Peer Review File

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Reviewer A

Comment 1: Several similar studies have indicated that serum HDL-C was a potential biomarker and a prognostic factor in gastric cancer patients, e.g. Guo E, Chen L, Xie Q, Chen J, Tang Z, Wu Y. Serum HDL-C as a potential biomarker for nodal stages in gastric cancer. Ann Surg Oncol. 2007 Sep;14(9):2528-34; Tamura T, Inagawa S, Hisakura K, Enomoto T, Ohkohchi N. Evaluation of serum high-density lipoprotein cholesterol levels as a prognostic factor in gastric cancer patients. J Gastroenterol Hepatol. 2012 Oct;27(10):1635-40; Sun H, Huang X, Wang Z, Zhang G, Mei Y, Wang Y, Nie Z, Wang S. Triglyceride-to-high density lipoprotein cholesterol ratio predicts clinical outcomes in patients with gastric cancer. J Cancer. 2019 Nov 1;10(27):6829-6836. In the present study, more novel information or study results are mandatory for readers.

Reply 1: We fully understand what the reviewer's means to say. The role of lipid profile levels in gastric cancer was investigated in previous studies, as the reviewer mentioned above. The difference was that the present study enrolled more lipid profiles and assess the role of lipid profiles both in cancer progression and prognosis in gastric cancer. Moreover, we using ROC analysis to determine the cutoff value for lipid profiles, which was quite different to other studies mention above. The results of the present study, as well as previous reports, may provide additional information on the influence of lipid profiles in gastric cancer patients.

Changes in the text: We added Tamura T's study results in the discussion section (see Page9, line 190-194).

Comment 2: In Table 2. Relationship between serum HDL-C and clinical characteristics in 358 patients with gastric cancer. Several important clinicopathologic features were missing, e.g. T factor, N factor, perineural invasion,

lymphovascular invasion and serum CEA level. In addition, authors should reform the Table 2 to identify the potential clinicopathologic features related to oncologic outcomes by univariate and multivariate analyses.

Reply 2: We fully understand the reviewer's questions. Actually, in table 2, the T and N factor was included. According to TNM T staging, T1 and T2 was classified as no serosal invasion, and T3 and T4 as serosal invasion, According to N staging, N0 was classified as no lymph node metastasis, and N1-3 as lymph node metastasis. We agree that it will be more useful if perineural invasion, lymphovascular invasion and serum CEA level can be evaluated in this study, we added perineural invasion, lymphovascular invasion variables in table 2. Unfortunately, data for CEA level was not available in the study. We fully understand that potential clinicopathologic features related to oncologic outcomes by univariate and multivariate analyses should be included in the study, however, the aim of Table 2 was to show the difference of clinicopathological features between high HDL-C group and low HDL-C group. The oncologic outcomes was described in the last paragraph of "results" section (see page 7, line 139-146).

Changes in the text: we added the data of perineural invasion, lymphovascular invasion in the table 2 with red color.

Comment 3: Likewise, Table 3 should be extensively revised to find out the independent risk factor of oncologic outcomes, not just for serosal invasion, LN metastasis and TNM stage only. Moreover, some data were inconsistent between Table 2 and Table 3.

Reply 3: We fully understand what the reviewer's means to say. The aim of Table 3 was to present the potential variables for patients who were have more risk to have tumor with serosal invasion, lymph node metastasis as well as advanced TNM stages, respectively. The independent factor of oncologic outcome was shown in the last paragraph of "results" section. We agree the reviewers comment that some data such as age, tumor size, were inconsistent between table 2 and table 3. In table 3, we use logistic regression analysis to find the risk factors for patient with more aggressive disease, so the variables entered into the analysis model should be categorical, thus, we set up age, tumor size according to the cutoff value in the study. We made the location variable in table 2 and table 3 as the same.

Changes in the text: We made some corrections in table 3 with red color.

Comment 4: Table 4. Univariate and multivariate analysis of gastric cancer with survival. This table is confusing, authors should presented the survival time in each variable.

Reply 4: We fully understand the reviewer's questions. The aim of table 4 was to present the different survival outcomes between high and low levels of lipid profiles, the univariate analysis was performed by using Kaplan–Meier method, and the multivariate analysis was performed using Cox regression model. We have considered the reviewer's comments and we added the mean survival time in the table 4.

Changes in the text: we added the survival time data in the table 4 with red color.

Comment 5. A survival curve analysis by using the Kaplan–Meier method, and the log-rank test was used to compare time-to-event distribution between high vs. low serum HDL-C groups that is needed to confirm the role of serum HDL-C.

Reply 5: We fully understand what the reviewer's point. Actually, the comparison of survival outcome between high vs. low serum HDL-C groups by a survival curve analysis was presented in table 4. The mean survival time was 55.8 and 58.9 months in patients with high and low level of HDL-C, the p value with 0.810, and no significance of survival was found between both groups.

Changes in the text: we added the survival data of HDL-C in the "results" section (see Page7, line 140-143).

Comment 6: In Results section: Among the total of 358 patient, three hundred patients (83.8%) performed radical surgery, and others were treated palliative. The percentage of GC patients receiving radical resection was relatively higher compared to other Asian countries. In addition, only 18.6% of patients were categorized into stage IV? Please make a consort flow diagram to show the details of all enrolled patients.

Reply 6: We fully understand the reviewer's intent. The patient enrolled in the study was from a single institute of surgical oncology, patient with potentially operable would be treated at the department of surgical oncology, otherwise, patients with clinically late stage diseases who were not suitable to have surgical treatment would transfer to medical oncology department, thus, a comparatively earlier stage disease were treated at our department, which may be one reason why radical surgical resection rate was high in this study. On the other hand, we performed neoadjuvant chemotherapy for patients with locally advanced gastric cancer, thus the radical surgical rate can be increased, as the same results with previous study publish in

New England journal of medicine [Ref].

In the present study, 18.6% patients were categorized as stage IV, we think it is reasonable, since most of patients with palliative surgery were found to be stage IV during the operation. Furthermore, patients with more than 15 lymph node metastasis was also classified to stage IV according to TNM stage classification.

[Ref] Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355:11-20

Changes in the text: we added the information of neoadjuvant chemotherapy in the "Materials and Methods" section (see Page5, line 91-92).

Comment 7: Finally, low level of serum high-1 density lipoprotein cholesterol in gastric cancer correlates with cancer progression but not survival. Moreover, none of the lipid profiles was an independent prognostic factor predicting the survival of gastric cancer. The negative results in the current study were not consistent with previous researches, of which it would not raise attention of readers for the subsequent interest.

Reply 7: We fully understand what the reviewer's means to say. As mentioned in the study, the relationship between HDL-C and patient outcome was controversial, we shared our single institution data with something new as compared with the previous studies, although with negative result in the present study, there may also give additional information for the influence of lipid profiles in patient outcomes in gastric cancer.

Changes in the text: We added a previous study results in the discussion section (see Page9, line 190-194).

Comment 8: Please correct the typos and grammatical error by English-editing with the certificate enclosed.

Reply 8: We have considered the reviewer's suggestions, the manuscript was corrected by an English native editor.

Changes in the text: The correction was made in red color in the revised manuscript.

Comment 9: Table 1. Why authors classified tumor size at 3 cm of cut-off level?

Reply 9: We classified tumor size at 3cm of cut-off level based on the previous studies as reference [Ref 1-2].

[Ref 1] Kim TJ, Lee H, Min YW, et al. One-dimensional and 2-dimensional tumor size measurement for prediction of lymph node metastasis in differentiated early gastric cancer with minute submucosal invasion. Gastrointest Endosc.

2017;85(4):730‐736.
[Ref] Xu C, Shen J, Xie S, Jiang Z, Chen W, Wang L. Impact of malignant ulcer size on lymph node stages in gastric cancer with ulcerative growth. Hepato-gastroenterology. 2012; 59(114):612‐615.
Changes in the text: no changes was made on this point in the revised manuscript.

Comment 10: Table 2 needs to be corrected as both groups were HDL-C<54.2mg/dl?

Reply 10: Thanks for the reviewers finding. We corrected the mistake in the revised manuscript.

Changes in the text: We corrected the mistake in the table 2 with red color.

Reviewer B

Comment 1: The manuscript is interesting. A linguistic revision is necessary

Reply 1: We have considered the reviewer's suggestions, the manuscript was corrected by an English native editor.
Changes in the text: The correction was made in red color in the revised manuscript.

Reviewer C

Comment 1: In Table 2, "Serosal invasion" means what? In many cases, the serosal invasion is positive. However, T4 cases are only less than 10% in Figure 1. Are T3 cases included in the serosal invasion? These points are unclear and so important.
Reply 1: We fully understand what the reviewer's point. According the TNM staging system, T3 and T4 tumor was serosal invasion positive.
Changes in the text: No changes was made on this point in the revised manuscript.

Comment 2: In Table 2, serosal invasion and LN metastasis are confounding factors of TNM stage and this logistic regression analysis is nonsense.
Reply 2: We fully understand what the reviewer's means to say. The aim of the table 2 was to show the differences of clinicopathologic features between high HDL-C group and low HDL-C group. The relationship between clinical variables and HDL-C level was analyzed by one-way ANOVA.

Changes in the text: no changes was made on this point in the revised manuscript.

Comment 3: In Table 4, correlations with the other clinicopathological features in survival should be shown.

Reply 3: We agree with the reviewer's comments. Actually, we did univariate and multivariate analysis with all candidate variables including clincopathological parameters and all lipid profiles, the reason why we only presented the lipid profiles data in table 4 was to emphasize the relationship between lipid profiles and patients survival in gastric cancer. According to the reviewer's suggestions, we added other clinicopathological variables data in the "results" section.

Changes in the text: We added other clinicopathological variables in the results section (see Page7, line 139-140).

Comment 4: There are some careless mistakes; for example, "HDL-C< 54.2" in Table 2, "HDL-C" in page 6 line 127, and so on.

Reply 4: We corrected the mistakes in the revised manuscript.

Changes in the text: We corrected the mistakes both in the results section and tables with red color in the revised manuscript.