Received: 28 October 2017 | Revised: 21 December 2017 | Accepted: 10 January 2018

DOI: 10.1002/hon.2498

ORIGINAL RESEARCH ARTICLE

WILEY

Presence of autoimmune disease affects not only risk but also survival in patients with B-cell non-Hodgkin lymphoma

Geffen Kleinstern[1,2*] | Mor Averbuch[1*] | Rania Abu Seir[3,4] | Riki Perlman[3] | Dina Ben Yehuda[3] | Ora Paltiel[1,3]

[1] School of Public Health, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

[2] Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA

[3] Department of Hematology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

[4] Department of Medical Laboratory Sciences, Al Quds University, Abu Deis, Jerusalem

Correspondence
Ora Paltiel, School of Public Health, Hadassah-Hebrew University, POB 12000, Jerusalem 9112001, Israel.
Email: orap@hadassah.org.il

Funding information
Hadassah University Hospital Compensatory Fund; Israel Science Foundation (ISF), Grant/Award Number: 877/10; United States Agency for International Development (USAID)/MERC, Grant/Award Number: TA-MOU-11-M31-025

Abstract

Although autoimmune diseases (AIDs) are known to predispose to non-Hodgkin lymphoma (NHL), their association with NHL prognosis has rarely been investigated. We examined associations between autoimmunity and B-cell NHL onset by comparing AID history (determined by self-report and medication review and supplemented by chart review where possible) among 435 adult B-NHL patients in Hadassah-Hebrew University Medical Center, diagnosed 2009-2014, and 414 age-and-sex frequency-matched controls. We examined AIDs as a whole, B- and T-cell–mediated AIDs, and autoimmune thyroid diseases. Among cases, we used Kaplan-Meier and Cox regression models to assess the association of AID with overall survival and relapse-free survival, adjusting for prognostically important patient and disease characteristics such as Ki67% staining, International Prognostic Index, rituximab treatment, and histological subgroup.

Autoimmune diseases were associated with B-NHL (odds ratio [OR] = 1.95; 95% confidence interval (CI), 1.31-2.92), especially AIDs mediated by B-cell activation (OR = 5.20; CI, 1.90-14.3), which were particularly associated with marginal zone lymphoma (OR = 19.3; CI, 4.59-80.9). We found that time to relapse for all B-NHL patients with AIDs was significantly shorter (mean of 49.21 mo [±3.22]) than among patients without AID (mean of 59.74 mo [±1.62]), adjusted hazard ratio [HR_{adj}] = 1.69 (CI, 1.03-2.79). Specifically, in patients with diffuse large B-cell lymphoma, of whom 91.8% had received rituximab, a history of B-cell–mediated AIDs was associated with shorter relapse-free survival and overall survival, HR_{adj} = 8.34 (CI, 3.01-23.1) and HR_{adj} = 3.83 (CI, 1.20-12.3), respectively.

Beyond confirming the well-known association between AIDs and B-NHL, we found that AID is an adverse prognostic factor in B-cell lymphoma, associated with a shortened time to relapse, suggesting that there are specific therapeutic challenges in the subgroup of patients suffering from both these diseases. Further work is required to address mechanisms of resistance to standard treatment in the setting of AID-associated B-NHL. In the era of immunotherapy, these findings have particular relevance.

KEYWORDS

autoimmune disease, diffuse large B-cell lymphoma, non-Hodgkin lymphoma, risk, survival

1 | INTRODUCTION

The association between autoimmune diseases (AIDs) and the risk of developing non-Hodgkin lymphoma (NHL) has been reported in many clinical and epidemiological studies, including both cohort and case-control studies. In an early study conducted in Finland between 1967 and 1973, which included 46 101 patients with rheumatoid arthritis (RA) followed for 213 911 person-years, the authors found a 2.8-fold increased risk for NHL.[1] Another study in Finland followed 676 RA or Sjögren syndrome (SS) patients between 1970 and 1991 and found

[*] Geffen Kleinstern and Mor Averbuch have equal contributions.

among the primary SS cases an 8.7-fold increased risk for NHL.[2] In addition, a cohort study from Canada followed 724 systemic lupus erythematosus (SLE) cases and found a 5.4-fold increased risk for NHL.[3] In a meta-analysis including 20 cohort studies published between 1974 and 2005, the relative risk of NHL for a variety of AIDs ranged between 2.5 and 37[4]; specifically, a high risk of NHL development was found for SS (18.8-fold increased risk), moderate risk for SLE (7.4-fold increased risk), and lower risk for RA (3.9-fold increased risk). These findings are further supported by population-based studies in the United States, which included 44 350 cases with lymphoid neoplasms and 122 531 population-based controls, and found strong associations for diffuse large B-cell lymphoma (DLBCL) with RA (1.4-fold increased risk) and SS (2.0-fold increased risk); T-cell lymphoma with haemolytic anaemia (9.7-fold increased risk), psoriasis (3.1-fold increased risk), SLE (4.4-fold increased risk), and coeliac disease (5.0-fold increased risk); and marginal zone lymphoma (MZL) with SS (6.6-fold increased risk), SLE (2.8-fold increased risk), and haemolytic anaemia (7.4-fold increased risk).[5] In addition, in a cohort study from the Swedish Cancer Registry in Sweden, which followed 878 161 patients for a mean of 9.4 years, with 33 different AIDs, 3096 of them were diagnosed with NHL during follow-up resulting in overall standardized incidence ratios for NHL of 1.6 after any AIDs; 27.2 for autoimmune haemolytic anaemia; 7.5 for immune thrombocytopenic purpura; 4.1 to 4.9 for polymyositis/dermatomyositis, SS, coeliac disease, and SLE; 2.0 to 2.6 for RA, systemic sclerosis, Crohn disease, myasthenia gravis, and sarcoidosis; and 1.4 to 1.5 for polymyalgia rheumatica, Hashimoto/hypothyroidism and psoriasis and ulcerative colitis.[6]

It is now recognized that NHL is a biologically and clinically heterogeneous malignancy.[7] The International Lymphoma Epidemiology Consortium (InterLymph), including 17 471 cases and 23 096 controls from 20 studies,[7] reported that AIDs mediated by B-cell activation were associated with specific B-cell lymphoma subtypes and AIDs mediated by T-cell activation were mainly related to T-cell lymphoma to varying degrees.[7-9]

The association between AID and prognosis in B-cell NHL (B-NHL) has rarely been documented. In contrast, poorer survival for Hodgkin lymphoma patients with a discharge diagnosis of AID was clearly shown by Landgren et al[10]; among 7414 Hodgkin lymphoma patients and 29 240 controls, they found that female and male patients with Hodgkin lymphoma had a 1.8-fold and 1.7-fold increased relative risk of dying at 5 years of follow-up, respectively.[10] Only a few studies, most involving small samples and conducted prior to the near-universal use of rituximab, have suggested poorer outcomes among NHL cases with AIDs.[11,12] A study conducted in Sweden among 1523 cases, with mean follow-up of 8.8 years, reported that the overall survival (OS) was marginally poorer among AIDs versus non-AID–associated NHL, hazard ratio (HR) = 1.4 (95% confidence intervals [CIs], 1.0-1.8).[13] In contrast, a study in which only patients with extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue were included, found comparable estimated median time to relapse in those both with and without AIDs.[14] The association of AID with lymphoma prognosis has become increasingly relevant in the era of immunotherapies, since autoimmunity is a major toxicity of these promising treatments and clinical trials generally exclude patients with AIDs.

Herein, we aim to examine the association between AIDs and B-NHL and the influence of AIDs on OS and relapse-free survival (RFS) after the introduction of rituximab as standard of care.

2 | METHODS

We performed a hospital-based case-control study among B-NHL adult (>18 y) patients diagnosed between 2009 and 2014 and healthy age-and-sex frequency-matched controls who accompanied patients to the hospital.[15] Participants answered interviewer-administered

TABLE 1 Demographic characteristics for controls and cases with overall B-NHL and subtypes

Characteristics		DLBCL		FL		MZL		Overall B-NHL		Controls		*P**
		N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	
Total no.		182	(41.8)	116	(26.7)	65	(14.9)	435	(100)	414	(100)	
Sex	Male	84	(46.2)	52	(44.8)	34	(52.3)	211	(48.5)	184	(44.4)	.23
	Female	98	(53.8)	64	(55.2)	31	(47.7)	224	(51.5)	230	(55.6)	
Age	<35	19	(10.4)	4	(3.4)	1	(1.5)	28	(6.4)	45	(10.9)	.001
Years	35-54	48	(26.4)	36	(31.0)	23	(35.4)	122	(28.0)	111	(26.8)	
	55-64	40	(22.0)	37	(31.9)	17	(26.2)	114	(26.2)	111	(26.8)	
	65-74	44	(24.2)	23	(19.8)	13	(20.0)	97	(22.3)	111	(26.8)	
	≥75	31	(17.0)	16	(13.8)	11	(16.9)	74	(17.0)	36	(8.7)	
Marital	Single	14	(7.7)	5	(4.3)	3	(4.6)	26	(6.0)	14	(3.4)	<.0001
Status	Married	127	(69.8)	86	(74.1)	49	(75.4)	311	(71.5)	382	(92.3)	
	Other	41	(22.5)	25	(21.6)	13	(20.0)	98	(22.5)	18	(4.3)	
Ethnicity	Ashkenazi	110	(60.5)	73	(62.9)	44	(67.7)	271	(62.3)	289	(70.0)	.02
	Sephardic	14	(7.7)	6	(5.2)	3	(4.6)	28	(6.5)	34	(8.2)	
	North African	27	(14.8)	24	(20.7)	10	(15.4)	68	(15.6)	46	(11.1)	
	West Asian	31	(17.0)	13	(11.2)	8	(12.3)	68	(15.6)	44	(10.97)	
Education	0-8	20	(11.0)	5	(4.3)	3	(4.6)	33	(7.6)	7	(1.7)	<.0001
Years	9-12	50	(27.5)	29	(25.0)	16	(24.6)	117	(27.0)	110	(26.6)	
	>12	112	(61.5)	82	(70.7)	46	(70.8)	284	(65.4)	297	(71.7)	

Abbreviations: B-NHL, B-cell non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MZL, marginal zone lymphoma.

*P value calculated for overall B-NHL versus controls.

questionnaires (see detailed methods[15]) including a history of AIDs and medications. Autoimmune disease status was confirmed using medication history (for both cases and controls) and review of medical records where possible including the presence of specific autoantibodies. Sociodemographic variables in cases and controls were compared using 2-sided Fisher exact and χ^2 tests. We examined the associations of AIDs as a whole, B- and T-cell–mediated AIDs (as per InterLymph criteria[16]), and autoimmune thyroid diseases with overall B-NHL, and specifically DLBCL, follicular lymphoma (FL), and MZL subtypes. B-cell–mediated AIDs included RA, SS, SLE, autoimmune haemolytic anaemia, antiphospholipid syndrome, polymyalgia rheumatica, cryoglobulinaemia vasculitis, and undefined B-cell AIDs; T-cell AIDs included coeliac disease, ulcerative colitis, Crohn disease, psoriasis, polymyositis, chronic inflammatory demyelinating polyneuropathy, sarcoidosis, multiple sclerosis, scleroderma, and immune thrombocytopenic purpura; autoimmune thyroid diseases included Hashimoto thyroiditis and Grave disease. We used logistic regression to assess the association of AID with lymphoma odds, adjusting for education (y), marital status, and ethnicity on the basis of grandparents' origin.

Among cases only, we measured OS (date of diagnosis to date of death or last follow-up) and RFS (remission date to date of first relapse or last follow-up) comparing those with/without AID using Kaplan-Meier curves for the AID and non-AID group and the log rank test for statistical comparison. We then constructed multivariable Cox regression models adjusting for Ki67% staining, International Prognostic Index[17] score, rituximab treatment, and histological subgroup.

Agreement of self-reported AIDs and medication history with medical records including the presence of specific autoantibodies was assessed using the Kappa score with 95% CIs.

3 | RESULTS AND DISCUSSION

Among 435 B-NHL cases and 414 healthy controls, the median age at diagnosis/interview was 60 years, with 48.5% and 44.4% males, respectively. The most common B-NHL subtype was DLBCL (41.8%) followed by FL (26.7%) and MZL (14.9%). During the study period, 90% of eligible B-NHL cases were recruited.[15] Demographic characteristics are shown in Table 1. Rituximab treatment was common

TABLE 2 History of autoimmune diseases for controls and cases with overall B-NHL and subtypes and rituximab treatment for cases

Characteristics	DLBCL		FL		MZL		Overall B-NHL		Controls		*P**
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	
Total no.	182	(41.8)	116	(26.7)	65	(14.9)	435	(100)	414	(100)	
AIDs (any)	41	(22.5)	24	(20.7)	15	(23.1)	97	(22.5)	57	(13.8)	.001
AIDs B-cell mediated	8	(4.4)	5	(4.3)	7	(10.8)	26	(5.9)	5	(1.2)	<.0001
Rheumatoid arthritis	3	(37.5)	3	(60.0)	2	(28.6)	10	(38.5)	3	(60.0)	
Sjogren's syndrome	1	(12.5)	1	(20.0)	1	(14.3)	3	(11.5)	…	…	
Systemic lupus erythematosus	3	(37.5)	…	…	2	(28.6)	5	(19.2)	2	(40.0)	
Autoimmune haemolytic anaemia	…	…	…	…	2	(28.6)	4	(15.4)	…	…	
Antiphospholipid syndrome	1	(12.5)	…	…	…	…	1	(3.8)	…	…	
Polymyalgia rheumatica	…	…	1	(20.0)	…	…	1	(3.8)	…	…	
Cryoglobulinaemic vasculitis	…	…	…	…	…	…	1	(3.8)	…	…	
Undefined B-cell	…	…	…	…	…	…	1	(3.8)	…	…	
AIDs T-cell mediated	14	(7.7)	7	(6.0)	5	(7.7)	31	(7.1)	19	(4.6)	.14
Coeliac disease	…	…	…	…	1	(20.0)	1	(3.2)	1	(5.3)	
Ulcerative colitis	3	(21.4)	…	…	2	(40.0)	6	(19.4)	…		
Crohn disease	1	(7.1)	1	(14.3)	…	…	2	(6.5)	2	(10.5)	
Psoriasis	9	(64.3)	5	(71.4)	1	(20.0)	17	(54.8)	12	(63.2)	
Polymyositis	…	…	…	…	1	(20.0)	1	(3.2)	…	…	
Chronic inflammatory demyelinating polyneuropathy	…	…	1	(14.3)	…	…	1	(3.2)	…	…	
Sarcoidosis	1	(7.1)	…	…	…	…	2	(6.5)	1	(5.3)	
Multiple sclerosis	…	…	…	…	…	…	…	…	2	(10.5)	
Scleroderma	…	…	…	…	…	…	…	…	1	(5.3)	
Immune thrombocytopenic purpura	…	…	…	…	…	…	1	(3.2)	…	…	
AID—thyroid	22	(12.1)	13	(11.2)	6	(9.2)	51	(11.8)	34	(8.2)	.08
Hypothyroidism (other)	21	(95.5)	12	(92.3)	6	(100)	49	(96.0)	32	(94.1)	
Graves hyperthyroidism	1	(4.5)	1	(7.7)	…	…	2	(4.0)	2	(5.9)	
Rituximab treatment[a]	167	(91.8)	77	(66.4)	27	(41.5)	308	(70.8)	…	…	

Abbreviations: AIDs, autoimmune diseases; B-NHL, B-cell non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MZL, marginal zone lymphoma.

Values were missing for ≤1% of exposure variables.

[a]Some cases with indolent lymphoma were untreated at the time of follow-up, observed by watchful waiting.

*P value calculated for overall B-NHL versus controls.

among B-NHL cases with 70.8%; it was most common among DLBCL cases with 91.8% followed by FL with 66.4% and MZL with 41.5%. Concordance between self-reported AID and medical records was moderate (Kappa = 0.60; 95% CI, 0.53-0.66).

Autoimmune diseases were present in 97 (22.5%) B-NHL cases and 57 (13.8%) controls; specifically, AIDs were most common in MZL (23.1%), followed by DLBCL (22.5%) and FL (20.7%) (Table 2). Autoimmune diseases were positively associated with B-NHL (odds ratio [OR] = 1.95; 95% CI, 1.31-2.92), DLBCL (OR = 1.96; 95% CI, 1.16-3.31), FL (OR = 2.13; 95% CI, 1.18-3.84), and MZL (OR = 2.38, 95% CI, 1.15-4.93). Autoimmune diseases mediated by B-cell activation were present in 26 (5.9%) B-NHL cases and 5 (1.2%) controls; specifically, AIDs mediated by B-cell activation were most common in MZL with 10.8%, followed by DLBCL with 4.4% and FL with 4.3% (Table 2). Autoimmune diseases mediated by B-cell activation were strongly associated with B-NHL overall (OR = 5.20; 95% CI, 1.90-14.26), notably with MZL (OR = 19.3; 95% CI, 4.59-80.9) and less with FL (OR = 4.27; 95% CI, 1.08-16.9) subtypes. Autoimmune diseases mediated by T-cell activation were present in 31 (7.1%) B-NHL cases and 19 (4.6%) controls; specifically, AIDs mediated by T-cell activation were most common in both DLBCL and MZL with 7.7%, followed by FL with 6.0% (Table 2); however, no significant association was found between AIDs mediated by T-cell activation and B-NHL or subtypes. Autoimmune thyroid diseases were present in 51 (11.8%) B-NHL cases and 34 (8.2%) controls; specifically, autoimmune thyroid diseases were most common in DLBCL with 21.1% followed by FL with 11.2% and MZL with 9.2% (Table 2); here again, no associations between autoimmune thyroid diseases and B-NHL or subtypes were observed.

After a median follow-up of 42 months (range, 2-75), we found that mean time to relapse was significantly shorter (49.21 mo [±3.22]) for B-NHL patients with AIDs compared with those without (59.74 mo [±1.62]) (adjusted HR [HR_{adj}] = 1.69; 95% CI, 1.03-2.79), especially for AIDs mediated by B-cell activation (HR_{adj} = 3.41; 95% CI, 1.77-6.55). In DLBCL in particular, both RFS and OS were markedly shortened in the presence of B-cell–mediated AIDs (Figure 1), HR_{adj} = 8.34 (95% CI, 3.01-23.1) and HR_{adj} = 3.83 (95% CI, 1.20-12.3) after adjusting for International Prognostic Index, Ki67 and rituximab, respectively. In addition, among MZL cases, RFS was adversely affected in those with B-cell mediated AIDs (HR_{adj} = 13.4; 95% CI, 2.48-72.6).

Our study included some limitations. One limitation was that medical records were largely unavailable to confirm AID status among controls (in whom only self-report and medication history were available). Resulting misclassification or information bias could have affected the OR estimates (but not the survival findings) biasing them toward the null in the assessment of the association of autoimmunity with NHL. We may have underestimated the prevalence of AID among cases; however, the prevalence of AIDs mediated by B-cell activation among controls (1.2%) was consistent with reports in the American population (approximately 1%).[18]

The distribution of specific AIDs differed from other studies. Specifically, among MZL cases with AID, 23.1% in our series and

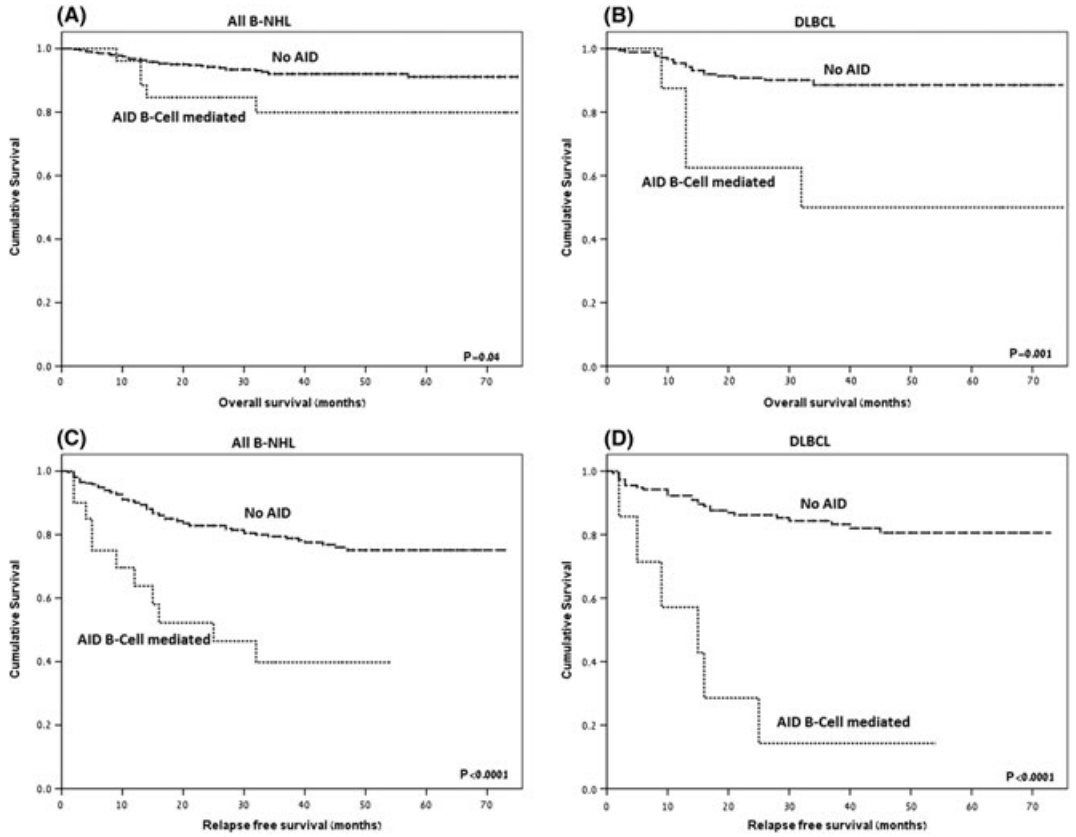

FIGURE 1 Overall and relapse-free survival by B-cell–mediated autoimmune diseases for all B-cell non-Hodgkin lymphoma and diffuse large B-cell lymphoma. Kaplan-Meier survival curves by B-cell–mediated autoimmune diseases (AIDs): (A) overall survival for overall B-cell non-Hodgkin lymphoma (B-NHL); (B) overall survival for diffuse large B-cell lymphoma (DLBCL); (C) relapse-free survival for overall B-NHL; (D) relapse-free survival for DLBCL. *P* values derive from log rank tests

30% in the InterLymph series[9] had Sjogren syndrome, while they represented 71% in Wöhrer study, which concentrated solely on extranodal. A distinction between MZL subtypes was not made in our study and is not always possible in case control studies.

Our strict definition of autoimmunity among cases may have affected the survival analysis, since it may have excluded milder cases in the AID subgroup. Compared with our study, the follow-up in the Wöhrer study of extranodal MZL was longer than our series and during the first 3 years of follow-up relapses indeed appeared to be more common in the autoimmune group. Longer follow-up of our patients and further studies examining extranodal vs nodal and splenic MZL are indeed warranted to further examine the effect of AID on survival and risk of relapse in all subtypes of B-NHL. Our findings should not call for overtreatment in extranodal MZL cases, but do call for increased vigilance, especially in DLBCL accompanied by AID.

In conclusion, beyond confirming the well-known association between B-NHL and AIDs, we found that AID is an adverse prognostic factor in B-NHL, associated with poorer OS and RFS in DLBCL. These findings are somewhat surprising given the beneficial effects of rituximab in many B-cell mediated AIDs[19] and its nearly ubiquitous use in current therapy of DLBCL. They are also of concern given the limitation (and frequent contraindication) of immunotherapy administration in patients with active AIDs.

The inferior RFS and OS in DLBCL suggest the presence of mechanisms of resistance to traditional chemoimmunotherapy in AID-associated lymphoma. While mechanisms for lymphoma transformation in AID have been suggested,[18] none have yet been raised regarding prognosis or response to therapy. Further work should examine cell-of-origin and molecular prognostic markers in AID-associated NHL, and attention to this risk group should lead to more effective therapies in these unusual lymphomas.

ETHICS STATEMENT

The study was approved by the ethics committee of Hadassah Medical Organization.

ROLE OF THE FUNDING SOURCE

The funding sources played no role in the study's design, execution or analysis.

ACKNOWLEDGEMENTS

This study was made possible by the generous support of the American people through the United States Agency for International Development (USAID)/MERC grant no. TA-MOU-11-M31-025. The contents are the responsibility of the authors and do not necessarily reflect the views of USAID or the United States Government; Israel Science Foundation (ISF) grant no. 877/10; and the Hadassah University Hospital Compensatory Fund. We thank Noemie Cohen for data entry.

CONFLICT OF INTEREST

All authors declare no competing financial interests.

AUTHORS' CONTRIBUTIONS

G.K. contributed to data collection, data analysis, data interpretation, literature search, and writing of the manuscript.

M.A. contributed to data collection, literature search, initial data analysis, data interpretation, writing of the manuscript, which comprises part of her requirements for her master degree in public health.[1]

R.A.S. contributed to data collection and interpretation and writing of the manuscript.

R.P. participated in training of study personnel, obtaining funding, data collection and interpretation, and reviewing the manuscript.

D.B.Y. involved in study design, facilitated patient recruitment, aided in obtaining IRB approval and funding, data interpretation, and writing of the manuscript.

O.P. was responsible for the study design, obtaining IRB approval and funding, data collection, review of clinical data, interpretation of data, and writing of the manuscript.

All authors reviewed and approved the final manuscript.

ORCID

Geffen Kleinstern http://orcid.org/0000-0001-6148-0421
Rania Abu Seir http://orcid.org/0000-0002-4625-9742
Ora Paltiel http://orcid.org/0000-0001-8324-3873

REFERENCES

1. Hakulinen T, Isomaki H, Knekt P. Rheumatoid arthritis and cancer studies based on linking nationwide registries in Finland. *Am J Med*. 1985;78(1A):29-32.
2. Kauppi M, Pukkala E, Isomäki H. Elevated incidence of hematologic malignancies in patients with Sjögren's syndrome compared with patients with rheumatoid arthritis (Finland). *Cancer Causes Control: CCC*. 1997;8(2):201-204.
3. Abu-Shakra M, Gladman DD, Urowitz MB. Malignancy in systemic lupus erythematosus. *Arthritis Rheum*. 1996;39(6):1050-1054.
4. Zintzaras E, Voulgarelis M, Moutsopoulos HM. The risk of lymphoma development in autoimmune diseases: a meta-analysis. *Arch Intern Med*. 2005;165(20):2337-2344. https://doi.org/10.1001/archinte.165.20.2337
5. Anderson LA, Gadalla S, Morton LM, et al. Population-based study of autoimmune conditions and the risk of specific lymphoid malignancies. *Int J Cancer*. 2009;125(2):398-405. https://doi.org/10.1002/ijc.24287
6. Fallah M, Liu X, Ji J, Försti A, Sundquist K, Hemminki K. Autoimmune diseases associated with non-Hodgkin lymphoma: a nationwide cohort study. *Ann Oncol: official journal of the European Society for Medical Oncology / ESMO*. 2014;25(10):2025-2030. https://doi.org/10.1093/annonc/mdu365
7. Morton LM, Slager SL, Cerhan JR, et al. Etiologic heterogeneity among non-Hodgkin lymphoma subtypes: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. *J Natl Cancer Inst Monogr*. 2014;2014(48):130-144. https://doi.org/10.1093/jncimonographs/lgu013
8. Cerhan JR, Kricker A, Paltiel O, et al. Medical history, lifestyle, family history, and occupational risk factors for diffuse large B-cell lymphoma: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. *J Natl Cancer Inst Monogr*. 2014;2014(48):15-25. https://doi.org/10.1093/jncimonographs/lgu010
9. Bracci PM, Benavente Y, Turner JJ, et al. Medical history, lifestyle, family history, and occupational risk factors for marginal zone lymphoma: the InterLymph Non-Hodgkin Lymphoma Subtypes Project.

J Natl Cancer Inst Monogr. 2014;2014(48):52-65. https://doi.org/10.1093/jncimonographs/lgu011

10. Landgren O, Pfeiffer RM, Kristinsson SY, Björkholm M. Survival patterns in patients with Hodgkin's lymphoma with a pre-existing hospital discharge diagnosis of autoimmune disease. *J Clin Oncol Off J Am Soc Clin Oncol*. 2010;28(34):5081-5087. https://doi.org/10.1200/JCO.2010.29.2243
11. Sarris AH, Papadimitrakopoulou V, Dimopoulos MA, et al. Primary parotid lymphoma: the effect of International Prognostic Index on outcome. *Leuk Lymphoma*. 1997;26(1-2):49-56. https://doi.org/10.3109/10428199709109157
12. Suvajdzic N, Djurdjevic P, Todorovic M, et al. Clinical characteristics of patients with lymphoproliferative neoplasms in the setting of systemic autoimmune diseases. *Med Oncol (Northwood, London, England)*. 2012;29(3):2207-2211. https://doi.org/10.1007/s12032-011-0022-x
13. Simard JF, Baecklund F, Chang ET, et al. Lifestyle factors, autoimmune disease and family history in prognosis of non-Hodgkin lymphoma overall and subtypes. *Int J Cancer*. 2013;132(11):2659-2666. https://doi.org/10.1002/ijc.27944
14. Wöhrer S, Troch M, Streubel B, et al. MALT lymphoma in patients with autoimmune diseases: a comparative analysis of characteristics and clinical course. *Leukemia*. 2007;21(8):1812-1818. https://doi.org/10.1038/sj.leu.2404782
15. Kleinstern G, Abu Seir R, Perlman R, et al. Ethnic variation in medical and lifestyle risk factors for B cell non-Hodgkin lymphoma: a case-control study among Israelis and Palestinians Chu P-Y, ed. *PLoS One* 2017;12(2):e0171709. https://doi.org/10.1371/journal.pone.0171709.
16. Wang SS, Vajdic CM, Linet MS, et al. Associations of non-Hodgkin lymphoma (NHL) risk with autoimmune conditions according to putative NHL loci. *Am J Epidemiol*. 2015;181(6):406-421. https://doi.org/10.1093/aje/kwu290
17. International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med*. 1993;329(14):987-994. https://doi.org/10.1056/NEJM199309303291402
18. Hemminki K, Liu X, Ji J, Försti A. Origin of B-cell neoplasms in autoimmune disease. Dolcetti R, ed. *PLoS One* 2016; 11(6):e0158360. https://doi.org/10.1371/journal.pone.0158360.
19. Tony H-P, Burmester G, Schulze-Koops H, et al. Safety and clinical outcomes of rituximab therapy in patients with different autoimmune diseases: experience from a national registry (GRAID). *Arthritis Res Ther*. 2011;13(3):R75. https://doi.org/10.1186/ar3337

How to cite this article: Kleinstern G, Averbuch M, Abu Seir R, Perlman R, Ben Yehuda D, Paltiel O. Presence of autoimmune disease affects not only risk but also survival in patients with B-cell non-Hodgkin lymphoma. *Hematological Oncology*. 2018. https://doi.org/10.1002/hon.2498