Dear Prof. Andrzej S Tarnawski,

We are pleased to be informed that our manuscript (Manuscript NO: 78044) is acceptable for publication after appropriate revision in your journal. We also thank the reviewers for the constructive comments and suggestions. We have revised the manuscript accordingly.

With best wishes,

Yours sincerely,

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First of all, we would like to express our sincere gratitude to the editors for their constructive and positive comments.

Reviewer #1:

Comment 1. Regarding patient characteristics, the distribution of etiology of AP is odd (alcohol only 3%), but maybe typical for the Asian population. This should be discussed, as we know that some forms of AP are associated with higher severity.

Response: In most high-income countries, gallstones (45%) and alcohol abuse (20%) are the most frequent causes of AP [27]. In our study, gallstones (63.2%) were even more frequent while alcohol (3.0%) was a less common etiology of AP, which is consistent with the conclusion of a Chinese study conducted by Zhu Y et al [28] over an 8-year period. We have discussed the differences in distribution of AP etiology in Europe and China in the Discussion section.

Comment 2. In order to increase the value of the paper, a correlation with other markers would be recommended, particularly with similar biomarkers such as procalcitonin.

Response: Thank you for your comment. There was positive correlation between presepsin and procalcitonin levels on day 1 and 3 after admission, and presepsin and C-reactive protein levels on day 3 and 7 (Table 4). We have added the correlation between presepsin and other markers (procalcitonin and C-reactive protein) in the Result and Discussion sections.

Comment 3. Also, regarding the association of presepsin clearance and AP severity – this might be explained by the renal failure in severe AP.

Response: Presepsin levels have been shown to increase as the glomerular filtration rate decreases and are markedly high in patients with chronic renal failure or receiving hemodialysis [23]. Recently, presepsin was found to be a predictor of septic acute kidney injury and renal replacement therapy initiation in sepsis patients [25]. Masson *et al.* found that presepsin levels are significantly higher in septic patients with shock than those without shock [10]. Potential explanations could be a reduced clearance of presepsin in non-mild patients due to reduced kidney function [22-24] and circulatory dysfunction [10]. This information has been added to the Discussion section.

Reviewer #2:

Comment 1. There are many pitfalls that the Authors acknowledged in the Discussion section (mainly, the influence of renal dysfunction on presepsin levels; the comparison of a serum biomarker with clinical scores but not with other biomarkers of inflammation, as CRP or PCT).

Response: Thank you for your comment. Presepsin levels have been shown to increase as the glomerular filtration rate decreases and are markedly high in patients with chronic renal failure or receiving hemodialysis [23]. There was positive correlation between presepsin and procalcitonin levels on day 1 and 3 after admission, and presepsin and C-reactive protein levels on day 3 and 7 (Table 4). We have added the influence of renal dysfunction on presepsin levels and the comparison of presepsin with other biomarkers (PCT and CRP) in the Discussion section.

Comment 2. I think that a brief comment about the sample size should be added.

Response: A brief comment regarding sample size has been added to the Methods section. With two-sided $\alpha = 0.05$, $\beta = 0.2$ and 70% of patients with mild pancreatitis [13], we would need 106 patients with 74 mild pancreatitis and 32 non-mild pancreatitis. This study enrolled 137 patients to account for 20% of patients lost to follow up.

Comment 3. What were the organs who failed?

Response: The most common organ systems to fail in non-survivors were circulatory [71.4% (5/7 patients)], respiratory [85.7% (6/7 patients)] and renal [42.8% (3/7 patients)] systems. This information has been added to the

Comment 4. How many infection (e.g., cholangitis) occurred?

Response: Con-infections that occurred in this study included biliary tract infections (63.2%), respiratory tract infections (15.0%) and urinary tract infections (2.3%).

Comment 5. What could be the role of presepsin in the clinical setting? Would it useful to rule out severe or moderate AP in the first days, allowing a rapid discharge? Indeed, a low PSP value at day 3 or day 5 may be of help more in identifying mild vs non mild disease than moderate vs severe.

Response: Thank you for your comments. Both presepsin and clearance rate of presepsin on day 3 may be used as early biomarker to predict the severity and prognosis of AP. The presepsin concentrations on day 3, 5, and 7 (but not day 1) increased with the severity of AP. A high presepsin value and low clearance rate of presepsin at day 3 could be valuable for the early identification of mild or moderate vs severe disease. We have added this information in the manuscript.

Comment 6. Are there other studies that investigated the role of PSP in patients with AP? If yes, were the PSP values comparable between studies?

Response: A gender- and age-matched study on patients with severe AP compared to healthy volunteers revealed that presepsin was an independent predictor of local complications, organ failure, and in-hospital mortality [26]. Furthermore, we observed dynamic changes in plasma presepsin levels and clearance rates of presepsin over time in patients with mild, moderate and severe AP and found that the presepsin concentrations on day 3, 5, and 7 (but

not day 1) increased with the severity of AP. A high presepsin value and low clearance rate of presepsin on day 3 were found to be more valuable for the early identification of mild or moderate vs severe disease.