

Round-1

Dear Editor,

Thank you for the pertinent observations and suggestions that helped us increase the quality of our manuscript “Extrapancreatic necrosis volume – a new tool in acute pancreatitis severity assessment?” (Manuscript NO.: 66849).

We assure the Editorial Team and Reviewers that we did all our best to improve the quality of the manuscript following the recommendations.

Please find below our answers for each of the reviewer’s observations and recommendations, point by point.

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On behalf of the authors

Reviewer 1

The authors' objective is to demonstrate the high predictive value of measuring the extrapancreatic necrosis volume in the estimation of acute pancreatitis (AP) severity. Reading the paper and the similar works from the literature, there is no doubt that CT images can detect important morphological alterations within the pancreas and in the surrounding tissues.

Answer 0

Thank you for all the kind observations regarding our work.

1) The question is: when? There is an agreement that early CT images can underestimate the severity of AP and the characteristic lesions appear parallel to the clinically severe course. The authors should emphasize this limitation: the predictive value of CT images is low at the onset of the disease and the values obtained by the authors come from the third day after the onset.

Answer 1

We added the following limitation in the **Discussions** section, according to the Reviewer's observation:

“Secondly, early CT images underestimate the extension of the pancreatic necrosis lesions and therefore CT examinations were performed at 48-72 hours after the disease onset.”

2) Comments, questions and criticisms - The objectives and the methods are clearly described. - “Many scores have been suggested to assess the severity of pancreatitis upon onset, consisting of clinical, biological, and imagistic markers (Ranson score, APACHE II, Glasgow) [3-5], which have not demonstrated significant discriminatory power. Computed tomography severity index (mCTSI) [7] imaging scores remain the most widely used in assessing the severity of pancreatitis.” - I am not agree neither with so negative opinion about clinical scores, nor with the dominant use of CT index, with real discriminatory power only > 48-72 hours of clinical evolution. Both types of scores are widely used.

Answer 2

The reviewer is right. We rephrased the quoted paragraph as follows:

“Many scores have been suggested to assess the severity of pancreatitis upon onset, consisting of clinical, biological, and imagistic markers (Ranson score, APACHE II, Glasgow) [3-5] ~~which have not demonstrated significant discriminatory power~~. The Computed tomography severity index (CTSI) [6] and the modified Computed tomography severity index (mCTSI) [7] ~~imaging scores~~ remain the most widely used **imaging scores** in assessing the severity of pancreatitis.”

3) Table 1. The same numbers cannot represent different percent values. The sum of numbers is 123 and not 139. The table requires revision and corrections.

Answer 3:

Thank you for pointing this out. We apologize for the inconsistency.

We revised Table 1 and made the corrections.

4) The distribution of severity is somewhat surprising: the low proportion of mild cases and frequent moderate AP is unusual in the literature.

Answer 4:

The atypical distribution of severity in our study is due to the particularity of our center as mild AP do not have clinical indication for CT assessment and therefore the CT exams were not performed.

We added this point in the limitations section, quote:

“Thirdly, the atypical distribution of severity in our study (low proportion of mild cases and frequent moderate AP) is due to the particularity of our center as mild AP do not have clinical indication for CT assessment and therefore the CT exams were not performed.”

5) The etiology of AP is not reported

Answer 5:

Imaging severity scores do not include the etiology of AP in the calculations and are not influenced by it. For this reason, reporting the etiology was not the subject of our research.

6) I did not find a clear explanation for the figures. I suppose that the numbers 1,2 and 3 represent the mild, moderate and severe disease. But what is the “0” and “4”? We can see several values corresponding a “0”.

Answer 6:

Thank you. We removed the values of “0” and “4” from the images. The values of “1”, “2”, “3” represent indeed the mild, moderate and severe disease.

We added these explanations in the Results section:

“The rAC values of “1”, “2”, “3” represent the mild, moderate and severe disease, respectively.”

7) Extrapancreatic fluid collections and necrosis are not clearly distinguished in the text. For example, the title of Fig. 3. is Correlation between extrapancreatic necrosis and rAC, but the fluid collection volume is depicted on the same figure. The definition of necrosis is lacking.

Answer 7:

Thank you. We modified the picture accordingly. The figure referred to extrapancreatic necrosis, not all the fluid collection volume. We added the explanation and the definition in the **Methods** section.

“Extrapancreatic necrosis included peripancreatic and contiguous retroperitoneal fat necrosis defined by fat infiltration, collection of fluid, or collection of both fluid and solid components. Peritoneal fluids were excluded using anatomical landmarks (specific peritoneal spaces for fluid accumulation have typical localizations, such as parieto-colic gutters, perihepatic and perisplenic spaces, others are located between the intestinal loops, and lack vascular structures). The results were expressed in milliliters.”

8) In how much cases the extrapancreatic necrosis was absent?

Answer 8:

The extrapancreatic necrosis was absent in 12 cases that we considered mild pancreatitis according to rAC.

We added the explanation in the **Results** section:

“The extrapancreatic necrosis was absent in 12 cases that were included in the mild pancreatitis category according to rAC.”

10) “...radiological scores were calculated following the computed tomography examination (CTSI, mCTSI, extrapancreatic necrosis volume), within 48-72 hours from the onset of symptoms.” It means that these scores, while predict early the severity of AP, are not useful at the onset of the AP...

Answer 10:

According to current guidelines ([https://www.gastrojournal.org/article/S0016-5085\(18\)30076-3/fulltext](https://www.gastrojournal.org/article/S0016-5085(18)30076-3/fulltext)) the evaluation of the pancreatic lesion by CT scan must be performed at 48-72 hours due to the fact that early CT images underestimate the extension of the pancreatic necrosis lesions. We added this limitation in the “**Discussions**” section, as stated above (point 1).

Reviewer 2

This is a paper investigating the association between extrapancreatic necrosis and severity of acute pancreatitis. Please add the frequency of pancreatic necrosis and necrosis sites (Ph, Pb, Pt) in this study. See the literature below. Kitamura K, et al. The Prognosis of Severe Acute Pancreatitis Varies According to the Segment Presenting With Low Enhanced Pancreatic Parenchyma on Early Contrast-Enhanced Computed Tomography: A Multicenter Cohort Study. Pancreas. 2017 Aug;46(7):867-873. Compare the severity of pancreatitis in pancreatic necrosis and extrapancreatic necrosis.

Answer:

Thank you for this important recommendation and for having brought this article to our attention. Indeed, comparing the severity of pancreatitis in pancreatic necrosis and extrapancreatic necrosis is a great topic for our next research. However, we are unable to include these comparisons in the current article due to space limitations (it will exceed the maximum number of words), time limitations and lack of data regarding necrosis sites (as these topics were not the subject of our study). We added some comments on the **Discussion** section, quote: “**In a recent study, Kitamura et al demonstrate that low enhanced pancreatic parenchyma in**

pancreatic head and tail on early contrast-enhanced computed tomography was independently associated with increased mortality in SAP." [24].

Reviewer 3

1) Although all the imaging scores showed a strong correlation with the severity of the acute pancreatitis, the evaluation of extrapancreatic necrosis volume had the best diagnostic accuracy in severe form in this study. However, the conclusion is not an innovation one. The original findings or hypotheses in this study are not new. In a 2015 study, Meyrignac et al. had already concluded the similar conclusion. (1.Meyrignac O, et al. Radiology. 2015;276(1): 119-28; 2.Çakar İ, et al. AbdomRadiol (NY). 2020;45(5): 1507-1516.)

Answer 1:

These two authors were cited in the article. The study was not intended to be innovative. Our aim was to increase the overall quality of evidence by bringing additional evidence for the inclusion in current practice of this score which proved to be more useful in predicting severe forms of pancreatitis compared to widely used imaging scores. The difference between the data obtained by us compared to the other mentioned authors consists in finding a different *cut-off* value. In this sense, we consider that as many studies on this subject are necessary in order to be able to identify a common *cut-off* value that can be used in clinical practice.

We added this to the conclusions, quote:

“This study increases the overall quality of evidence by bringing additional evidence for the inclusion in current practice of this score which proved to be more useful in predicting severe forms of pancreatitis compared to widely used imaging scores. The difference between the data obtained by us compared to the other mentioned authors consists in finding a different cut-off value. In this sense, we consider that as many studies on this subject are necessary in order to be able to identify a common cut-off value that can be used in clinical practice.”

2) Furthermore, there are many mistakes/spell errors in the manuscript. Introduction 1. “...Promisingly, one of the recently studied scores is the extrapancreatic necrosis volume.”

Answer 2:

Thank you for the observation. We revised the article and corrected the spelling errors. We revised the mentioned sentence:

~~“Promisingly, one of the recently scores studied is the extrapancreatic necrosis volume.~~
A promising score recently studied is extrapancreatic necrosis volume”.

3) Authors should use a reference. Meyrignac O, Lagarde S, Bournet B, Mokrane FZ, Buscail L, Rousseau H, Otal P. Acute Pancreatitis: Extrapancreatic Necrosis Volume as Early Predictor of Severity. Radiology. 2015;276(1): 119-28 [PMID: 25642743 DOI: 10.1148/radiol.15141494].

Answer 3.

This reference is already included in our article (Reference:21)

4) Material and method 1. This retrospective study was on 139 patients, how were those patients enrolled in the study by authors? How many patients were excluded during that period of time?

Answer 4:

The study enrolled all patients with AP who underwent CT examination. Patients were admitted to the Institute of Gastroenterology and Hepatology, Iasi during the study period. The exclusion criteria specified in the **Methods** section were: “patients with other pancreatic diseases (chronic pancreatitis, pancreatic neoplasm), patients who did not undergo a CT examination within 48-72 hours from the onset of symptoms”.

There were 42 patients excluded of which 23 cases had other pancreatic diseases and 19 cases underwent a CT scan within 48-72 hours from the onset of the symptoms, because of the subevaluation of lesions in this interval.

We added that the Method section, quote:

“There were 42 patients excluded of which 23 cases had other pancreatic diseases and 19 cases underwent a CT scan within 48-72 hours from the onset of the symptoms, because of the subevaluation of lesions in this interval.”

5) The CT examination was performed with a Siemens Somatom Emotion 16 system. Please give the CT scanner information in detail. Also, Iopamiro 370 mg I/ mL, please reveal the contrast agent original information.

Answer 5

We added the CT scanner information in the Methods section, as follows:

„The CT examination was performed with a Siemens Somatom Emotion 16 system (Erlangen, Germany). CT examinations were enhanced with contrast material and were performed with a 70-second scanning delay after intravenous injection of 100 mL of iopromide (370 mg iodine per milliliter, Ultravist 370; Berlex Laboratories, Wayne,NJ) injected at a rate of 3 mL/sec–the volume was adjusted according to the patient’s mass (maximum 1 mL/ kg body weight. The CT was performed at 130 kVp, maximum current 300 mAs, 16 x 1.5 mm collimation, dose modulation applications (CARE4Dose), 3 mm thick reconstructed images, 1.5 mm increment, B41s filter. The field of view was 42 cm and the matrix was 512 × 512. CT studies were retrospectively reviewed on picture archiving and communication system workstations (syngo 2007, Siemens, Erlangen, Germany)”.

6) We are very interested in the measurement about areas of extrapancreatic necrosis. So how can we accurately differentiate pancreatic ascites from intra-abdominal fluid or mixed (solid and liquid) collections by a CT examination?

Answer 6

We added the following explanations in the **Methods** section:

“Extrapancreatic necrosis included peripancreatic and contiguous retroperitoneal fat necrosis defined by fat infiltration, collection of fluid, or collection of both fluid and solid components. Peritoneal fluids were excluded using anatomical landmarks (specific peritoneal spaces for fluid accumulation have typical localizations, such as parieto-colic gutters, perihepatic and perisplenic spaces, others are located between the intestinal loops, and lack vascular structures). The results were expressed in milliliters.”

7) Another issue, with regard to a measure of volume, was this value measured only once, twice or other times? The intra- or inter-observer agreement should be considered in this study.

Answer 7

We added these informations to the **Methods** section:

“All the CT studies were reviewed by two radiologists specialized in abdominal imaging. To assess interobserver and intraobserver agreement, the images were interpreted at 3 months interval and the average of the two values was determined. The results that differed by more than 20 ml of extrapancreatic necrosis between baseline and 3 months determinations were excluded. Both radiologists were blinded to clinical data.”

8) The statistical analysis was performed using SPSS-18. Please depict the using SPSS edition in detail. As for statistical analysis on the non-Gaussian data distribution, please demonstrate data or evidence.

Answer 8

We added the detailed information about SPSS in the **Methods** section:

“The statistical analysis was performed using **SPSS Inc. Released 2009. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.**”

We also added the following information about the statistical analysis on the non-Gaussian data distribution:

“Because of the non-Gaussian data distribution, highlighted by the average level being at a distance from the median of the set of values, the correlations between the parameters were analysed using the Spearman rank correlation coefficient.”

9) Results 1. As for Figures (Fig1.-Fig 4.), what are these numbers “0, 1, 2, 3” of the revised Atlanta criteria (rAC) referring to?

Answer 9:

Thank you. We removed the value of “0” and “4” from the images. The values of “1”, “2”, “3” represent indeed the mild, moderate and severe disease.

We added these explanations in the Results section:

“The rAC values of “1”, “2”, “3” represent the mild, moderate and severe disease, respectively.”

10) In Fig 3., there is no unit on extrapancreatic necrosis volume. 3. In Fig.5., “Correlations between the volume of the pancreatic necrosis and the severity forms of acute pancreatitis”, “the pancreatic necrosis” should be modified as the extrapancreatic necrosis. 4. In Fig. 6., ROC curve. “CTSI_m” should be modified as mCTSI, and “PCR” should be modified as CRP. 5. “...PCR proves to be a good predictor of pancreatitis severity...”, “PCR” should be modified as CRP.

Answer 10

Thank you for the observations. We revised the Figures 3, 5 and 6 and the “PCR” abbreviation accordingly.

11) **Discussions 1. Too long.**

Answer 11:

Thank you for the observation. We remove some parts of the discussions, as follows:

~~“There are numerous studies reporting a strong correlation between CTSI and the clinical severity of acute pancreatitis.”~~

~~“Our study attempted to predict the severe acute pancreatitis using the volume of extrapancreatic fluid collections. In 1999, Lankish et al. highlighted the fact that pancreatic necrosis and extrapancreatic fluid collections are predictive factors for the identification of severe acute pancreatitis. The authors noticed a significant and direct correlation between the volume of extrapancreatic fluid collections and clinical parameters. The mCTSI score is highly accurate in assessing the severe form of pancreatitis^[22].”~~

11) For the assessment of severe pancreatitis, the best predictor turns out to be the volume of necrosis (AUC=0.993), followed by the mCTSI score (2007) (AUC=0.972), and the CTSI score (1990) (AUC=0.969). So, how can we conclude that the volume of necrosis is significantly better than CTSI or mCTSI score?

Answer 11

The majority of scientific studies compare the AUC values by its absolute value. Statistical analyses including the report of p-values for differences between AUCs using average-

based tests cannot be sufficiently reasoned (<https://journals.sagepub.com/doi/pdf/10.1177/172460080301800312>). Because of this, in our article we aimed to identify the best AUC by its absolute value.

Round-2

Dear Editor,

Thank you for the pertinent observations and suggestions that helped us increase the quality of our manuscript “Extrapancreatic necrosis volume – a new tool in acute pancreatitis severity assessment?” (Manuscript NO.: 66849).

We assure the Editorial Team and Reviewers that we did all our best to improve the quality of the manuscript following the recommendations.

Please find below our answers for the second round of reviews.

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On behalf of the authors

Reviewer 1

You should investigate whether extrapancreatic necrosis is associated with pancreatitis-related mortality.

Answer

Thank you for this important recommendation. Indeed, investigating whether extrapancreatic necrosis was associated with pancreatitis-related mortality can be insightful. Unfortunately, data on mortality could not be collected due to our local hospitals' circuits and lack of access to

mortality data, as the patients with severe pancreatitis are usually transferred to other different Clinics (Surgery).

However, we consider that our results have significant impact and value, as severity and mortality are strongly related and documented in numerous evidence-based papers (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5141403/>) and in order to prevent mortality, the prediction of disease severity is the single most important indicator of negative prognosis, for which early recognition and intervention could be lifesaving (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3071387/>).