

Peer Review File

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Reviewer Comments

1. The paper has English language problems and extensive language editing is necessary. In the title, “diagnostic clues” is a lay term, which should be the clinical characteristics and outcomes of patients with cancer who are first diagnosed with AP. Lien 16, page 3, “or” should be “and”.

Reply: We thank the Reviewer for his/her in-depth evaluation of our work. As suggested, we have revised the title to "Clinical characteristics and outcome of tumor-associated acute pancreatitis: a single-center cohort study" and changed the "or" in line 50 on page 4 to "and".

Changes in the text: we have modified our text as advised and all revisions have been highlighted in yellow in the revised manuscript. Please refer to page 1, line 1, “Clinical characteristics and outcome of tumor-associated acute pancreatitis: a single-center cohort study”, page 1, line 3, “Running title: Clinical characteristics and outcome of tumor-associated AP”, page 3, line 36, “assess the clinical characteristics and outcome...”, and page 4, line 50, “The median survival period of AP patients with PC, PAC, and NPC was ...”.

2. Abstract. Details of methods should be briefly described here, including the selection criteria of patients, data collection on clinical variables and outcomes, follow up procedures, and statistical analysis.

Reply: We thank the Reviewer for his/her comment of our work. We agree that the information is essential. As suggested, we have modified the methods section as follows: Patients who presented with AP and were diagnosed with tumor after admission were included according to the inclusion and exclusion criteria and followed up by hospital notes, telephone, WeChat and/or e-mail. The clinical characteristics and outcome were analyzed with multivariable logistic regression and were compared with AP patients without tumor.

Changes in the text: we have modified our text as advised and all revisions have been highlighted in yellow in the revised manuscript. Please refer to page 3, line 37-41, “Patients who presented with AP and were diagnosed with tumor after admission were included according to the inclusion and exclusion criteria and followed up by hospital notes, telephone, WeChat and/or e-mail. The clinical characteristics and outcome were analyzed with multivariable logistic regression and were compared with AP patients without tumor”.

3. Introduction. Line 15-16, page 4, the authors may consider to summarize the clinical characteristics of AP patients who were diagnosed with cancer later from these available case reports, such information may provide more insights on the research topic of this study. Line 12-15, page 4, the authors may provide some examples to explain why AP was an early sign of cancers and why it is neglected in clinical practice. Line 4, page 5, please provide examples for adverse impact. Line 8, page 5, this is an observational study, so CONSORT is not suitable for it.

Reply: We thank the Reviewer for his/her kind evaluation of our work. As suggested, we have summarized the clinical characteristics of tumor-associated AP from these available case

reports, such as elderly, mild AP that were non-specific. In the discussion section, we have made discussion on the possible mechanisms why AP was an early sign of cancers (please see page 15, line 275-281) and the reasons why tumors were overlooked in the early stage (please see page 15, line 226-238). Due to words limitations, we will not expand the description here. Moreover, we have added examples of adverse impact based on Reference 9, such as late stage of tumor, poor quality of life and short survival time, etc. We are sorry for the wrong description of reporting checklist and have changed “CONSORT” on page 5, line 75 to “STROBE”.

Changes in the text: we have modified our text as advised and all revisions have been highlighted in yellow in the revised manuscript. Please refer to page 5, line 67, “... (such as elderly, mild AP) ...”, page 5, line 70-72, “...can adversely impact survival, resulting in late stage of tumor, poor quality of life and short survival time, etc.”, page 5, line 75, “...accordance with the STROBE reporting checklist”.

4. Methodology. I suggest the authors to re-organize this part according to following subtitles: patients and settings, measures and outcomes, procedures, and statistical analysis. Line 14, page 6, the authors need to describe factors that were matched. Because this is 1:4 matching, please also provide the details of individual matching.

Reply: We thank the Reviewer for this important comment. It does improve this paper a lot. As suggested, we have re-organized the methodological part. Moreover, we have provided the details of individual matching, that is controls were randomly selected from the database of AP without tumor using stratified random sampling, and matched to each study subject by gender and length of stay at a case-to-control ratio of 1:4. This matching method was previously

reported by Jonathan C Routh in the Journal of Urology (J Urol . 2015 Jan;193(1):268-73. doi: 10.1016/j.juro.2014.06.085.).

Changes in the text: we have modified our text as advised and all revisions have been highlighted in yellow in the revised manuscript. Please refer to methods section (page 5-9, line 78-134), and page 7, line 97-100, “AP without tumor (controls) were randomly selected from the AP database, which had been described elsewhere (11, 12), using stratified random sampling. Controls were matched to each study subject by gender and length of stay at a 1:4 ratio”.

5. Statistics. Student’s t test cannot be used for comparing “continuous nonparametric variables”. In fact, the term “continuous nonparametric variables” is confusing, which may be continuous variables with a skewed distribution. In addition to Chi-square test, please also consider Fisher’s exact test as appropriate. Please also specify the statistical method for multiple analysis, logistic or Cox regression? Further, I do not agree with the term “risk factors”, which should be clinical features associated with cancer diagnosis. Risk factors are factors causing cancers such as smoking.

Reply: We thank the Reviewer for his/her kind reminding. We are sorry for the insufficient statistical methodological description. As suggested, we have modified this section with pertinent points and rechecked our data.

Changes in the text: we have modified our text as advised and all revisions have been highlighted in yellow in the revised manuscript. Please refer to page 9, line 129-132, “We use the Student’s t test, Wilcoxon rank-sum test or Kruskal-Wallis test to compare continuous

variables, and the Chi-square test or Fisher's exact test to compare categorical variables. Univariable and multivariable logistic regression analysis was then applied to identify clinical features for tumors".

6. Discussion. Dilation of MPD, vascular invasion, mild AP and anemia are clinical characteristics of AP patients with cancer, not "risk factors". Further, this study is not an interventional study, so "timely detection may lead to favorable outcomes" is inappropriate. Please revise the conclusion and make it with cautions.

Reply: We thank the Reviewer for his/her kind evaluation of our work. As suggested, we have changed the term of "risk factors" to "clinical characteristics" and revised the conclusion and discussion with pertinent points.

Changes in the text: we have modified our text as advised and all revisions have been highlighted in yellow in the revised manuscript, see page 4, line 52-54, "Mild AP patients with dilation of MPD, vascular invasion, and anemia were more frequently suggested a tumor etiology. Thus, clinical vigilance is needed for timely detection of tumor-associated pancreatitis with these characteristics". Page 13, line 203-205, "and if AP had been appropriately investigated, it might result in an earlier diagnosis of tumor".