Annals of Hematology (2019) 98:445–455
https://doi.org/10.1007/s00277-018-3515-2

ORIGINAL ARTICLE

Autoimmune disease-associated non-Hodgkin's lymphoma—a large retrospective study from China

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Received: 5 May 2018 / Accepted: 4 October 2018 / Published online: 29 October 2018

Abstract

The incidence and clinical implications of autoimmune diseases (ADs) in patients with non-Hodgkin's lymphoma(NHL) remain unclear. The aim of this study was to examine the prevalence of ADs in NHL and define the clinical characteristics and prognosis of AD-associated NHL patients. Patients diagnosed with NHL in our institute between 1995 and 2017 were retrospectively reviewed to assess the incidence of ADs. Of 4880 patients with NHL, 140 (2.9%) presented with autoimmunity, with a total of 24 ADs. The most common AD was Sjögren syndrome, followed by autoimmune cytopenia, psoriasis, rheumatoid arthritis, etc. Psoriasis and rheumatoid arthritis were significantly associated with pre-existing ADs, whereas autoimmune cytopenia was significantly associated with secondary AD. Sjögren syndrome was significantly associated with B-cell lymphoma, and systemic vasculitis was significantly associated with T-cell lymphoma. Patients with AD-associated NHL had a high frequency of extranodal involvement(87%), with significant associations between specific extranodal sites of lymphoma and subtypes of ADs. Among patients with available data on pre-treatment peripheral blood Epstein-Barr virus (EBV) DNA($n = 68$), elevated EBV-DNA load was observed in a variety of NHL subtypes, including 20% of marginal zone lymphoma and 14.3% of follicular lymphoma patients. In a matched-pair analysis, survival did not differ significantly between NHL patients with and without ADs. However, for NHL patients with pre-existing ADs, a prior history of systemic corticosteroids therapy was significantly associated with worse survival (HR = 7.33, $P = 0.006$). Taken together, our data suggest that a broad spectrum of ADs is associated with NHL, and AD-associated NHL has distinct features with regard to clinical manifestations and prognosis.

Keywords Non-Hodgkin's lymphoma · Autoimmune disease · Prevalence · Clinical characteristics · Prognosis

Introduction

Non-Hodgkin's lymphoma (NHL) is a heterogeneous group of lymphoid neoplasms with variations in cellular origin, biological behavior, clinical manifestation, and prognosis. It is the eighth most commonly diagnosed malignancy worldwide [1]. In China, it was estimated that 882,000 patients were diagnosed with lymphoma in 2015 with NHL comprising the majority of cases [2].

The causes of NHL remain poorly understood, yet autoimmune disorders(ADs) have been increasingly identified as an important predisposing factor. Several large epidemiological studies from different countries have showed a consistent risk increase of lymphoma associated with certain ADs, such as Sjögren syndrome (SS), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), celiac disease, etc. [3–5]. Conversely, autoimmune conditions were also reported to occur during the course of lymphoma [6, 7], suggesting a bidirectional inter-relationship between autoimmunity and lymphoid neoplasms.

The biological mechanisms underpinning this bilateral relation between AD and lymphoma remain largely unknown.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00277-018-3515-2) contains supplementary material, which is available to authorized users.

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A number of AD-related risk factors have been linked to lymphoma development in the literature, with the prime example being disease severity and the degree of inflammatory activity [8]. It has been suggested that chronic inflammation and/or antigen stimulation in patients with active ADs could lead to the proliferation and clonal expansion of B or T cells, which in turn increased the risk of accumulating genetic events and ultimately resulted in the development of lymphoma [8]. Other proposed predisposing factors include the use of immunosuppressive agents [9, 10], genetic susceptibility [8], and environmental factors such as Epstein-Barr Virus (EBV) infection [11, 12], yet the evidence linking these factors to increased lymphoma risk was not as strong as that for chronic inflammation. In the case of autoimmunity developing during the course of lymphoma, the literature suggested that impaired cellular and humoral-mediated immunity that are often present in patients with lymphoma might promote the development of autoimmune alterations in this population [13].

In contrast to the substantial amount of work carried out to investigate the risk and pathophysiology of lymphoma development in patients diagnosed with ADs, there is limited data to describe the incidence and spectrum of ADs in patients diagnosed with lymphoma. The majority of literature on AD-associated lymphomas were case reports and small retrospective series, thus it is unsurprising that the prevalence and distribution of ADs in patients with lymphoma varied widely between different studies [14–17]. Furthermore, due to a lack of adequate data in the literature, the clinical manifestations and prognosis of the patients with NHL in association with various ADs remain largely unclear.

Given that there is no large Chinese series of AD-associated lymphoma reported in the literature, we conducted this single-center retrospective study to investigate the incidence and spectrum of ADs in Chinese patients with NHL, and to define the clinical characteristics and prognosis of these patients.

Methods

Patients

We retrospectively reviewed patients with NHL treated at our hospital between January 1995 and December 2017. Patients were considered eligible for analysis if they had pathologically confirmed diagnosis of NHL and a diagnosis of autoimmune disease.

We recorded data on the histological subtypes of NHL, characteristics and treatment of ADs, time between lymphoma and AD diagnosis, clinical parameters and treatment of NHL, and time to death or last follow-up. The histological diagnoses of NHL were established based on the 2008 WHO classification [18]. ADs were diagnosed and classified by using international diagnostic criteria for each AD type (1996 American College of Rheumatology criteria for SLE [19], 2010 European League Against Rheumatism criteria for rheumatoid arthritis [20], etc). The Ann Arbor Staging system and their Cotswold's modification were used for staging of NHL patients. Overall survival was calculated from the date of lymphoma diagnosis to the date of death or last follow-up. In order to investigate the prognostic impact of ADs on patients with NHL, we performed a matched-pair analysis: patients with AD-associated NHL were matched to those with NHL and without ADs treated during the same period at our hospital at ratio of 1:1 for each of the following factors: age, histology of lymphoma and first-line treatment. Data on the clinical characteristics and follow-up of patients in the matched cohort were also recorded as stated above.

Statistical analysis

Continuous variables were presented as mean ± SD or median (interquartile range), and compared by the one-way ANOVA test followed by post hoc Scheffe's test in cases of normal distribution and otherwise the non-parametrical Kruskal–Wallis test. Categorical variables were presented as numbers and percentages and compared by χ^2 or Fisher exact test as appropriate. Overall survival was estimated by Kaplan–Meier curves. Log-rank test and Cox regression methods were used to analyze time-to-event data. All tests were two-sided and $P < 0.05$ was considered statistically significant. Statistical analyses were carried out using the SPSS 19.0 Package.

Results

The incidence and spectrum of ADs in patients with NHL

Of 4880 patients with NHL, 140(2.9%) presented with autoimmune conditions, with a total of 24 ADs. The frequencies of each AD in our cohort of patients with NHL are detailed in Table 1. The most common AD was SS, followed by autoimmune cytopenia, psoriasis, RA, SLE, Hashimoto thyroiditis (HT), dermatomyositis/polymyositis (DM/PM), etc.

The temporal relations between ADs and NHL

The diagnosis of AD was prior to the diagnosis of lymphoma in 65% of patients, concomitant with the diagnosis of lymphoma in 28% of patients, and after lymphoma diagnosis in 7% of patients. The time between AD diagnosis and onset of NHL differed significantly by AD subtypes ($P < 0.001$, Fig. 1). In order to assess the importance of one disease as a predisposing factor for the development of the other, we separated the cases with initial diagnosis of ADs (pre-existing ADs) from those

Table 1 Spectrum and frequency of ADs in patients with NHL ($n = 4880$)

Subtypes of AD	Number of cases (%)	Frequency in patients with NHL (‰)
Sjögren syndrome	31 (22.1)	6.4
Autoimmune cytopenia	29 (20.7)	5.9
Autoimmune hemolytic anemia	22 (15.7)	4.5
Immune thrombocytopenia	6 (4.3)	1.2
Evan's syndrome	1 (0.7)	0.2
Psoriasis	17 (12.1)	3.4
Rheumatoid arthritis	13 (9.3)	2.6
Systemic lupus erythematosus	11 (7.9)	2.2
Hashimoto thyroiditis	10 (7.1)	2.0
Dermatomyositis/polymyositis	6 (4.3)	1.2
Systemic vasculitis	5 (3.6)	1.0
Giant cell arteritis	1 (0.7)	0.2
Granulomatosis with polyangiitis	1 (0.7)	0.2
Behcet disease	1 (0.7)	0.2
Cryoglobulinemic vasculitis	1 (0.7)	0.2
Unclassified vasculitis	1 (0.7)	0.2
Primary glomerulonephritis/nephropathy	5 (3.6)	1.0
Membranous nephropathy	2 (1.4)	0.4
Mesangial proliferative glomerulonephritis	2 (1.4)	0.4
Minimal change disease	1 (0.7)	0.2
Inflammatory bowel disease	3 (2.1)	0.6
Ulcerative colitis	1 (0.7)	0.2
Crohn disease	2 (1.4)	0.4
Ankylosing spondylitis	3 (2.1)	0.6
Mixed connective tissue disease	2 (1.4)	0.4
Systemic sclerosis	2 (1.4)	0.4
Myasthenia gravis	2 (1.4)	0.4
Celiac disease	1 (0.7)	0.2

with initial diagnosis of NHL ('secondary' ADs). Patients with simultaneous diagnosis of the two disorders were included in the latter group. Among the major subtypes of ADs in this study, psoriasis and RA were significantly associated with pre-existing ADs, whereas autoimmune cytopenia was significantly associated with 'secondary' AD (Table 2). There was no significant difference in the distribution of the other ADs in this study.

In the patients with pre-existing ADs, the most common AD was Sjögren's syndrome, followed by psoriasis, RA, HT, SLE, etc. The median time from the diagnosis of AD to the development of NHL was 8.5 years(interquartile range 3.3–18.1 years). The time from AD diagnosis to the development of NHL differed significantly by the subtypes of ADs ($P < 0.01$, Fig. 2). Notably, the median time from the diagnosis of AD to the onset of NHL was < 2 years for DM/PM and primary glomerulonephritis/nephropathy, and > 2 years for the other ADs.

In the patients with "secondary" ADs, the most frequent AD was autoimmune hemolytic anemia (AIHA), followed by SS and immune thrombocytopenia (ITP). The median time from the diagnosis of lymphoma to the diagnosis of AD was 2.6 years (interquartile range 0.1–7.7 years) for the patients who developed ADs after the onset of NHL ($n = 10$). Among these patients, three developed ADs during the first-line treatment of lymphoma, four developed ADs while lymphoma was in complete remission, and the other three patients experienced ADs at relapse of lymphoma.

The distribution of ADs within the subtypes of NHL

The subtypes of NHL in this study and the distribution of ADs within these subtypes are detailed in Table 3. B-cell lymphoma comprised 74.3% of all cases, with diffuse large B-cell lymphoma (DLBCL) being the most common (34.3%). Significant associations were observed between specific subtypes of ADs and NHL histologies. Overall, SS was significantly associated with B-cell lymphoma ($P = 0.005$), whereas systemic vasculitis was significantly associated with T-cell lymphoma ($P = 0.021$). Specifically, significant associations between marginal zone lymphoma (MZL) and SS ($P = 0.004$), between angioimmunoblastic T-cell lymphoma (AITL) and AIHA ($P = 0.003$), and between subcutaneous panniculitis-like T-cell lymphoma (SPTL) and SLE ($P = 0.013$) were observed in our cohort of patients.

Clinical characteristics of patients with AD-associated NHL

The clinical characteristics of the 140 patients are shown in Table 4. Eighty-six (61%) patients were female, with a median age of 54 years at lymphoma diagnosis. Thirty-seven percent of patients had a Eastern Cooperative Oncology Group performance status (ECOG-PS) ≥ 2, and 66% of patients had stage IV disease at presentation. Extranodal involvement was present in 87% of patients at diagnosis. The most frequent extranodal site was the bone marrow (23.6%), followed by lung (16.4%), gastrointestinal tract (15%), and liver (10%). The associations between the extranodal sites of NHL and the subtypes of associated ADs are detailed in Table 5. Notably, consistencies between the extranodal locations of lymphoma and the major organs affected by ADs were observed in a proportion of patients. Significant associations were found between SS and lymphoma of the salivary glands ($P = 0.037$), between HT and lymphoma of thyroid gland ($P < 0.001$), between immune-mediated interstitial lung disease (e.g., interstitial lung diseases secondary to a systemic AD such as RA, SS, DM, etc.) and lymphoma of the lung ($P = 0.007$), and between IBD and lymphoma of the intestine ($P = 0.016$). In addition, one patient with pre-existing ankylosing spondylitis developed primary

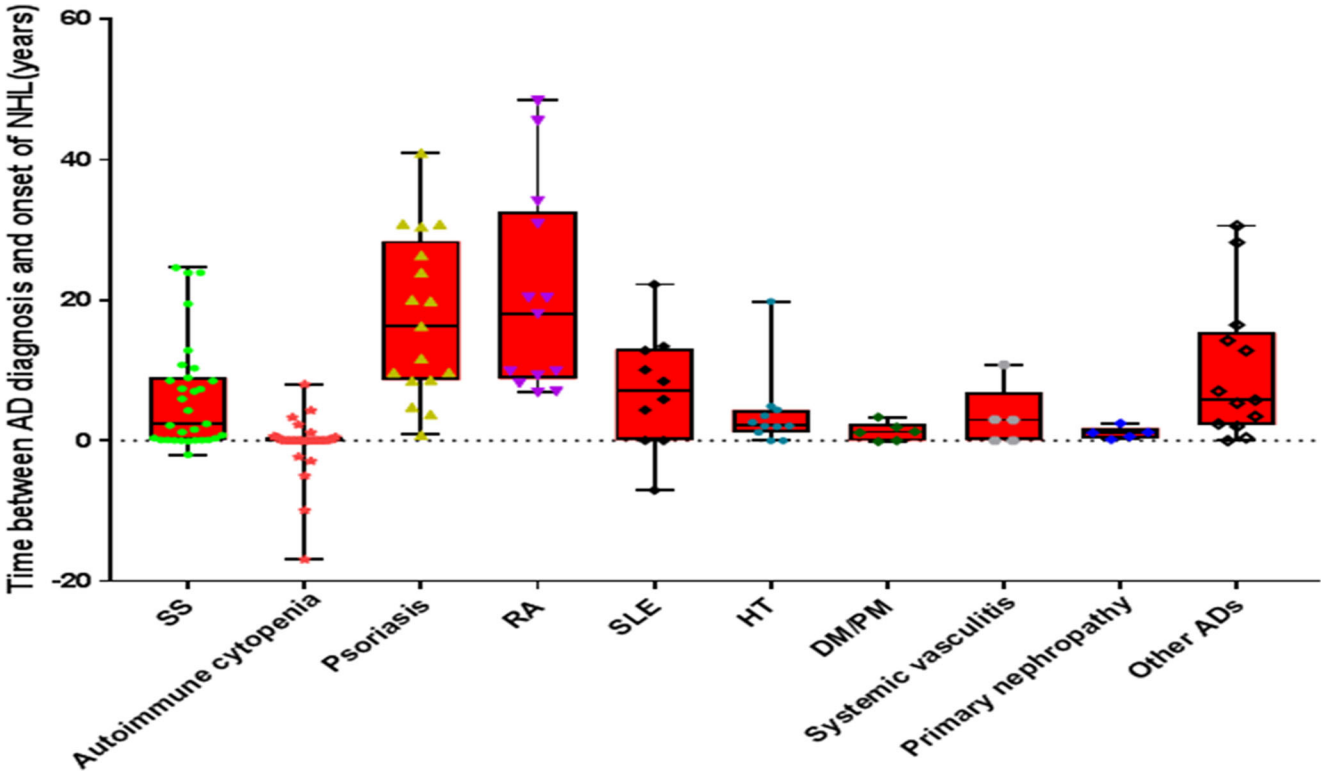

Fig. 1 Boxplots demonstrating the temporal relations between different ADs and NHL (e.g., the time between each AD diagnosis and onset of NHL). A positive value indicates the diagnosis of AD preceded onset of NHL, and a negative value indicates the diagnosis of AD after onset of NHL. The line in the box shows the median time, the upper and lower borders of the box indicate the upper and lower quartile, lines below and above the box indicate the minimum and maximum time

DLBCL of the lumbar vertebrae. One patient with psoriasis and one patient with DM developed mycosis fungoides.

Among the 68 patients in whom pre-treatment peripheral blood levels of EBV-DNA were available, the EBV-DNA load was elevated (e.g., ≥ 500 copies/ml) in 19% of patients with DLBCL and 55% of patients with T-cell lymphoma. Notably, elevated levels of pre-treatment EBV-DNA were also observed in 2 out of 10 (20%) patients with MZL and 1 out of 7 (14.3%) patients with follicular lymphoma (FL), respectively. None of these three patients had a record of systemic corticosteroids and/or immunosuppressive therapy prior to the diagnosis of lymphoma.

When clinical characteristics were analyzed according to the subtypes of ADs, the only significant difference

Table 2 Distribution of ADs according to the time occurred in relationship to lymphoma

Subtypes of AD	AD diagnosed prior to lymphoma ($n = 92$)	AD diagnosed concomitantly with or after lymphoma ($n = 48$)	P value
SS	19	12	0.556
Autoimmune cytopenia	5	24	**< 0.001**
Psoriasis	17	0	**0.001**
RA	13	0	**0.015**
HT	9	2	0.305
SLE	7	3	1.000
DM/PM	4	2	1.000
Systemic vasculitis	3	2	1.000
Primary nephropathy	4	1	0.837
IBD	3	0	0.516
Ankylosing spondylitis	3	0	0.516
Other ADs	5	2	1.000

Psoriasis and RA were significantly associated with pre-existing ADs, autoimmune cytopenia was significantly associated with secondary AD ($P < 0.05$)

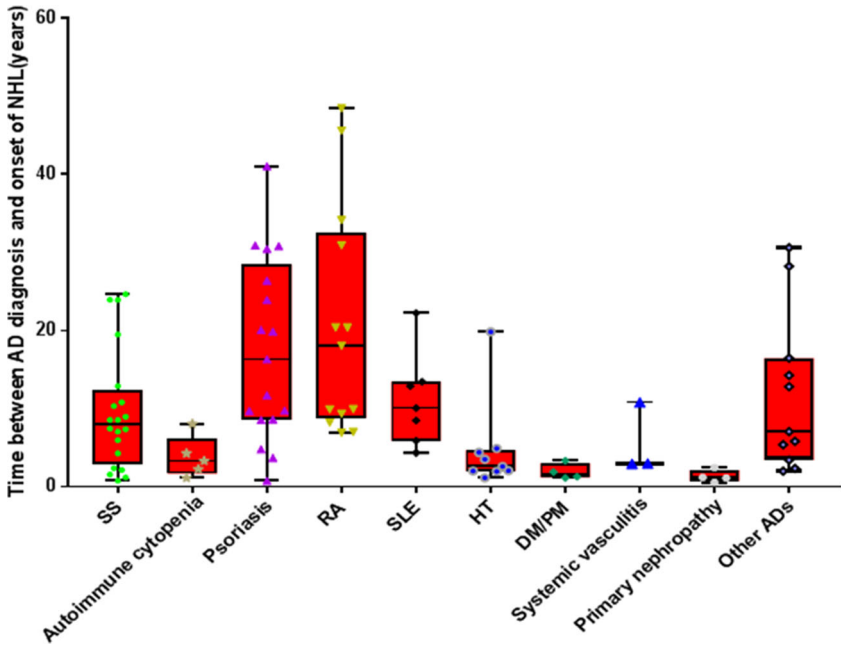

Fig. 2 Boxplots showing the time duration from the diagnosis of ADs to the onset of NHL in patients with pre-existing ADs. The line in the box shows the median time, the upper and lower borders of the box indicate the upper and lower quartile, lines below and above the box indicate the minimum and maximum time duration

between groups of patients with different ADs was the gender distribution ($P < 0.001$). A female predominance was observed in the majority of patients with AD-associated NHL except for patients with psoriasis (77% male), primary nephropathy (100% male), and ankylosing spondylitis (67% male).

Treatment outcome and prognosis of patients with AD-associated NHL

The first-line treatment for patients with NHL in association with ADs was similar to that for NHL patients without AD. In brief, 83.1% of patients underwent systemic

Table 3 The distribution of autoimmune disorders by NHL subtype

Autoimmune disorder	B-cell NHL							T-cell NHL							
	All	DLBCL	MZL	FL	MCL	LPL/WD	Other B-NHL	All	PTCL-NOS	ALCL	AITL	ENKL	SPTL	MF	Other T-NHL
SS	29	10	11	3	0	1	4	2	1	0	0	0	0	0	1
AIHA	17	10	3	0	0	1	3	7	1	0	4	0	0	0	1
ITP	5	3	0	2	0	0	0	1	0	0	0	0	0	0	1
Psoriasis	12	6	1	1	2	0	2	5	1	0	0	1	0	1	2
RA	10	7	2	1	0	0	0	3	1	0	1	0	0	1	0
SLE	6	2	2	0	1	0	1	4	1	0	0	0	2	0	1
HT	11	3	4	2	0	0	2	0	0	0	0	0	0	0	0
DM/PM	4	2	1	0	0	0	1	2	0	0	0	0	0	1	1
Vasculitis	1	0	0	0	0	0	1	4	1	1	0	1	1	0	0
Primary nephropathy	2	1	0	0	0	0	1	3	0	2	0	1	0	0	0
IBD	0	1	0	0	0	0	0	2	0	0	0	1	0	0	1
AS	3	1	1	0	1	0	0	0	0	0	0	0	0	0	0
Other AD	3	2	0	0	0	1	0	4	1	1	0	1	0	0	1
Total number	104	48	25	9	5	3	14	36	7	4	5	5	3	3	9

DLBCL diffuse large B-cell lymphoma; *MZL* marginal zone lymphoma; *FL* follicular lymphoma; *MCL* mantle cell lymphoma; *LPL/WD* lymphoblastic lymphoma/Waldenström's macroglobulinemia; *PTCL-NOS* peripheral T-cell lymphoma, not otherwise specified; *ALCL* anaplastic large cell lymphoma; *AITL* angioimmunoblastic T-cell lymphoma; *ENKL* extranodal NK/T-cell lymphoma; *SPTL* subcutaneous panniculitis-like T-cell lymphoma; *MF* mycosis fungoides

Table 4 Clinical characteristics of 140 AD-associated NHL patients at diagnosis

Parameter	Number (%)
Age	
Median	54
Range	16–81
Sex	
Male	54 (39)
Female	86 (61)
ECOG-PS	
0	34 (24)
1	55 (39)
2	35 (25)
3–4	16 (12)
History of AD treatment	
Systemic corticosteroids[a]	38 (27)
Immunosuppressants[b]	26 (19)
Presence of B symptoms	83 (59)
Ann Arbor stage	
I–II	34 (24)
III–IV	106 (76)
Presence of extranodal involvement	122 (87)
Lactate dehydrogenase	
Elevated	69 (49)
Normal	56 (40)
Unknown	15 (11)
EBV-DNA	
Elevated	20 (14)
Normal	48 (34)
Unknown	72 (52)
Absolute lymphocyte count	
Low	50 (36)
Normal	68 (49)
Unknown	22 (16)

[a] Systemic corticosteroids included prednisone, prednisolone, methylprednisolone, and dexamethasone

[b] Immunosuppressants included cytotoxic drugs (e.g., azathioprine, methotrexate, cyclophosphamide, vincristine), cyclosporine, mycophenolate mofetil, thalidomide, tacrolimus, and anti-CD20 antibody (e.g., rituximab). The doses of each agent varied according to the subtypes and severity of ADs and the general condition of individual patients

chemotherapy, 5% received radiotherapy, 2.6% underwent surgery, and 11% (mostly indolent NHL) employed a "watch and wait" strategy. The first-line chemotherapy regimens are detailed in Table S1. Eighty-one percent of patients received anthracycline-containing regimens (mostly CHOP, other regimens including CHOEP, EPOCH, hyperCVAD, etc.), and the remaining patients received non-anthracycline-containing regimens (e.g., SMILE, gemcitabine-based regimens, etc.). Rituximab was given to 58% of patients. Two patients received first-line high-dose therapy and autologous stem cell transplantation.

At a median follow-up of 23 months (range 0.1–202 months), 36 patients had died. The causes of death were lymphoma progression (75%), treatment-related infection (17%), secondary primary malignancies (3%), and others (5%). The 5-year OS for the entire cohort was 64%(95% CI 51.8–76.4%, Fig. 3a). The 5-year OS for patients with indolent NHL (e.g., low-grade FL, MZL, lymphoblastic lymphoma, SPTL, mycosis fungoides), aggressive B-cell lymphoma (e.g., DLBCL, mantle cell lymphoma, grade 3b FL), and aggressive T-cell lymphoma (e.g., peripheral T-cell lymphoma not otherwise specified, anaplastic large cell lymphoma, AITL, and extranodal NK/T cell lymphoma) were 90.5%, 58.7, and 43.5%, respectively ($P = 0.005$, Fig. 3b).

AD-specific survival analyses were performed in the subtypes of ADs with a decent sample size (e.g., at least 10 cases for each AD) in the study. Survival of NHL patients did not differ significantly by the subtypes of co-existent ADs ($P = 0.725$, Fig. 4a). Likewise, there was no significant survival difference between the groups of patients with pre-existing, concomitant, and subsequent ADs ($P = 0.479$, Fig. 4b). A prior history of systemic corticosteroids therapy was associated with significantly worse survival in the subgroup of patients with pre-existing ADs ($P = 0.024$, Fig. 5a). A similar trend toward decreased OS was observed in the patients with prior use of immunosuppressants, although it is not statistically significant ($P = 0.106$, Fig. 5b). In multivariate analyses, prior use of systemic corticosteroids remained statistically significant after adjusting for age, ECOG-PS, histologies of NHL, Ann Arbor stage, pretreatment LDH, and prior use of immunosuppressants (Table 6).

In the matched-pair analysis comparing patients with AD-associated NHL and patients with NHL without AD, the baseline clinical characteristics were similar between the study cohort and matched cohort except for a higher frequency of B symptoms in patients with AD-associated NHL (Table S2). There was no significant difference in OS between patients with AD-associated NHL and those with NHL and without ADs (5-year OS 64 vs. 76%, $P = 0.25$, see Fig. 6a). In subgroup analyses according to different histologies of NHL, no significant difference in OS was found between the study cohort and the matched cohort in subgroups of patients with indolent NHL, aggressive B-cell NHL or aggressive T-cell NHL (Fig. 6b–d).

Discussion

Despite the long-standing recognition of the inter-relationship between ADs and lymphoma, the exact prevalence and spectrum of ADs in the patients with NHL remain poorly defined.

Table 5 The associations between autoimmune disorders and extranodal sites of NHL

Extranodal sites of NHL	SS ($n = 31$)	AIHA/ ITP ($n = 29$)	Psoriasis ($n = 17$)	RA ($n = 13$)	SLE ($n = 11$)	HT ($n = 10$)	DM/ PM ($n = 6$)	Systemic vasculitis ($n = 5$)	Kidney disease ($n = 5$)	IBD ($n = 3$)	AS ($n = 3$)	Other AD ($n = 7$)
Salivary glands ($n = 9$)	5	1	0	2	0	0	0	0	0	0	1	0
Nasal cavity/ paranasal sinus ($n = 12$)	4	1	2	1	1	0	0	1	0	1	0	1
Thyroid gland ($n = 6$)	0	0	0	0	0	6	0	0	0	0	0	0
Lung ($n = 27$)	8	6	0	1	2	2	1	1	0	0	0	2
Gastrointestinal tract ($n = 21$)	5	4	3	1	1	2	0	0	1	2	0	2
Liver ($n = 14$)	1	5	1	1	0	1	2	2	1	0	0	0
Kidney/adrenal glands ($n = 10$)	3	1	**3**	0	0	2	0	0	0	0	0	1
Bone ($n = 9$)	2	1	1	2	1	0	0	1	0	0	1	0
Bone marrow ($n = 33$)	9	9	3	1	1	4	1	1	1	0	0	3
Skin ($n = 10$)	1	0	2	1	0	1	2	1	2	0	0	0
Central nervous system ($n = 3$)	0	1	1	0	0	0	0	0	1	0	0	0
Other sites ($n = 17$)	1	3	2	1	3	3	0	3	1	0	0	0

Psoriasis and RA were significantly associated with pre-existing ADs, autoimmune cytopenia was significantly associated with secondary AD ($P < 0.05$)

SS Sjögren syndrome, *AIHA* autoimmune hemolytic anemia, *ITP* immune thrombocytopenia, *RA* rheumatoid arthritis, *SLE* systemic lupus erythematosus, *HT* Hashimoto thyroiditis, *DM/PM* dermatomyositis/polymyositis, *IBD* inflammatory bowel disease, *AS* ankylosing spondylitis

The present study investigated the frequency and distribution of ADs in a large cohort of Chinese patients with NHL, and analyzed the clinical and prognostic profiles of these patients. To the best of our knowledge, this is the first large-scale report on AD-associated NHL in Chinese population.

Although the spectrum of ADs in our study was generally consistent with the published literature [14–17], the frequency of AD (2.9%) was lower in our cohort than that in previous reports. In a recent multicenter retrospective study of French patients with NHL ($n = 2503$), 4.3% of patients presented with autoimmune manifestations [17]. A similar rate of autoimmune conditions (4.6%) was also observed in a large cohort study of American patients with DLBCL ($n = 5924$) [21]. In other smaller series, this frequency ranged from 7.6 to 12.9% [14–16]. A possible explanation for the lower frequency in our cohort is that our study population has a different geographic and ethnic background from those in other series. However, as this is a single-center study and there is currently no other large-scale report on AD-related NHL from China, we could not draw a definitive conclusion on whether the incidence of AD-associated NHL was indeed lower in the Chinese population.

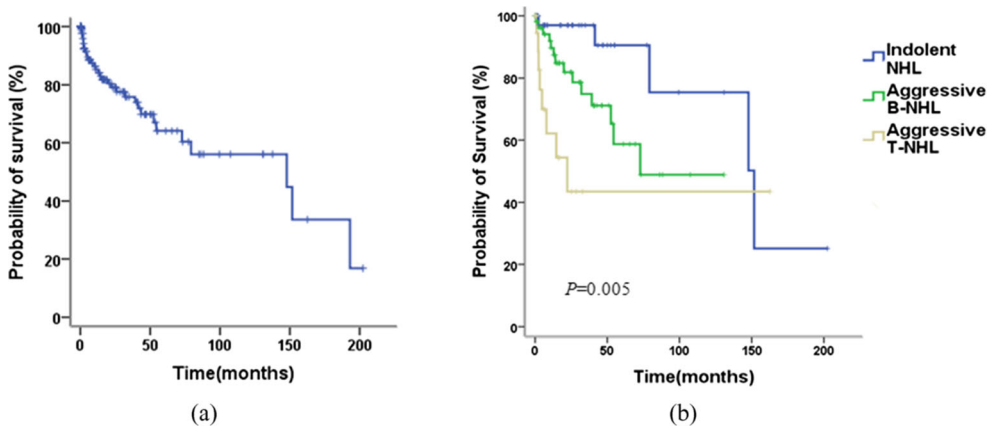

Fig. 3 Survival of NHL patients in the entire cohort (**a**) and according to the subtypes of NHL (**b**)

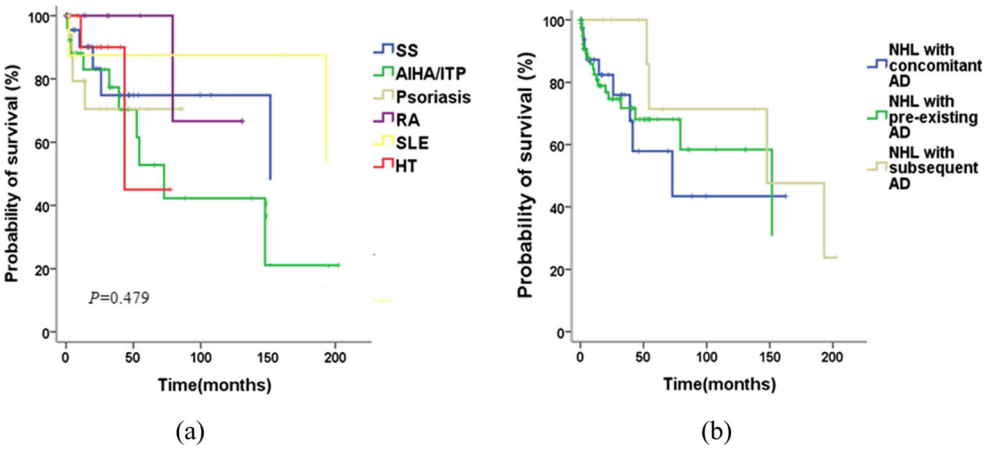

Fig. 4 Survival of NHL patients by the subtypes of ADs (**a**) and according to the subgroups of patients with pre-existing, concomitant, and subsequent ADs (**b**)

Our study revealed distinct patterns of temporal relations between specific ADs and NHL. We found that this relationship could be one-way or two-way depending on the subtypes of ADs. The "one-way" relationship is exemplified by psoriasis, RA, and autoimmune cytopenia. RA and psoriasis almost invariably preceded the development of NHL, whereas most cases of autoimmune cytopenia occurred concomitantly with or subsequent to the onset of NHL. By contrast, ADs such as SS and SLE were fairly distributed in the pre-existing AD and secondary AD groups, suggesting that these ADs could be both a predisposing factor and a secondary effect of lymphomagenesis. Although previous studies have noted this bi-directional inter-relationship between ADs and lymphoma [13–17], our results expand their findings and highlight the heterogeneity of this relationship between different subtypes of ADs. Even in the patients with pre-existent ADs, the time duration from the diagnosis of AD to the development of NHL varied significantly by the subtypes of ADs, suggesting that the mechanisms of lymphomagenesis in the background of autoimmunity was different for various subtypes of ADs. However, it should be noted that some ADs that closely preceded the onset of NHL, as in the cases of DM/PM and glomerulonephritis in this study, might not be truly primary disorders but rather secondary autoimmune manifestations of the underlying lymphoma, thus the distinction between 'primary' and 'secondary' AD might be difficult under some circumstances. In light of this ambiguity, we suggest that clinicians should be more aware of the possibility of covert lymphoma in the management of ADs that was found to be associated with incipient or concomitant occurrence of lymphoma in this study.

The present study identified a number of correlations between the subtypes of NHL and subtypes of ADs. Among these findings, the association between SS and marginal zone lymphoma has been well established in the literature [22, 23]. As to the other associations (e.g., T-cell lymphoma and systemic vasculitis, SPTL, and SLE), relevant data in the current literature is limited. In support of our results, a multicenter retrospective study of 63 SPTL patients found that 19% had autoimmune conditions among which SLE was the most common [24]. The correlation between systemic vasculitis and T-cell lymphoma has not been explicitly described in previous studies. Although these novel findings are hypothesis-generating, given the small number of cases with vasculitis-associated lymphoma and AD-associated SPTL in this study, these associations should be regarded as suggestive rather than definitive and need further validation from large cohort studies.

A prominent clinical feature of the patients with AD-associated NHL in this study was the high frequency of

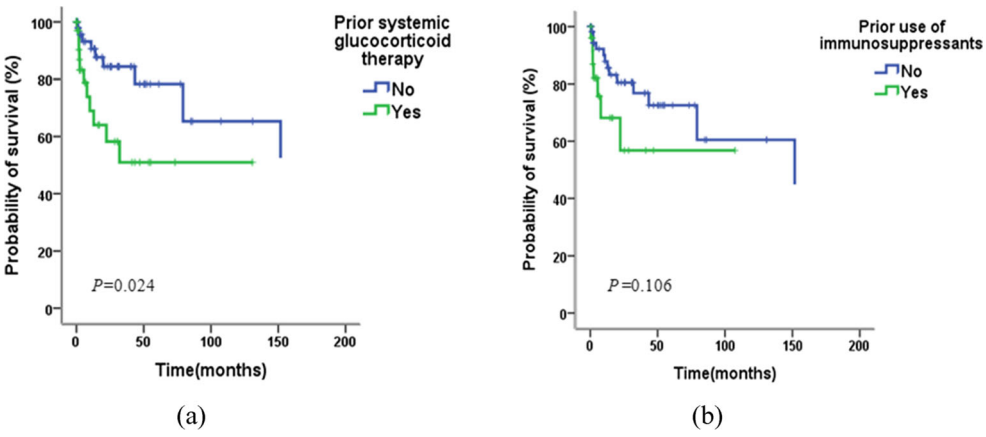

Fig. 5 Survival of NHL patients with pre-existing ADs according to prior use of systemic corticosteroids (**a**) or immunosuppressants (**b**)

Table 6 Analyses of factors associated with survival in NHL patients with pre-existing ADs

Factor	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age > 60 years	3.43	1.29–9.13	0.014	1.20	0.34–4.30	0.776
ECOG-PS ≥ 2	8.45	3.13–22.83	< 0.001	16.65	2.50–110.75	**0.004**
Aggressive histologies of NHL	8.51	1.11–65.20	0.039	1.45	0.14–14.98	0.754
Stage III/IV	7.25	0.97–54.42	0.054	4.07	0.39–42.67	0.241
LDH	4.07	1.43–11.54	0.008	0.60	0.11–3.27	0.554
Prior glucocorticoids	2.90	1.15–7.28	0.024	7.33	1.76–30.49	**0.006**
Prior immunosuppressants	2.19	0.85–5.64	0.106	0.68	0.17–2.78	0.595

Psoriasis and RA were significantly associated with pre-existing ADs, autoimmune cytopenia was significantly associated with secondary AD ($P < 0.05$)

HR hazard ratio, *CI* confidence interval

extranodal disease and the consistencies between extranodal sites of lymphoma and the primarily affected organs in AD. These findings provide further evidence for role of persistent local inflammation in the pathogenesis of lymphoma within the framework of AD. The frequency of EBV infection in the patients with AD-related lymphoma has been of particular interest since EBV might be a potential driving force of lymphoma development. In our study, the frequencies of elevated EBV-DNA loads in the peripheral blood of patients with DLBCL and T-cell lymphoma were generally comparable to those reported for patients with corresponding lymphoma histologies and without autoimmune complications [25–27]. However, it is noteworthy that elevated levels of EBV-DNA in peripheral blood were also detected in 20% (2 out of 10) of patients with MZL and 15% (1 out of 7) of patients with FL. Since EBV has rarely been associated with these indolent B-cell lymphomas [28] and there is a scarcity of data in the literature regarding the associations of peripheral blood EBV-DNA with FL or MZL, these findings were interesting and might suggest a potential role of EBV in the development of these AD-related indolent B-cell lymphomas. Although the small sample size requires caution in interpretation of these results, this finding is hypothesis-generating and worthy of further exploration.

Our survival analyses found no significant difference in survival between NHL patients with AD and those without ADs. This finding is consistent with several previous reports

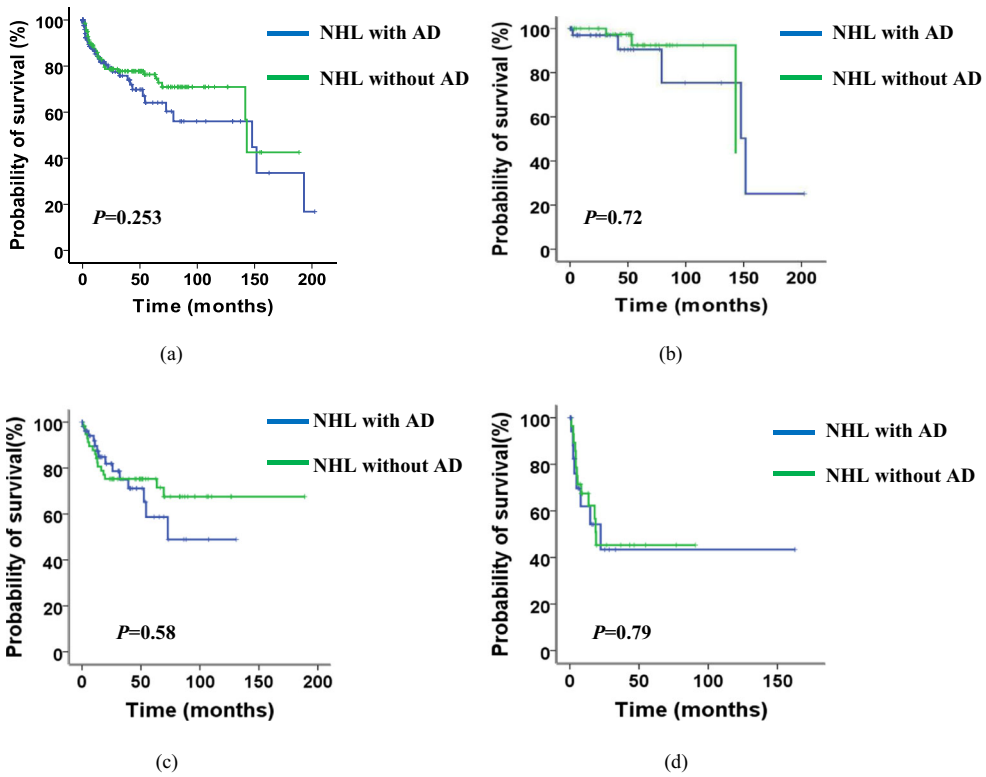

Fig. 6 Survival of patients with AD-associated NHL ($n = 140$) and patients with NHL without ADs (n = 140) in the entire cohort (**a**) and in the subgroups with indolent NHL (**b**), aggressive B-cell NHL (**c**), and aggressive T-cell NHL (**d**)

[16, 21, 29], suggesting that AD as a whole has no significant impact on the prognosis of NHL. Although a recent multicenter study by Jachiet et al. [17] reported contrary findings pointing to an adverse prognostic effect of ADs, this study has different inclusion criteria and distribution of ADs compared with our study. Specifically, the study by Jachiet et al. excluded a proportion of patients with well-defined pre-existing ADs such as Sjögren's syndrome, systemic lupus erythematosus, and rheumatoid arthritis, thus these ADs were under-represented in the study cohort whereas other ADs such as autoimmune cytopenia were relatively over-represented. These differences might serve as a confounding factor in the comparison and analysis of survival outcomes.

Another notable finding in prognostic analyses was that prior systemic corticosteroid therapy was significantly associated with worse survival in NHL patients with pre-existent ADs, even after adjusting for the other established prognostic factors. No previous study tried to determine the impact of prior AD-directed therapy on the survival of patients who developed lymphoma. The mechanisms underlying this observation were not entirely clear and might be attributable to several factors. First, the immunosuppressive effects of prolonged glucocorticoids therapy might impair the patients' immune responses against lymphoma. Xing et al. recently reported that dexamethasone could enhance PD-1 expression in human $CD4^+$ and $CD8^+$ T cells and suppress T-cell functions via inhibition of cytokines production and induction of T-cell apoptosis [30]. Second, the immunosuppressive state resulting from protracted corticosteroid therapy might increase the risk of severe treatment-related infection during the subsequent treatment of lymphoma. Notably, among the patients with lymphoma and pre-existent ADs in our study, death from treatment-related infection occurred in 5.3% of patients with a prior history of corticosteroids therapy compared with 0% of patients without previous use of corticosteroids. Third, long-term chronic exposure to glucocorticoids can lead to the development of glucocorticoid resistance [31] and result in failure of responsiveness to glucocorticoid in the subsequent treatment of lymphoma.

The present study has several limitations. Firstly, this is a single-center study, thus our data might not be well representative of the profiles of AD-associated NHL in the entire Chinese population. In addition, given the wide heterogeneity in the histologies of NHL, it is difficult to focus our analysis on the impact of ADs upon a specific subtype of lymphoma.

In conclusion, this study provides a comprehensive analysis of NHL in connection with ADs in a large cohort of Chinese patients. Our results expand previous findings in this field and provide new lines of evidence that AD-related NHL might be considered a different spectrum of entities with distinct characteristics in terms of pathobiology, clinical manifestations, and prognostic profiles as compared to NHL patients without autoimmunity. It will be important to incorporate genetic and molecular analyses into future studies of AD-related NHL in order to unravel the key pathogenic events, genetic alterations, and signaling pathways that eventually might lead to a more tailored therapeutic approach for these patients.

Acknowledgments The authors thank the patients, medical staff, and physicians who participated in this study. The authors thank the assistance of department of hematology and department of rheumatology for study collaboration. The authors also acknowledge the department of medical record library for medical record provision.

Authors' contributions S.H., D.Z., and W.Z. designed the research study; all authors contributed to the acquisition of data and the statistical analysis and interpretation of data; all authors contributed in drafting the article or revising it critically for important intellectual content; all authors gave the final approval of the version published.

Compliance with ethical standards

Conflict of interest disclosures The authors declare no competing financial interests for this study.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients for being included in the study.

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