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LETTER TO THE EDITOR

Can serum immunoglobulin G4 levels and age serve as reliable predictors of relapse in autoimmune pancreatitis?

Jun-Min Song, Si-Yu Sun

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Abstract

We are writing in response to the paper published in the *World Journal of Gastroenterology* by Zhou *et al*. The authors identified higher serum immunoglobulin (Ig) G4 levels and age over 55 years as independent risk factors for disease relapse. Despite notable strengths, it is crucial to address potential biases. Firstly, the cohort study included 189 patients with autoimmune pancreatitis (AIP) type 1 (with higher IgG4 seropositivity and higher relapse) and 24 with type 2 (with lower IgG4 seropositivity and lower relapse). Consequently, most, if not all, AIP type 2 patients were assigned to the normal group, possibly inflating the association of higher serum IgG4 levels with relapse and potentially exaggerating the association of older age with relapse. Secondly, the authors did not provide sufficient details regarding AIP diagnosis, such as the ratio of definitive *vs* probable cases and the proportion of biopsies. In cases where histological evidence is unavailable or indeterminate, AIP type 2 may be misdiagnosed as definitive type 1, and type 1 may also be misdiagnosed as probable type 2, particularly in cases with normal or mildly elevated serum IgG4 levels. Lastly, in this retrospective study, approximately one-third of the consecutive patients initially collected were excluded for various reasons. Accordingly, the impact of non-random exclusion on relapse outcomes should be carefully considered. In conclusion, the paper by Zhou *et al* offers plausible, though not entirely compelling, evidence suggesting a predictive role of elevated serum IgG4 levels and advanced age in AIP relapse. The foundation for future investigations lies in ensuring a reliable diagnosis and accurate disease subtyping, heavily dependent on obtaining histological specimens. In this regard, endoscopic ultrasound-guided fine-needle biopsy emerges as a pivotal component of the diagnostic process, contributing to mitigating biases in future explorations of the disease.

Key Words: Autoimmune pancreatitis; Immunoglobulin; Endoscopic ultrasound; Relapse; Age

Core Tip: This paper assesses the strengths and potential biases of the provided study. Accurate diagnosis and subtyping are crucial for both clinical practice and research. In this context, endoscopic ultrasound-guided fine-needle biopsy emerges as a pivotal component of the diagnostic process, playing a key role in mitigating the introduction of various biases in future investigations of autoimmune pancreatitis.

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TO THE EDITOR

We are writing in response to the recent clinical research paper published in the *World Journal of Gastroenterology* by Zhou *et al*[1]. In their study, the authors presented a cohort of 213 patients diagnosed with autoimmune pancreatitis (AIP), assigned to two groups based on serum immunoglobulin (Ig) G4 levels. Specifically, 148 patients were assigned to the abnormal group with serum IgG4 levels exceeding 2-fold the upper limit of the reference range, while 65 patients belonged to the normal group with serum IgG4 levels at or below this threshold. Through a comprehensive comparison of clinical characteristics and outcomes between these two groups, Zhou *et al*[1] identified higher serum IgG4 levels and age over 55 years as independent risk factors for disease relapse.

The significance of this large-sample study, considering the relative rarity of AIP, lies in its potential to contribute valuable insights to the management of patients with AIP. The findings suggest that monitoring serum IgG4 levels, particularly when exceeding 2-fold the upper limit of the reference range, can serve as a useful predictive indicator for disease relapse. Furthermore, the identification of age over 55 years as an independent risk factor adds dimension to the prognostic considerations for AIP. The implications of these results are noteworthy, as they may guide clinicians in developing more targeted and effective management strategies for AIP patients. The study conducted by Zhou *et al*[1] provides a solid foundation for further discussions and investigations in the field of AIP, shedding light on potential paths for improved patient care and outcomes.

AIP represents a distinctive form of chronic pancreatitis triggered by aberrant autoimmune or inflammatory reactions. The disease encompasses two clinical subtypes, namely type 1 (histologically defined as lymphoplasmacytic sclerosing pancreatitis) and type 2 (histologically defined as idiopathic duct-centric pancreatitis). Despite sharing indistinguishable imaging manifestations and exhibiting a complete response to steroid treatments, these two subtypes display distinct clinical, histological, and prognostic features[2]. Notably, patients with AIP type 1 exhibit higher IgG4 seropositivity (60%-80%)[3-5] and a more elevated relapse rate (up to 60%)[4] compared to those with type 2, where IgG4 seropositivity is lower (approximately 20%)[4,5], and the relapse rate is correspondingly reduced (approximately 20%)[6,7]. Additionally, individuals with type 1 are, on average, two decades older than their type 2 counterparts[2].

One of the outstanding challenges in clinical practice is identifying reliable risk factors associated with the relapse of AIP type 1. Presently, the most pertinent factors include proximal bile duct involvement (*vs* no involvement), diffuse pancreatic enlargement (*vs* focal enlargement), and initial treatment with steroids (*vs* surgical resection)[8]. However, the role of elevated serum IgG4 levels and older age remains contentious, as discussed in this paper and other sources[8]. The primary contribution of this study is to underscore the significance of elevated serum IgG4 levels and older age in predicting relapse. However, it is crucial to interpret this contribution cautiously due to potential biases. Firstly, the cohort study included 189 patients with AIP type 1 and 24 with type 2, resulting in a proportion of type 2 patients of approximately 10%, consistent with an international multicenter study[9]. Consequently, most, if not all, AIP type 2 patients (with lower IgG4 seropositivity and lower relapse rates) were assigned to the normal group, possibly inflating the association of higher serum IgG4 levels with relapse. Similarly, the abnormal group mostly comprised AIP type 1 patients with older age (as indicated in the study, male patients in the abnormal group were older than their normal group counterparts) and higher IgG4 seropositivity, potentially exaggerating the association of older age with relapse. Secondly, the authors did not provide sufficient details regarding AIP diagnosis, such as the ratio of definitive *vs* probable cases and the proportion of biopsies. According to international consensus diagnostic criteria, biopsy is mandatory for AIP type 2 but not for type 1[10]. However, in cases where histological evidence is unavailable or indeterminate, AIP type 2 may be misdiagnosed as definitive type 1[11], and type 1 may also be misdiagnosed as probable type 2, particularly in cases with normal or mildly elevated serum IgG4 levels. Lastly, in this retrospective study, a total of 308 consecutive patients were initially collected, but 95 patients (approximately one-third) were excluded for various reasons. As the exclusion was not random (*e.g.*, patients with no relapse were more likely to be excluded due to incomplete follow-up data), the impact of exclusion on relapse outcomes should be carefully considered.

In conclusion, the clinical research paper authored by Zhou *et al*[1] provides plausible, albeit not entirely compelling, evidence suggesting a predictive role of elevated serum IgG4 levels and advanced age in the relapse of AIP. These findings, while intriguing, warrant further validation through prospective, multi-center studies with larger sample sizes.

The cornerstone of such investigations lies in ensuring a reliable diagnosis and accurate disease subtyping, a task heavily reliant on obtaining histological specimens. In this regard, endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) and biopsy (FNB) emerge as pivotal components of the diagnostic process. While EUS-FNA proves valuable in distinguishing between the two subtypes of AIP, particularly in seronegative cases[12], the overall performance of FNB surpasses that of FNA. A recent clinical research paper published in the *Endoscopic Ultrasound* by Thomsen *et al*[13] sheds light on this aspect. Their examination of 852 consecutive pancreatic EUS-SharkCore FNB procedures, spanning both benign and malignant lesions, revealed the successful acquisition of sufficient tissue cylinders for histological diagnosis in 93.4% (796/852) of cases. Despite immediate and late complications occurring in 5.4% and 4.7% of procedures, respectively, only 0.2% required intervention. Notably, among the FNB procedures from 15 patients with AIP (10 type 1 and 5 type 2), the study reported a sensitivity of 83.3%, a specificity of 99.5%, and an accuracy of 99.2%. Furthermore, EUS, especially ultrasound elastography, provides distinctive features that enhance the diagnosis of AIP, while concurrently aiding in its differentiation from pancreatic cancer[14,15]. Collectively, these studies underscore the potential of EUS-FNB as an optimal approach for diagnosing and subtyping AIP, offering a high level of efficacy and safety. This contributes to mitigating the introduction of various biases in future explorations of the disease.

FOOTNOTES

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