Immunological relationship between autoimmune liver disease and autoimmune thyroid disease:a cross-sectional study

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Abstract

Background: High prevalence of autoimmune thyroid disease (AITD) in patients with autoimmune liver disease (AILD) has been observed. Data on the clinical relationship between AILD and AILD remain scanty. We aimed to evaluate the immunological relationship between AILD and AITD. Results: 324 patients with AILD were enrolled, 113 out of 324 patients were concurrent AITD (34.9%). Patients with autoimmune hepatitis (AIH) were more likely to develop AITD (45.8%), followed by autoimmune hepatitis-primary biliary cholangitis overlap syndrome (AIH-PBC OS) (39.5%) and PBC (22.6%). AILD patients with concurrent AITD showed higher levels of IgG (21.5 g/L vs 16.3 g/L, P<0.0001) and gamma globulin (γ-globulin)(27.1% vs 21.9%, P<0.0001), and IgG were positively correlated with thyroid antibodies [thymoglobulinantibody (TGAb), thyroid peroxidase antibody (TPOAb)] (r=0.396, 0.322; P<0.0001, P=0.002, respectively). The frequency of TPOAb positivity was highest in PBC patients with concurrent AITD (83.9%). The AIH concomitant with AITD had a higher nuclear homogenizing antinuclear antibody (ANA) positivity compared with the AIH alone (P=0.019). PBC patients with concurrent AITD were significantly older than the PBC patients without AITD (P=0.0004). Thyroid dysfunction in AILD patients with concurrent AITD was principally characterized by Hashimoto's thyroiditis (65.5%) and diffuse lesions were mainly indicated in thyroid ultrasound (53.1%). Conclusions: The high incidence of AILD concomitant with AITD, as well as the higher levels of serum IgG and γ-globulin, and the strong correlation between thyroid antibody and IgG, suggesting that we should strengthen the screening of autoimmune thyroid disease when diagnosing and treating autoimmune liver disease.

Background

Autoimmune liver disease (AILD), caused by the imbalance of immune tolerance and leading to liver and gallbladder system damage, is a group of autoimmune diseases. The spectrum of AILD includes autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), and overlap syndrome (OS). Autoimmune thyroid diseases (AITD), featured by the production of autoantibody which induced by abnormal autoimmune responses and targets thyroid cells, is a class of organ-specific autoimmune disease, and mainly including Hashimoto's thyroiditis (HT) and Graves' disease (GD). AILD frequently overlap other extrahepatic autoimmune disease (EHAID) [1-3], AITD is the commonest concurrent EHAID in AILD patients (10-23%) [4-6]. The high incidence of AILD concomitant with AITD may be closely relevant to its underlying pathogenesis. Dr. Daya CM [7]proposed the concept of molecular mimicry, that is, infection with a virus or bacterium that contains a protein similar to a thyroid protein may result in the activation of thyroid-specific T cells, triggering immune system disorders and giving rise to thyroid dysfunction. Whether hepatocytes or cholangiocytes and thyroid cell have similar proteins, which cross-react with each other and activate specific T cells, leading to the concurrence of AILD and AITD, remains yet to be determined.

The incidence rate, clinical features, and outcomes in AILD patients concomitant with EHAID have been analyzed by previous studies [8-15]. No targeted study on the correlation between AITD and AILD has been conducted. Therefore, our study intends to analyze the differences in biochemical and

immunological indicators between AILD patients with and without AITD and to explore the possible association of clinical immunology between the two diseases.

Methods

Patient selection

Retrospectively recruited 324 inpatients with AILD at Department of Hepatology, Tianjin Second People's Hospital, Tianjin, between January 2013 and January 2019. 113 out of 324 were concurrent autoimmune thyroid disease. This study was approved by the Ethics Committee of Tianjin Second People's Hospital and all subjects have given informed.

The diagnosis of AIH was made based on the revised IAIHG scoring system issued in 1999 by the International Autoimmune Hepatitis Group [16]. The diagnosis of PBC was made based on the European Association for the Study of the Liver (EASL) PBC Clinical Practice Guidelines (2017) [17]. The diagnosis of PSC was made based on the consensus of experts in the diagnosis and treatment of primary sclerosing cholangitis (2015) [18]. The diagnosis of AIH-PBC OS was made based on EASL Clinical Practice Guidelines for the management of cholestatic liver disease (2009) [19]. Viral hepatitis, non-hepatotropic virus infection, alcoholic liver disease, drug-induced hepatitis, and hereditary metabolic liver disease were excluded.

Associated diagnosis of EHAID and family history of autoimmune diseases were searched and retrieved via the hospital electronic records, clinical letters and medical case notes. All these diseases have been diagnosed and confirmed based on the international criteria. The diagnosis of GD was based on the American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis (2016) [20]. The diagnosis of HT was based on the Chinese Guidelines for diagnosis and treatment of Adult Hypothyroidism (2017) [21].

Laboratory methods

Patients' case records, such as age, sex, symptoms, personal and family history, were systematically reviewed and examined. Clinical liver enzymes like serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP) and immunological indicators like immunoglobulin G (IgG), immunoglobulin M (IgM), gamma globulin (γ-globulin) were measured by Turbidimetric inhibition immunoassay (Hitachi 7180 Automatic Biochemical Analyzer). Antinuclear antibody (ANA), anti-mitochondrial antibody (AMA), anti-smooth muscle antibody (ASMA), anti-mitochondrial antibody M2 (AMA-M2), anti-dsDNA antibody and anti-centromere antibody were analyzed by indirect immunofluorescence or immunoblotting (Cycleblot 48 Automatic Western blotting).

Total triiodothyronine (TT3), total thyroid hormone (TT4), free triiodothyronine (FT3), free thyroxine (FT4), thyroid stimulating hormone (TSH), thyroglobulin antibody(TGAb) and thyroid peroxidase antibody

(TPOAb) were detected with electro-chemiluminescence (Roche cobas e 411 Analyzer, Switzerland).

Thyroid ultrasounds were performed by a well-trained physician (PHILIPSIU22, Netherlands).

A liver biopsy was performed in 187 patients with AILD. Histological assessment of the severity of liver inflammation and the degree of fibrosis was based on the scoring system proposed by Batts and Ludwig [22]. Biopsies were evaluated by two experienced pathologists that were unaware of the subjects' identity or clinical information.

Statistical analysis

Results were analyzed using SPSS version 23.0 (IBM Corp, USA). Continuous variables satisfied normality were expressed as mean±standard deviation (x±SD), and Student t-test was used to compare the differences in variable between the two groups. Non-normal continuous variables were expressed as median and inter-quartile range [M(P25~P75)], and Mann-Whitney test was applied. Categorical variables are expressed as actual numbers and percentages. Group comparisons of variables were analyzed with χ^2-test or Fisher's exact test if the expected cell frequency is <5. Bivariate Spearman correlation test was used to analyze the correlation of two pair random variables. P<0.05 was considered significant.

Results

Sociodemographic and biochemical indicators

Among the 324 patients with AILD, AIH, 142 (43.8%) patients; PBC, 137 (42.3%) patients; PSC, 2 (0.6%) patients; AIH-PBC OS, 43 (13.3%) patients. AITD was the commonest EHAID in AILD patients (34.9%) (Table 1).

Patients with AIH were more likely to develop AITD (45.8%), followed by AIH-PBC OS (39.5%) and PBC (22.6%). (Figure 1)

There were no significant differences in sex and biochemical parameters such as liver enzymes (ALT, AST, GGT, ALP) between AILD patients with and without AITD (P>0.05). PBC patients with concurrent AITD were significantly older than the PBC patients without AITD (P=0.0004). (Table 2, Table 3, Table 4)

Immunological indicators

AILD patients with concurrent AITD showed higher levels of IgG (21.5 g/L vs 16.3 g/L, P<0.0001) and γ-globulin (27.1% vs 21.9%, P<0.0001). (Table 5)

The serum IgG levels in the three subgroups of AILD patients with concurrent AITD was higher than those of patients without concurrent AITD (21.7g/L vs 17.5g/L, P<0.0001; 20.3g/L vs 15.4g/L, P<0.0001;24.3g/L vs 18.6g/L, P=0.035, respectively). The serumγ-globulin levels were noticed significantly different between AIH or PBC patients with and without AITD (26.4% vs 22.4%, P<0.0001;

26.7% vs 21.3%, P=0.0004, respectively); no differences emerged between AIH-PBC OS with and without AITD (P=0.081). (Table 2, Table 3, Table 4)

Significant correlation exists between IgG and TGAb or TPOAb in AILD patients with concurrent AITD (r=0.396,0.322; P<0.0001, P=0.002, respectively). (Table 6)

Autoantibody profile

No significant differences were observed in ANA between PBC/AIH-PBC OS patients with and without AITD (P>0.05) (Table 3, Table 4). But the nuclear homogenous ANA between AIH patients with and without AITD was excluded (P=0.019). (Table 2)

Thyroid function

Thyroid dysfunction were mainly manifest as Hashimoto's thyroiditis and thyroid antibody positivity in AILD concomitant with AITD, and ultrasound indicated diffuse thyroid lesions. The frequency of TPOAb positivity differed significantly among the three subgroups of AILD concomitant with AITD (P=0.035), especially the highest positivity in the PBC concomitant with AITD. And AITD more frequently coincided with or posterior to AILD’s onset. (Table 7)

Discussion

With improvement in awareness towards AILD and advancements in modern immunodiagnostic technology, a growing number of patients attacked by AILD are detected, the coexistence of extrahepatic autoimmune disease (EHAID) increases as well, especially the most prevalence of autoimmune thyroid disease (AITD) [3, 4, 23]. We recorded a high frequency of AITD in AILD (34.9%), with AIHconcomitant with AITD being the commonest, followed by AIH-PBC OS and PBC. Our data showed that thyroid disease was mainly manifest as Hashimoto's thyroiditis, which was in consonance with studies by Floreani A [24] and Crowe J P [25]. And diffuse thyroid damage was more prevalent.

This is hitherto the first study to elaborate the immunological relationship between AILD and AITD. TGAb and TPOAb are mainly IgG, TGAb in HT patients are predominantly IgG1, IgG2 and IgG4and TPOAb in HT patients are mostly IgG1 and IgG4 [26-28]. Kawashima ST et al [29] have reported that 25.5% of patients with HT had elevated serum IgG levels. Similarly, the levels of IgG and γ-globulin in AILD concomitant with AITD were higher than those in AILD alone, and IgG in the three subgroups of AILD patients with concurrent AITD was higher than those of patients without concurrent AITD as well. Further exploration of the correlation between IgG and thyroid antibodies revealed a positive correlation. It is possible, therefore, that presence of AITD could increase serum levels of IgG. Meanwhile, some AILD patients with concurrent AITD had undergone or were undergoing antithyroid or immunosuppressive therapy. Related literature has established that anti-thyroid therapy reduces thyroid antibody titers [30], signifying that IgG may be higher before controlling thyroid disease. Whether there is cross-reactivity of antithyroid autoantibodies in the presence of autoreactive T cells or similar epithelial antigens in both the liver and the thyroid, remains

unclear. And further studies on molecular biology are required to be undertaken. The findings of this research provided insights that it is noteworthy screening for thyroid antibodies when distinctly elevated IgG was detected in patients with AILD; especially in PBC individuals, once IgG was found to be elevated dramatically, not only AIH-PBC overlap but also closely monitoring of thyroid function should be considered.

This study revealed that nuclear homogenization ANA positivity was more prevalent in AIH concomitant with AITD compared to AIH alone. However, the result may be limited by the retrospective and small sample sizes of this study, whereby considerable multicenter and prospective cohort is necessary to estimate the probability. No statistical significance in other autoantibodies was attained between AILD patients with and without AITD, indicating that the specificity of autoantibodies in thyroid diseases was not evident and the screening of AITD susceptible individuals in AILD merely by certain autoantibodies was inappropriate.

Our study observed that the TPOAb positivity was the highest in PBC patients with concurrent AITD compared with other AILD patients with concurrent AITD, which was in parallel with Nakamura H's findings [31]. Nevertheless, further research remains to be carried out whether it can be identified as a serological clue to distinguish AIH from PBC when the diagnosis is equivocal. Consequently, we set about exploring the expression of TPO (a membrane-bound glycoprotein containing a heme prosthetic group) and cholangiocytes surface proteins to establish a probable interplay of molecular mechanism.

Murillo Perez CF et al [32]demonstrated that PBC patients diagnosed in recent decades are older than patients diagnosed in earlier decades over a 44-year follow-up. The PBC patients with concurrent AITD in our study were shown to be clustered in elderly subjects, which was in accord with that of Tojo J et al [33] who observed that PBC concomitant with CREST syndrome was older than that of PBC alone. There may be two possible hypotheses. Firstly, autoimmune diseases presented occult progression, leading to an older age at presentation. Secondly, AILD and AITD were detected by accident when patients see their physician to undergo routine testing of liver and thyroid function, which occurs more frequently in older individuals. It seems that closely monitoring thyroid function is indispensable in the elderly PBC patients. However, Floreani A et al [34] did not observe an age difference between PBC patients with and without EHAID. Therefore, whether the difference exists is yet to be further confirmed by a comprehensive study.

Interestingly, our data showed that AITD more frequently coincided with AILD's onset or occurred years after the diagnosis of AILD, which was conflict with Guan-Wee Wong's [6] findings that EHAID predated AIH diagnosis. Actually, controversy still exists on the above results. Firstly, Thyroid abnormality was unveiled by accident during active stages of hepatitis, which was ignored or missed in previous clinical practice. Secondly, Patients, prior to AILD, who have suffered from thyroid disease and have accepted antithyroid therapy, whereas the liver function was not systematically screened then. After all, AILD tended to be asymptomatic at presentation. Lastly, it's well-recognized that patients with autoimmune disease are prone to involve multiple organs, liver and thyroid might be affected simultaneously or successively. As a consequence, an uncertain sequence still exists in AILD and AITD. Meanwhile, the

selection bias cannot be avoided, opinions on the onset time of disease vary from hepatologists to endocrinologists. Hence, it is of vital importance to strengthen the consultation between hepatologist and endocrinologist and promote the development of the MDT diagnosis and treatment model.

Conclusions

In summary, AITD was found to be the most prevalent concurrent autoimmune disease in AILD patients with concurrent EHAID. It seems reasonable to recommend routine screening for autoimmune thyroid disease in patients with AILD when IgG and γ-globulin were significantly elevated.

Abbreviations

EHAID: extrahepatic autoimmune disease; AILD: autoimmune liver disease; AITD: autoimmune thyroid disease; HT: Hashimoto's thyroiditis; GD: Graves' disease; AIH-PBC OS: autoimmune hepatitis-primary biliary cholangitis overlap syndrome;ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma glutamyl transferase; ALP: alkaline phosphatase; IgG: immunoglobulin G; IgM: immunoglobulin M; γ-globulin: gamma globulin; ANA: antinuclear antibody; AMA: anti-mitochondrial antibody; AMA-M2: anti-mitochondrial antibody M2; TGAb: thyroglobulin antibody; TPOAb: thyroid peroxidase antibody.

Declarations

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Availability of data and materials

All data and analysis results are included in this article. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author'contributions

Jia Li and Qingmin Zeng conceived and designed the study; Jia Li, Min Gao, Chunyan Wang supervised the study; Qingmin Zeng, Chunhua Tu, Ping Han collected data; Qingmin Zeng, Xu Han, Chen Chen, Lili Zhao analyzed data statistically; Qingmin Zeng wrote the manuscript; Jia Li, Min Gao, Chunyan Wangand

Qingmin Zengrevised the manuscript. All authors reviewed the results and approved the final version of the manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Tianjin Second People's Hospital. Written informed consent was obtained from all study participants.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Frequency of EHAID in AILD patients

EHAID	Frequency, n=324 (%)
AITD	113(34.9)
HT	74(22.8)
GD	25(7.7)
Other	14(4.3)
Rheumatoid arthritis	12(3.7)
Sjogren's syndrome	16(4.9)
Systemic lupus erythematosus	5(1.5)
Systemic sclerosis	2(0.6)
Vitiligo	4(1.2)
Psoriasis	3(0.9)
Ulcerative colitis	2(0.6)
Raynaud's phenomenon	2(0.6)
Eczema	5(1.5)
Still's disease	1(0.3)
Mixed connective tissue disease	4(1.2)

EHAID, extrahepatic autoimmune disease; AILD, autoimmune liver disease; AITD, autoimmune thyroid disease; HT, Hashimoto's thyroiditis; GD, Graves' disease.

Table 2 Comparison of clinical features between AIH patients with and without AITD

	AIH(n=77)	AIH with AITD(n=65)	P-value
Male/Female	12/65	4/61	1.000
Age, year	54.36 ± 1.40	53.66 ± 1.20	0.710
Family history of AID	5	8	0.257
ALT(IU/L)	363.0(182.5~710.0)	378.0(171.0~566.5)	0.584
AST(IU/L)	300.0(149.5~614.5)	319.0(161.0~577.5)	0.634
IgG(g/L)	17.5(14.9~19.9)	21.7(17.6~29.1)	< 0.0001*
γ-globulin(%)	22.4(19.4~25.6)	26.4(22.4~32.3)	< 0.0001*
ANA			
cytoplasmic granules	26	17	0.363
nuclear granules	33	28	1.000
nuclear homogenous	9	18	0.019*
centromere	1	2	0.593
Anti-dsDNA	11	15	0.197
Cirrhosis	23	21	0.856

Data were shown as mean ± SD and/or median (range).

AIH, autoimmune hepatitis; AITD, autoimmune thyroid disease. ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; ALP, alkaline phosphatase; IgG, immunoglobulin G; IgM, immunoglobulin M; γ-globulin, gamma globulin; ANA, antinuclear antibody; AMA, anti-mitochondrial antibody; AMA-M2, anti-mitochondrial antibody M2. *P<0.05.

Table 3 Comparison ofclinical features between PBC patients with and without AITD

	PBC(n=106)	PBC with AITD(n=31)	P-value
Male/Female	9/28	1/12	0.258
Age, year	55.19 ± 1.03	62.81 ± 1.62	0.0004*
Family history of AID	5	2	0.656
GGT(IU/L)	322.5(160.5~569.3)	314.0(123.0~552.0)	0.601
ALP(IU/L)	202.5(155.0~422.0)	266.0(122.0~496.0)	0.744
IgG(g/L)	15.4(12.2~18.0)	20.3(16..9~24.7)	<0.0001*
IgM(g/L)	3.1(1.8~4.4)	3.6(2.7~4.9)	0.115
γ-globulin(%)	21.3(17.9~25.7)	26.7(21.7~30.4)	0.0004*
ANA			
cytoplasmic granules	63	17	0.682
nuclear granules	13	2	0.520
centromere	18	6	0.790
AMA	63	18	1.000
AMA-M2	69	16	0.209
Anti-centromere antibody	21	7	0.801
Cirrhosis	36	13	0.523

Data were shown as mean ± SD and/or median (range).

PBC, primary biliary cholangitis; AITD, autoimmune thyroid disease. GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase; IgG, immunoglobulin G; IgM, immunoglobulin M; γ-globulin, gamma globulin; ANA, antinuclear antibody; AMA, anti-mitochondrial antibody; AMA-M2, anti-mitochondrial antibody M2. *P<0.05.

Table 4 Comparison of clinical features between AIH-PBC OS patients with and without AITD

	AIH-PBC OS(n=26)	AIH-PBC OS(n=17) +AITD	P-value
Male/Female	3/23	1/16	0.642
Age, year	57.38± 1.23	58.41 ±3.16	0.731
Family history of AID	2	3	0.369
ALT(IU/L)	122.0(51.3~300.8)	71.0(28.5~232.5)	0.243
AST(IU/L)	147.0(71.5~393.8)	104.0(36.5~192.0)	0.117
GGT(IU/L)	245.5(116.8~523.8)	231.0(143.55~433.0)	0.619
ALP(IU/L)	197.0(136.3~474.3)	187.0(129.0~252.0)	0.315
IgG(g/L)	18.6(15.7~21.9)	24.3(17.3~26.1)	0.035*
IgM(g/L)	2.2(1.5~4.4)	3.7(2.1~5.3)	0.129
γ-globulin(%)	25.8(19.4~29.0)	29.6(22.2~36.2)	0.081
ANA			
cytoplasmic granules	17	12	1.000
nuclear granules	7	4	1.000
centromere	4	2	1.000
AMA	15	11	0.755
AMA-M2	11	11	0.215
Cirrhosis	11	8	1.000

Data were shown as mean ± SD and/or median (range).

AIH-PBC OS, autoimmune hepatitis-primary biliary cholangitis overlap syndrome; AITD, autoimmune thyroid disease. ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase; IgG, immunoglobulin G; IgM, immunoglobulin M; γ-globulin, gamma globulin; ANA, antinuclear antibody; AMA, anti-mitochondrial antibody; AMA-M2, anti-mitochondrial antibody M2. *P<0.05.

Table 5 Comparison of immunological indicators between AILD patients with and without AITD

	AILD(n=211)	AILD+AITD(n=113)	P-value
Family history of AID	12	13	0.080
EHAID	32	24	0.170
IgG(g/L)	16.3(13.5~19.5)	21.5(17.5~26.1)	<0.0001*
γ-globulin(%)	21.9(18.9~26.4)	27.1(21.9~31.8)	<0.0001*
ANA			
cytoplasmic granules	106	46	0.104
nuclear granules	53	34	0.359
centromere	23	10	0.701

Data were shown as mean ± SD and/or median (range).

AILD, autoimmune liver disease; AITD, autoimmune thyroid disease; AID, autoimmune disease; EHAID, extrahepatic autoimmune disease. IgG, immunoglobulin G; γ-globulin, gamma globulin; ANA, antinuclear antibody. *P<0.05.

Table 6 Correlation between IgG and thyroid antibodies in AILD with concurrent AITD

Thyroid antibody	r-value	P-value
TGAb(IU/mL)	0.396	<0.0001*
TPOAb(IU/mL)	0.322	0.002*

AILD, autoimmune liver disease; AITD, autoimmune thyroid disease; TGAb; thyroglobulin antibody; TPOAb, thyroid peroxidase antibody.*P<0.05.

Table 7 Thyroid manifestation in AILD with concurrent AITD

	AIH, n=65	PBC, n=31	AIH-PBC OS,n=17	P-value
AITD				
HT	42	20	12	0.891
GD	17	5	3	0.438
Other	6	6	2	0.371
Thyroid antibody positivity				
TGAb	45	20	13	0.717
TPOAb	39	26	9	0.035*
TSH				
>4.20 uIU/mL	27	10	10	0.203
<0.27 uIU/mL	4	2	1	1.000
Ultrasounds				
Nodule	14	4	2	0.538
Diffuse lesion	32	15	13	0.125
Time of onset of AITD				
Previous	7	5	2	0.788
Posterior or simultaneous	58	26	15	0.788

AIH, autoimmune hepatitis; PBC, primary biliary cholangitis; AIH-PBC OS, autoimmune hepatitis-primary biliary cholangitis overlap syndrome; AILD, autoimmune liver disease; AITD, autoimmune thyroid disease; HT, Hashimoto's thyroiditis; GD, Graves' disease;TGAb, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody; TSH, thyroid stimulating hormone. *P<0.05.

Figures

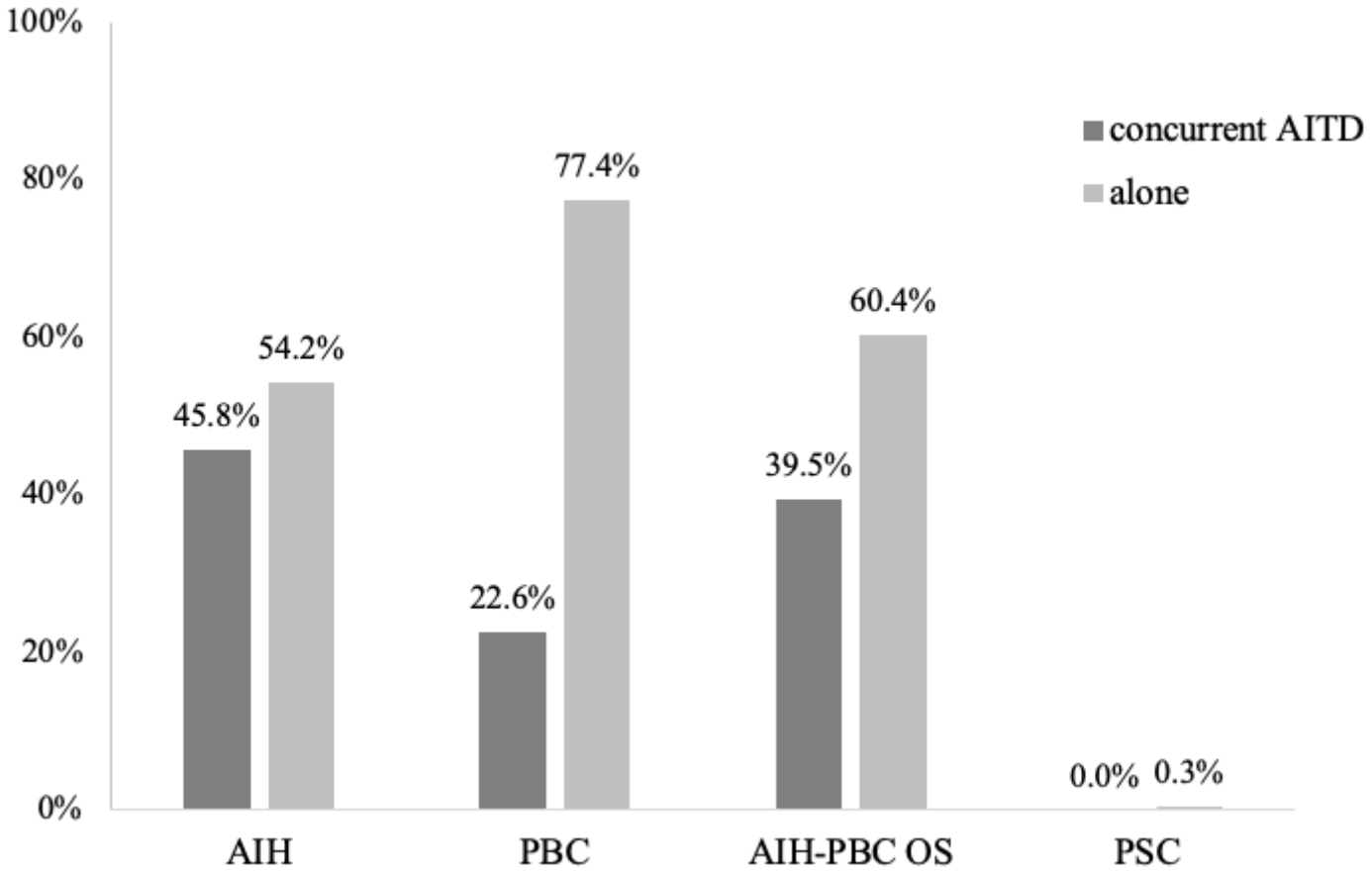

Figure 1

Frequency of AITD in AILD patients.AIH, autoimmune hepatitis; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; AIH-PBC OS, autoimmune hepatitis-primary biliary cholangitis overlap syndrome; AITD, autoimmune thyroid disease.