

7 April, 2015

Dear Editor,

**Title:** Prognostic significance of the lymphocyte-to-monocyte ratio in patients with metastatic colorectal cancer

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**Name of Journal:** World Journal of Gastroenterology

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The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

**Reviewer 1**

**Major Revisions**

(1) The NLR, which was reported to correlate with the survival in patients with colorectal cancer, is similar to the LMR. There was a significant relationship between the LMR and the NLR. According to a univariate analysis, both the LMR and the NLR significantly correlated with the survival. However, in a multivariate analysis neither of them were independent prognostic factors. (Table 4) However, only the LMR significantly correlated with the chemotherapeutic response. Moreover, in relation to the normalization of the value after chemotherapy, only the LMR significantly correlated with the survival.

(2) We used a ROC curve to determine the appropriate cut-off value for LMR. Based on the results, the appropriate cut-off value was 3.38. Therefore, we set 3.38 as the cut-off value. (Figure 1)

(3) We added the more detailed information for patient characteristics such as the performance status and response to treatment, which have been reported to correlate with

survival. (Table 1, 2, 4)

(4) We also added some information about the KRAS and molecular targeted therapy. (Table 1, 2, 4)

(5) The objective response rate did not differ according to the LMR. However, the high-LMR group had a significantly higher disease control rate than the low-LMR group. (Table 3)

(6) We added some information about the resection of primary tumor. (Tables 1, 2, 4)

### **Minor Revision**

(1) In abstract, we changed 'LMR' to 'Lymphocyte to monocyte ratio (LMR)'.

### **Reviewer 2**

#### **Major revisions**

(1) We used a ROC curve to determine the appropriate cut-off value for LMR. Based on the results, the appropriate cut-off value was 3.38. Therefore, we set 3.38 as the cut-off value. (Figure 1)

(2) We added the information about the sensitivity, specificity, positive predictive value and negative predictive value in main text and figure legends.

(3) We performed the analysis again based on the new cut-off value for the LMR (Table 2-4 and Figure 2, 3)

### **Reviewer 3**

#### **Major revisions**

(1) Although long-term chemotherapy may lead to a decrease in the number of lymphocytes, the lymphocyte count, which was measured 8 weeks after the initiation of chemotherapy, was not affected by chemotherapy regardless of the regimen of chemotherapy. (Table 5)

(2) All patients underwent first-line chemotherapy and there was no initiation of palliative chemotherapy for recurrence while the patients underwent adjuvant chemotherapy. Therefore, we believed that there was no effect on the pretreatment lymphocyte count. However, there was a possibility that chemotherapy might affect the white blood cell counts. Therefore, we evaluated the pretreatment and posttreatment white blood cell counts. Although the absolute lymphocyte count did not change after chemotherapy, the absolute neutrophil count significantly decreased and the absolute monocyte count significantly increased. Because the absolute neutrophil count tends to decrease after chemotherapy, the NLR tends to improve regardless of whether the tumor is controlled. On the other hand, because the absolute monocyte count tends to increase, the LMR tends to worsen regardless of whether the tumor progresses. The normalization of the LMR after chemotherapy despite

such situations is considered to reflect the tumor control. This is because the prognostic significance of the normalization after chemotherapy varied between the LMR and NLR.

(3) We provided more detailed information on patient characteristics, such as their performance status and KRAS, and greater detail on the treatments that were administered, such as the resection of primary tumor and molecular targeted therapy, which have been reported to correlate with survival. (Tables 1, 2) According to a multivariate analysis for overall survival, we added these factors. (Table 4)

#### **Minor revision**

(1) The manuscript was checked by a native speaker (Brian Quinn who provided medical writing services on behalf of JMC, Ltd).

3 Reference and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*

Sincerely yours,

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