Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitl "The prognostic significance of pretreatment serum carcinoembryonic antigen (CEA) levels in Gastric Cancer with pathological lymph node-negative(pN0): a large sample single-center retrospective study". (ID: 33617).

Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in red in the paper. The main corrections in the paper and the responds to the reviewer' s comments are as flowing:

Responds to the reviewer' s comments:

Reviewer #1:

1.There are several typos, which should be corrected.

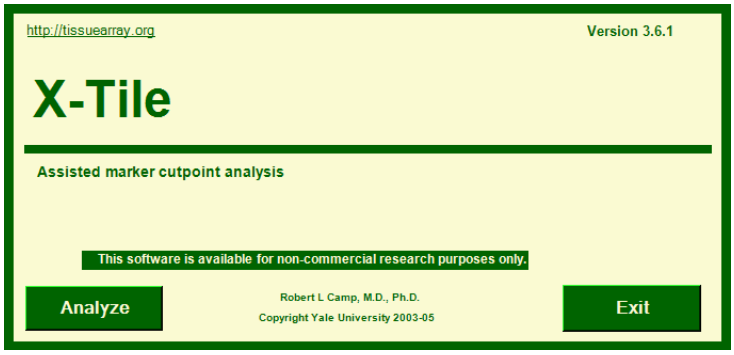
Response: We are very sorry for our incorrect writing, and several typos in our manuscript were revised.

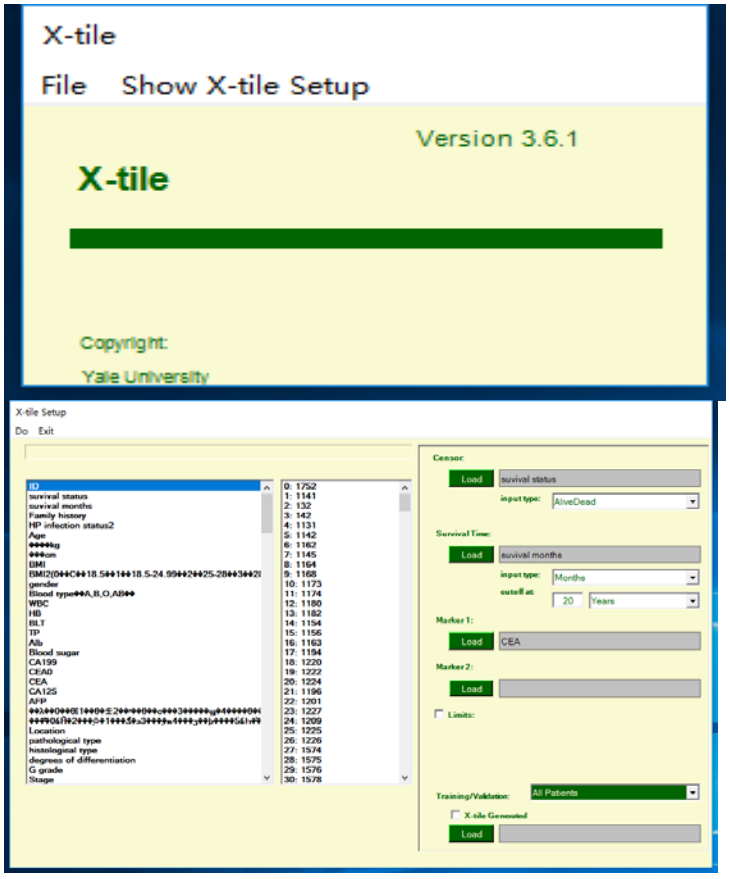
2.Since this study was retrospectively planned, Authors should make it explicit in the title.

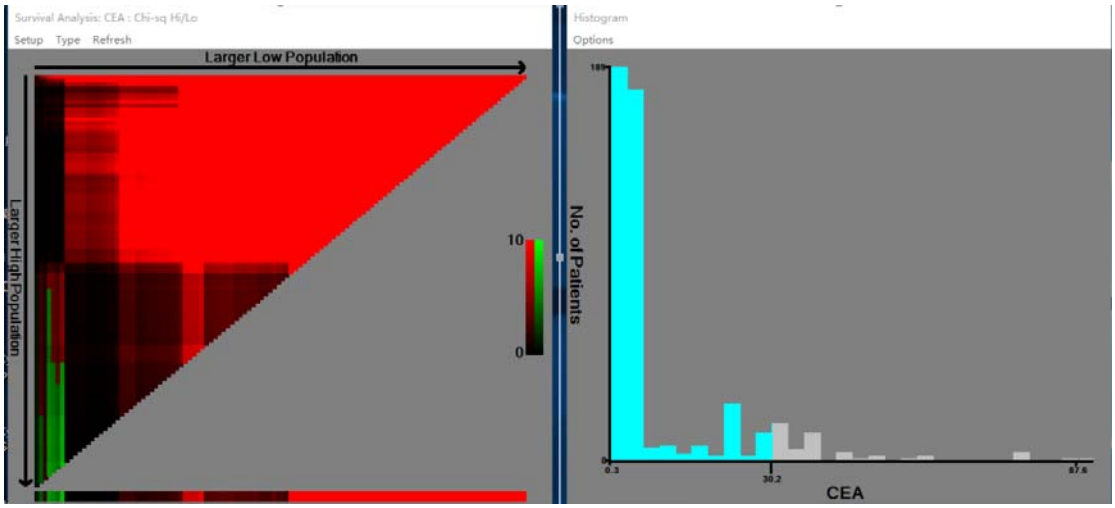
Response: The title was revised as: The prognostic significance of pretreatment serum carcinoembryonic antigen (CEA) levels in Gastric Cancer with pathological lymph node-negative (pN0): a large sample single-center retrospective study

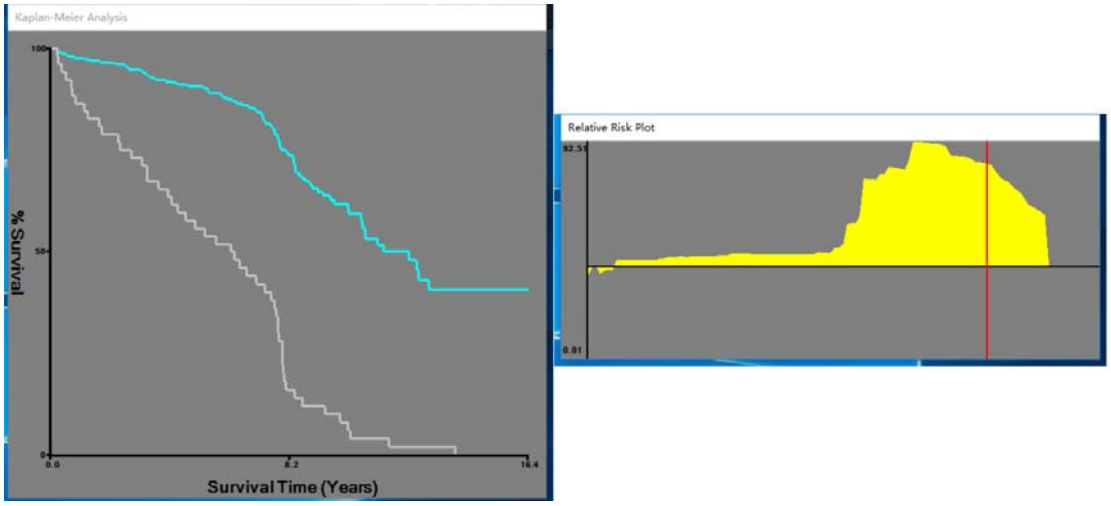
3.The X-tile plot has been recently elaborated to establish cut-offs for biomarkers in cancer (see Camp RL et al, Clin Cancer Res 2004). Therefore Authors should provide more detail about this test in the appropriate section of the article, and add the reference as well.

Response: The process of the X-tile plot was as follow:









4.Data about Lauren classification of GC is lacking.

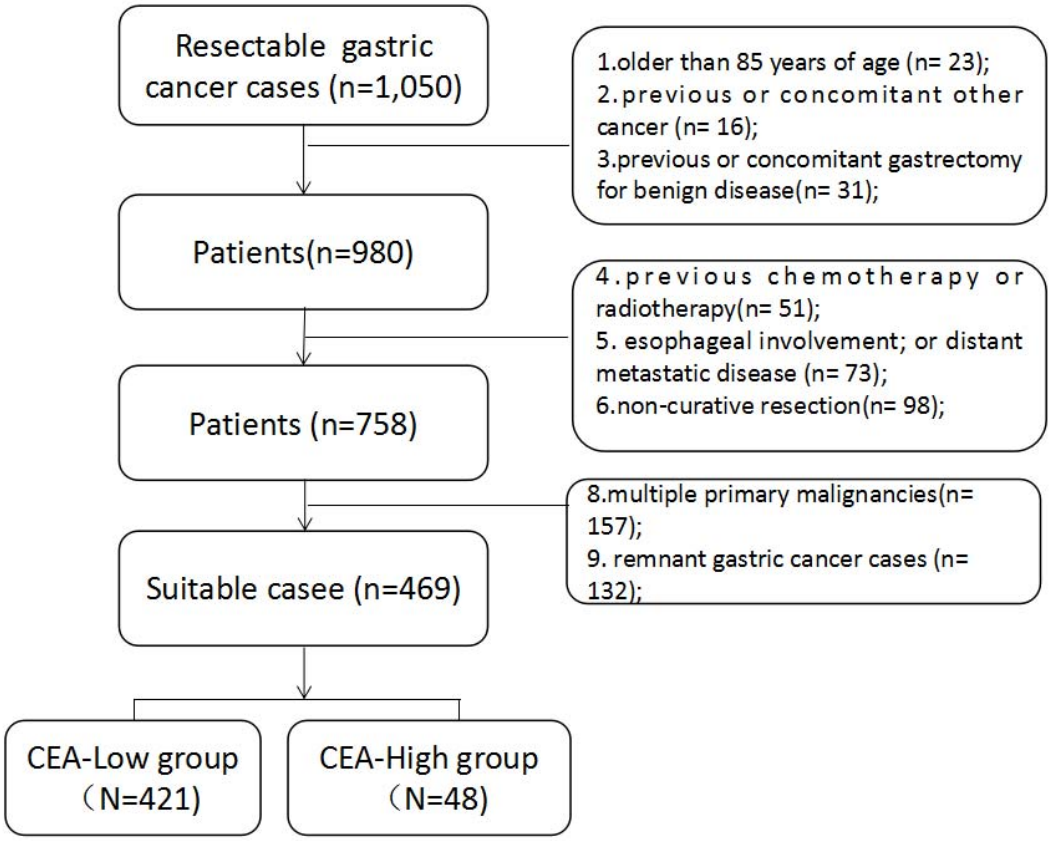
Response: We have re-written this part according to the Reviewer's suggestion, and data about Lauren classification was make up.

5.It is unclear whether GC of the cardia were included. Indeed, it is known that this subtype of GC has a different pathogenesis and singular natural history. Please clarify this point.

Response: Considering the Reviewer's suggestion, we have re-written this part, and data about Location was make up.

6.Authors should report how many GC have been excluded from the initial pool of cases due to inclusion/exclusion criteria. A figure with a flowchart may be useful.

Response: A figure with a flowchart about the inclusion and exclusion criteria were as follows:



Reviewer #2:

1 However the statistical analyses should be controlled by a statistician. The authors compared two CEA groups: high-CEA 421 patients-v/s low CEA 48 patients. Is this difference enough for safe statistical analyses 421v/s 48? (did the patients performed power calculation for safe results? It seems that the 48 patiens group is too small in comparison to 421 patients group.

Response: This study is retrospective, with its own weaknesses such as confounding factors. We had consulted some statistics experts, to ensure the strength of statistics.

2 Did all patients receive similar post-op treatment? Eg How many of them received adjuvant radiochemotherapy?

Response:

The exclusion criteria were as follows: 1. older than 85 years of age; 2.previous or concomitant other cancer; 3.previous or concomitant gastrectomy for

benign disease; 4. previous chemotherapy or radiotherapy; 5.esophageal involvement; or 6.distant metastatic disease; 7.non-curative resection, 8.multiple primary malignancies, 9. remnant GC, 10. mortality within 30 days after surgery.

So none of the case received adjuvant radiochemotherapy.

3 According to table 1. There was statistical significant difference in T1a between two groups. (in Low CEA group more patients were T1a in comparison to high CEA group. So the worse outcome could be attributed to worse T staging. So high CEA levels is a predictor to worse T stage?

Response:

This study is retrospective, with its own weaknesses such as confounding factors. In the CEA-high group, the proportion of was slightly higher than the negative group in poor differentiation(54.2% vs 46.3%), and nerve invasion(22.92% vs 16.6%). What is more, percentage was dramatically higher in CEA-high group than CEA-low counterparts in stage of T2-4b (81.25% vs 65.32%, P=0.026), vessel carcinoma embolus(31.35% vs 17.1%, P=0.017) among the CEA-positive goup.

Multivariate survival analysis showed that CEA (OR = 4.924), and T category (OR = 2.214) were significant prognostic factors for stage pN_0 GC (all $P < 0.05$). Besides, only T category (OR = 1.962) was an independent hazard factor in the CEA-hgih group ($P < 0.05$).

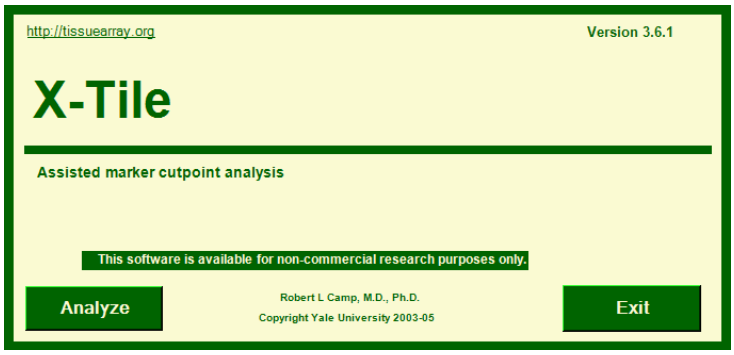
Thus, T category might be considered as contributing to high CEA levels, and affecting the prognosis.

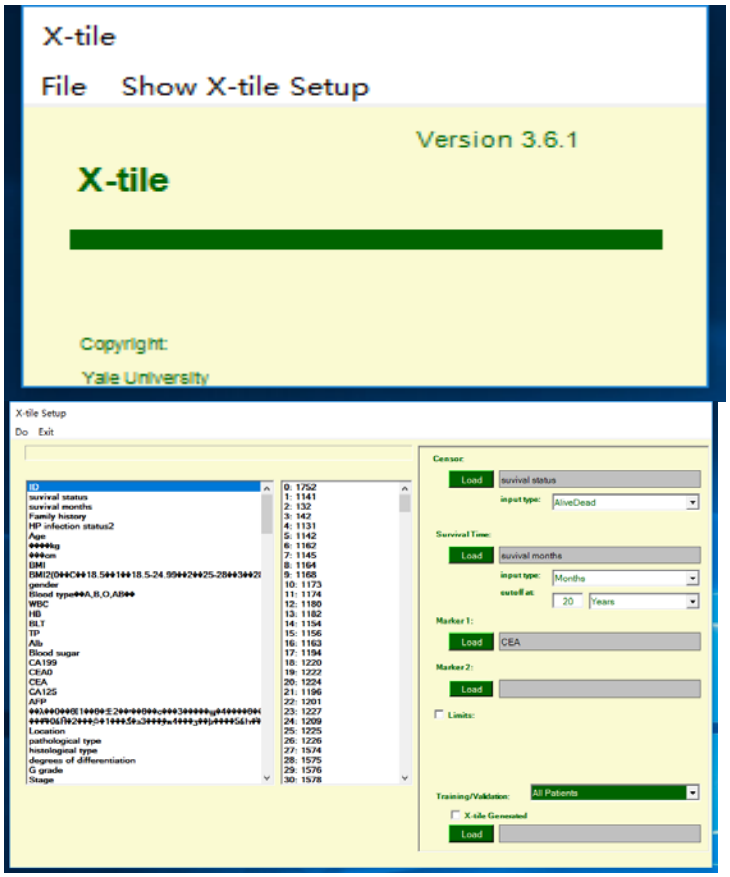
4 In the discussion last sentence the authors reported subgroup T1N3. However, the protocol include only pNo patients. Please clarify what the meaning of this last sentence.

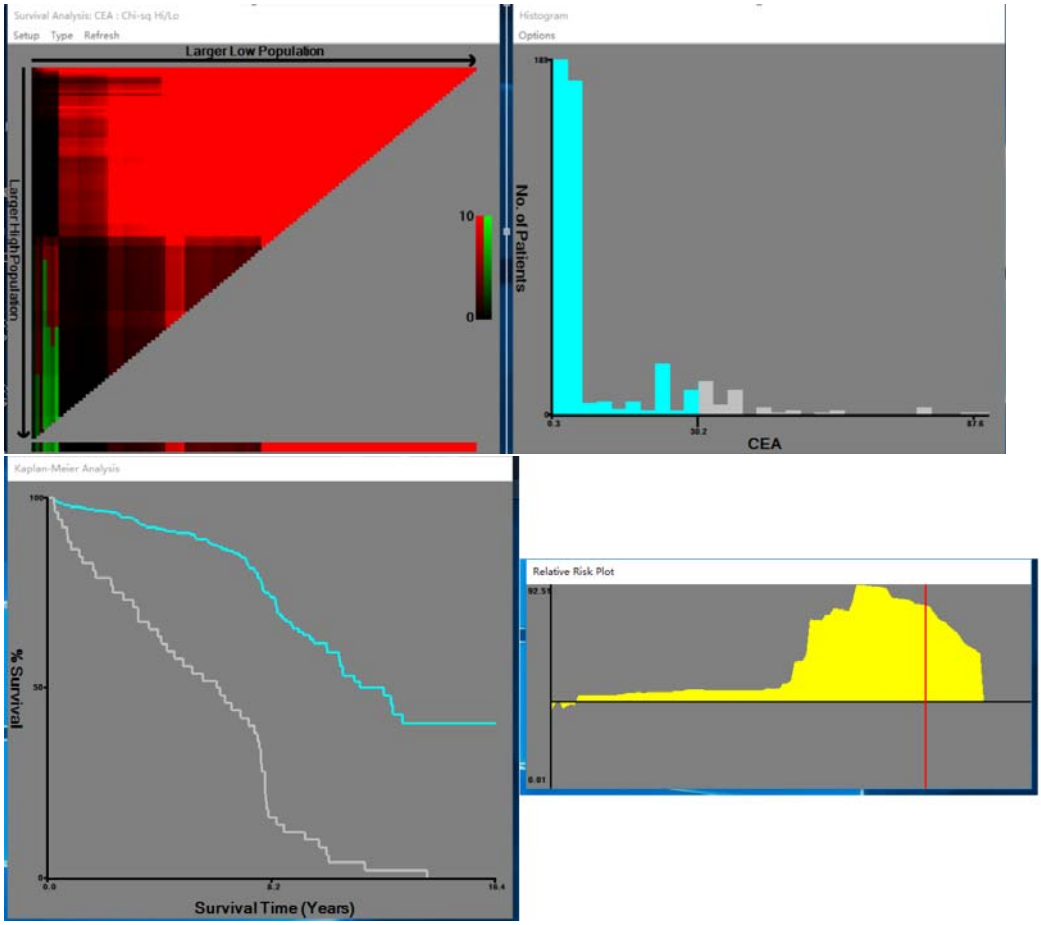
Response: We are very sorry for our negligence of this part, and the discussion last sentence was removed.

5.Figure 1 is not well understood. Please clarify better.

Response: The process of the X-tile plot was as follow:







We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. And here we did not list the changes but marked in red in revised paper.

We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.