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Title: Chitinase 3-Like 1(CHI3L1) secreted by peritumoral macrophages in esophageal squamous cell carcinoma is a favorable prognostic factor for survival

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Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled '**Chitinase 3-Like 1(CHI3L1) secreted by peritumoral macrophages in esophageal squamous cell carcinoma is a favorable prognostic factor for survival**'. Those comments are all valuable and very helpful for revising and improving our paper. We have studied comments carefully and have made corrections which we hope meet with approval. We have highlighted the changes with a different color in the revision. The point-by-point answers to the comments and suggestions were listed as below.

Editor:

1. Thanks for your suggestions about the format. The format of reference and figure has been revised and highlighted in the manuscript.
2. As for the language, with the help of American Journal Experts, we modified the manuscript and corrected the grammar errors using the "Track Changes" function. The certificate letter has been uploaded.

Reviewer #1:

why the total number of patients in pT Status are 141, and in pN Status are 141, but the total number of patients in pM Status is 144, in the stage are 144 again.

Thank you for pointing this out. We are very sorry for leaving out three patients'

information about T classification and N classification by mistake. The information has been included and highlighted in Table 1 on the page 24 of the manuscript.

Reviewer #2:

1. The treatment options in these cohort of patients have not been reported. We would like to know if they received chemotherapy and the type of chemotherapeutic regimens and surgery.

Thank you for pointing it out. Of the included patients, 73 patients underwent surgery. Of the 73 patients who underwent surgery, 3 patients received chemotherapy followed by surgical resection, 2 received radiation before surgery and others did not undergo chemotherapy or radiation additionally. 57 patients received combined adjuvant chemoradiotherapy. All of them received chemotherapy administered concurrently with radiation therapy. 11 subjects underwent systemic chemotherapy. A variety of chemotherapy regimens were employed, most commonly cisplatin and 5-Fluorouracil. The type of chemotherapeutic regimens for the patients underwent chemoradiotherapy or chemotherapy are listed below:

Chemotherapeutic regimens	No of patients
DDP+5-Fu	25
DDP+FuDR	4
DDP+NVB	9
DDP+4-quinlones	2
Taxol+CBP	7
Taxol+5-Fu	5
Taxol+DDP	4
DDP	2
Other/unknown	10
Total	68

The information was listed and highlighted on the page 9 of the manuscript and table 1.

2. The association of OS with type of treatment regimens should be considered. The correlation of CHI3L1 with treatment options and OS then should be evaluated.

Thanks for your suggestion.

Univariate Cox regression analysis showed that the type of treatment regimens was significantly associated with OS ($P < 0.001$). However, the relationship between type of treatment regimens and OS was not significant ($P = 0.084$) after adjustment for other covariates analysed by the multivariate Cox regression model. The information has been included and highlighted on the page 9 of the manuscript and Table 2.

The correlation of CHI3L1 with treatment options was listed in and highlighted in Table 1 on the page 24 of the manuscript. The chi-square test result show that their correlation is not significant ($P = 0.138$).

Multivariate Cox regression analysis in Table 2 showed that after adjustment for other covariates including treatment options, CHI3L1 is still an independent predictor for OS. The information has been included and highlighted on the page 9 of the manuscript and Table 2.

In addition, Separate analyses of the prognostic effect of CHI3L1 in patients treated with surgery also showed a significant effect for predicting OS ($P = 0.014$).

Information was shown below:

Cox analysis of overall survival (OS) in patients treated with surgery

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age	0.999	0.960-1.040	0.976	-	-	-
Sex	0.378	0.147-0.972	0.043 ^a	0.299	0.114-0.785	0.014 ^a
Smoke Status	0.751	0.522-1.079	0.122	-	-	-
Alcohol Intake	0.887	0.451-1.745	0.729	-	-	-
G grade	1.456	0.887-2.39	0.138	-	-	-

TNM stage	2.068	1.377-3.160	<0.001 ^a	2.418	1.561-3.746	<0.001 ^a
CHI3L1	1.004	1.001-1.008	0.025 ^a	1.005	1.001-1.009	0.014 ^a
SCCA	1.097	0.913-1.318	0.323	-	-	-
CEA	1.089	0.984-1.206	0.099	-	-	-

Variables: age, ≥ 60 vs. < 60 ; gender, female vs. male; smoke, smoker vs. non-smoker; alcohol intake, yes vs no; grade, grade 3 vs. grade 2 vs. grade 1; stage, IV vs. III vs. II vs. I ; - represent "date not available"; ^arepresent $P < 0.05$. HR, hazard ratio; CI, confidence interval.

3. English language should be improved.

Thank you for pointing it out. With the help of American Journal Experts, we modified the manuscript and corrected the grammar errors using the "Track Changes" function.

Sincerely,

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