PEER REVIEW HISTORY

eGastroenterology publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Early Clinical Predictors of Infected Pancreatic Necrosis: A Multicentre Cohort Study
AUTHORS	Song, Kai; He, Wenhua; Wu, Zuoyan; Meng, Jie; Tian, Wei; Zheng, Shicheng; Mu, Dong; Wang, Ruifeng; Chen, Hongda; Zhu, Yin; Wu, Dong

VERSION 1 - REVIEW

REVIEWER NAME	Huang, Haojie
REVIEWER AFFILIATION	N/A
REVIEWER CONFLICT OF INTEREST	I have no competing interest.
DATE REVIEW RETURNED	25-Jun-2024

GENERAL COMMENTS	Thank you for inviting me to review the paper titled “Clinical Characteristics Within 24 Hours of Admission as Predictors of Infected Pancreatic Necrosis: Multicenter Cohort Study.” In this study, Kai and his colleagues constructed a predictive model for infected pancreatic necrosis based on clinical characteristics and multivariate logistic regression. The research is intriguing and holds considerable clinical value. However, several shortcomings need to be addressed or clarified. Major Concerns: Study Design Limitations: As a retrospective study, there is a potential for selection bias. Additionally, the absence of prospective validation data could impact the accuracy of the model’s predictions. Details of Statistical Analysis Methods: While the article used LASSO regression for variable selection, it lacks a detailed explanation of the model selection and evaluation process. Providing more information on model diagnostics, variable selection, and cross-validation would enhance the transparency of the methodology. Balancing Sensitivity and Specificity: The article should include a more extensive discussion on the model's sensitivity and specificity and how to balance these factors in clinical practice to minimize overtreatment and missed diagnoses. Minor Concerns: The authors compared the ROC index of the IPN model with several severity scores, including APACHEII, Marshall, SOFA, and BISAP. However, the decision curve analysis only compares the IPN model with BISAP. It would be beneficial to include other scores in the decision curve analysis for a more comprehensive evaluation.

REVIEWER NAME	Huang, Yuting

REVIEWER AFFILIATION	Mayo Clinic in Florida
REVIEWER CONFLICT OF INTEREST	No conflict of interest to disclose.
DATE REVIEW RETURNED	03-Jul-2024

GENERAL COMMENTS	I read this manuscript with great interest, it addresses an important clinical question to have an early prediction for infection in pancreatic necrosis. The manuscript is overall well written. There are some comments Major comments: 1. the authors used data from Peking Union Medical College hospitals as a validation set, while the rest of the data was used as a development set. However, the patient populations might differ in Peking Union Medical College Hospitals as a popular referral center. I suspect their patient population might be more complicated than other hospitals. Will this difference impact the accuracy of the results? 2. There are several similar studies published recently, to name some of them: PMID: 38577189, 38779802, 36057565, 36996800. Some of them have very similar study designs to the current study. Also, PMID 36579141 is a clinical trial evaluating the PASS-4 model. The current study is a retrograde study. The authors mentioned mostly the study by Zhu et al. What would be the advantage/uniqueness of the current study compared to the rest? Minor comments: 1. Please double-check that abbreviations have full spelling when showing up the first time, for example, AP in line 47, SAP in line 197, MSAP in line 200, et al. 2. Please consider using "antibiotics overuse/misuse" instead of "antibiotics abuse". 3. Please keep the format consistent in the tables. Sometimes there is a space between the number and (), sometimes there is not.

REVIEWER NAME	Huang, Wei
REVIEWER AFFILIATION	West China Hospital of Sichuan University
REVIEWER CONFLICT OF INTEREST	No competing interest.
DATE REVIEW RETURNED	09-Jul-2024

GENERAL COMMENTS	I have reviewed the current study, entitled “Clinical Characteristics Within 24 Hours of Admission as Predictors of Infected Pancreatic Necrosis: Multicenter Cohort Study” with great interests. This study included 3224 acute pancreatitis patients (189 were diagnosed infected pancreatic necrosis, IPN) from 8 centres in China. Albeit respective in nature, the study utilised routine clinical available parameters within 24 hours to compose a predictive model (temperature, respiratory rate, calcium, and BUN) for early identification of IPN. The AUC (95% CI) for discovery set, internal validation set, and external validation set was 0.80 (0.76-0.84), mean 0.80, and 0.85 (0.81- 0.90), respectively. The AUC of the predictive model for IPN was consistently better than BISAP, APACHE II, Marshall, and SOFA scores. This study endeavoured to address an important clinical question and has its merits. However, there are some improvements need to be made before considering for acceptance:

	Major points: 1. How these parameters (temperature, respiratory rate, calcium, and BUN) were selected to compose the predictive model for IPN? For example, why blood glucose and positive peritoneal irritation signs were removed? Was there a multivariate analysis? 2. Please can the authors provide sensitivity, specificity, PPV, NPV, pre-test probability and post-test probability of the predictive value? 3. I would strongly against that a model with AUC over 0.7 is considered to have a good discriminatory ability. An AUC of 0.7 or a little above does not advance clinical practice for decision-making. 4. In my opinion, comparing sterile necrosis and IPN would be a better comparison group. The comparison between non-IPN and IPN can be placed in the supplementary tables. 5. How do the authors deal with data for patients who developed multiple organ failure early in the disease course and died prematurely who did not have a chance to have a CT scan or to be diagnosed as IPN? 6. Lancet Gastroenterol Hepatol. 2022 Oct;7(10):913-921. This type of study needs to be in the introduction. 7. Did the author have some available data for serum CRP, PCT (Int J Mol Sci. 2024 Jan 20;25(2):1273.), and IL-6 (Pancreatology. 2020 Oct;20(7):1302-1311) to compare the predictive value of the predictive model with these parameters for IPN? At least the authors should discuss these points for dynamically assessing the risk of IPN in the discussion part. 8. Did the author compare the predictive model with PASS or any modified PASS (United European Gastroenterol J. 2023 Feb;11(1):69-78) for IPN? If the authors do have the data for modified PASS, it is very important to add this in the study. Did the authors collect pancreas imaging data (i.e. non-enhanced CT scan) thus to add these imaging data to enhance the predictive value of the predictive model for IPN? Minor points: 1. The study claimed that IQR was used but in fact, 25th-75th percentile was used. Please correct. 2. This study “Predicting need for intervention in acute necrotizing pancreatitis following discharge- A single center experience in 525 patients (Pancreatology. 2022 Dec;22(8):1063-1070) is highly relevant and need to be discussed in the discussion. 3. The authors need to be aware that IPN without persistent organ failure had low mortality (PMID: 38037512). Therefore, in the introduction the authors need to find a better approach to describe the importance for IPN. The DBC, mDBC, and multiple centre studies from Spain (PMID: 29672416), Dutch (PMID: 29950344), and Chengdu (PMID: 31233394) need to be discussed. 4. When the authors were citing TRACE-1 trial for discussion, the authors need to point out the lack of accurate predictor for acute necrotising pancreatitis with or without infection. In fact, this should be placed in the introduction and can be explained for better trial design. 5. Data between 2017-2020 were retrospectively collected for now. How in the methods, the authors described data were collected within 24 hours after admission immediately? Why follow 2020 AGA guideline? 6. When describing results, mortality in SAP patients is important, mortality in IPN within SAP patients is important, mortality in MSAP patients with IPN is also important.

REVIEWER NAME	Ke, Lu
REVIEWER AFFILIATION	Nanjing Jinling Hospital, Department of Critical Care Medicine
REVIEWER CONFLICT OF INTEREST	None
DATE REVIEW RETURNED	14-Jul-2024

GENERAL COMMENTS	This is a large cohort study assessing the value of early admission characteristics in predicting IPN. Predicing IPN is of clinical value, which may help facilitata appropriate treatment. However, though based on a large cohort, I have serveral comments to make the paper better. 1. The event rate is relatively low, though postive events seem enough with large sample size. This will make the model unstable. In pratice, usually in the very early phase, predicing whether the patient would develop necrotizing pancreaitits is more clinically relevant. Consider change the dependent endpoint wihich better suits the data and setting; 2. Similar to the above comments, LASSO is too data driven, espeically when you have a lot of low-risk patients. Better try different modes of variable selction to test the robustness of the model. 3. The authors should be cautious stating that IPN increased mortality. With modern minimally invasive techniques, IPN mains increase morbidity rather than mortality. 4. Please state the treatment strategies for IPN in the participating sites. The problem is if you use antibiotics first for IPN ,there may be a good part of patients successfully treated by antibiotics thus missed the IPN diagnoses as used in this study. 5. For the vital signs, how was those defined? Worst in a day? or data at admission. 6. DAC curve makes very limited sense, especailly tested in the same cohort.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comments to the Author

Thank you for inviting me to review the paper titled “Clinical Characteristics Within 24 Hours of Admission as Predictors of Infected Pancreatic Necrosis: Multicenter Cohort Study.” In this study, Kai and his colleagues constructed a predictive model for infected pancreatic necrosis based on clinical characteristics and multivariate logistic regression. The research is intriguing and holds considerable clinical value. However, several shortcomings need to be addressed or clarified.

Major Concerns:

1. Study Design Limitations: As a retrospective study, there is a potential for selection bias. Additionally, the absence of prospective validation data could impact the accuracy of the model’s predictions.

Response: Thank you for your in-depth insights and review comments. Although our findings were robust in validation, the data were retrospectively collected, which is a major limitation of our study.

We have described this limitation in the limitation section. Therefore, the conclusions of our study still require additional prospective validation.

2. Details of Statistical Analysis Methods: While the article used LASSO regression for variable selection, it lacks a detailed explanation of the model selection and evaluation process. Providing more information on model diagnostics, variable selection, and cross-validation would enhance the transparency of the methodology.

Response: We apologize for any confusion caused by our unclear description in the previous manuscript. We have revised our variable selection method in the revised manuscript. Initially, variables with $p < 0.1$ were identified through univariate analysis. These variables were then subjected to LASSO regression for further selection to reduce the number of variables. The LASSO logistic regression model was used with penalty parameter tuning conducted by 10-fold cross-validation according to minimum criteria. Finally, the variables selected by LASSO were included in a multivariate analysis to identify independent risk factors for IPN. This process resulted in the identification of five independent risk factors in final model.

3. Balancing Sensitivity and Specificity: The article should include a more extensive discussion on the model's sensitivity and specificity and how to balance these factors in clinical practice to minimize overtreatment and missed diagnoses.

Response: Thank you very much for your professional insights. We have added a description of sensitivity and specificity in the discussion section: In our IPN model, the risk of IPN can be defined through the model. When using the model score of 0.068 at the optimal AUC as the cutoff value, the IPN probability threshold is 0.51. The sensitivity and specificity of the model reach 0.75 and 0.85, respectively. Increasing the probability threshold to 0.60 reduces sensitivity but increases specificity (to 0.23 and 0.99, respectively), thus lowering the risk of overtreatment while raising the risk of missed diagnoses. Conversely, if higher sensitivity is desired, the model threshold can be lowered. For instance, when the cutoff model score is 0.03, sensitivity reaches 0.84, but specificity drops to 0.67, increasing the risk of overtreatment. Therefore, a threshold that maximizes classification accuracy can be found based on acceptable levels of false-positive and false-negative rates. In this way, the model allows flexible selection of thresholds to define risk groups.

Minor Concerns:

4. The authors compared the ROC index of the IPN model with several severity scores, including APACHEII, Marshall, SOFA, and BISAP. However, the decision curve analysis only compares the IPN model with BISAP. It would be beneficial to include other scores in the decision curve analysis for a more comprehensive evaluation.

Response: Thank you for your constructive criticism. We have supplemented this section and conducted comparisons in both the training and validation sets. The IPN model has shown more net benefit than others over a wide range of probability thresholds, suggesting better clinical decision value for our IPN model.

Reviewer: 2

Comments to the Author

I read this manuscript with great interest, it addresses an important clinical question to have an early prediction for infection in pancreatic necrosis. The manuscript is overall well written. There are some comments

Major comments:

1. the authors used data from Peking Union Medical College hospitals as a validation set, while the rest of the data was used as a development set. However, the patient populations might differ in Peking Union Medical College Hospitals as a popular referral center. I suspect their patient population might be more complicated than other hospitals. Will this difference impact the accuracy of the results?

Response: Thank you for your professional and insightful review comments. In the initial manuscript, we compared the clinical characteristics of AP patients at PUMCH with those from other hospitals and indeed found significant differences in the distribution of etiologies and severity of patients at PUMCH compared to those from other hospitals. To address this potential bias, we revised the selection of the derivation and validation sets. We divided all patients into a 7:3 ratio for the training and validation sets. The model's performance was validated, demonstrating its robustness.

2. There are several similar studies published recently, to name some of them: PMID: 38577189, 38779802, 36057565, 36996800. Some of them have very similar study designs to the current study. Also, PMID 36579141 is a clinical trial evaluating the PASS-4 model. The current study is a retrograde study. The authors mentioned mostly the study by Zhu et al. What would be the advantage/uniqueness of the current study compared to the rest?

Response: Thank you for your insightful perspectives and keen insight into cutting-edge scientific research directions. We have provided a more detailed description in the discussion section regarding the existing models. Overall, our model has certain distinctions and advantages compared to other prediction models. Firstly, our model is based on a larger multicenter cohort of AP patients in China, making the patient characteristics more representative. Secondly, the variables we included are all measurable within 24 hours of admission, which enhances the convenience of use while achieving good discrimination and robustness in predictive performance. Furthermore, some studies lack validation and risk overfitting, whereas our model has undergone multiple validations.

Regarding the research about mPASS-4 score in the prediction of IPN, it is based on a rigorously designed prospective clinical study, giving it the highest level of evidence among all existing models. Although its reported performance is lower than that of our model, comparisons of models require validation within the same cohort. Since our data set is insufficient to evaluate the mPASS-4 and PASS scores, it’s a pity that a direct comparison cannot be performed in our cohort. Should the opportunity arise in the future, we will conduct further comparative studies of the models.

Minor comments:

1. Please double-check that abbreviations have full spelling when showing up the first time, for example, AP in line 47, SAP in line 197, MSAP in line 200, et al.

Response: Thank you for your kind reminder. We have made the necessary corrections to ensure that abbreviations are fully spelled out upon their first appearance

2. Please consider using "antibiotics overuse/misuse" instead of "antibiotics abuse".

Response: Thank you for your professional suggestion. We have revised the text to use "antibiotics overuse/misuse" instead of "antibiotics abuse."

3. Please keep the format consistent in the tables. Sometimes there is a space between the number and (), sometimes there is not.

Response: Thank you for your careful review of our manuscript. We have standardized the format in the tables to ensure consistency, eliminating any discrepancies in spacing between the number and parentheses.

Reviewer: 3

Comments to the Author

Dear Editor,

I have reviewed the current study, entitled “Clinical Characteristics Within 24 Hours of Admission as Predictors of Infected Pancreatic Necrosis: Multicenter Cohort Study” with great interests. This study included 3224 acute pancreatitis patients (189 were diagnosed infected pancreatic necrosis, IPN) from 8 centres in China. Albeit respective in nature, the study utilised routine clinical available parameters within 24 hours to compose a predictive model (temperature, respiratory rate, calcium, and BUN) for early identification of IPN. The AUC (95% CI) for discovery set, internal validation set, and external validation set was 0.80 (0.76-0.84), mean 0.80, and 0.85 (0.81- 0.90), respectively. The AUC of the predictive model for IPN was consistently better than BISAP, APACHE II, Marshall, and SOFA scores. This study endeavoured to address an important clinical question and has its merits. However, there are some improvements need to be made before considering for acceptance:

Major points:

1. How these parameters (temperature, respiratory rate, calcium, and BUN) were selected to compose the predictive model for IPN? For example, why blood glucose and positive peritoneal irritation signs were removed? Was there a multivariate analysis?

Response: Thank you for your constructive criticism. We have revised our approach to variable selection and included the steps for multivariate analysis. Initially, we performed univariate analysis to identify candidate variables with a p-value < 0.1. These variables were then subjected to further selection using LASSO regression, and the remaining variables were ultimately included in the multivariate analysis to identify independent risk factors for IPN. The final model included five variables, among which blood glucose levels were identified as an independent risk factor for IPN and were included in the final model.

2. Please can the authors provide sensitivity, specificity, PPV, NPV, pre-test probability and post-test probability of the predictive value?

Response: Thank you for your professional comments. We have included this data in the manuscript, which shows a sensitivity of 0.75 and a specificity of 0.85 (positive predictive value 76.7%, negative predictive value 95.7%, pre-test probability 5.4%, post-test probability 50.1%). The calculation formulas are as follows:

PPV = TP / (TP + FP)

NPV = TN / (TN + FN)

where TP represents True Positives, FP represents False Positives, TN represents True Negatives, and FN represents False Negatives.

The post-test probability is calculated using the formula:

post-test probability= LR+* pre-test probability / (1 - pre-test probability + LR+ * pre-test probability)

LR+ is the positive likelihood ratio, calculated as: LR+ = PPV / (1 - NPV) .

3. I would strongly against that a model with AUC over 0.7 is considered to have a good discriminatory ability. An AUC of 0.7 or a little above does not advance clinical practice for decision-making.

Response: Thank you for your rigor in the review of manuscript. We have streamlined this statement. Our model demonstrated good performance, with an AUC of 0.85 (95% confidence interval 0.81–0.89). The mean AUC in internal validation was 0.84, and in the validation set, the AUC was 0.82 (95% CI 0.77–0.87). This indicates that our model's performance is robust.

4. In my opinion, comparing sterile necrosis and IPN would be a better comparison group. The comparison between non-IPN and IPN can be placed in the supplementary tables.

Response: Thank you for your professional and kind suggestion. We have supplemented the manuscript accordingly in supplementary material. However, we regret that we did not conduct a specific evaluation of necrotizing pancreatitis in the data collection stage, which has resulted in a lack of data on this aspect. Additionally, our assessment of acute necrotic collection was based on the CT scans obtained at admission. Using acute necrotic collection presented at admission as a substitute for patients with necrotizing pancreatitis would likely lead to an underestimation of necrotizing pancreatitis. Therefore, we cannot distinguish between sterile necrosis and IPN based on necrotizing pancreatitis in our population. Nonetheless, we did compare the clinical characteristics of patients with IPN and non-IPN patients based on those who presented with acute necrotic collection at admission, and we have included these findings in the supplementary table.

5. How do the authors deal with data for patients who developed multiple organ failure early in the disease course and died prematurely who did not have a chance to have a CT scan or to be diagnosed as IPN?

Response: We appreciate your professionalism and insightful comments. Unfortunately, such patients do exist in clinical practice, particularly in China. When a disease is deemed beyond treatment, a small proportion of patients' families may choose to forgo further treatment. Although these patients have medical records, their notable characteristics include severe disease and short hospital stays. During our data collection, we have excluded the data of these patients. Consequently, the final dataset only includes patients with complete hospitalization records, either those who improved and were discharged or those who deteriorated and died with comprehensive examination and treatment details.

For patients who were discharged prematurely due to a lack of hope for recovery, we did not collect data as their final clinical outcomes were unknown. Therefore, one of our exclusion criteria is

premature discharge. Therefore, this also highlights an issue: for patients with rapidly progressing and more severe diseases, our model may not be applicable due to the lack of data for validation.

6. Lancet Gastroenterol Hepatol. 2022 Oct;7(10):913-921. This type of study needs to be in the introduction.

Response: Thank you for your professional suggestions. We have added a description of this study in the introduction section, to further highlight the importance of early prediction of IPN in reducing the overuse of antibiotics and the disease burden associated with IPN.

7. Did the author have some available data for serum CRP, PCT (Int J Mol Sci. 2024 Jan 20;25(2):1273.), and IL-6 (Pancreatology. 2020 Oct;20(7):1302-1311) to compare the predictive value of the predictive model with these parameters for IPN? At least the authors should discuss these points for dynamically assessing the risk of IPN in the discussion part.

Response: Thank you for thorough review of our manuscript. Among the 8 centers included in our study, some hospitals utilize hsCRP (high-sensitivity C-reactive protein) for CRP testing, while others use standard CRP tests. The hsCRP can display specific values exceeding 150, whereas CRP values exceeding 150 are shown as ">150". Therefore, for the sake of rigor, we decided not to analyze CRP, also considering the higher number of missing values for CRP.

Regarding IL-6 and PCT, most centers did not consistently use IL-6/PCT for initial testing within 24 hours of patient admission, and the timing of IL-6/PCT testing after admission was inconsistent, which could be influenced by the disease course. Therefore, out of caution, we did not collect these data retrospectively for this study. This is a limitation of our model, and we greatly appreciate the reviewer's insight. We have added the following to the limitations section of our manuscript: "Besides, in our multicenter research, we did not include other inflammatory markers such as interleukin-6, other peripheral blood information including proteomics, radiomics, and other potential factors. This may potentially decrease the predictive accuracy of our model."

8. Did the author compare the predictive model with PASS or any modified PASS (United European Gastroenterol J. 2023 Feb;11(1):69-78) for IPN? If the authors do have the data for modified PASS, it is very important to add this in the study. Did the authors collect pancreas imaging data (i.e., non-enhanced CT scan) thus to add these imaging data to enhance the predictive value of the predictive model for IPN?

Response: Thanks for your constructive criticism. The article "United European Gastroenterol J. 2023 Feb;11(1):69-78" evaluates the PASS-4 model and proposes modifications to the PASS score. The PASS score requires information on patients' abdominal pain, opioid requirements, and tolerance to enteral nutrition. We have added a description of this study in the discussion section. However, our retrospective study lacked sufficient data dimensions to evaluate the PASS score in patients, preventing us from further comparing the mPASS-4 score. Additionally, regarding the CT imaging data, we only collected diagnostic results after reviewing the imaging studies during the data collection phase, and we did not gather radiomics information. Given the increasing importance of radiomics in many studies, we have initiated corresponding research and believe that radiomics can play a significant role in the field of acute pancreatitis in the future.

Minor points:

1. The study claimed that IQR was used but in fact, 25th-75th percentile was used. Please correct.

Response: Thank you for your kind reminder. We have made the necessary revisions in the manuscript.

2. This study “Predicting need for intervention in acute necrotizing pancreatitis following discharge- A single center experience in 525 patients (Pancreatology. 2022 Dec;22(8):1063-1070) is highly relevant and need to be discussed in the discussion.

Response: Thank you for your insights in this field. We have added the relative discussion in revised manuscript. The work by Trikudanathan et al. differs from our study on early prediction of IPN, as it focuses on whether there are indications for intervention after discharge in patients with necrotizing pancreatitis and constructs a predictive model for intervention needs based on single-center data, achieving a best AUC of 0.88. This model provides a powerful tool for managing IPN patients from a different perspective.

3. The authors need to be aware that IPN without persistent organ failure had low mortality (PMID: 38037512). Therefore, in the introduction the authors need to find a better approach to describe the importance for IPN. The DBC, mDBC, and multiple centre studies from Spain (PMID: 29672416), Dutch (PMID: 29950344), and Chengdu (PMID: 31233394) need to be discussed.

Response: Thank you for your professional suggestions. IPN increases the incidence of persistent organ failure, which significantly raises mortality rates and leads to a considerable economic burden. We have cited relevant literature in the introduction. In the introduction section, we have revised the description of the importance of IPN as follows: "However, approximately 18% of AP patients may encounter infected pancreatic necrosis (IPN), increasing the morbidity of persistent multiple organ failure, which further escalates the mortality rate. IPN also significantly prolongs patients' hospital stays, imposing a substantial socioeconomic burden." Additionally, we modified the description in the "What is already known on this topic" section to read: "Infected (peri)pancreatic necrosis (IPN) greatly increases the morbidity of persistent multiple organ failure and mortality in the absence of appropriate treatment."

4. When the authors were citing TRACE-1 trial for discussion, the authors need to point out the lack of accurate predictor for acute necrotising pancreatitis with or without infection. In fact, this should be placed in the introduction and can be explained for better trial design.

Response: Thank you for your insightful comments. Before introducing the purpose of our study, we provided a description of the TRACE trial. Although it is based on a rigorous prospective clinical trial design, the mPASS-4 model still shows unsatisfactory predictive performance. Therefore, we aim to develop a more robust predictive model based on multicenter data.

5. Data between 2017-2020 were retrospectively collected for now. How in the methods, the authors described data were collected within 24 hours after admission immediately? Why follow 2020 AGA guideline?

Response: We apologize for any confusion caused by our unclear description in the manuscript. Regarding data collection, we would like to clarify that we collected the initial set of data after patient admission, such as laboratory indicators. Specifically, we gathered the results of the first blood tests conducted within 24 hours of admission. We have revised the statement to: "The demographic and clinical data were the first set of information collected within 24 hours of admission for each patient."

Our standards for data collection and the diagnosis of complications primarily refer to the "Classification of Acute Pancreatitis—2012: Revision of the Atlanta Classification and Definitions by International Consensus" (Gut 2013; 62:102-11). We did not reference the 2020 AGA guidelines for diagnostic criteria. We cited the 2020 AGA guidelines to emphasize that, in addition to confirmed cases of IPN, the guidelines also recommend the use of antibiotics in cases with a high suspicion of IPN, thereby highlighting the importance of IPN prediction.

6. When describing results, mortality in SAP patients is important, mortality in IPN within SAP patients is important, mortality in MSAP patients with IPN is also important.

Response: Thank you for your expertise in the field of pancreatology. We have added this information to the main text: "The mortality rates in patients with SAP and moderate severe AP were 7.1% (52 out of 730) and 0.2% (2 out of 992), respectively."

Reviewer: 4

Comments to the Author

This is a large cohort study assessing the value of early admission characteristics in predicting IPN. Predicing IPN is of clinical value, which may help facilitata appropriate treatment. However, though based on a large cohort, I have serveral comments to make the paper better.

1. The event rate is relatively low, though postive events seem enough with large sample size. This will make the model unstable. In pratice, usually in the very early phase, predicing whether the patient would develop necrotizing pancreaitits is more clinically relevant. Consider change the dependent endpoint wihich better suits the data and setting;

Response: Thank you for your in-depth suggestion. However, since we did not conduct a specific evaluation of necrotizing pancreatitis in data collection stage, we lack data on this aspect. Our assessment of acute necrotic collection was based on CT scans obtained at admission, and using acute necrotic collection presented at admission as a substitute for patients with necrotizing pancreatitis would likely lead to an underestimation of the actual incidence of necrotizing pancreatitis. Therefore, we ultimately chose IPN as our endpoint. Given that the mortality rate for IPN is higher than that for non-infected necrotizing pancreatitis, we hope that our model can provide early warning for IPN.

Regarding the robustness of the model, it underwent internal cross-validation and validation set testing within our cohort, indicating that the model's performance is relatively consistent. However, the lack of an external validation cohort remains a concern regarding the model's robustness and is one of our study's limitations.

2. Similar to the above comments, LASSO is too data driven, espeically when you have a lot of low-risk patients. Better try different modes of variable selction to test the robustness of the model.

Response: Thank you for your insightful comments. Considering the suggestion from multiple reviewers, we have revised our variable selection method and included the steps for multivariate analysis. Initially, we performed univariate analysis to identify candidate variables with a p-value < 0.1. These candidate variables were then subjected to LASSO regression for further selection. The LASSO logistic regression model was utilized with penalty parameter tuning conducted through 10-fold cross-validation based on minimum criteria. The remaining variables from the previous steps were ultimately included in the multivariate analysis, which corrected for covariates to identify the independent risk factors for IPN. The final model incorporated five independent risk factors for IPN.

3. The authors should be cautious stating that IPN increased mortality. With modern minimally invasive techniques, IPN mains increase morbidity rather than mortality.

Response: Thank you for your careful reading of the article and your professional suggestions. We have revised the descriptions in the abstract and discussion sections as follows: "Infected pancreatic necrosis exacerbates the burden on patients with acute pancreatitis and increases mortality rates in the absence of appropriate treatment."

Additionally, we have stated, "Given that IPN without appropriate treatment significantly increases the mortality rate of AP, the prevention of SAP and IPN will be an important direction."

4. Please state the treatment strategies for IPN in the participating sites. The problem is if you use antibiotics first for IPN, there may be a good part of patients successfully treated by antibiotics thus missed the IPN diagnoses as used in this study.

Response: Thank you for your constructive criticism. The use of antibiotics is very important for studying the course and prognosis of IPN. However, we regret that we could not include an analysis of antibiotic use and other treatments due to the lack of data collected during the retrospective data gathering. Current research evidence indicates that the prophylactic use of antibiotics does not effectively reduce the incidence of IPN, which is one of the reasons guidelines (Gastroenterology 2020;158:67-75 e1.) do not recommend the routine use of prophylactic antibiotics. Therefore, theoretically, the timing of antibiotic administration may not affect the incidence of IPN. However, there is a possibility that clinicians may overlook imaging diagnoses or microbiological confirmations of IPN due to ongoing antibiotic use. Unfortunately, due to missing data, we cannot conduct a corresponding analysis. In the future, we will further investigate this aspect of research. Once again, thank you for your insightful suggestions.

5. For the vital signs, how was those defined? Worst in a day? or data at admission.

Response: We sincerely apologize for any misunderstanding caused by our description. Regarding data collection, the information we included pertains to patients' data at admission. For example, concerning laboratory indicators, we collected the results of the first set of blood tests conducted within 24 hours of admission. We have revised the statement to: "The demographic and clinical data were the first set of information collected within 24 hours of admission for each patient."

6. DAC curve makes very limited sense, especailly tested in the same cohort.

Response: Thank you for your kind suggestions. We have decided to follow your advice and reduce the analysis of the clinical value in this section, incorporating it as a small part of the supplementary

information on model performance. Additionally, we have placed the comparison results of the IPN model with other severity scoring systems in the appendix.

VERSION 2 - REVIEW

REVIEWER NAME	Huang, Haojie
REVIEWER AFFILIATION	N/A
REVIEWER CONFLICT OF INTEREST	No competing interest.
DATE REVIEW RETURNED	15-Aug-2024

GENERAL COMMENTS	Thank you for your response, now this paper is qualified to be published in your respected journal

REVIEWER NAME	Huang, Yuting
REVIEWER AFFILIATION	Mayo Clinic in Florida
REVIEWER CONFLICT OF INTEREST	There is no conflict of interest to declare.
DATE REVIEW RETURNED	18-Aug-2024

GENERAL COMMENTS	The authors addressed the previous raised concerns sufficiently. With other reviewer's comments, this revised version of manuscript reads much improved. No more concerns have been raised during this round of review.

REVIEWER NAME	Huang, Wei
REVIEWER AFFILIATION	West China Hospital of Sichuan University
REVIEWER CONFLICT OF INTEREST	No competing interest.
DATE REVIEW RETURNED	28-Aug-2024

GENERAL COMMENTS	The authors have adequately addressed my concerns.

VERSION 2 – AUTHOR RESPONSE

Responses to reviewers

Thank you for your kind reminder. We have carefully reviewed the entire manuscript again and made the necessary revisions. Age was also presented using the median (25th percentile- 75th percentile), and we have included a note below the table.

We added the following to the ‘Conclusion’ section: ‘We developed a simple model for early prediction of IPN based on a multi-center cohort, exhibiting good performance and robustness. The model can assist clinicians in devising personalized treatment strategies, potentially helping to

reduce AP-related healthcare costs and mortality rates.’