ROUND 1

Editor in Chief

World Journal of Gastroenterology

July 21th, 2023

Dear Editor in Chief,

Thank you very much for your letter and advice. We also thank the reviewers for the valuable comments and suggestions. Accordingly, we have revised the manuscript, and would like to re-submit it for your consideration. We have addressed the comments raised by the reviewers, and the amendments are highlighted in yellow in the revised manuscript. Point by point responses to the reviewers' comments are listed below this letter.

We hope that the revised version of the manuscript is now acceptable for publication in your journal.

Looking forward to hearing from you soon.

With best wishes.

Yours sincerely,

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Reviewer 1

The authors analyzed 213 patients diagnosed with autoimmune pancreatitis (AIP) based on the International Consensus Diagnostic Criteria (ICDC) to compare clinical features and outcomes of AIP stratified by IgG4 level and analyze predictors of relapse. The results of this study suggested a more active immune system and a higher relapse rate in those with abnormally elevated serum IgG4 levels. In addition, elevated serum IgG4 and IgA levels were detected to be independent risk factors of relapse. The following concerns should be addressed before it can be considered for publication.

Comments:

1. In the Cox regression analyses, the authors treated age and serum IgG4 and IgA levels as binomial variables with specific cutoff values. The authors should perform additional Cox regression analyses in which these variables are treated as continuous variables.

2. Maintenance glucocorticoid treatment is known to prevent relapse. The authors are recommended to compare initial and maintenance doses of glucocorticoid and presence or absence of maintenance therapy between the two group and add these variables as candidates of risk factors of relapse or at least important covariates.

Reply:

Thanks for your suggestions.

1. We have already performed Cox regression analyses in which those variables mentioned above are treated as continuous variables. The results are shown as follows (Age, HR 1.023; 95%CI 0.992-1.056; P=0.149; IgA, HR 1.000; 95%CI 0.994-1.006, P=0.949; IgG4, HR 1.000; 95%CI 1.000-1.000; P=0.735). We did not show complete results due to the limited space. Furthermore, based on other studies and guidelines, we treated some variables as binomial variables and chose the twice of upper limit of normal as cutoff values [1-5]. We also added the explanation of the cutoff values in the manuscript.

Revised manuscript (Part of Univariate and multivariate analyses)

Univariate analyses revealed an association between relapse and age over 55 years (hazard ratio [HR]: 2.254; 95% confidence interval [CI]: 1.074-4.731; *P*=0.032). Similarly, serum IgG4 levels (>402 mg/dL, 2×ULN) and IgA levels (>400 IU/mL, 1×ULN) were found to be significant contributors to relapse (IgG4, HR: 3.381, 95% CI: 1.176-9.726, *P*=0.024; IgA, HR: 6.271, 95% CI: 1.294-30.389, *P*=0.023).

2. We have compared the initial doses of glucocorticoid and presence or absence of maintenance therapy between the two group and add these variables as candidates of

risk factors of relapse. In the relapse group, the median dose of initial prednisolone is 40 (35-100) mg/d, 8 of 30 (26.7%) patients received 5mg/d prednisolone as maintenance therapy. In the group of patients without relapse, the median dose of initial prednisolone is 40 (30-50) mg/d (P=0.745), 95 of 163 (58.3%) patients (P=0.002) received 5mg/d prednisolone as maintenance therapy. We also added these variables as candidates of risk factors of relapse. The results are shown below.

Variates	HR	95% CI	*P* value
Initial dose of prednisolone (mg/d)	0.997	0.991-1.004	0.439
Maintenance therapy	0.61	0.269-1.386	0.238

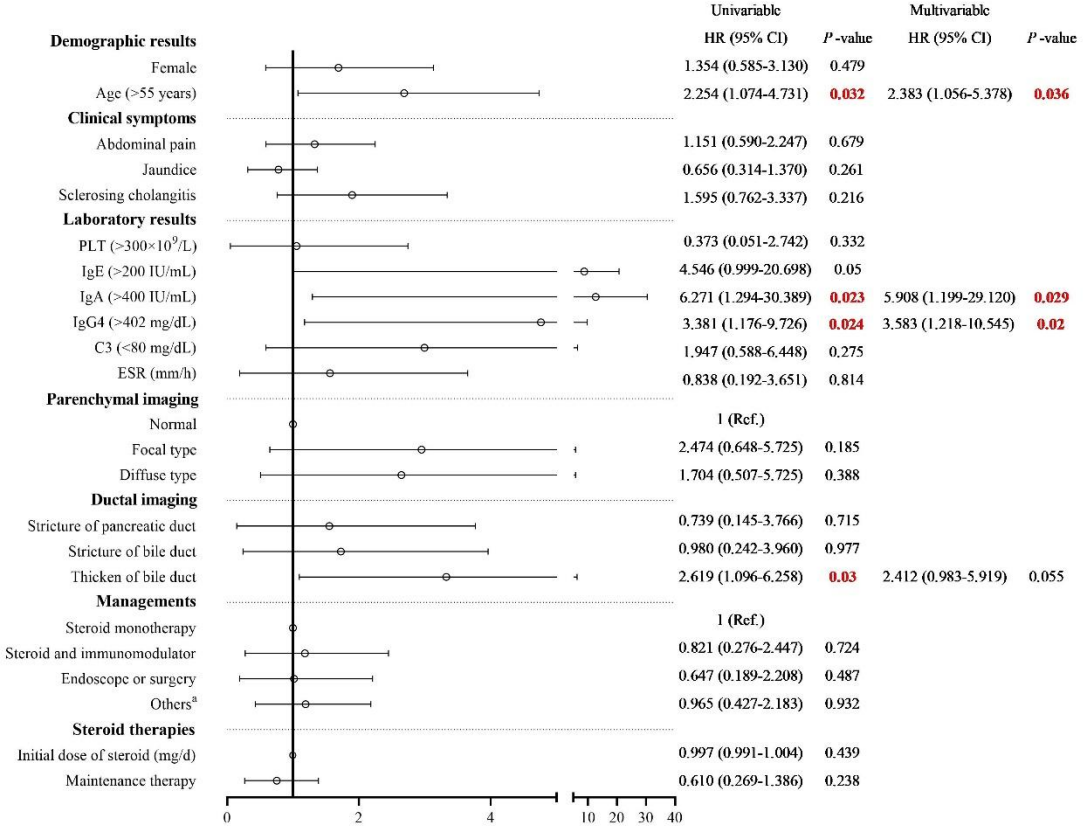
Revised manuscript (Part of Univariate and multivariate analyses)

Patients with a thickened bile duct seen on imaging scans also showed a higher risk of relapse (HR: 2.619; 95% CI: 1.096-6.258, P=0.030). The presence of some clinical symptoms such as abdominal pain, type of parenchymal imaging, type of managements, initial dose of steroid and absence of maintenance therapy, were not significantly different between the relapse and non-relapse groups.

Revised manuscript (Part of Discussion)

Maintenance therapy was recommended in various studies to prevent relapse[1,45], while in our study, the absence of maintenance therapy did not seem a predictor of relapse.

Revised manuscript (Figure 3)



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Reviewer 2

Dear Authors,

1. please state the type of AIP of the patient cohorts described in the Manuscript.

2. Also, please add info on the duration and dose of steroid therapy.

Reply:

Thanks for your important advices. We supplemented the information in our manuscript with your suggestions and details are presented as below:

1. Revised manuscript (Part of Demographic characteristics)

Baseline data are summarized in Table 1. Overall, 65 and 148 patients in the normal and abnormal groups, respectively, were included. There are 189 patients with type 1 AIP and 24 patients with type 2 AIP.

2. Revised manuscript (Part of Remission and relapse)

In the normal group, twenty-six (40.0%) patients received steroid monotherapies, fourteen (21.5%) received steroids plus immunomodulators, twelve (18.5%) underwent endoscopies or surgeries, and thirteen (20.0%) received other therapies such as hepatic protectors, the median duration and dose of prednisolone therapy are 8 (6-9) weeks and 40 (30-50) mg/d. In the abnormal group, eighty-one (54.7%) patients received steroid monotherapies, thirty (20.3%) received steroids plus immunomodulators, nine (6.1%) underwent endoscopies or surgeries, and twenty-eight (18.9%) received other therapies, the median duration and dose of prednisolone therapy are 8 (6-9) weeks (P=0.200) and 42.5 (40-100) mg/d (P=0.750).

ROUND 2

Responses to Reviewer To Reviewer 1

In the Cox regression analyses in which age and serum IgG4 and IgA levels are treated as continuous variables, the authors showed that these variables, especially serum IgG4 and IgA levels, were not associated with relapse at all. The results indicated that there was a weaker and limited association between relapse and serum IgG4 and IgA levels than expected. The authors should clearly describe these results in the Results section to avoid the misconception that there was a strong association between relapse and serum IgG4 and IgA levels.

Answer: We thank the reviewer for raising this important issue. Firstly, we would like to express our highest respect to your professional and careful review. Upon receipt of your article comment, we immediately conducted a detailed and profound meeting to discuss the research with the professional bio-statistician. We reviewed and analyzed the distribution type of these variables carefully and performed histograms in the supplemental materials (Supplemental Figure 1-3). The results showed that these variables are skewed distribution rather than normally distributed. Therefore, it was inappropriate to perform the Cox regression analyses in which these variables are treated as continuous variables in the last response letter. After a thorough discuss with the professional bio-statistician, we decided to retain the Cox regression analyses in which these variables are treated as binary variables and adapted the current cut-off value based on many important published studies and guidelines [1-6]. Our statistical analysis was based on most published studies. We sincerely hope that you can understand us and support us. In the future, we will insist to enlarge and continue this study and make multicenter study among many hospitals. Supplemental Figure 1 Frequency histogram of Age Supplemental Figure 2 Frequency histogram of serum IgA concentration Supplemental Figure 3 Frequency histogram of serum IgG4 concentration Reference: 1. Ishikawa, T., Kawashima, H., Ohno, E., Iida, T., Suzuki, H., Uetsuki, K., Yamada, K., Yashika, J., Yoshikawa, M., Gibo, N., Aoki, T., Kataoka, K., Mori, H., & Fujishiro, M. (2020). Risks and characteristics of pancreatic cancer and pancreatic relapse in autoimmune pancreatitis patients. Journal of gastroenterology and hepatology, 35(12), 2281–2288. https://doi.org/10.1111/jgh.15163 2. Lee, H. W., Moon, S. H., Kim, M. H., Cho, D. H., Jun, J. H., Nam, K., Song, T. J., Park, D. H., Lee, S. S., Seo, D. W., & Lee, S. K. (2018). Relapse rate and predictors of relapse in a large single center cohort of type 1 autoimmune pancreatitis: long-term follow-up results after steroid therapy with short-duration maintenance treatment. Journal of gastroenterology, 53(8), 967–977. https://doi.org/10.1007/s00535-018-1434-6 3. Hart, P. A., Kamisawa, T., Brugge, W. R., Chung, J. B., Culver, E. L., Czakó, L., Frulloni, L., Go, V. L., Gress, T. M., Kim, M. H., Kawa, S., Lee, K. T., Lerch, M. M., Liao, W. C., Löhr, M., Okazaki, K., Ryu, J. K., Schleinitz, N., Shimizu, K., Shimosegawa, T., ⋯ Chari, S. T. (2013). Long-term outcomes of autoimmune pancreatitis: a

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2. In addition, referring to other previous studies in which serum immunoglobulin levels were treated as continuous variables (reference 40 and Mizushima I, et al. Rheumatology (Oxford). 2020;59:513-518.) or divided into quartiles (Wallace ZS, et al. Rheumatology (Oxford). 2016;55:1000-8. and Liu Z, et al. J Intern Med. 2022;292:91-102.), the authors should discuss association between relapse and serum IgG4 and IgA levels in more detail. Answer: Thanks for your constructive suggestions. It's important for our manuscript. we revised our manuscript and discussed the association between the relapse and serum IgG4 and IgA level in more detail (please see the Discussion Part of Manuscript). Besides, we also performed Cox regression analyses in which serum IgG4 levels were divided into quartiles (Table 1), which indicates an association between serum IgG4 level with relapse. Lots of published studies investigated the association between relapse with serum IgG4 level which was treated as binary variables [7-18]. Besides, it is more convenient to adapt the binary variables to evaluate the risk of relapse in the clinical practice. We sincerely hope that we could get your understanding. Table 1 Univariate Cox regression analyses for risk factors associated with relapse of AIP Serum IgG4 concentration Hazard ratio (95% CI) First quartile (median 252 mg/dL) Ref Second quartile (median 500 mg/dL) 1.108 (0.304-4.033) Third quartile (median 1040 mg/dL) 1.597 (0.471-5.414) Fourth quartile (median 1970 mg/dL) 2.814 (0.906-8.744) P for trend 0.025 Reference: 7. Ishikawa, T., Kawashima, H., Ohno, E., Iida, T., Suzuki, H., Uetsuki, K., Yashika, J., Yamada, K., Yoshikawa, M., Gibo, N., Aoki, T., Kataoka, K., Mori, H., Yamamura, T., Furukawa, K., Nakamura, M., Hirooka, Y., & Fujishiro, M. (2021). Clinical characteristics and long-term prognosis of autoimmune pancreatitis with renal lesions. Scientific reports, 11(1), 406. https://doi.org/10.1038/s41598-020-79899-3 8. Kuraishi, Y., Uehara, T., Watanabe, T., Ashihara, N., Ozawa, M., Kanai, K., & Kawa, S. (2020). Corticosteroids prevent the progression

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