Peer Review File

Article information: http://dx.doi.org/10.21037/gs-21-116

Reviewer A

As AF is common in the population the question about the impact of AF on postop. outcome of patients after pancreaticoduodenectomy is reasonable and the large cohort of 12,785 patients allows a sufficient analysis.

However, before acceptance of the manuscript major revisions are necessary.

1. Most important, the authors identify critical consequences of AF and conclude that surgeons should develop an appropriate preoperative evaluation plan (p. 14, l. 4-5).

The authors should present an evaluation plan and suggest potential preoperative treatment strategies (e.g. preoperative consultation of cardiologist?)

How should surgeons deal with patients being treated with new oral anticoagulants like Apixaban or Rivaroxaban? Who should receive bridging therapy and who not?

Reply 1: For pancreatic cancer patients with atrial fibrillation undergoing PD, a thorough and careful evaluation of cardiac function and adjustment of the use of anticoagulants before surgery would be beneficial. Patients with atrial fibrillation often take anticoagulant drugs like warfarin, rivaroxaban or apixaban regularly. Since PD is associated with high risk for bleeding, while pancreatic cancer coupling with atrial fibrillation is associated with high risk of thromboembolism, we have to take perioperative anticoagulation plan seriously.

For patients with atrial fibrillation who take warfarin orally, omitting warfarin for five days before surgery and checking the INR on the day before surgery has been recommended. The use of bridging while holding oral anticoagulants has become common clinical practice, though some current evidence argue that bridging may not significantly reduce thromboembolic events, yet increasing major adverse cardiovascular events and bleeding. Douketis et al. concluded that forgoing bridging anticoagulation was noninferior to perioperative bridging in patients with atrial fibrillation. According to the ACC Expert Consensus, if the patient's thrombosis risk is low (CHA_2DS_2-VASc Score <=4), bridging is not recommended; if the patient's thrombosis risk is medium-to-high (CHA_2DS_2-VASc Score 5 and above) or with prior stroke or TIA, clinical judgment need to be used. For patients who have previously taken apixaban or rivaroxaban, it is suggested that the anticoagulants should be omitted 2-3 days before surgery and bridging is not required. However, there has been limited evidence regarding bridging, specifically for pancreatic cancer patient, in the 2017 ACC periprocedural management of anticoagulation guideline. In this case, if a

complicated case is encountered, multidisciplinary team approach involving cardiologists and anesthesiologists would likely be beneficial.
Thank you for your comment and we have added relevant content in the manuscript.
Changes in the text: we have modified our manuscript (see Page 16, line 19-21, Page 17, line 1-21).

2. Language editing is required – I suggest editing of a native English speaker. Use one term for pancreatic head resection throughout the manuscript: e.g. pancreaticoduodenectomy and do not switch between Whipple's procedure etc. and PD.

Reply 2: We have unified all the terms describing pancreaticoduodenectomy in the manuscript and finished the editing work by native English speaker.
Changes in the text: we have modified our manuscript (throughout the manuscript).

3. The term "gastrointestinal leakage" is misleading, because this term focuses on the duodenojejunostomy or gastrojejunostomy after PD. Insufficiencies of the DJ or GJ occur significantly less often than leakages of the pancreatic anastomosis or the hepaticojejunostomy. A major documental problem is that the large NIS database and ICD-9 does not differentiate between the different kinds of anastomotic leakages. This should be indicated early and throughout the manuscript – where appropriate - to avoid confusion.

Reply 3: The ICD-9 codes of gastrointestinal (GI) anastomotic leakage is 44.61, 44.63, 44.69, 46.71, 46.72, 46.79 (procedure codes). Due to the limitation of database and ICD-9 code, different kinds of anastomotic leakages like leakages of the pancreatic anastomosis or hepaticojejunostomy cannot be differentiated. We appreciate your comment and indicated this point in the Methods session.
Changes in the text: (see Page 7, line 14-17).

4. What is the definition of a postoperative shock?

Reply 4: In our study, we used ICD 9 code 998.0 to include patient who developed shock during or resulting from a surgical procedure, including hemorrhagic shock, hypovolemic shock, septic shock and distributive shock, yet excluding shock that are anaphylactic due to serum, anesthetic, electric, following abortion, obstetric and traumatic.
Changes in the text: None

5. p.10 – l. 5: more literature and current literature should be quoted:

Cameron JL, He J. Two thousand consecutive pancreaticoduodenectomies. J Am Coll Surg. 2015;220:530–6.

Shrikhande SV, Sivasanker M, Vollmer CM, Friess H, Besselink MG, Fingerhut A, et al. Pancreatic anastomosis after pancreatoduodenectomy: a position statement by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2017;161:1221–34.

Luu AM, Krasemann L, Fahlbusch T, Belyaev O, Janot-Matuschek M, Uhl W, Braumann C. Facing the surgeon's nightmare: Incidence and management of postoperative pancreatic fistulas grade C after pancreaticoduodenectomy based on the updated definition of the International Study Group of Pancreatic Surgery (ISGPS). J Hepatobiliary Pancreat Sci. 2020 Apr;27(4):171-181. doi: 10.1002/jhbp.713. Epub 2020 Feb 14. PMID: 31951086.

6. p. 10 l.17: these sources do not focus on long-term survival of patients with PDAC. Although technical and medical advances have been achieved within the last decades, long-term survival occurs still in 20,4 %. However, with new chemotherapy regimens, better survival outcomes are expected in near future (54.4 months survival).

Please include:

Luu AM, Braumann C, Belyaev O, Janot-Matuschek M, Rudolf H, Praktiknjo M, Uhl W. Long-term survival after pancreaticoduodenectomy in patients with ductal adenocarcinoma of the pancreatic head. Hepatobiliary Pancreat Dis Int. 2020 Dec 9:S1499-3872(20)30244-7. doi: 10.1016/j.hbpd.2020.12.006. Epub ahead of print. PMID: 33349608.

Conroy T, Hammel P, Hebbar M, Ben Abdelghani M, Wei AC, Raoul JL, Choné L, Francois E, Artru P, Biagi JJ, Lecomte T, Assenat E, Faroux R, Ychou M, Volet J, Sauvanet A, Breysacher G, Di Fiore F, Cripps C, Kavan P, Texereau P, Bouhier-Leporrier K, Khemissa-Akouz F, Legoux JL, Juzyna B, Gourgou S, O'Callaghan CJ, Jouffroy-Zeller C, Rat P, Malka D, Castan F, Bachet JB; Canadian Cancer Trials Group and the Unicancer-GI–PRODIGE Group. FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer. N Engl J Med. 2018 Dec 20;379(25):2395-2406. doi: 10.1056/NEJMoa1809775. PMID: 30575490.

Neoptolemos JP, Palmer DH, Ghaneh P, Psarelli EE, Valle JW, Halloran CM, Faluyi O, O'Reilly DA, Cunningham D, Wadsley J, Darby S, Meyer T, Gillmore R, Anthoney A, Lind P, Glimelius B, Falk S, Izbicki JR, Middleton GW, Cummins S, Ross PJ, Wasan H, McDonald A, Crosby T, Ma YT, Patel K, Sherriff D, Soomal R, Borg D, Sothi S, Hammel P, Hackert T, Jackson R, Büchler MW; European Study Group for Pancreatic Cancer. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. Lancet. 2017 Mar 11;389(10073):1011-1024. doi: 10.1016/S0140-6736(16)32409-6. Epub 2017 Jan 25. PMID: 28129987.

Reply 5: We have cited these references in the manuscript.
Changes in the text: (see Page 12, line 14-15, Page 12, line 17-19)

Reviewer B

The authors evaluated short-term outcomes following open pancreatoduodenectomy for pancreatic cancer with or without atrial fibrillation (AF) within National Inpatient Sample Database (NIS), which is an inpatient database. Among All patients aged ≥18 years undergoing pancreaticoduodenectomy, 10% had AF. As results, Patients with AF were found to have significantly higher cost, but similar mortality and LOS (was this an abbreviation of Length of stay?) compared to those without AF. In older patients (> 65 y), AF was found to be associated with a significantly higher cost, longer hospital stay, higher incidence of cardiac complications, respiratory complications and postoperative shock, yet similar mortality. The authors concluded that atrial fibrillation was found to be associated with higher cost in pancreatic cancer patients undergoing open pancreaticoduodenectomy, as well as increased some complications as above. This study includes several new findings. However, I have several criticisms as follow.

1. As for the population, there was a significant difference in age, so it is assessed that it is evaluated at 65 years of age or older, but it is necessary to present a founding separated by 65 years. Because the median age was 71.9 Years Old in AF group, you may be a bit higher boundary. Alternatively, how is Propensity Score Matching statistical analysis, as there are many cases?

Reply 1: We appreciate your comment. The reason we are using age 65 as cutoff, is because 65 is the age separating elderly patients and middle ages. As reviewer B kindly pointed out, the median age was 71.9 years old in AF group and we possibly could be at a bit higher boundary. Therefore, we implanted Propensity Score Matching model in our study to help validate our result and decrease statistical errors.
Changes in the text: we have added Propensity Score Matching model in our manuscript (see Page 8, line 10-17, Page 9, line 19-20, Page 10, line 8-9, Page 10, line 16-18, Page 11, line 19-20, Page 12, line 1-6 and table 3).

2. In the AF group, it is necessary to consider what perioperative management was connected to the cost increase. It is also considered to be a useful study as presence of perioperative management for anticoagulant specifically.

Reply 2: Adjustment of anticoagulant and a thorough evaluation of cardiac function like echocardiography and exercise tolerance test might be connected to the cost increase. What is more, higher incidence of perioperative complications such as

gastrointestinal anastomotic leakage, cardiac complications, respiratory complications, pulmonary embolism, and perioperative shock in AF group might contribute to the higher expenditure.

For pancreatic cancer patients with atrial fibrillation undergoing PD, a thorough and careful evaluation of cardiac function and adjustment of the use of anticoagulants before surgery would be beneficial. Patients with atrial fibrillation often take anticoagulant drugs like warfarin, rivaroxaban or apixaban regularly. Since PD is associated with high risk for bleeding, while pancreatic cancer coupling with atrial fibrillation is associated with high risk of thromboembolism, we have to take perioperative anticoagulation plan seriously.

For patients with atrial fibrillation who take warfarin orally, omitting warfarin for five days before surgery and checking the INR on the day before surgery has been recommended. The use of bridging while holding oral anticoagulants has become common clinical practice, though some current evidence argue that bridging may not significantly reduce thromboembolic events, yet increasing major adverse cardiovascular events and bleeding. Douketis et al. concluded that forgoing bridging anticoagulation was noninferior to perioperative bridging in patients with atrial fibrillation. According to the ACC Expert Consensus, if the patient's thrombosis risk is low (CHA_2DS_2-VASc Score <=4), bridging is not recommended; if the patient's thrombosis risk is medium-to-high (CHA_2DS_2-VASc Score 5 and above) or with prior stroke or TIA, clinical judgment need to be used. For patients who have previously taken apixaban or rivaroxaban, it is suggested that the anticoagulants should be omitted 2-3 days before surgery and bridging is not required. However, there has been limited evidence regarding bridging, specifically for pancreatic cancer patient, in the 2017 ACC periprocedural management of anticoagulation guideline. In this case, if a complicated case is encountered, multidisciplinary team approach involving cardiologists and anesthesiologists would likely be beneficial.

We appreciate your comments and have added relevant content into our Discussion session.

Changes in the text: we have modified our manuscript (see Page 16, line 19-21, Page 17, line 1-21).

3.The authors concluded that Surgeons should pay special attention to these patients and formulate an appropriate perioperative evaluation plan . What kind of the special attention and the perioperative evaluation plan is recommended in details?

Reply 3: Patients with atrial fibrillation with cardiac insufficiency may not tolerate anesthesia and surgery. So, Surgeons should pay special attention to these patients and

formulate an appropriate perioperative management plan. Commonly used clinical evaluation methods of cardiac function include echocardiography and exercise tolerance test. If a complicated case is encountered, the best way for the surgeon is to consult with cardiologists and anesthesiologists. Thank you for your helpful comments, we have revised our manuscript and added relevant content in the manuscript.
Changes in the text: we have modified our manuscript (see Page 16, line 19-21, Page 17, line 1-21).

4. Since post-operative shock increased in the AF group, it could be related not only cardiac complications but also abdominal bleeding owing to pancreatic fistula after PD. Abdominal bleeding on pancreatic fistula after PD for the patient using anticoagulant therapy may be directly linked to mortality. As the authors mentioned in limitations, it was difficult in this study design using the Database to mention the postoperative abdominal bleeding, however, it may be better to add considered to be substituted by blood transfusion and postoperative shock. I think it would be better to discuss the relationship between Post-operative shock, Blood transfusion and LOS.

Reply 4: We appreciate your suggestion. The NIS database cannot determine the amount of bleeding, therefore, we tried using blood transfusion as a suboptimal measure to indirectly identify intraoperative bleeding. On the other hand, the post-operative shock was not limited to hemorrhagic, but also cardiogenic shock (possibly related to cardiac complications) and septic shock (possibly related to GI anastomotic leakage).
In our result, we got significantly more incidence of post-operative shock in AF group than the non-AF group, yet no statistical difference in blood transfusion was found between the two groups. We suspected that the cause of post-operative shock in AF group is more cardiogenic and / or infectious than hemorrhagic, however this is only correlation not causality limited by the retrospective character of our study.
We witnessed a significant rise of LOS in AF group, and this could be related to significantly high complications (post-operative shock, blood transfusion, etc) in the AF group.
Changes in the text: we have modified our manuscript (see Page 15, line 9-17).

Reviewer C
The idea for the study is original and the topic is of clinical relevance. The study population is theoretically large enough to ensure reliable statistical conclusions. However, some issues of concern should be addressed by the authors in order to allow acceptance of the manuscript:
Unfortunately, the NIS database doesn't provide several important parameters, which would have been of relevance for the manuscript. data on typical surgical complications

such as POPF and PPH are absent, 90-day mortality, tumor characteristics etc are missing. At the same time table 1 includes a myriad of parameter, which have nothing to do with the aims of the study, such as type of insurance or ethnicity of patients.
Especially, data on the type of antocoagulation medication before surgery and the management of antithrombotic therapy postoperatively are not given. This allows no conclusions on the importance of the reported data. What proportion of patiets were treted with warfarin, DOACs or not therapy at all? was bridging applied or not and if yes how long perioperatively?

Reply 1: The NIS database has limitations due to its own characteristics. Some important parameters such as POPF, PPH, 90-day mortality and tumor characteristics are not able to extract from NIS. In addition, NIS does not contain the data of anticoagulation medication and antithrombotic therapy, so further study is needed to explore the anticoagulation in the perioperative period of PD surgery, and we discussed this point in the Discussion session. Based on the results obtained from NIS database, we will conduct further study to explore the impact of atrial fibrillation on the prognosis of pancreatoduodenectomy. Respectfully, we have revised Table 1 according to your comments.
Changes in the text: we have modified our manuscript (see Page 16, line 19-21, Page 17, line 1-21 and Table 1).

In conclusion atrial fibrillation is a common finding in the elderly group of patients scheduled for PD. However, the limited and inspecific volume of data provided by NIS does not allow any clinically relevant insights concerning the management of AF in this collective. The authors should try to focus on a more detailed discussion of other published data on AF in PD and summarize i a systematic manner available evidence on the topic in order to compensate for the lacking NIS data. A management algorithm for AF in PD should be proposed and critically discussed.

Reply 2: For pancreatic cancer patients undergoing PD surgery with AF, evaluation of cardiac function and adjustment of the use of anticoagulants are required before surgery. Commonly used clinical evaluation methods of cardiac function include echocardiography and exercise tolerance test. Patients with atrial fibrillation often take anticoagulant drugs like warfarin, rivaroxaban or apixaban regularly. Since PD is associated with high risk for bleeding, while pancreatic cancer coupling with atrial fibrillation is associated with high risk of thromboembolism, we have to take perioperative anticoagulation plan seriously.
For patients with atrial fibrillation who take warfarin orally, omitting warfarin for five days before surgery and checking the INR on the day before surgery has been

recommended. The use of bridging while holding oral anticoagulants has become common clinical practice, though some current evidence argue that bridging may not significantly reduce thromboembolic events, yet increasing major adverse cardiovascular events and bleeding. Douketis et al. concluded that forgoing bridging anticoagulation was noninferior to perioperative bridging in patients with atrial fibrillation. According to the ACC Expert Consensus, if the patient's thrombosis risk is low (CHA_2DS_2-VASc Score <=4), bridging is not recommended; if the patient's thrombosis risk is medium-to-high (CHA_2DS_2-VASc Score 5 and above) or with prior stroke or TIA, clinical judgment need to be used. For patients who have previously taken apixaban or rivaroxaban, it is suggested that the anticoagulants should be omitted 2-3 days before surgery and bridging is not required. However, there has been limited evidence regarding bridging, specifically for pancreatic cancer patient, in the 2017 ACC periprocedural management of anticoagulation guideline. In this case, if a complicated case is encountered, multidisciplinary team approach involving cardiologists and anesthesiologists would likely be beneficial.
We are grateful for the suggestion and we have modified the manuscript according to your comment. In the Discussion section of the manuscript, we have added a management algorithm for patients with preoperative atrial fibrillation and we will conduct further study to explore the impact of atrial fibrillation on PD.
Changes in the text: we have modified our manuscript (see Page 16, line 19-21, Page 17, line 1-21).

Reviewer D

Inpatient Sample

1. Robot and laparoscopic PD were excluded. Considering interest of current MI-PD, it would be more attractive if the authors include these patients group and investigate the impact of AF on MI-PD.

Reply 1: We are grateful for the suggestion. We were planning to analyze LPD and RPD separately in our subgroup analysis section. However, the NIS database could not accurately differentiate LPD and RPD and would possibly lead to biased results. Therefore, we excluded robot and laparoscopic PD.
Changes in the text: None.

2. How about long-term oncologic outcomes?

Reply 2: NIS database has its own inherent shortcomings, follow-up information is not included within the NIS database, and it is one of the limitations of the present study.
Changes in the text: None.

3. Cancer stage cannot be correlated?

Reply 3: Like follow-up information, cancer stage is not included within the NIS database. We have described in detail the limitations caused by the inherent shortcomings of NIS database in the discussion section.
Changes in the text: None.

4. It is unfair to compare between two groups. Table 1 shows some deviation of the basal clinical characteristics. I recommend PSM analysis.

Reply 4: We appreciate reviewer D's suggestion. We have included Propensity Score Matching model in our analysis and included the result into our manuscript.
Changes in the text: we have added Propensity Score Matching model in our manuscript (see Page 8, line 10-17, Page 9, line 19-20, Page 10, line 8-9, Page 10, line 16-18, Page 11, line 19-20, Page 12, line 1-6 and table 3).

5. In multivariable analysis, mortality was not found statistically difference, but its clinical meaning should be placed because OR>3, p=0.08)

Reply 5: Thank you for pointing this out. We have revised the manuscript.
Changes in the text: we have modified our manuscript (see Page 14, line 1-2).

Minor
6. How could you access the data of US. All authors are Chinese?

Reply 6: This study was made possible by scholars from different institutes from both the U.S. and China, including surgeon from NYU Langone. We have obtained the assess of the NIS database, which is a publicly available, deidentified database.
Changes in the text: None.

7. Remove the head number in result session. Is it Journal requesting style?

Reply 7: Thanks very much for the suggestion, and we have removed the head number.
Changes in the text: All the head number in result session.

8. Significant finding need to be specifically described in result session.

Reply 8: We appreciate your comment and we have updated our result session.

Changes in the text: throughout the result session.