**Name of Journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 88369

**Manuscript Type:** LETTER TO THE EDITOR

**Clinical characteristics and outcomes of autoimmune pancreatitis based on serum immunoglobulin G4 levels: A single-center, retrospective cohort study**

Jaber F *et al*. AIP based on serum immunoglobulin G4 level

Fouad Jaber, Khaled Elfert, Saqr Alsakarneh, Azizullah Beran, Mohammed Jaber, Manesh Kumar Gangwani, Yazan Abboud

**Fouad Jaber, Saqr Alsakarneh,** Department ofInternal Medicine, University of Missouri-Kansas City, Kansas, MO 64108, United States

**Khaled Elfert,** Department of Internal Medicine, SBH Health System, New York, NY 10457, United States

**Azizullah Beran,** Department of Gastroenterology, Indiana University, 420 University Blvd, Indianapolis, IN 46202, United States

**Mohammed Jaber,** Department of Medical Education, Al Azhar University School of Medicine, Gaza P.O.Box 108, Palestine

**Manesh Kumar Gangwani,** Department of Internal Medicine, The University of Toledo, Toledo, OH 43606, United States

**Yazan Abboud,** Department of Internal Medicine, Rutgers New Jersey Medical School, Newar, NJ 57873, United States

**Author contributions:** Jaber F conceived the research; Jaber F, Alsakarneh S, Elfert K designed the research workflow; Jaber F, Alsakarneh S, Abboud Y, and Jaber M wrote the final manuscript; Beran A and Gangwani MK supervised the project; all authors have read and agreed to the final version of the manuscript.

**Corresponding author: Fouad Jaber, MD, Doctor, Master's Student,** Department of Internal Medicine, University of Missouri-Kansas City, No. 5000 Holmes St, Kansas, MO 64108, United States. fouad.jaber.md@gmail.com

**Received:** September 22, 2023

**Revised:** November 10, 2023

**Accepted:** November 21, 2023

**Published online:**

**Abstract**

Autoimmune pancreatitis (AIP) is a complex, poorly understood disease gaining increasing attention. "Clinical Characteristics and Outcome of AIP Based on Serum IgG4 levels," investigated AIP with a focus on serum immunoglobulin (Ig) G4 levels. The 213 patients with AIP were classified according to serum IgG4 levels: Abnormal (elevated) and normal. Patients with higher IgG4 levels exhibited a more active immune system and increased relapse rates. Beyond IgG4, the IgA levels and age independently contributed to relapse risk, guiding risk assessment and tailored treatments for better outcomes. However, limitations persist, such as no IgA correlation with IgG4 levels, absent data on autoantibody-positive AIP cases critical for Asian diagnostic criteria, and unexplored relapse rates in high serum IgG AIP by subtype. Genetic factors and family histories were not addressed. As the understanding and referral of seronegative AIPs increase, there's a growing need for commercially available, highly sensitive, and specific autoantibodies to aid in diagnosing individuals with low or absent serum IgG4 levels.

**Key Words:** Autoimmune pancreatitis; Relapse; Immunoglobulin G; Immune System, Immunoglobulin A; Outcomes

Jaber F, Elfert K, Alsakarneh S, Beran A, Jaber M, Gangwani MK, Abboud Y. Clinical characteristics and outcomes of autoimmune pancreatitis based on serum immunoglobulin G4 levels: A single-center, retrospective cohort study. *World J Gastroenterol* 2023; In press

**Core Tip:** The study on autoimmune pancreatitis (AIP) based on serum immunoglobulin (Ig) G4 levels offers valuable insights into this complex condition. Elevated IgG4 and IgA levels in patients with AIP were associated with more active immune system and higher relapse rates, highlighting the potential of IgG4 as a biomarker. However, limitations include the lack of analysis on IgA levels in relation to IgG4 levels, the absence of data on autoantibodies, and the lack of reporting on family history and genetic factors. As awareness of AIP grows, there is a need for highly sensitive and specific autoantibodies to aid in diagnosis, especially for IgG4-negative AIP patients.

**TO THE EDITOR**

We read with great interest a recent article published in your esteemed journal, titled "Clinical Characteristics and Outcome of Autoimmune Pancreatitis Based on Serum IgG4 levels" by Zhou *et al*[1]. Autoimmune pancreatitis (AIP) is a complex and poorly understood condition that has garnered considerable attention in recent years. This study by Zhou *et al* offers valuable insights into the characteristics and outcomes of AIP, focusing on the role of serum immunoglobulin (Ig) G4 levels[1]. We believe that the findings presented in this research hold significant clinical implications and merit further discussion and dissemination.

The authors meticulously investigated a cohort of 213 patients with AIP, and their decision to categorize them into two groups based on serum IgG4 levels, the abnormal group with high IgG4 levels and the normal group, is particularly noteworthy[1]. By comparing these groups, the study reveals several compelling findings that deserve attention from the medical community.

Firstly, in line with other studies[2-4], this study highlights that patients with AIP and elevated IgG4 levels have distinct clinical features, such as a higher relapse rate[1]. This observation contributes to our understanding of the heterogeneity within the population of patients with AIP and highlights the potential importance of serum IgG4 levels as a biomarker of disease activity.

Furthermore, identifying factors associated with AIP relapse is of utmost importance for clinical management. The multivariate analyses performed in this study suggest that not only serum IgG4 levels but also IgA levels and patient age play independent roles in predicting relapse[1]. This information could help physicians stratify risks and adjust treatment strategies for patients, ultimately improving their long-term outcomes.

However, a few limitations are worth mentioning. While the study found an association between IgA levels and higher relapse rates[1], no further analysis of IgA levels relative to serum IgG4 levels was performed. One study mentioned that serum IgA and IgM levels were lower in patients with high-level serum IgG4 AIP than in patients with normal serum level IgG4 AIP[5], while another study reported an inverse correlation between serum IgG4 and IgM or IgA in 20 cases of AIP[6]. Further stratification based on IgA levels could expand our knowledge of the association between IgG4 and IgA in AIP.

Furthermore, the proportion of patients with AIP with positive autoantibodies was not discussed in this study[1]. While serum IgG levels and anti-nuclear antibody positivity were previously part of the classical criteria for AIP[7], neither the current international consensus diagnostic criteria for AIP[8] nor the Japanese revised clinical diagnostic criteria for AIP[9] included these two elements. Nonetheless, some studies have reported lower IgG4 levels in patients with positive serum autoantibodies compared to patients without autoantibodies. This finding may contribute to demonstrating the presence of AIP with an association of autoantibodies alone in a subset of patients. Furthermore, in one study, higher serum IgM and IgA levels were observed in serum autoantibody-positive (+) patients with AIP compared to serum autoantibody-negative (-) patients with AIP, suggesting that examining the properties of high serum IgG4 AIP and serum autoantibodies could provide valuable insights[5]. With increasing understanding and prevalence of seronegative AIP among general clinicians, there is a growing demand for commercially available autoantibodies with superior sensitivity and specificity to aid in the identification and diagnosis of AIP in individuals with low or absent serum IgG4 levels.

Another limitation to consider is that the study did not examine relapse rates in patients with high serum IgG levels based on the type of AIP[1]. Previous research has suggested different relapse rates, with type 1 AIP in patients with high serum IgG4 having higher rates (20%-40%) compared to type 2 AIP[5,10,11]. The lack of this information limits our understanding of how serum IgG levels may impact relapse risk in different AIP subtypes.

Finally, Zhou *et al*[1] reported neither family history nor genetic factors. It is important to note that HLA-DRB1 haplotypes are associated with AIP susceptibility[12] as well as other diseases, such as rheumatoid arthritis[13]. This genetic aspect requires further study to better understand the complex interplay between genetics and AIP.

In conclusion, the research conducted by Zhou *et al*[1] sheds light on the clinical aspects of AIP and highlights the importance of serum IgG4 levels as a prognostic indicator. It also provides valuable insights into risk factors for relapse, which can serve as a basis for more targeted therapeutic interventions. As AIP continues to be a challenge for physicians worldwide, studies such as these contribute significantly to our knowledge and have the potential to improve patient care.

**REFERENCES**

1 **Zhou GZ**, Zeng JQ, Wang L, Liu M, Meng K, Wang ZK, Zhang XL, Peng LH, Yan B, Pan F. Clinical characteristics and outcome of autoimmune pancreatitis based on serum immunoglobulin G4 level: A single-center, retrospective cohort study. *World J Gastroenterol* 2023; **29**: 5125-5137 [PMID: 37744294 DOI: 10.3748/wjg.v29.i35.5125]

2 **Culver EL**, Sadler R, Simpson D, Cargill T, Makuch M, Bateman AC, Ellis AJ, Collier J, Chapman RW, Klenerman P, Barnes E, Ferry B. Elevated Serum IgG4 Levels in Diagnosis, Treatment Response, Organ Involvement, and Relapse in a Prospective IgG4-Related Disease UK Cohort. *Am J Gastroenterol* 2016; **111**: 733-743 [PMID: 27091321 DOI: 10.1038/ajg.2016.40]

3 **Pelkmans LG**, Hendriksz TR, Westenend PJ, Vermeer HJ, van Bommel EFH. Elevated serum IgG4 levels in diagnosis and treatment response in patients with idiopathic retroperitoneal fibrosis. *Clin Rheumatol* 2017; **36**: 903-912 [PMID: 28105551 DOI: 10.1007/s10067-017-3542-8]

4 **Kubota K**, Watanabe S, Uchiyama T, Kato S, Sekino Y, Suzuki K, Mawatari H, Iida H, Endo H, Fujita K, Yoneda M, Takahashi H, Kirikoshi H, Kobayashi N, Saito S, Sugimori K, Hisatomi K, Matsuhashi N, Sato H, Tanida E, Sakaguchi T, Fujisawa N, Nakajima A. Factors predictive of relapse and spontaneous remission of autoimmune pancreatitis patients treated/not treated with corticosteroids. *J Gastroenterol* 2011; **46**: 834-842 [PMID: 21491208 DOI: 10.1007/s00535-011-0393-y]

5 **Matsubayashi H**, Sawai H, Kimura H, Yamaguchi Y, Tanaka M, Kakushima N, Takizawa K, Kadooka M, Takao T, Hebbar S, Ono H. Characteristics of autoimmune pancreatitis based on serum IgG4 level. *Dig Liver Dis* 2011; **43**: 731-735 [PMID: 21515099 DOI: 10.1016/j.dld.2011.03.006]

6 **Taguchi M**, Kihara Y, Nagashio Y, Yamamoto M, Otsuki M, Harada M. Decreased production of immunoglobulin M and A in autoimmune pancreatitis. *J Gastroenterol* 2009; **44**: 1133-1139 [PMID: 19626266 DOI: 10.1007/s00535-009-0106-y]

7 **Kim MH**, Kwon S. Diagnostic criteria for autoimmune chronic pancreatitis. *J Gastroenterol* 2007; **42 Suppl 18**: 42-49 [PMID: 17520223 DOI: 10.1007/s00535-007-2050-z]

8 **Shimosegawa T**, Chari ST, Frulloni L, Kamisawa T, Kawa S, Mino-Kenudson M, Kim MH, Klöppel G, Lerch MM, Löhr M, Notohara K, Okazaki K, Schneider A, Zhang L; International Association of Pancreatology. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. *Pancreas* 2011; **40**: 352-358 [PMID: 21412117 DOI: 10.1097/MPA.0b013e3182142fd2]

9 **Kawa S**, Kamisawa T, Notohara K, Fujinaga Y, Inoue D, Koyama T, Okazaki K. Japanese Clinical Diagnostic Criteria for Autoimmune Pancreatitis, 2018: Revision of Japanese Clinical Diagnostic Criteria for Autoimmune Pancreatitis, 2011. *Pancreas* 2020; **49**: e13-e14 [PMID: 31856100 DOI: 10.1097/MPA.0000000000001443]

10 **Kamisawa T**, Notohara K, Shimosegawa T. Two clinicopathologic subtypes of autoimmune pancreatitis: LPSP and IDCP. *Gastroenterology* 2010; **139**: 22-25 [PMID: 20639082 DOI: 10.1053/j.gastro.2010.05.019]

11 **Maire F**, Le Baleur Y, Rebours V, Vullierme MP, Couvelard A, Voitot H, Sauvanet A, Hentic O, Lévy P, Ruszniewski P, Hammel P. Outcome of patients with type 1 or 2 autoimmune pancreatitis. *Am J Gastroenterol* 2011; **106**: 151-156 [PMID: 20736934 DOI: 10.1038/ajg.2010.314]

12 **Ota M**, Katsuyama Y, Hamano H, Umemura T, Kimura A, Yoshizawa K, Kiyosawa K, Fukushima H, Bahram S, Inoko H, Kawa S. Two critical genes (HLA-DRB1 and ABCF1)in the HLA region are associated with the susceptibility to autoimmune pancreatitis. *Immunogenetics* 2007; **59**: 45-52 [PMID: 17119950 DOI: 10.1007/s00251-006-0178-2]

13 **Gonzalez-Gay MA**, Garcia-Porrua C, Hajeer AH. Influence of human leukocyte antigen-DRB1 on the susceptibility and severity of rheumatoid arthritis. *Semin Arthritis Rheum* 2002; **31**: 355-360 [PMID: 12077707 DOI: 10.1053/sarh.2002.32552]

**Footnotes**

**Conflict-of-interest statement:** All authors declare no conflict of interest.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Corresponding Author's Membership in Professional Societies:** American College of Gastroenterology; American Association for the Study of Liver Diseases.

**Peer-review started:** September 22, 2023

**First decision:** November 1, 2023

**Article in press:**

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** United States

**Peer-review report’s scientific quality classification**

Grade A (Excellent): A

Grade B (Very good): 0

Grade C (Good): C, C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Liu C, China; Mizushima I **S-Editor:** Qu XL **L-Editor: P-Editor:**