

Response to reviewer comments on the manuscript of ESPS 17735 for 'world Journal of Gastroenterology' entitled 'Comparison of Selected Inflammation-based Prognostic Markers in Relapsed or Refractory Metastatic Colorectal Cancer Patients'.

June 30. 2015

Dear Dr. Jing Yu,

We are grateful for your handling the manuscript of ESPS 17735 entitled ' Comparison of Selected Inflammation-based Prognostic Markers in Relapsed or Refractory Metastatic Colorectal Cancer Patients'. And we also appreciate the insightful comments and supportive suggestions provided by the valued reviewers, which have improved the quality of manuscript.

We have revised the manuscript on the basis of the comments and suggestions with our best. We hope that the modified manuscript is considerably improved enough to accept for the publication in 'World Journal of Gastroenterology'. Detailed point by point responses to the reviewer comments are provided below. All of the changed parts of manuscript were highlighted in yellow.

Thank you very much for your time and consideration.

Best regards,  
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## Point by point response to the reviewers' comments

Reviewer : 1

We deeply appreciate your precise comments and suggestions to improve the quality of our manuscript. All the pointed issues on the manuscript have been revised faithfully as you advised, and we wrote simple answers on the comments as shown below.

Song A et al reported, in 177 metastatic colorectal cancers (mCRC), the correlation between systemic inflammation-based prognostic markers and overall survival. The authors demonstrated the prognosis value of modified Glasgow Prognostic Score (mGPS), Lymphocyte Monocyte ratio (LMR) and CA 19.9 in multivariate analysis. Patients were mostly refractory mCRC. The strength of this study is to have excluded patients with chemotherapy within 4 weeks what could skew the biological results. The results can help decision making in refractory mCRC and selected patients for other chemotherapy regimen or best supportive care. Nevertheless, this study has some minor limitations. The results data are well described and analysed. Moreover, discussion is well written and relevant.

### Major comments

✓ In the Methods section, authors should describe which significant variables in univariate analysis where introduce in multivariate analysis (if  $p < 0.05$  ?).

Thank you for your meticulous comments which we missed to describe. We didn't clarify the detail of proportional hazards model. The result of multivariate analysis was based on the manuscript was based the Cox's multivariate proportional hazard models with stepwise selection process.

And this comment was related with 2<sup>nd</sup> and 3<sup>rd</sup> comments in major comments, so we described the details on multivariate analysis separately at the end of major comments.

✓ ROC curve need to be shown and also the method used to select the cut-off value for each variable.- I think that authors could analysed only absolute cell count and not % in univariate and multivariate analyses. Which one was selected for multivariate analyses?

Thank you for this point. The details of ROC curve including figure of curves and results of analysis were shown in the figure 2. The results of the key prognostic factors of this study, such as cut-off values, AUCs, and significances of LMR and PNI were described in the 'result' section of manuscript.

Regarding the variables entered in multivariate analysis, we answered at the end of major comments.

✓ In table 3, authors should showed non-significant variables introduced in the multivariate analysis.

We analyzed the multivariate analysis using the Cox proportional hazard model in a stepwise manner. Stepwise model is an automated process of building a model by adding and removing significant variables for making the best set of survival predictors. So all of the variables resulted from stepwise model was showed in table 3 of manuscript and described the details in the 'result' and 'discussion' of manuscript.

Regarding the multivariate analysis

Initially, we entered all the significant factors from univariate analysis for multivariate proportional hazards regression. In final stepwise modeling, we could get the result with mGPS, LMR, CA 19-9 which you saw in the first manuscript. However, after reading your comment on entering the white blood cell count and percentage in multivariate analysis, we realized our failure to notice on many overlapped variables which was entered in multivariate analysis. As you indicated, the absolute count and the percentage of white blood cell were overlapped and the systemic inflammation markers calculated by the formula containing the variables of white blood cell count, albumin and CRP. After removing overlapped and correlated variables, we could the result of multivariate analysis with mGPS, LMR, CA19-9, AST, treatment duration which were reported in this revision manuscript.

Regarding non-significant variables in multivariate analysis, we performed both of simple proportional hazards regression and stepwise proportional hazards regression with forward and backward process. The potential predictors from simple multivariate analysis and stepwise multivariate analysis revealed consistently through the models, as you see in the below tables. As you see in the tables, the stepwise multivariate models regardless of forward or backward process were showed us the same model function for predicting survival. Therefore, we selected the result of multivariate analysis from stepwise model which showed more powerful predictors for survival time.

All the results of multivariate proportional hazards regression were attached in below tables. Thank you again for your advice what we missed.

The simple multivariate Cox proportional hazards regression \_ using enter process in SPSS software

Variable		Hazard Ratio (95% CI)	<i>p</i> -value
Liver metastasis	No vs. Yes	1.136(0.742-1.738)	0.558
CA19-9 (U/mL)	≤27 vs. >27	1.435(0.962-2.141)	0.077
CEA (ng/mL)	≤5 vs. >5	1.127(0.638-1.989)	0.681
Hb (g/dL)	≤12.1 vs. >12.1	0.697(0.430-1.130)	0.143
ECOG - PS	0-1 vs. 2-4	1.199(0.793-1.813)	0.389
AST (IU/L)	<40 vs. ≥40	2.738(1.251-5.993)	0.012
ALT (IU/L)	<40 vs. ≥40	0.637(0.280-1.450)	0.283
mGPS			0.046
	0 vs. 1	0.907(0.521-1.578)	0.729
	0 vs. 2	2.933(1.104-7.791)	0.031
NLR	<5 vs. ≥5	1.724(0.951-3.123)	0.073
PLR			0.423
	<150 vs. 150-300	0.753(0.457-1.239)	0.264
	<150 vs. >300	0.963(0.434-2.139)	0.927
LMR	>3.4 vs. ≤3.4	1.630(1.006-2.639)	0.047
PNI	≤45.3 vs. >45.3	1.348(0.741-2.452)	0.328
Treatment duration (months)	≥2.9 vs. <2.9	1.900(1.238-2.914)	0.003

The forward stepwise multivariate Cox proportional hazards regression \_ using forward process in SPSS software

Variable		Hazard Ratio (95% CI)	<i>p</i> -value
mGPS			0.017
	0 vs. 1	1.135(0.717-1.797)	0.588
	0 vs. 2	3.212(1.437-7.716)	0.004
LMR	>3.4 vs. ≤3.4	1.658(1.092-2.518)	0.018
CA19-9 (U/mL)	≤27 vs. >27	1.482(1.007-2.182)	0.046
AST (IU/L)	<40 vs. ≥40	2.377(1.359-4.155)	0.002
Treatment duration (months)	≥2.9 vs. <2.9	1.718(1.160-2.543)	0.007

The backward stepwise multivariate Cox proportional hazards regression \_ using backward process in SPSS software

Variable		Hazard Ratio (95% CI)	<i>p</i> -value
mGPS			0.017
	0 vs. 1	1.135(0.717-1.797)	0.588
	0 vs. 2	3.212(1.437-7.716)	0.004
LMR	>3.4 vs. ≤3.4	1.658(1.092-2.518)	0.018
CA19-9 (U/mL)	≤27 vs. >27	1.482(1.007-2.182)	0.046
AST (IU/L)	<40 vs. ≥40	2.377(1.359-4.155)	0.002
Treatment duration (months)	≥2.9 vs. <2.9	1.718(1.160-2.543)	0.007

#### Minor comments

- ✓ In the abstract and in the text, KM is not defined.

Thank you for this comment. As you pointed, we missed the description on Korean Medicine (KM) although it was described in the result. We added it in the abstract and the treatment section of materials and methods briefly.

- ✓ In the abstract, authors should replace “mGPS 1” by “mGPS at 1 versus 0” and “mGPS 2” by “mGPS at 2 versus 0”.

Thank you for this good suggestion to improve understanding of the detail. It was corrected as you suggested.

- ✓ In the discussion, page 9, I do not understand the sentence “AST elevation was observed in 30 patients and liver metastasis was shown in 29 patients in the study”. What is the total number of patients? What is the association with overall survival?

Thank you for pointing the wrong number. Among enrolled patients, AST elevation was observed in 30 patients and ALT elevation was observed in 20 patients, whereas liver metastasis was showed in 108 patients. It was modified correctly in the discussion of manuscript.

- ✓ In Table 1, there is a problem with the % of prior chemotherapy lines “11,9/15,8/30,5/4”, the total is not 100%.

Thank you for pointing this. Because of the space of table, all characters of number were not shown. It was corrected as you commented.

Reviewer : 2

Dear authors, Your work is excellent and very interesting idea. I think that all these prognostic markers can be easy incorporated in everyday practice work.

We appreciate your evaluation and opinion.