly, in our study, patients with EM involvement showed an obvious lower OS.

The peripheral blood LMR, as a surrogate marker of host immunity (i.e. ALC) and tumor microenvironment (i.e. AMC), is a predictive biomarker for clinical outcomes in lymphoma [23, 24]. However, up to now, there is no consistent cut-off value for the LMR in all these studies. As we know, inflammatory responses can lead to chronic oxidative stress and generate oxygen free radicals, which have been shown to stimulate cancer initiation, promotion and progression. Moreover, tumor-associated macrophages (TAMs) are derived from circulating monocytes and act as an important inflammatory infiltrating component [25]. TAMs, which are linked to the growth, angiogenesis and metastasis of a variety of tumors, may interact with tumor cells and promote tumor development by producing various cytokines and chemokines [26]. Just as our data demonstrated LMR was a practical and convenient prognostic marker for those newly-diagnosed MM patients with EM involvements. However, there is no statistical significance of LMR in those without EM involvement.

Molecular differences between EM lesions are documented in small case series. The correlative factor is described as an invasion-metastasis cascade, which may include decreased adhesion molecule expression and downregulation of chemokine receptors. For example, CD56, a cell adhesion molecule, positive in about 70% of all MM, can facilitate disease dissemination by impairing the adherence of myeloma cells to the bone marrow microenvironment, downregulation of P-selectin, low expression of chemokine receptors, such as CCR1, CCR2, or downregulation of CXCR4 and its ligand SDF-1alpha, which are critically linked to the occurrence of EM [27]. Sheth N et al. [28] noted that p53 expression was more prevalent in EM sites of MM, interestingly, CD56 was not differentially expressed in the cohort of MM with EM involvement. Conflicting data were shown by Dahl and colleagues [29], who demonstrated that in all seven EM cases, CD56 was completely downregulated. As we can see, the numbers documented are still in small case series, and further studies warranted investigating molecular differences between the two.

In conclusion, despite novel insights into the pathobiology of MM and the availability of new research platforms and therapeutics, innovative treatment strategies are urgently needed, especially for what have been invested in this

category of newly-diagnosed MM patients with EM involvements. Indeed, LMR provides an easily, generally available and low price biomarker since it is directly derived from routine blood cell counts and might represent a novel and useful marker for patient stratification in MM management. However, we acknowledged that our finding was limited to a retrospective study in a small-scale analysis, and thus, further studies performed in a multi-centric clinical study are needed for the exploration of prospective manner and prognostic marker of this disease.

Acknowledgements

The research is granted by National Natural Science Foundation of China 2013, NO.8127-2562.

Disclosure of conflict of interest

None.

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