

Dear Mr. Lian-Sheng Ma,

Thank you for giving us the opportunity to submit a revised draft of the manuscript “EPIDEMIOLOGICAL TRENDS IN ACUTE PANCREATITIS - A RETROSPECTIVE COHORT IN A TERTIARY CENTER OVER A SEVEN YEAR PERIOD” for publication in the World Journal of Methodology. We appreciate the time and effort that you and the reviewers dedicated to providing feedback on our manuscript and are grateful for the insightful comments and valuable improvements that they have inspired us to make on our paper. We have incorporated most of the suggestions made by the reviewers. Please see below, in blue, for a point-by-point response to the reviewer’s comments and concerns. All page numbers & rows refer to the revised manuscript file as outputted from F6Publishing AI editing tool, file name: **84697\_Auto\_Edited.docx**.

**Review ID 05722857:**

Interesting paper comparing epidemiology data on acute pancreatitis. While it does not bring new breakthrough informations it is important to see and compare evolution of epidemiology data and differences if different geografic regions and different time periods. It is a respectable fact, that this it the first study of its kind form Romania. Comments: in text is biliary AP defined as imaging findings with a high direct bilirubi. Biliary AP is however defined by elevation of aminotransferases (AST and/or ALT). Elevated bilirubin does not statistically corelate with biliary ethiology of AP. This shloud be corrected.

**Correspondent author response:** We would like to thank the reviewer for its comments. The reviewer is correct, and we have modified the Results/Etiology section, changing the bilirubine reference to the transaminase one and we have also added a new reference in regard to this topic (no. 8 – C. E. Forsmark, S. S. Vege, and C. M. Wilcox, “Acute Pancreatitis,” <https://doi.org/10.1056/NEJMra1505202>, vol. 375, no. 20, pp. 1972–1981, Nov. 2016, doi: 10.1056/NEJMRA1505202.)

The revised text reads as follows on page 8, line 3-4: 2. *Biliary – imagistic findings (ultrasonographic, computer tomography or magnetic-resonance) with elevated aminotransferases (ALT or AST).*

**Review ID 06176936:**

Dear colleagues, Digital material must be of the same type. I would change like this: We estimated the incidence of AP at 29,2 episodes that required hospitalization per 100,000 people. The majority of our cases were found in males (68,9%) and were related to alcohol abuse (45,7%). Out of the patients we were able to find data regarding tobacco usage, a vast majority of the patients were active smokers (68,5%).

**Correspondent author response:** We would like to thank you for pointing this out. We fully understand the reviewer concern and we took the appropriate measures. This error was due to the fact that in Romanian the demarcation between the integer digit and decimals is made by comma. As we all know the process of writing a manuscript involves multiple drafts, and as all the authors are Romanian-native speakers most of our initial drafts were in our language and this error might have slipped in the process of translation to English. As suggested by the reviewer, we have modified the entire article by reporting all data with a single decimal (trough approximation), and using a point instead of a comma for demarcation as this is the normative in English language.

**Review ID 05924725:**

This is a retrospective epidemiological analysis. It is not adequately describe the background, present status and significance of the study. The methods of data analysis in the study is too simple with insufficient evidence. In the it discuss of the manuscript, paper's scientific is not significance relevance to clinical practice sufficiently.

**Correspondent author response:**

While we accept the reviewer's opinion, we respectfully disagree. Both the corresponding author and the last author, in our quality of clinical practioners in a

ward of gastroenterology that is caring for around 4000 patients / year consider that the topic of this paper is suitable in clinical practice in regard with: improving the interview skills for identifying alcohol abuse as almost half of the cases are alcohol related, improving the necessity for imagistic investigation as a quarter of the patients didn't had any of them, the estimate for incidence and costs can be of help in predicting the material and financial necessity of gastroenterological services around our region and not the least we should seek better tobacco-withdrawal strategies as more the two thirds of this patients are active tobacco users. Our opinion is also in accordance to the other three reviewers, as I understand. Besides, there are several studies that highlight: the lack of studies regarding AP in a predicted high incidence area (Eastern Europe) of which we are part and also the necessity to improve *geographically targeted considerations* in our region. To this regard I must recommend the conclusion section of a high-quality paper based on data from Global Burden of Disease Study 2019 published recently by a collective of Chinese colleagues (Li *et al.* *BMC Gastroenterol* (2021) 21:332 <https://doi.org/10.1186/s12876-021-01906-2>), from which I would like to cite: *"There were substantial differences in the burden of acute pancreatitis across regions, geographically targeted considerations are needed to tailor future interventions to relieve the burden of acute pancreatitis in specific countries, especially for Eastern Europe."*

Also, we do accept the reviewer opinion regarding the simplicity of our statistical test but we consider that for the aims of our study more sophisticated statistical test are beyond the scope of this paper and might become more difficult to emphasise the results of our work.

Although we cared and were interested about the third part of the review regarding the section of discuss, probably due to the fact that we are not English-native speakers we find quite difficult to understand the remarks made by the reviewer, but we are open for suggestion if the reviewer finds the necessary time to explain us exactly what can be improved.

**Review ID 02547753:**

Thanks for the authors' work. This study provides us with valuable data for the

epidemiological trends for acute pancreatitis in Romania , which is lacking in related work on Pubmed. However, I do have some questions: 1, “The objective of this paper is to estimate the incidence, cost and tobacco usage of hospitalized AP cases in Romania”(last paragraph of Introduction), and the authors’ hospital “admitting half of the AP patients in our hospital as the other half being admitted to surgical wards”(first paragraph in Results). As the authors' hospital is a tertiary referral center, how can they ensure that the AP patients in their district are representative of AP patients throughout Romania? Have they considered any potential district-level heterogeneity? 2, The conclusion that "the incidence of acute pancreatitis in Romania is 2924 episodes per 100,000 people" is significant, as it is almost 10-20 times higher than the average level observed in East Europe (ref 8). Therefore, it is important to discuss in detail the potential reasons behind this discrepancy." 3, In this study, the etiology is classified as “alcohol related, biliary, hypertriglyceridemia, trauma,DM, and others”. Could you please provide more details on the criteria used for this classification? Are there any related references that were consulted in making these classifications? 4. The table formatting in this article should be polished.

### Corresponding author response:

I thank for the reviewer’s very well stratified and constructive suggestions. In regard to those I would like to respond point-by-point:

1. We agree that there might exist district-level heterogeneity regarding our estimate of incidence, this is why we modified one of our aims as: *estimating the incidence of AP in southern Romania*. To sustain my point of view, I should give you some additional data not included in the paper, like:
  - Although in Romania the hospitals that are designated for emergency have a great degree of territorialization, according to our law patients have the liberty to choose their hospital regardless of their domicile. A great part of our patients (including the one from the study) are coming from the districts around Bucharest, as healthcare access is difficult in small urban & countryside of Romania. Our hospital (University Emergency Hospital of Bucharest) is the largest emergency hospital in south-eastern Romania with

1099 beds as it is presented on Romanian Ministry of Public Health official website (<https://ms.ro/ro/unitati-sanitare/spitalul-universitar-de-urgenta-bucuresti/> link in Romanian, I will be happy to translate it in English if the reviewer consider adequate).

- We took into consideration in BUC-API – Gastroenterology cohort also the domicile of the patients in regard only to the district (county) of origin so anonymity can be preserved. So I present you the following data: 612 (64.6%) cases from patients residing in Bucharest (population: 1.9 million), the rest of them from counties all around Romania with the most residing in: Giurgiu county (population 0.25 million) – 100 cases (10.6%), Ilfov county (population: 0.4 million in 2011) – 87 cases (9.2%) and Teleorman county (population: 0.36 million) – 27 cases (2.9%), all of them at the southern tip of Romania. Also I must mention that we are a teaching hospital rank 1 hospital which is obliged by the law to accept transfers (if required) from rank 2 hospitals (county hospitals) from the aforementioned counties.
- 2. In regard to the report we have made on the estimated incidence, in the first draft of the manuscript we reported an incidence of 29.24 (twenty-nine point twenty-four) cases per 100,000 inhabitants which fits the interval the reviewer mentioned. As in regard to the changes we made for the review ID 06176936 there was an error regarding the fact that we used commas instead of point to split integral digits from their decimals. We addressed that, all our fractional data are now reported with point instead of commas and rounded up to the first decimal. So, in the latest version there will be an estimated incidence of 29.2 (twenty-nine point two) cases per 100,000 people. (Page 11, conclusion section, 1<sup>st</sup> line) and also anywhere this report is made throughout the entire article.
- 3. We agree on this topic, so we addressed it in the following manner: we have added Sleisenger and Fordtrans – Gastrointestinal and Liver diseases – 10th edition (reference no. 7) as the source for our classification of etiology (page 7, 3<sup>rd</sup> and 4<sup>th</sup> row of etiology subsection); we added references to alcoholic etiology and we have mentioned the impossibility to quantify the usage of CAGE questionnaires from medical records that were available to us, even if they are

used by some of our fellow colleagues (reference no. 8, 9, 10); we improved our criteria for biliary etiology changing from bilirubine criteria to transaminase one and adding reference to it (reference no. 8) and we improved our hypertriglyceridemia criteria by stating exactly why we choose 750mg/dL as our threshold (page 7) and adding references to it (references no. 8 and 11).

4. We agree, thank you for this suggestion. We changed tables 2-4 design so now all our tables have a unitary appearance.

In conclusion, I am open to offer to the reviewer any supplementary data related to the aforementioned issues and we are glad to make supplementary changes if those are deemed necessary by him/ she.