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Autoimmune disease and risk of lymphoma: analysis from real-world data and Mendelian randomization study

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Abstract

Background Autoimmune diseases (AIDs) appear to be the primary predisposing factors for lymphoma. This study aims to investigate the causal effects between AIDs and lymphomagenesis.

Methods A two-sample Mendelian randomization (MR) framework was employed to estimate the causal effect through UK Biobank (UKB) and FinnGen cohorts. Patients with histories of AIDs and diagnosed with lymphoma were enrolled in real-world studies.

Results MR analysis investigated the potential causal effect of AIDs on the risks of lymphoma [odd ratio (OR) = 1.001, 95% confidence interval (CI) = 1.000-1.002, $p = 0.040$]. In our real-world data, there are no significantly increased risks for lymphoma when analyzing ORs for the history of rheumatoid arthritis (RA) and psoriasis (PsO) (OR 1.027, 95% CI = 0.516–2.04 for RA, and OR 1.022, 95% CI = 0.442–2.365 for PsO). The serum albumin (ALB) and sialic acid (SA) levels were independent prognostic factors for both progression-free survival (PFS) and overall survival (OS) in AIDs-associated lymphoma (AAL) patients.

Conclusions Our results confirmed the causal relationships between AIDs and risks of lymphoma. Serum ALB and SA levels have demonstrated a vital influence on outcomes of AAL patients, in which the IL-17 pathway might play an active role.

Keywords Autoimmune disease, Lymphoma, Mendelian randomization, Genome-wide association studies, Clinical characteristics, Prognosis

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Introduction

The dysregulation of B cell development is a well-established phenomenon in specific forms of immunodeficiency, leukemia/lymphoma, and autoimmune diseases (AIDs) [1]. Among them, lymphoma, consisting of Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL), ranks among the top ten most prevalent cancers globally [2]. Lymphoma exhibits diverse clinical and morphological presentations, with etiological factors varying across its subtypes. Despite extensive research spanning several decades, a comprehensive comprehension of the underlying causes of lymphoma remains elusive. Also,

immunosuppressive conditions including human immunodeficiency virus (HIV) infection and autoimmune diseases have emerged as significant risk factors for lymphoma [3, 4]. In the context of active AID, antigen stimulation and chronic inflammation promote the clonal expansion of B and T cells, thereby elevating the risk of accumulating multiple genetic events and potentially resulting in lymphoma [5]. According to previous investigations, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and idiopathic thrombocytopenic purpura (ITP) are associated with heightened lymphoma risks [6–12]. Various factors influence the hazard, including AID types, immunosuppressant applications, and inflammation [12–14]. Previous studies have established a correlation between autoimmune conditions, specifically those mediated by B or T-cell responses, and lymphoma subtypes [15–17].

However, the specific mechanisms through which AIDs affect lymphoma risks remain ambiguous. It is reported that genetic variants associated with the immune system may contribute to NHL progression and AIDs. A range of genetic polymorphisms could induce impaired lymphocyte regulation or a decreased activation threshold [18]. Wang et al. conducted a study to investigate the impact of single nucleotide polymorphisms (SNPs) of cytokines on the development of lymphomas in individuals with AIDs [19]. Their findings suggested that the autoimmune conditions mediated by B cells may contribute to an increased susceptibility to NHL. Whereas, the meta and retrospective analyses were conducted only involved case-control and cohort studies, making them vulnerable to several biases that hinder the evaluation of causal relationships. Mendelian randomization (MR) is an epidemiological approach used to infer causal links from observational data, similar to randomized controlled trial, which has emerged as a preferred method for gene-level research to investigate causal links in complex diseases. In this study, we utilized Genome-wide association studies (GWAS) data to clarify the genetic links between AIDs and lymphoma using the MR method and real-world data, offering new perspectives on the pathogenesis of AID-associated lymphoma (AAL).

Materials and methods

Study design

The MR research was conducted under Epidemiology-MR (STROBE-MR) guidelines. The STROBE-MR checklist is included as a supplementary file 2. The MR model is shown in Fig. 1. The GWAS data on lymphoma cases and control samples were obtained from the UK Biobank (UKB), with 1,752 cases and 359,442 controls [20]. The summary statistics for AIDs were obtained from a recently published GWAS, with 42,202 European AID cases and 176,590 control cases [21].

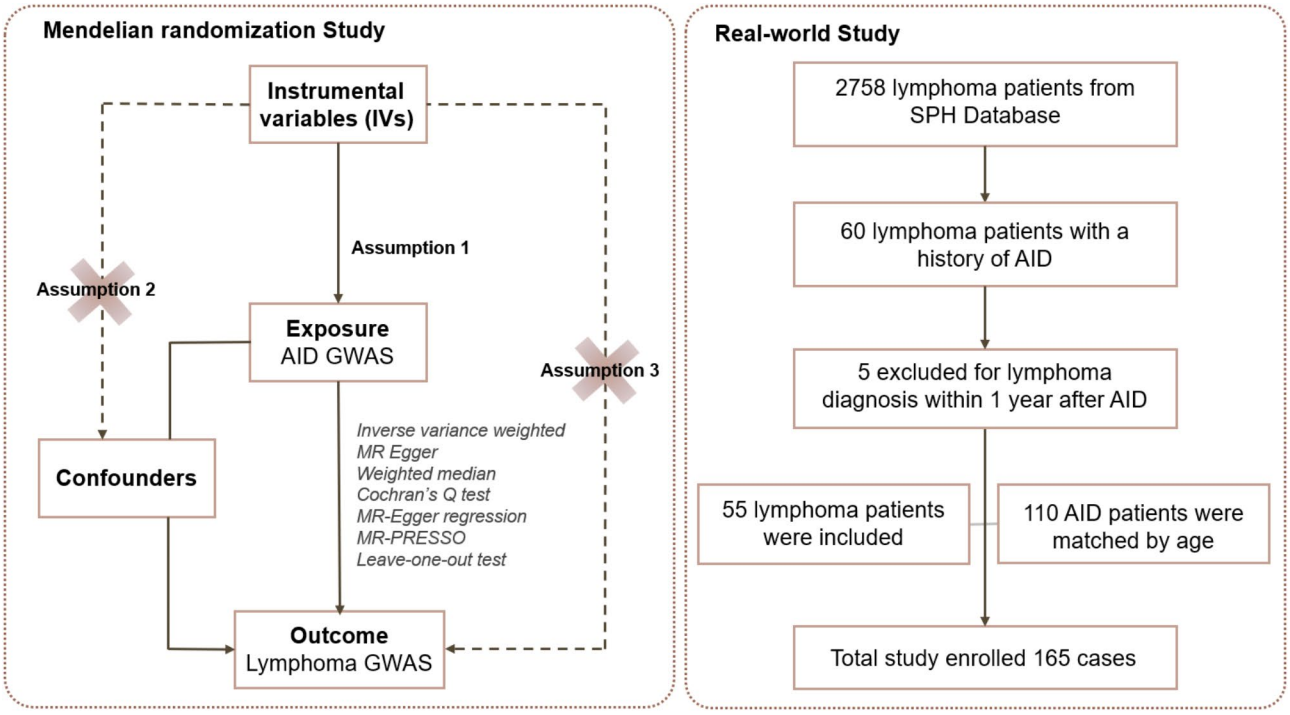

Fig. 1 Flow chart of the study. In an MR study, instrumental variables (IVs) need to satisfy three main assumptions: (1) they must be associated with the exposure (relevance assumption), (2) IVs should not be linked with confounding variables (independence assumption) and (3) IVs should affect the result solely through the exposure (the exclusion restriction assumption) [51]. MR, Mendelian randomization; AID, autoimmune disease; GWAS, Genome-wide association studies; SPH, Shandong Provincial Hospital

A two-sample MR approach was implemented to investigate the potential causal effect of AIDs on lymphoma. Genetic variants that reached the genome-wide significance ($p < 5 \times 10^{-8}$) were selected as instrumental variables (IVs). IVs were grouped based on linkage disequilibrium (LD, $r^2 = 0.001$) and genomic region (clump window 10,000 kilobases). To evaluate the correlation strength and avoid bias caused by weak IVs, we calculated F-statistic (< 10) [22]. Using a two-sample design, we conducted a harmonization process on the SNPs-exposure and SNPs-outcome datasets to exclude palindromic SNPs by comparing the allele frequencies. After the steps mentioned above, the remaining SNPs were eventually employed as genetic instruments.

Mendelian randomization and sensitivity analysis

To assess the causal relationship between AIDs and lymphoma, we employed various statistical methods including the conventional inverse-variance weighted (IVW) method, the MR-Egger regression method, the weighted median estimator, and the weighted mode method. The risks of lymphoma were quantified using an odds ratio (OR) with a 95% confidence interval (CI) per unit increase in the logarithm of odds of AID. For each SNP, heterogeneity was assessed using Cochran's Q test [23]. The pleiotropy of the genetic instruments was evaluated through PhenoScanner. Leave-one-out analysis was conducted to examine the impact of SNP outliers for analyzing sensitivity. Statistical analysis was conducted using a Two-sample MR R package.

Patient selection

The data set for this study consisted of patients diagnosed with lymphoma at Shandong Provincial Hospital (SPH) from Jan 1st, 2010 to May 1st, 2022. Patients concluded met the following inclusion criteria: (1) Patients were histopathologically confirmed as lymphoma by at least two independent pathologists, and (2) they had a history of autoimmune disorders and sufficient available clinical information. AIDs were diagnosed and classified by using international diagnostic criteria for each AID type, supported by their previous medical materials. The exclusion criteria were as follows: (1) Patients with an autoimmune disorder-free interval of less than 1 year since their lymphoma diagnosis, as the presence of autoimmune phenomena related to incipient lymphoma could not be ruled out, and (2) patients with a previous history of malignancy. Since the first AAL patient was diagnosed in 2012. Controls were selected at random from individuals diagnosed with AIDs at SPH since 2012, completing a minimum of one year of follow-up. All AID patients received comprehensive evaluations, including medical history reviews and physical exams focusing on lymphoma-related symptoms like lymphadenopathy, fever, and weight loss. Suspected cases underwent imaging, and biopsies were performed if lymphadenopathy or other abnormalities were found. For each lymphoma case, a lymphoma-free AID individual was identified as a control, ensuring they were alive and had not been diagnosed with lymphoma at the time the match cases were diagnosed. Age was used as a matching criterion, with cases and controls matched based on age at lymphoma diagnosis for cases and age at the last follow-up for controls. Informed consent was obtained from all patients on their first visit, and the study received approval from the Medical Ethical Committee of Shandong Provincial Hospital. This study adhered to the principles outlined in the Declaration of Helsinki.

We retrospectively gathered clinical and demographic data from electronic medical records of the SPH database, encompassing information such as demographics, baseline characteristics, laboratory results, image examination, bone marrow tests, and treatment outcomes. All patients were subject to regular follow-up visits. We documented treatments administered to patients before lymphoma diagnosis, as well as during the AID course.

Statistical analysis of the observational study

Baseline characteristics of the case and control cohorts were compared, utilizing frequencies and percentages to summarize categorical variables and medians and interquartile ranges (IQRs) to summarize continuous variables. Demographic and individual baseline clinical characteristics of the case and control cohorts were compared by using Pearson's chi-square test for categorical variables and the Mann-Whitney U test for continuous variables. Logistic regression was conducted to calculate the ORs and 95% CIs for the cases and their matched controls. The primary endpoint was overall survival (OS), determined from the diagnosis date to the date of death or censoring. The secondary endpoint was progression-free survival (PFS) and was measured from the diagnosis date to disease progression, death, or censoring. PFS and OS of AAL patients were described by Kaplan-Meier estimates and compared using the log-rank tests. Prognostic variables were identified using univariate and multivariate Cox Proportional Hazards (Cox) regression analysis. The Youden index was used to determine optimal cut-off values of serum ALB and SA levels for receiver operating characteristic (ROC) curves. A two-sided $P < 0.05$ was considered statistically significant. All statistical analysis was carried out using SPSS 22.0 software and the R software.

Gene expression analysis

Gene expression profiling data from microarray datasets GSE32018, GSE20874, and GSE13996 were utilized, with RNA normalization performed using log2

transformation. Probes were converted to homologous gene symbols based on platform annotation information. Probes that matched multiple genes were excluded, and the average expression values were calculated for genes corresponding with numerous probes. Principal component analysis (PCA) was employed as an initial quality control measure.

Results

MR analysis of causal effects of AID on lymphoma

In the MR study, we utilized 36 AID-related SNPs and found strong evidence suggesting a potential causal effect of AID on lymphoma risk (OR = 1.001, 95% CI = 1.000-1.002, $p = 0.040$). Additionally, we obtained similar risk estimates through the MR-Egger regression and weighted median approaches (Table 1). Although heterogeneity was observed, as indicated by a Cochran Q-test derived p of 0.002 for MR-Egger and p of 0.001 for IVW, we deemed it acceptable given the consistency of the MR estimates from MR-Egger and IVW. The slopes of the MR regressions and causal estimates correlated to each SNP are depicted in Fig. 2a-b. What's more, based on the leave-one-out sensitivity analysis, it was determined that no individual single SNP strongly disrupted the overall effect of AID on lymphoma (Fig. 2c). The symmetric funnel plot indicated the absence of either unbalanced horizontal pleiotropy or evident heterogeneity (Fig. 2d).

Moreover, we examined the association between single AID and lymphoma using multivariable MR (MVMR) analysis. It was found that the only potential causal effect of Sjögren's syndrome (SS) on risks of lymphoma was detected (OR = 1.002, 95% CI = 1.001–1.002, $p < 0.01$). The same direction of association was obtained using other MR estimators. A Cochran Q-test derived p value was 0.056 of IVW and 0.063 of MR-Egger, showing no heterogeneity. Other sensitivity analyses suggested that these effects were robust to various MR assumptions.

Clinical characteristics of AAL patients in SPH

In our observational study, a total of 55 cases of HL and NHL were collected from SPH and matched with 110 randomly selected controls. The flowchart illustrating the study design can be found in Fig. 1, while the characteristics of the study participants are presented in Table 2. The distribution of patients based on AID and lymphoma subtypes is visualized using a heatmap (Fig. 3). The median age at AID was 40 years (range, 5–80 years), while the median age of lymphoma diagnosis was 60 years (range, 11–81 years). The clinical progression from AIDs to lymphoma exhibited significant variability, with a median duration of 10 years (range, 1–40 years). A female predominance was observed (52.7%, $n = 29$). Patients with a history of RA accounted for 32.73% ($n = 18$) of the cases, followed by psoriasis (PsO) (16.36%, $n = 9$).

Among ALL patients, the most prevalent subtype was NHL (81.82%, $n = 45$), with 15 patients diagnosed with diffuse large B-cell lymphoma (DLBCL), which was compatible with the previous literature [18]. In DLBCL patients, a more precise diagnosis was available for 8 individuals, with 7 classified as germinal center B cell type (GCB) type and 1 as non-GCB type. Based on incomplete immunohistochemical results, CD20 expression was detected in 23 of 28 patients (82.1%). A total of 11 cases (20.0%) exhibited a Ki67 index below 60%, while 15 patients (27.3%) had a Ki67 index equal to or exceeding 60%. Additional details were provided in Supplemental Table 1.

In our research, 49 individuals were newly diagnosed, with a median follow-up duration of 49.5 months. Throughout the observation period, 14 out of 40 cases succumbed to the disease (excluding 9 cases due to lost follow-up). The one-, three-, and five-year OS rates were determined to be 72.5%, 45%, and 22.5%, respectively. The majority of cases (85.71%, $n = 42$) had an Eastern Cooperative Oncology Group (ECOG) score ranging from 0 to 1. While the baseline ECOG score was 2–3 in 7 patients, with none scoring 4. Lymph node involvement was observed in 13 patients (26.53%), and extranodal involvement was detected in 36 patients (73.47%), with 19 of them exhibiting marrow infiltration. Additionally, 6 cases (12.2%) exhibited more than one instance of extranodal invasion. It is noteworthy to mention that the primary origin of nodal/extranodal involvement was not influenced by factors such as sex, ECOG status, age at lymphoma, disease duration, PFS, or OS, as depicted in Table 3.

Clinical risk factors of AAL

There were no significant differences observed between AAL patients and controls in terms of sex ($p = 0.373$), age at onset of AID ($p = 0.514$), age of matching time ($p = 0.805$) or duration of AID ($p = 0.401$) (Supplemental Table 2). The cohorts generated through the matching process were found to be balanced. It is worth noting that 21 cases of lymphoma were diagnosed more than 20 years after the onset of the disease. The power analysis

Table 1 MR analysis for the causality of AID with the risk of lymphoma

MR Methods	AID			
	OR	95% CI	*p*-value	B
MR Egger	1.002	1.000-1.003	0.018	0.002
Weight median	1.001	1.000-1.002	0.152	0.001
IVW	1.001	1.000-1.002	0.04	0.001

MR: Mendelian randomization; AID, autoimmune disease; IVW: inverse-variance weighted; OR: odds ratio; 95% CI: 95% confidence interval

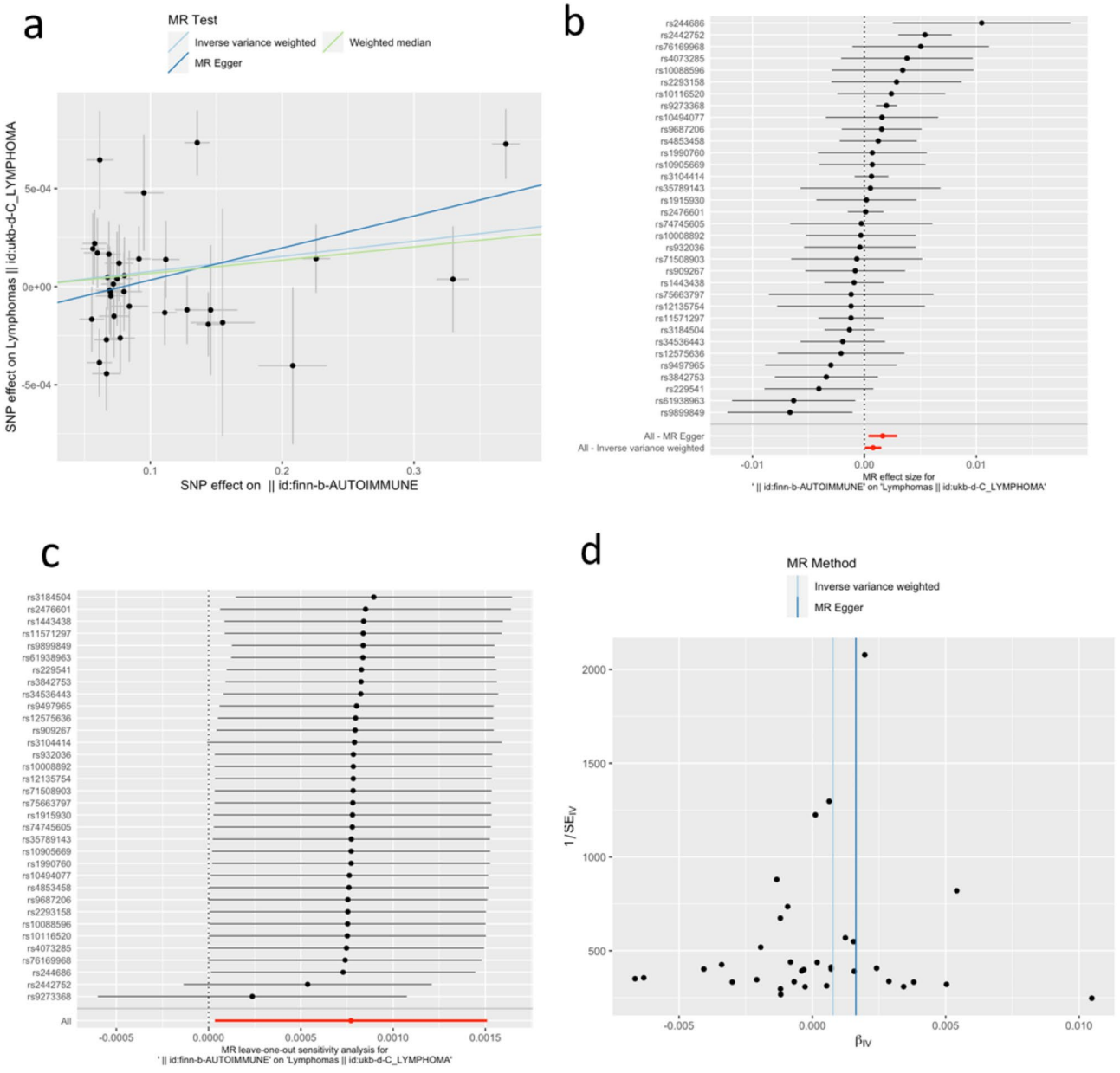

Fig. 2 Scatter plot (**a**), forest plot (**b**), leave-one-out (**c**) and funnel plot (**d**) of SNPs associated with AID and their risks of lymphoma. SNP, single nucleotide polymorphism; AID, autoimmune disease

was conducted to evaluate whether the sample size is sufficient to detect the hypothesized effect (>0.9). Univariate analysis indicated that factors such as sex, type of AID, age at AID/lymphoma, and disease duration were not associated with an increased risk of lymphoma. Furthermore, the assessment of ORs for the history of RA and PsO did not reveal any significantly elevated risks for lymphoma (OR 1.027, 95% CI = 0.516–2.045 for RA, and OR 1.022, 95% CI = 0.442–2.365 for PsO).

Survival risk factors of AAL

We collected data on levels of inflammatory markers and metabolites at the time of lymphoma diagnosis. Through univariate and multivariate Cox regression analysis, we determined that the serum albumin (ALB) and sialic acid (SA) levels were independent prognostic factors for both PFS and OS ($p < 0.05$). Using ROC curves, we identified ALB of 36 g/L and SA of 747 mg/L as the optimal cutoff points for survival analysis, with respective AUC values of 0.750 (95% CI 0.583–0.917, $p = 0.01$) and 0.697 (95% CI 0.525–0.870, $p = 0.043$), respectively (Supplemental

Table 2 Baseline characteristics of cases

	Cases (*n* = 55)
Sex	
Male	26 (47.3)
Female	29 (52.7)
Age at AID diagnosis, years, median (range)	60 (11–81)
Age at lymphoma diagnosis, years, median (range)	40 (5–80)
Disease duration, years, median (range)	10 (1–40)
AID	
RA	18 (32.7)
PsO	10 (18.2)
HSP	6 (10.9)
SS	3 (5.5)
AS	3 (5.5)
HT	3 (5.5)
Others	12 (21.8)

Data are n (%) unless otherwise stated. AID: autoimmune disease; RA: rheumatoid arthritis; PsO: psoriasis; HSP: Henoch-Schönlein purpura; SS: Sjögren's syndrome; AS: ankylosing spondylitis; HT: hashimoto's thyroiditis; Others including ITP: immune thrombocytopenia; SLE: systemic lupus erythematosus; sarcoidosis; ENL: erythema nodosum leprosum; gout; SSc: systemic sclerosis; MG: myasthenia gravis; AIHA: autoimmune hemolytic anemia: UC: ulcerative colitis; DM: dermatomyositis

Table 3 Baseline characteristics between patients with intranodal and extranodal involvement.

	Intranodal involvement (*n* = 13)	Extranodal involvement (*n* = 36)	*P*
Age, years, median (range)	49 (11–81)	58.5 (11–76)	0.489
Age, years			0.947
< 60	7 (53.9)	19 (52.8)	
≥ 60	6 (46.2)	17 (47.2)	
Sex			0.06
Male	9 (69.2)	14 (38.9)	
Female	4 (30.8)	22 (61.1)	
ECOG performance status			0.363
0 or 1	10 (76.9)	32 (88.9)	
≥ 2	3 (23.1)	4 (11.1)	
Disease duration, years, median (range)	10 (1–40)	10 (1–40)	
Status			0.702
Alive	7 (53.9)	19 (52.8)	0.887
Dead	3 (23.1)	11 (30.1)	
Losing follow-up	3 (23.1)	6 (16.7)	
PFS, months, median (range)	39 (1-115)	26 (0-113)	0.843
OS, months, median (range)	34.5 (1-115)	30 (0-113)	0.815

Data are n (%) unless otherwise stated. ECOG: Eastern Cooperative Oncology Group; PFS: progression-free survival; OS: overall survival

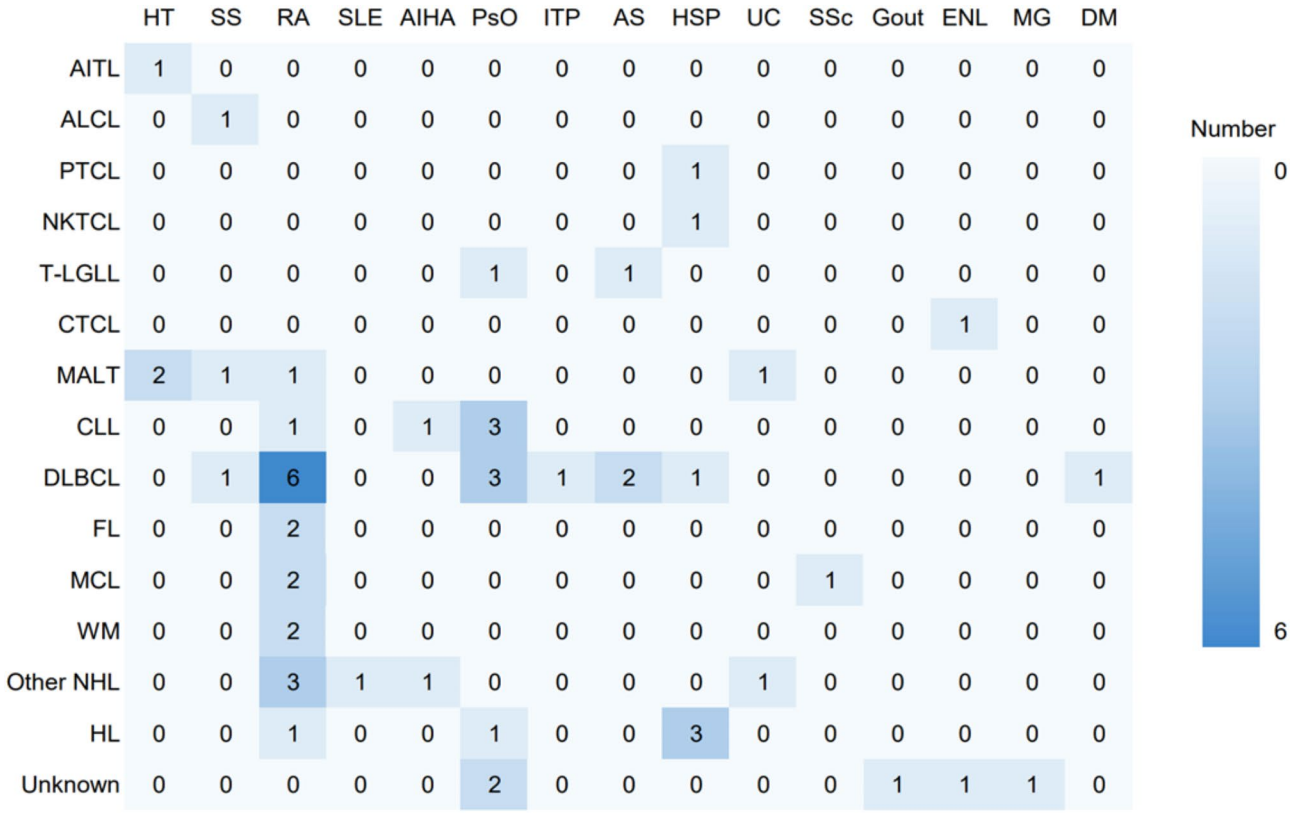

Fig. 3 Heatmaps of the patients with AID associated lymphoma (*n* = 55). AID, autoimmune disease; HT, Hashimoto's thyroiditis; SS, Sjögren's syndrome; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; AIHA, autoimmune hemolytic anemia; PsO, psoriasis; ITP, immune thrombocytopenia; AS, ankylosing spondylitis; HSP, Henoch-Schönlein purpura; UC, UC, ulcerative colitis; SSc, systemic sclerosis; ENL, erythema nodosum leprosum; MG, myasthenia gravis; DM dermatomyositis

Fig. 1). The clinical indicators corresponding to different levels of ALB and SA are presented in Table 4.

Patients who exhibited decreases in ALB levels (< 36 g/L) demonstrated unfavorable pre-treatment indicators, such as elevated levels of lymphocyte-to-monocyte ratio (LMR) ($p = 0.019$), beta-2-microglobulin (β2-MG) ($p = 0.022$) and lactate dehydrogenase (LDH) ($p = 0.002$). Conversely, there was no correlation between serum SA levels and these aforementioned factors. Subsequent survival analyses indicated that patients with lower ALB levels experienced significantly worse PFS ($p = 0.0024$) and OS ($p < 0.001$) outcomes (Fig. 4a-b). Furthermore, patients with higher SA levels (≥ 747 mg/L) exhibited poorer PFS ($p = 0.0339$) and OS ($p = 0.0093$) outcomes (Fig. 4c-d).

Analysis of differentially expressed genes of lymphoma in GEO database

Previous studies suggested that interleukin (IL)-2, IL-5, IL-6, IL-10, and tumor necrosis factor (TNF)-α, NOTCH, FAS and MHC receptor families are the proposed mechanisms for the association between AIDs and lymphoma [24]. The effect of SNPs on cytokines was reported in the progression of lymphomas in concurrence with AIDs [19]. To gain a deeper understanding, we identified 107 differentially expressed genes (DEGs) between HL, T-NHL, and B-NHL patients and healthy controls using the GEO database (Fig. 5a). Subsequently, we performed Gene Ontology (GO) and Kyoto Encyclopaedia of Genes and Genomes (KEGG) analyses on the upregulated DEGs to comprehensively investigate their biological functions. The analysis annotations indicated a strong association

Table 4 Correlation between ALB as well as SA and clinical characteristics of lymphoma patients with a history of AID

Variables	ALB < 36 g/L	ALB ≥ 36 g/L		SA < 747 mg/L	SA ≥ 747 mg/L	
	(*n* = 19)	(*n* = 29)	*P*	(*n* = 31)	(*n* = 17)	*P*
Sex			0.263			0.606
Male	11 (54.9)	12 (41.4)		14 (45.2)	9 (52.9)	
Female	8 (62.1)	17 (58.6)		17 (54.8)	8 (47.1)	
ECOG score			0.097			0.686
0 or 1	14 (73.7)	27 (93.1)		27 (87.1)	14 (82.4)	
≥ 2	5 (26.3)	2 (6.9)		4 (12.9)	3 (17.6)	
Extranodal involvement			0.571			0.077
Absence	6 (31.6)	7 (24.1)		11 (35.5)	1 (11.8)	
Presence	13 (68.4)	22 (75.9)		20 (64.5)	15 (88.2)	
Age			0.863			0.464
< 60	10 (52.6)	16 (55.2)		18 (58.1)	8 (47.1)	
≥ 60	9 (47.4)	13 (44.8)		13 (41.9)	9 (52.9)	
Disease duration			0.272			0.772
< 10 years	6 (31.6)	12 (48.0)		11 (39.3)	7 (43.8)	
≥ 10 years	13 (68.4)	13 (52.0)		17 (60.7)	9 (56.3)	
Chemotherapy			**0.039**			0.131
Yes	6 (31.6)	18 (62.1)		18 (58.1)	6 (35.3)	
No	13 (68.4)	11 (37.9)		13 (41.9)	11 (64.7)	
LMR			**0.019**			0.135
< 0.7	4 (22.2)	0 (0.0)		1 (3.4)	3 (17.6)	
≥ 0.7	14 (77.8)	28 (100.0)		28 (96.9)	14 (82.4)	
NLR			0.79			0.989
< 2	7 (38.9)	12 (42.9)		12 (41.4)	7 (41.2)	
≥ 2	11 (61.1)	16 (57.1)		17 (58.6)	10 (58.8)	
PLR			0.115			0.056
< 138	12 (66.7)	12 (42.9)		12 (41.4)	12 (70.6)	
≥ 138	6 (33.3)	16 (57.1)		17 (58.6)	7 (29.4)	
β2-MG			**0.022**			0.67
< 3.8 mg/L	9 (47.4)	23 (79.3)		20 (64.5)	12 (70.6)	
≥ 3.8 mg/L	10 (52.6)	6 (20.7)		11 (35.5)	5 (29.4)	
LDH			**0.002**			0.912
< 220U/L	1 (6.7)	13 (56.5)		9 (37.5)	5 (35.7)	
≥ 220U/L	14 (93.3)	10 (43.5)		15 (62.5)	9 (64.3)	

Data are n (%) unless otherwise stated. ALB: albumin; SA: sialic acid; LMR: lymphocyte-monocyte ratio; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-lymphocyte ratio

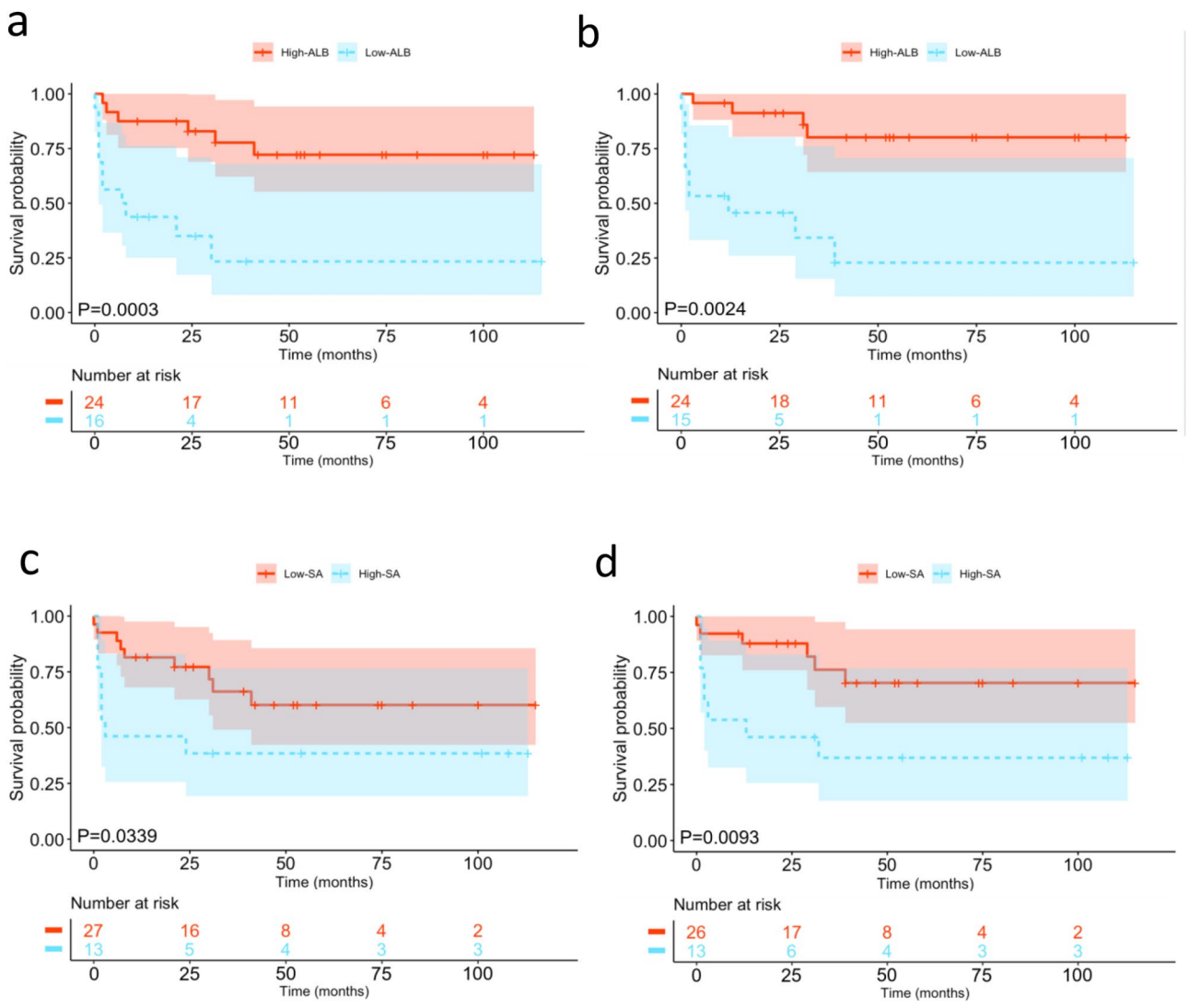

Fig. 4 PFS (**a**) and OS (**b**) according to the serum ALB level in AAL patients. PFS (**c**) and OS (**d**) according to the serum SA level in AAL patients

between the DEGs and various immune responses and cell death processes (Fig. 5b). Moreover, enrichment results highlighted the significance of pathways represented by IL-17, Estrogen, and TNF signaling pathways of apparent significance (Fig. 5c). The top 60 hub prognostic genes of the protein-protein interaction (PPI) network were identified and visualized (Fig. 5d). Certain genes, such as IL1B and chemokine c-c motif chemokine ligand 20 (CCL20), ranked highly in the network, indicating their significance as downstream signaling molecules in the IL-17 pathway.

Discussion

A recent large-scale prospective cohort study revealed that lymphoma had the most widespread links with various immune-mediated diseases among all cancers [25]. Epidemiological studies have consistently demonstrated an elevated risk of lymphoma in individuals with specific autoimmune/inflammatory conditions across diverse cohorts from various countries [5]. In a significant nested case-control study of over 44,000 lymphoid malignancy cases, it was reported that several autoimmune diseases were linked to an increased risk of NHL [11]. A comprehensive retrospective study conducted in China revealed a significant association between a history of RA and event-free survival (EFS) in patients with mantle cell lymphoma (MCL) and HL [26]. Despite the acknowledgment of the longstanding association between AIDs and lymphoma, the comprehensive understanding of the underlying mechanism and clinical characteristics of AAL patients remains limited.

Meanwhile, figuring out the mechanism can potentially elucidate the disparate prognostic outcomes. The presence of SNP in cytokines' genes could explain the association between AIDs and lymphoma [19]. Studies in epidemiology have looked into the co-localization

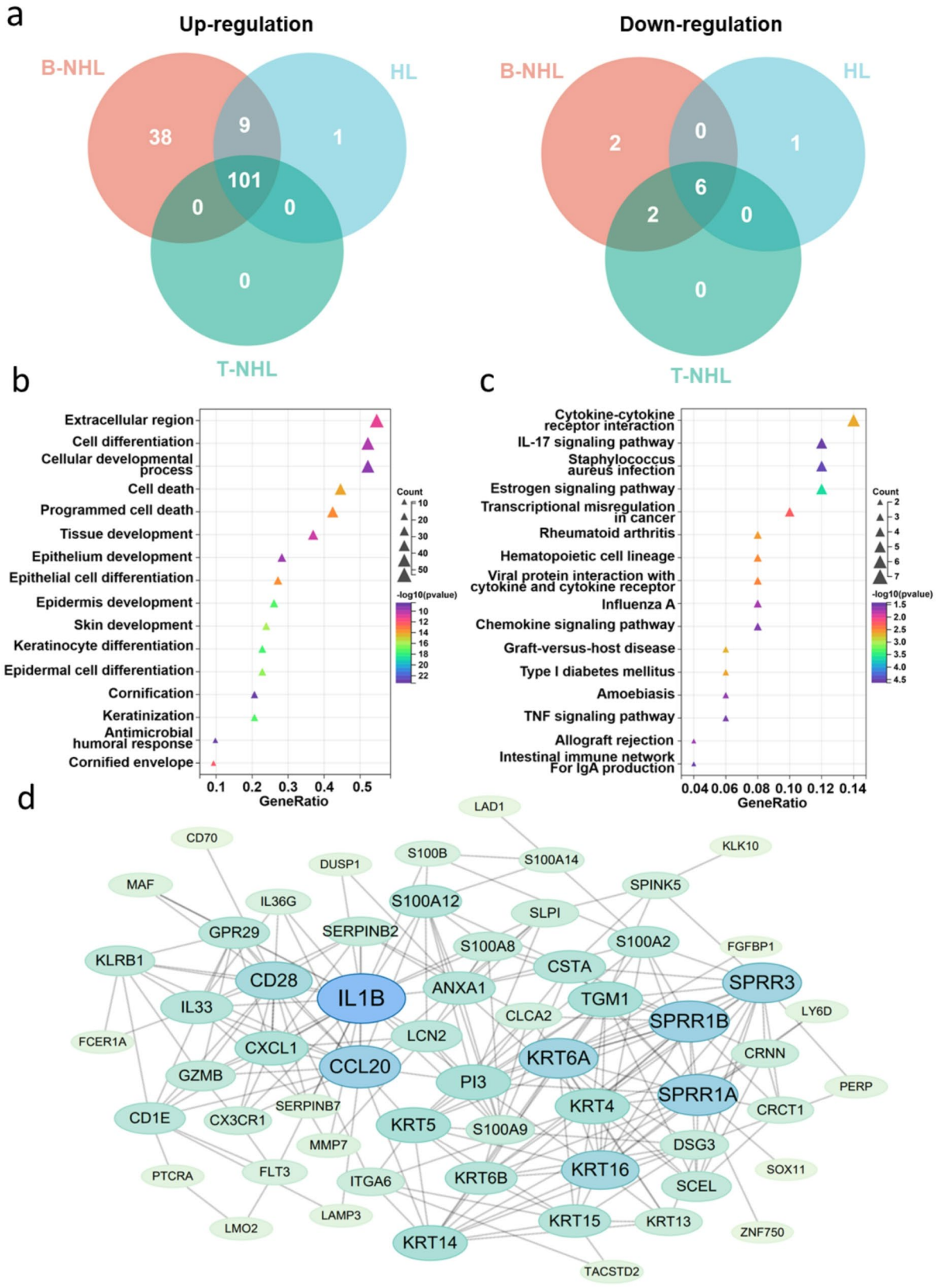

Fig. 5 (**a**) Venn diagram showing DEGs between HL, T-NHL, B-NHL and healthy control (HC) according to GSE32018, GSE20874 and GSE13996. (**b**) GO analysis of upregulated DEGs. (**c**) KEGG pathway of upregulated DEGs. (**d**) PPI network of top 60 hub prognostic genes

of susceptibility alleles in the MHC for NHL and AIDs, hinting at shared risk loci [11, 17]. Here, we focused on the association between AIDs and lymphoma using SNP as IV at the genetic level. The MR results revealed that AIDs were causally associated with lymphoma. Next, our investigation focused on the influence of AIDs-associated fundamental signatures on lymphoma. The findings are supported in part by other studies, which demonstrated that factors including sex, type of AIDs, age at AIDs/lymphoma, and disease duration were not identified as risk factors for lymphoma. While no overall association between any specific AID and lymphoma risk was found, patients with a history of RA or PsO showed a higher likelihood of developing lymphomas, consistent with prior reports [27, 28]. However, due to the low incidence, our study did not analyze the relationship between lymphoma and SS, despite multiple evidence reporting their relationships [29, 30]. Besides, the risk of SLE-associated lymphoma was previously shown to be significantly elevated, with a fold increase of more than four [31].

The prognostic implications of AIDs on lymphoma have been a subject of controversy. Simard et al. demonstrated a significant association between AIDs and mortality in patients with NHL [hazard ratios (HR) = 1.4, 1.0-1.8] [32]. In contrast, a study utilizing the Surveillance, Epidemiology, and End Results (SEER) database found no significant differences in survival patterns between patients with a history of AIDs and those without in the context of DLBCL [33]. What's more, data from the University of Iowa/Mayo Clinic Molecular Epidemiology Resource indicated that a history of immunosuppression did not impact subsequent prognosis in any lymphoma subtype [16, 34]. Otherwise, treatment for lymphoma is the same regardless of AIDs. Clinicians should be aware that patients with AAL might need more tailored therapeutic approaches based on genetic and molecular analysis, expecting a better OS. As a result, we analyzed the outcomes of AAL patients and identified risk factors that affect prognosis, which involved the examination of inflammatory markers and metabolites. It was determined that serum ALB and SA levels were closely related to the prognosis. Subgroup analysis revealed that patients with lower serum ALB levels tended to have poorer PFS and OS. Oppositely, patients with lower serum SA levels exhibited better PFS and OS. These findings highlighted the prognostic value of serum ALB and SA levels in AAL patients.

The continuous growth of B cells due to antigens may increase the risk of harmful genetic changes, leading to a neoplastic clone. Resistance to apoptosis in autoimmune diseases like RA and SLE, influenced by Bcl-2 expression and factors like nuclear factor-κB, can worsen these effects [35, 36]. Elevated B-cell activating factor (BAFF), also known as B-lymphocyte stimulator (BLyS) [37], crucial for B-cell development and antibody responses, may lead to harmful B-cell activation in autoimmune disorders and lymphomas [38]. BAFF levels are higher in those with SS, RA, and SLE, correlating with disease-specific autoantibodies in SS and rising in lymphoma patients regardless of autoimmunity [39, 40]. BAFF-related mechanisms might link autoimmunity and lymphoma. Among other potentially significant cytokines, IL-6, IL-10, and TNF-α are noteworthy. IL-10 is involved in the production of autoantibodies and may function as an autocrine growth factor in B-cell lymphomas. Genetic variations in the TNF-α and IL-10 genes have been linked to up to a 2-fold increased risk of DLBCL [41]. Consequently, the systematic collection and detailed molecular analysis of materials from autoimmune patients who develop lymphomas, both retrospectively and prospectively, are crucial for identifying key pathogenetic events.

It has been proposed that the level of inflammation and severity of the autoimmune condition may contribute to an elevated risk of lymphoma development. The prolonged systemic inflammation could potentially trigger lymphoma formation [42]. Chronic activation of self-reactive B cells might be particularly significant for lymphoma development in organ-specific autoimmune diseases. For instance, in SS, marginal zone autoimmune B cells are activated within salivary glands and other mucosal sites specifically affected by the autoimmune process, leading to an increased incidence of mucosa-associated lymphoid tissue (MALT) lymphoma and other marginal-zone B-cell lymphomas [43, 44]. Whereas, the observed rise in DLBCL risk in SS might suggest an involvement of a systemic inflammatory component. Consequently, assessing the predictive capability of systemic inflammatory markers and autoreactive B cell markers for lymphoma will be important. Our study demonstrated the crucial role of the IL-17 pathway in lymphomagenesis as revealed through GO and KEGG analyses. IL-17 (IL-17A), which was initially detected in 1993 [45], has been established as an essential driver of inflammation over the past decade [46, 47]. Consequently, targeting the IL-17 signaling axis has emerged as a promising therapeutic approach for various AIDs [48–50].

We should acknowledge the potential limitations of this study. Further verification is necessary to corroborate these findings, and larger sample sizes are warranted to comprehensively understand the role of AIDs in the management of lymphoma patients. As this is a single-center study there is currently no other large-scale report on AID-related NHL from China. Moreover, the varied histological types of NHL make it hard to narrow our analysis to the influence of AIDs on a specific lymphoma subtype. Nevertheless, our study had the strength that the SPH data was well representative of the general

population with built-in quality assurance. Our findings were given a distinct ethnic and geographic baseline compared to Western countries, which warranted further exploration in China and Asia.

In conclusion, associations between AIDs and lymphoma were analyzed from a genetic perspective and real-world insights in this study. The results supported that AID patients were at increased risk of developing lymphoma. In our real-world study, the primary origin of nodal/extranodal involvement was not affected by factors such as sex, ECOG status, age at lymphoma, disease duration, PFS, or OS in patients with AAL. What's more, indicators including gender, type of AID, age at AID/lymphoma diagnosis, and disease duration have been confirmed to have no association with an increased risk of lymphoma. Notably, serum ALB and SA levels have demonstrated a vital influence on outcomes of AAL patients, in which the IL-17 pathway might play an active role.

Abbreviations

AAL	AIDs-associated lymphoma
AID	Autoimmune disease
ALB	Albumin
β2-MG	Beta-2-microglobulin
BAFF	B-cell activating factor
BLyS	B-lymphocyte stimulator
CCL20	Chemokine c-c motif chemokine ligand 20
CI	Confidence interval
Cox	Cox Proportional Hazards
DEG	Differentially expressed gene
DLBCL	Diffuse large B-cell lymphoma
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
GCB	Germinal center B cell type
GO	Gene Ontology
GWAS	Genome-wide association studies
HIV	Human immunodeficiency virus
HL	Hodgkin's lymphoma
HR	Hazard ratios
IL	Interleukin
IQR	Interquartile range
ITP	Idiopathic thrombocytopenic purpura
IV	Instrumental variable
IVW	Inverse-variance weighted
KEGG	Kyoto Encyclopaedia of Genes and Genomes
LD	Linkage disequilibrium
LDH	Lactate dehydrogenase
LMR	Lymphocyte-to-monocyte ratio
MALT	Mucosa-associated lymphoid tissue
MCL	Mantle cell lymphoma
MR	Mendelian randomization
MVMR	Multivariable MR
NHL	Non-Hodgkin's lymphoma
OR	Odd ratio
OS	Overall survival
PCA	Principal component analysis
PFS	Progression-free survival
PPI	Protein-protein interaction
PsO	Psoriasis
RA	Rheumatoid arthritis
ROC	Receiver operating characteristic
SA	Sialic acid
SEER	Surveillance, Epidemiology, and End Results
SLE	Systemic lupus erythematosus
SNP	Single nucleotide polymorphism
SPH	Shandong Provincial Hospital
SS	Sjögren's syndrome
TNF	Tumor necrosis factor
UKB	UK Biobank

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Author contributions

LZ, SC and YL designed this work. LZ and TL, collected the data. YL and ZY performed data analysis. LZ, XW and XZ drafted and revised the manuscript. All authors approved the final manuscript.

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Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Medical Ethical Committee of Shandong Provincial Hospital.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Clinical trial

Not applicable.

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