Answering reviewers

Reviewer 1

Thank you for sending your manuscript. This manuscript was "Nomograms predicting long-term survival in patients with invasive intraductal papillary mucinous neoplasm of pancreas: a population-based study". This manuscript had well described, but had several problems. However, I wonder you should revise some parts of it Major)

Answer: Thank you very much for your kind comments. We highly appreciate your affirmation, and have tried our best to revise our paper accordingly.

1. This manuscript had collected in long time, and diagnostic level of IPMN had been changed. Further treatment and chemotherapy for invasive IPMN wad been improved. This prognosis was significantly changed. This design was difficult.

Answer: Thank you very much for your kind comments. Since IPMN was firstly defined by the WHO in 1996, the diagnostic criteria and therapeutic approaches of IPMN have been significantly changed. Given that the histological diagnosis is the golden standard of tumor diagnosis, we only included patients with histological diagnosis of invasive IPMN in this study to avoid the misdiagnosis of invasive IPMN. Patients were excluded if they were diagnosed with in situ carcinoma or their diagnosis was based on autopsy report or death certificated only. Moreover, because the detailed information of therapy, including radiotherapy and chemotherapy, were not available in the SEER database, we could not further explore the impact of the improvement of therapeutic approach on prognosis of IPMN. Instead, we have listed it as one of the limitations of this study. (Page 9, Line 367-369)

2. Nomogram predicting malignancy risk for IPMN was proposed in Ann Surg previously. You needed to discuss this nomogram.

Answer: Thank you very much for your kind comments. For IPMN, their malignancy risk is very different from their prognosis. Although several nomograms predicting malignancy risk of IPMN have been previously published in some authoritative magazines, such as Ann Surg and Ann Surg Oncol, there had no report on predictive models for prognosis in patients with invasive IPMN. Moreover, as a rare tumor, it's hard to develop a prognostic nomogram for IPMN of pancreas in a single institution, but the SEER database has provided a broad path for it. Thus, we developed these

first nomograms to quantify the probability of long-term survival of invasive IPMN of pancreas based on the SEER dataset.

3. You classified two group. What methods did you use?

Answer: Thank you very much for your kind comments. We divided the patients into two groups, namely the training and the validation groups, through the simple randomization grouping method with a proportion of 7:3. (Page 5, Line 177-178)

4. You should reveal the weighting of nomogram easily. Please try to consider again. Thank you.

Answer: Thank you very much for your kind suggestions. The nomogram works by ranking the effect estimates, and are influenced by the presence of the included variables. In nomogram model, each included factor is ascribed a weighted point, and the total score calculated from the various factors correspond to the predicted survival probability for a patient. Patients with a higher score indicated a worse prognosis. In this study, T stage had the strongest prognostic weight for OS and CSS; thus, it was converted into 100 points. The remaining variables were assigned a smaller number of points proportional to their effect size, which presented the relative importance of the remaining factors compared with the most significant factor. We have revealed this interpretation of the nomogram in the "Discussion" part (Page 8, Line 309-312 and 329-333).

Reviewer 2

The authors described the establishment and validation of nomogram for the assessment of the prognosis of invasive carcinoma associated with intraductal papillary mucinous neoplasm of the pancreas. The nomogram predicts the prognosis better than the staging system of American Joint Committee on Cancer. The data and discussion look reasonable. However, there are a couple of criticisms.

Answer: Thank you very much. We highly appreciate your affirmation and will perfect our manuscript by following your kind comments.

1. In the present study, the authors extracted patients of intraductal papillary mucinous neoplasm of the pancreas were extracted with ICD-O-3 codes. Some ICD codes are defined as in situ carcinoma.

Answer: Thank you very much for your kind comments. In this study, patients were included if

they were histologically diagnosed with invasive IPMN and patients were excluded if they were diagnosed with in situ carcinoma or their diagnosis was based on autopsy report or death certificated only. (Page 4, Line 153-155)

2. The authors intended to evaluate the prognosis of INVASIVE carcinoma derived from intraductal papillary mucinous neoplasm. The authors stated the limitation of data sets of Surveillance, Epidemiology, and End Results. It is not clear whether the patients are all INVASIVE intraductal papillary mucinous neoplasm. This needs to be verified. The issue is also related to the above issue.

Answer: Thank you very much for your kind comments. The identification of invasive IPMN in the SEER registry was based on ICD-O-3 codes, which does not allow for verification of pathological diagnoses and leads to potential miscoding or misclassification of these tumors. Given that the histological diagnosis is the golden standard of tumor diagnosis, we only included patients with histological diagnosis of invasive IPMN in this study to avoid the misdiagnosis of invasive IPMN. Patients with excluded if they were diagnosed with in situ carcinoma or their diagnosis was based on autopsy report or death certificated only. (Page 4, Line 153-155)

3. The WHO classification of intraductal papillary mucinous neoplasm has been changed this year. The nomogram needs to follow the newest classification and concept of the classification.

Answer: Thank you very much for your kind comments. Due to the hysteresis of the SEER's update, only the classification of IPMN based on ICD-O-3 was available in the SEER dataset. Thus, we can only adopt the current classification of the SEER database in this study. Moreover, a specific classification of IPMN, such as MD-IPMN, BD-IPMN, and MT-IPMN, were unavailable in the SEER dataset, and we could not conduct this study by following the newest classification and concept of the classification. This was also one of the limitations of this study. (Page 9, Line 361-362 and 366-369)

4. There are many strange sentences and wordings. There are also grammatical errors. The manuscript needs thorough revision.

Answer: Thank you very much for your kind comments. We have sent the revised manuscript to further English polishing. The certificate of English editing has been provided with the resubmission.

Reviewer 3

This is an interesting manuscript that essentially addresses prognostic scoring in patients undergoing resectional surgery for IPMN. These types of data have been carried out for pancreatic ductal adenocarcinoma extensively in the past and I am sure patients with adenocarcinoma on the background of IPMN were included. This manuscript is however a large series of patients with IPMN cancers. The problem with all of these scoring systems is that they are largely only useful once histology is available and are unlikely to significantly change treatment. The key for this disease is to predict those patients in whom the IPMN will turn malignant and when, this is particularly pertinent in those with BD-IPMN. Despite this the manuscript is well written and interesting, there are a small number of grammatical/typographical errors which need correction.

Answer: Thank you very much for your kind comments. As a rare tumor, it's hard to develop a prognostic nomogram for IPMN of pancreas in a single institution, but the SEER database has provided a broad path for it. To date, there has no previous study focused on the predictive model for prognosis of IPMN. In this study, we have developed nomograms for predicting the probability of overall survival and cancer-specific survival at different time points in patients with invasive IPMN of pancreas based on the SEER dataset. We highly appreciate your affirmation and have sent the revised paper to further English editing. The certificate of English editing has been uploaded as attachment with the revised submission.