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Frequency of seronegative cases in autoimmune hepatitis and their association with the systemic immune inflammation index

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ABSTRACT

Aims: It is suggested that a deficiency in B cells plays a role in pathogenesis of seronegative autoimmune hepatitis (snAIH). The lack of B cells leads to notable changes in the variety of leukocyte types within the bloodstream. This study aimed to determine the frequency of snAIH in patients with autoimmune hepatitis, as well as to explore the relationship between snAIH and leukocyte-based inflammatory indices.

Methods: In this retrospective study, 57 patients newly diagnosed with autoimmune hepatitis were included. According to clinical and pathological findings, patients were classified into seropositive autoimmune hepatitis (spAIH) and snAIH groups. The inflammation indices included the platelet to lymphocyte ratio (PLR), the neutrophil to lymphocyte ratio (NLR), and the systemic immune-inflammation index (SII).

Results: The frequency of snAIH was 26.3%. The snAIH group exhibited higher NLR (3.0 vs. 1.5, $p<0.001$) and SII (726.1 vs. 300.8, $p<0.001$) levels, along with a lower PLR level (118.2 vs. 151.1, $p=0.001$) than the spAIH group. The threshold value of SII in predicting snAIH was ≥488.4 (sensitivity=80.9%, specificity=86.7%), and it exhibited better diagnostic performance than other inflammatory indices.

Conclusion: In autoimmune hepatitis patients, snAIH exhibits by a notable prevalence and a different inflammatory landscape. For patients suspected of autoimmune hepatitis but negative for autoantibodies, the SII could serve as a straightforward, accessible, and affordable predictor prior to liver biopsy.

Keywords: Autoantibodies, autoimmune hepatitis, inflammation, liver diseases

INTRODUCTION

Autoimmune hepatitis (AIH) is a chronic condition characterized by immune-mediated destruction of hepatic cells, leading to liver inflammation and, potentially, cirrhosis and liver failure.[1] AIH is typically identified through the presence of autoantibodies and elevated immunoglobulin levels, with a definitive diagnosis confirmed through liver biopsy. However, in a subset of patients, biopsy results are positive even though serological markers are negative. This group, referred to as seronegative autoimmune hepatitis (snAIH), poses diagnostic challenges and highlights the heterogeneity of AIH.[2]

The pathogenesis of AIH involves the interaction between specific genetic characteristics and molecular mimicry in the development of the disease. This interaction includes impaired immune regulatory mechanisms played by the CD4+T cell population, Treg cells, CD8+cytotoxicity, and B cells involved in the production of autoantibodies.[3,4] This impairment of mechanisms triggers an autoimmune reaction, characterized by liver damage from interferon-γ produced by effector T cells.[5] While the precise mechanism underlying snAIH pathogenesis remains unidentified, the absence of autoantibodies could indicate a reduction or absence of B cell activity, alongside significantly preserved T cell activity.[6] Therefore, these two main lymphocyte types (B and T cells) may exhibit differences between snAIH and seropositive AIH (spAIH) groups. Additionally, platelet products induce interactions among innate or adaptive immune cells such as neutrophils, monocytes, macrophages, T cells, and B cells.[7] These findings suggest that inflammatory responses may differ between snAIH and spAIH groups.

Recent studies have emphasized the significance of extended inflammation indices, such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte

ratio (PLR), as potential markers of inflammation and prognosis in AIH.[8-11] However, we have not encountered a study evaluating the systemic immune-inflammation index (SII) in patients with AIH. Furthermore, the diagnostic performance of these inflammation indices in distinguishing between snAIH and spAIH groups has not yet been evaluated.

Given the absence and deficiency of B cells in snAIH, we hypothesized that inflammation indices might differ in snAIH compared to spAIH. This study aimed to determine the frequency of snAIH in AIH patients, as well as to explore the relationship between snAIH and inflammatory indices such as SII, NLR, and PLR.

METHODS

This retrospective study was conducted with AIH patients who admitted to the Gastroenterology Clinic of the Health Sciences University Ümraniye Training and Research Hospital between 01.01.2015 and 16.10.2023. The present study adhered to the ethical regulations and principles as stipulated in the Declaration of Helsinki. The study received approval from the Ethical Committee of Health Sciences University Ümraniye Training and Research Hospital (Date: 21.12.2023, Decision No: 565). The requirement for obtaining informed consent was exempted by the Ethics Committee, given the retrospective design of the study.

The sample size for our study was calculated based on the reported prevalence of seronegative autoimmune hepatitis (snAIH), which ranges between 7% and 36% in the literature.[6,12,13] To determine an adequate sample size for our prevalence study, we employed the following formula: $n=Z2\times P\times(1-P)/d2$. In this formula, n denotes the sample size, Z is the statistical value associated with the confidence level (Z=1.96 for a 95% confidence interval), P indicates the anticipated prevalence [(7%+36%)/2≈22%], and d reflects precision, aligning with the effect size (14%). Based on the calculation, the estimated sample size needed, with a 95% confidence level and a 14% margin of error, is approximately 34 patients.

Study Population

We retrospectively evaluated a total of 84 patients who were diagnosed with AIH for the first time. The diagnosis of AIH was based on the diagnostic criteria established by the International Autoimmune Hepatitis Group (IAIHG).[14] Patients under the age of 18, pregnant women, those with a history of AIH, those without a liver biopsy, those with any comorbid conditions such as malignancy, inflammatory diseases, heart diseases, kidney diseases or lung diseases, and those with an acute or chronic liver diseases (such as viral hepatitis, alcoholic liver disease, non-alcoholic fatty liver disease, and hereditary liver diseases), and those with missing clinical data were not included in the study. Subsequent to the exclusion process, 57 patients newly diagnosed with AIH were enrolled in this study.

Study Protocol

Demographic and clinical data were collected using the hospital's electronic information system and patient files. Venous blood was drawn from all patients on the same day as their liver biopsy during their initial diagnosis. According to clinical and pathological findings, patients were classified into spAIH and snAIH groups. For a spAIH diagnosis, patients were required to exhibit at least one typical non-organ-specific antibody (anti-nuclear antibody [ANA], anti-smooth muscle antibody [ASMA], and anti-liver kidney microsomal [anti-LKM] type 1 antibody), hypergammaglobulinemia, and characteristic liver histopathologic signs (interface hepatitis, predominantly lymphoplasmacytic or resetting of the liver cells), alongside the exclusion of other liver diseases. For snAIH, the diagnostic criteria include a lack of typical non-organ-specific antibody, the presence of characteristic liver histopathologic signs and successful response to immunosuppressive therapy, excluding other hepatic diseases.[2]

Blood samples were measured using Mindray MC6800 device (Mindray, Shenzhen, China) and Architect plus device (Abbot Diagnostics, Abbot Park, Illinois, USA). The electrical impedance method was employed to measure complete blood counts. The enzymatic colorimetric test was utilized to measure the concentrations of alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transferase (GGT), and albumin. Inflammation indices were calculated as follows: PLR=platelet count to lymphocyte count ratio, NLR=neutrophil count to lymphocyte count ratio, and SII=(neutrophil count×platelet count) to lymphocyte count ratio.[15]

Statistical Analysis

All data were analyzed with IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA). Numerical data determined to be normally distributed based on the results of Kolmogorov-Smirnov tests are given as mean±standard deviation (SD) values while non-normally distributed variables are given as median (25th-75th quartile) values. For comparisons between groups, Student T-test and Mann-Whitney U test were used in line with the normality of the considered distribution. Categorical variables are given as numbers and percentages, and inter-group comparisons were conducted with Chi-square and Fisher exact tests. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of the inflammation indices to predict snAIH. Significance was accepted at $P<0.05$ (*) for all statistical analyses.

RESULTS

The mean age of 57 AIH patients included in the study was 55.4±12.5 years, the majority of them were female (71.9%). The demographic features of AIH patients were reported in Table 1. Among the patients, 56.1% tested positive for ANA, 10.5% for AMA, 28.1% for ASMA, and 5.3% for anti-LKM. Every patient's liver biopsy revealed either interface hepatitis, a mainly lymphoplasmacytic infiltrate, or rosetting of the liver cells. The frequency of snAIH was 26.3%. Demographic findings did not differ between snAIH and spAIH groups (p>0.05) (Table 1).

Table 1. The demographic features of autoimmune hepatitis patients

Variables	All population n=57	Autoimmune hepatitis		p
		Seronegative	Seropositive	
		n=15	n=42	
Age, years	55.4±12.5	53.0±9.3	53.8±12.4	0.807
Gender, n (%)				
Female	41 (71.9)	13 (86.7)	28 (66.7)	0.139
Male	16 (28.1)	2 (13.3)	14 (33.3)	
BMI, kg/m2	28.5±8.2	29.4±7.5	28.2±8.6	0.716
Smoking, n (%)	27 (47.4)	7 (46.7)	20 (47.6)	0.949
Alcohol use, n (%)	8 (14.0)	2 (13.3)	6 (14.3)	0.927
Clinical presentation, n (%)				
Jaundice	53 (93.0)	13 (86.7)	40 (95.2)	0.598
Fatigue	23 (40.4)	7 (46.7)	16 (38.1)	0.760
Pruritus	18 (31.6)	5 (33.3)	13 (30.9)	0.991
Abdominal pain	13 (22.8)	3 (20.0)	10 (28.8)	0.994

Categorical variables were shown as number percentages. Numerical variables are mean±SD or median (IQR). BMI, body mass index.

The snAIH group exhibited higher median neutrophil counts (4.6 vs. 3.0×10^3/μL, p<0.001) and median lymphocyte counts (2.3 vs. 1.8×103/μL, p=0.001) compared to the spAIH group, with no significant differences in median platelet counts (218 vs. 234×10^3/L, p=0.154) and median monocyte counts (0.6 vs. 0.5×10^3/L, p=0.350). The snAIH group exhibited higher median levels of NLR (3.0 vs. 1.5, p<0.001) and SII (726.1 vs. 300.8, p<0.001), along with a lower median PLR level (118.2 vs. 151.1, p=0.001) compared to the spAIH group (Figure 1). Additionally, the median IgG level was significantly lower in the snAIH group (1530 vs. 1890, p<0.001). Other laboratory findings did not show significant differences between the groups (Table 2).

The diagnostic performance of inflammatory indices in predicting snAIH is shown in Figure 2. The threshold value of NLR in predicting snAIH was ≥1.9 with 71.4% sensitivity and 86.7% specificity. The threshold value of PLR in predicting snAIH was ≤100 with 73.8% sensitivity and 66.7% specificity. The threshold value of SII in predicting snAIH was ≥488.4 with 80.9% sensitivity and 86.7% specificity, and it exhibited better diagnostic performance than other inflammatory indices (Figure 2).

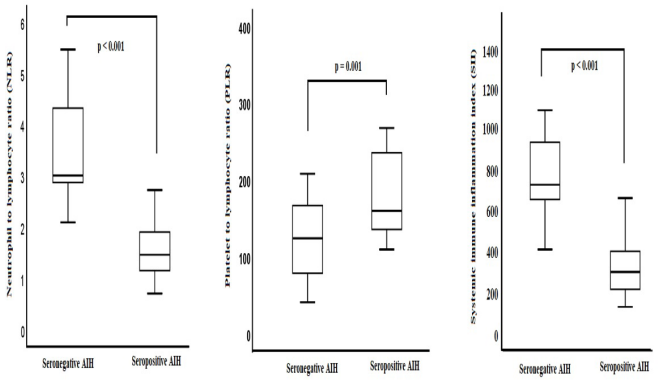

Figure 1. The distribution of immune inflammation indices among seronegative and seropositive patients with autoimmune hepatitis.

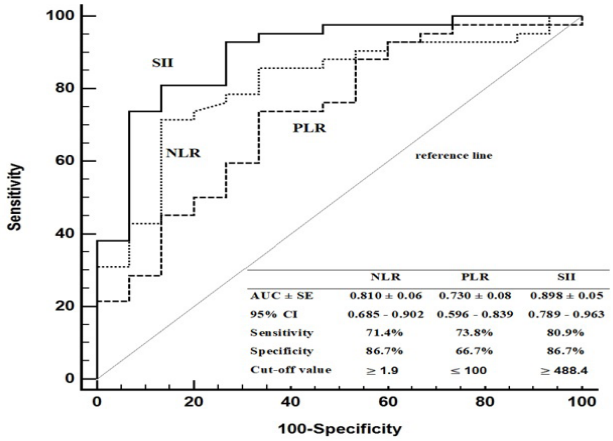

Figure 2. The diagnostic performance of immune inflammation indices in distinguishing between seronegative and seropositive autoimmune hepatitis patients

DISCUSSION

To our best knowledge, this is the first study to evaluate the diagnostic performance of the SII for distinguishing between snAIH and spAIH cases among AIH cohort. The main consequences are: 1) Higher levels of NLR and SII were observed in snAIH patients, while spAIH patients exhibited higher PLR levels. 2) In predicting snAIH patients, higher NLR levels and lower PLR levels exhibited similar sensitivity but differed in specificity. 3) SII levels demonstrated superior diagnostic performance compared to NLR and PLR in predicting snAIH patients.

Previous studies have reported that the incidence of snAIH among AIH patients varies widely, ranging from 7% to 36%.[6,12,13] In this study, the frequency of snAIH was determined to be 26.3%, consistent with the range reported in the literature. The lack of typical

Table 2. The laboratory findings of autoimmune hepatitis patients

Variables	All population n=57	Autoimmune hepatitis		p
		Seronegative	Seropositive	
		n=15	n=42	
Autoantibodies, n (%)				
ANA	32 (56.1)	-	32 (76.2)	-
AMA	6 (10.5)	-	6 (14.3)	-
ASMA	16 (28.1)	-	16 (38.1)	-
Anti-LKM	3 (5.3)	-	3 (7.1)	-
Laboratory findings				
Hemoglobin, g/dL	12.7±1.7	12.9±2.0	12.6±1.6	0.624
WBC,×103/µL	6.7±2.3	7.5±2.6	6.4±2.1	0.171
Neutrophils,×103/L	3.6 (2.7-4.6)	4.6 (3.9-5.8)	3.0 (2.6-3.8)	<0.001*
Lymphocytes,×103/µL	2.0 (1.4-2.5)	2.3 (1.1-2.0)	1.8 (1.1-2.8)	0.001*
Platelets,×103/µL	224.0 (167.5-270.4)	218.0 (145.0-276.0)	234.0 (157.0-292.0)	0.154
Monocytes,×103/µL	0.5 (0.4-0.7)	0.6 (0.4-0.8)	0.5 (0.4-0.7)	0.350
NLR	1.8 (1.2-2.7)	3.0 (2.8-4.3)	1.5 (1.2-1.9)	<0.001*
PLR	127.5 (90.3-195.4)	118.2 (86-164.3)	151.1 (130.5-233.8)	0.001*
SII	381.2 (244.1-605.3)	726.1 (620.8-949.8)	300.8 (215.8-401.4)	<0.001*
ALT, U/L	22.0 (15.0-38.0)	25.0 (17.0-38.0)	22.0 (14.2-35.5)	0.526
AST, U/L	23.0 (17.0-31.0)	23.0 (16.0-30.5)	23.5 (18.0-30.5)	0.696
ALP, U/L	85.0 (58.0-113.0)	66.0 (49.0-99.5)	85.5 (64.0-117.5)	0.205
GGT, U/L	29.0 (18.0-53.0)	31.0 (21.5-66.0)	29.0 (16.0-45.8)	0.379
IgG, mg/dL	1720 (1500-2340)	1530 (1281-2100)	1890 (1586-2615)	<0.001*
Albumin, g/dL	43.5±4.6	44.3±43.3	43.3±4.7	0.488
INR	1.1±0.2	1.0±0.1	1.1±0.2	0.339
Total bilirubin, mg/dL	0.6 (0.4-0.8)	0.4 (0.3-0.7)	0.6 (0.4-0.8)	**0.095**

Categorical variables were shown as number percentages. Numerical variables are mean±SD or median (IQR). AMA, antimitochondrial antibody; ANA, anti-nuclear antibody; ASMA, anti-smooth muscle antibody; anti-LKM, anti-liver kidney microsomal type 1 antibody; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; IgG, immunoglobulin G; INR, international normalized ratio; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; SII, systemic immune inflammation index; WBC, white blood counts.

serological markers complicates the diagnosis of SnAIH, necessitating histological examination and mandating the exclusion of other liver diseases.[2] The precise mechanism underlying the pathogenesis of snAIH is still unclear. While the lack of autoantibodies constitutes the primary diagnostic distinction, this feature might not indicate a fundamental difference in pathogenesis. Instead, it could be an epiphenomenon rather than a divergence in the underlying disease mechanisms.[12] The absence of positive serology is hypothesized to be related to variations in B cell activity, as opposed to a distinct defect in generating specific autoantibodies.[6] AIH is known as a T cell-mediated disease, and these cells are associated with auto-antibody titers, immunoglobulin levels, and specific antibodies in spAIH.[16-18] It has been reported that serum IgG concentrations are significantly lower in patients with snAIH compared to those with spAIH.[19,20] This finding has also been supported in the current study. A study conducted on mice model of AIH showed that treatment with B-cell depleting antibodies (anti-CD20) reduced T-cell proliferation but did not lead to significant changes in total IgG levels or autoantibodies.[3] In AIH, B cells play a crucial role in modulating the immune response, a function they accomplish through two primary mechanisms: the secretion of cytokines and the orchestration of the recruitment of other immune cells.[21] Thus, B cells, acting as antigen-presenting cells in spAIH, might also account for the inadequate auto-antibody production in snAIH.

In a study conducted on mice with a B cell deficiency, it was reported that there was an increase in the number of neutrophils in the circulating blood.[22] Patients with snAIH exhibited higher neutrophil counts than patients with spAIH. This finding supports the suggested involvement of B cell deficiency in the pathogenic mechanism of snAIH.[6,23,24] Furthermore, an increase in lymphocyte counts was observed in snAIH patients. The decrease in peripheral neutrophil and lymphocyte counts in spAIH patients may be attributed to depletion or the migration of these cells from the bloodstream to the liver.[25] Meanwhile, patients with spAIH showed a

trend towards elevated platelet counts. Platelets, which play a significant role in the adaptive immune response, can activate peripheral blood B cells and enhance immunoglobulin production.[26] This mechanism may account for the elevated platelet and IgG levels observed in spAIH patients. On the other hand, neutrophils can influence macrophages towards an anti-inflammatory state, while platelets have the ability to modify neutrophil functions.[27] This illustrates the complex interplay within the immune system, where different cell types can significantly impact each other's roles, affecting the overall immune response and potentially the progression or resolution of inflammation.

Considering AIH is an inflammatory disease, indices derived from leukocyte subtypes might serve as better indicators for distinguishing these patients. Previous studies have reported that patients with AIH exhibit higher NLR and lower PLR levels.[8,9] However, the correlation between snAIH and these indices has not been thoroughly investigated. In this study, the observed lower NLR levels in patients with spAIH could indicate a higher migration of lymphocytes from the peripheral blood to the liver compared to neutrophils. This might also shed light on the observed higher PLR levels in these patients, in addition to the role of platelets in activating peripheral blood B cells.[26] On the other hand, the SII, which encompasses components of both NLR and PLR, could serve as a better indicator in distinguishing these patients. Patients with snAIH had higher SII levels compared to those with spAIH. Furthermore, it displayed a sensitivity of 80.9% and a specificity of 86.7% in differentiating these patient groups, outperforming both NLR and PLR in diagnostic performance. These findings are also consistent with the prognostic performance of the SII in liver diseases.[28,29] For patients suspected of AIH but negative for autoantibodies, the SII could serve as a straightforward, accessible, and affordable predictor prior to liver biopsy.

Limitations

This study had several important limitations. The main limitations were its small sample size, being conducted in a single center, and its retrospective design. Secondly, it was not possible to evaluate the extent to which inflammation indices in AIH varied in relation to healthy controls or patients with different liver conditions. This analysis might have provided further insights into the significance of these inflammation indices in AIH pathology and their efficacy in diagnosis. Finally, this study did not explore the relationship between snAIH and B cell deficiency. Hence, there is a need for more comprehensive research that includes techniques like flow cytometry to explore the impact of systemic inflammation differences in snAIH.

CONCLUSION

In patients with AIH, snAIH exhibits by a notable prevalence and a different inflammatory landscape. SnAIH exhibits different inflammatory profiles characterized by reduced PLR, as well as elevated NLR and SII. For patients suspected of AIH but negative for autoantibodies, the SII could serve as a straightforward, accessible, and affordable predictor prior to liver biopsy.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was performed in accordance with the Declaration of Helsinki, and approved by the University of Health Sciences Ümraniye Training and Research Hospital, Clinical Researches Ethics Committee (Date: 21.12.2023, Decision No: 565).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The author declared that this study has received no financial support.

Financial Disclosure

The author declared that this study has received no financial support.

Author Contributions

The author declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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