

# Autoimmune cytopenias in patients with malignant lymphoma: A multicenter report by the Polish Lymphoma Research Group

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## Abstract

**Background.** Autoimmune cytopenias (ACs), including immune thrombocytopenia (ITP), autoimmune hemolytic anemia (AIHA) and autoimmune granulocytopenia, are rare complications observed in lymphoma patients. They may appear before, during or after lymphoma diagnosis, whether the patients had disease progression or not.

**Objectives.** This study aims to correlate ACs with lymphoma type, disease course and prognosis. We performed a multicenter retrospective analysis of adult patients with malignant lymphoma and ACs coexistence diagnosed and treated in centers aligned with the Polish Lymphoma Research Group (PLRG).

**Materials and methods.** The analysis covers the years 2016–2022 and included 51 patients comprised of 23 women and 28 men. Of these, 35 patients were diagnosed with AIHA, 15 patients with ITP and 1 patient with both AIHA and ITP.

**Results.** The most common type of lymphoma was Hodgkin lymphoma (HL) (12 patients) and diffuse large B-cell lymphoma (DLBCL) (14 patients). At the time of diagnosis, 31 (61%) of patients had stage 4 of HL or DLBCL, according to Ann Arbor classification. In total, the response to treatment was evaluated in 50 patients, with 25 being in complete remission and 6 in partial remission. We observed that B cell symptoms ( $p = 0.036$ ), bone marrow involvement ( $p = 0.073$ ), splenomegaly ( $p = 0.025$ ), and more than 2 lines of treatment were more common in AIHA compared to ITP patients. Conversely, eucopenia ( $p = 0.056$ ) and ACs without lymphoma progression ( $p = 0.002$ ) were more often diagnosed in ITP patients.

**Conclusions.** In the study group, relapsed and refractory disease was observed more often, and shorter overall survival (OS) was noted in patients with DLBCL. We found that AC is associated with a worse prognosis in comparison to the general population of lymphoma patients. There were no differences in response to AC therapy. To have more accurate data, a larger group, as part of a multicenter study, should be evaluated.

**Key words:** lymphoma, ITP, AIHA, immune complications, autoimmune cytopenia

## Cite as

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## Background

Autoimmune cytopenias (ACs) are a group of heterogeneous but closely related conditions defined by immune-mediated destruction of hematologic cell lineages, including white blood cells (neutrophils), red blood cells and platelets.<sup>1</sup> This destruction can be primary or secondary to other illnesses. Autoimmunity results from a complex interplay of genetic and environmental factors, including infections and drugs. Autoimmune cytopenias can be formally classified as idiopathic, consisting of single lineage destruction, including autoimmune hemolytic anemia (AIHA), immune thrombocytopenia (ITP) and, more rarely, autoimmune granulocytopenia (AG), as well as multi-lineage destruction, known as Evans syndrome.<sup>2</sup> The relative frequency of each of the clinical forms of ACs remains uncertain, with conflicting results from different studies. Older literature reported the highest rates of AIHA with lower rates of ITP and multi-lineage autoimmune cytopenia. The diagnosis of AC is usually made according to the criteria of the respective disease, and in some cases, antibodies are detected without symptomatic disease.

Secondary AC results from another cause, including medications, rheumatologic disorders, immunodeficiencies, lymphoproliferative disorders, malignancies, or as a complication of organ or hematopoietic stem cell transplant (HSCT).<sup>3</sup> The association between lymphoma and AC has long been noted. While definitive evidence linking the causality of these diseases is rare, there is compelling evidence of their co-occurrence. Autoimmune cytopenia may be diagnosed before, at presentation, or at any point during the course of lymphoma, and may also be observed in both untreated and treated patients. Autoimmune cytopenia occurs in approx. 5–10% of chronic lymphocytic leukemia (CLL) patients,<sup>4</sup> although so far, the exact prevalence of AC in lymphoma patients remains unclear. The frequency of AC varies among entities, with a high prevalence in certain types of lymphomas. Most AC are associated with B cell lymphomas and are much less frequent with T cell non-Hodgkin lymphomas (NSLs).

## Objectives

Because of the rarity of lymphoma-associated AC, the data on the clinical characteristics, treatment of the disease, as well as prognosis are extremely poor and based mostly on case reports, with some larger groups described. Therefore, taking into consideration the scarcity of data and simultaneously the need to increase physician awareness of the diagnosis of ACs in lymphoma patients, we conducted a retrospective study at the Polish Lymphoma Research Group (PLRG) between 2016 and 2022.

## Materials and methods

### Data source

The study was performed on behalf of the Extranodal Lymphomas Working Group of the PLRG, which is a voluntary organization comprising hematological and oncological centers in Poland that provide care for lymphoma patients. All member centers were invited to participate in this study and provide additional study-specific data about eligible patients.

### Study population and outcome

This study was a retrospective analysis of all patients who were diagnosed with ACs either simultaneously or sequentially with lymphoma. The analysis includes patients diagnosed during the period 2016–2022.

The primary objective of the study was to analyze the outcome of lymphoma treatment, i.e., overall survival (OS) of the patients with ACs and mortality. The secondary objectives were to examine the clinical presentation of lymphoma, the efficacy of lymphoma treatment, progression-free survival (PFS), and factors associated with OS and PFS.

### Diagnosis of autoimmune cytopenia

The presence of AC, namely AIHA, ITP and AG, was respectively recorded based on patients' medical records. The diagnosis of AIHA was based on the presence of anemia (a hemoglobin level below 12 g/dL), and laboratory evidence of hemolysis, namely strong direct antiglobulin test (DAT) positivity, elevated absolute reticulocyte count, an elevated lactate dehydrogenase (LDH), an elevated indirect bilirubin level, and a low serum haptoglobin level. Immune thrombocytopenia was diagnosed in patients with a platelet count below 100,000/ $\mu$ L in whom other causes of thrombocytopenia have been ruled out.

All cases had biopsy-confirmed lymphoma and were diagnosed with AC at any time before, concurrently or after. The histological lymphoma diagnosis was established based on the 2008 World Health Organization (WHO) classification.<sup>5</sup>

We assessed the incidence, clinical characteristics, treatment strategies, and outcome of lymphoma patients experiencing AC, and compared their data with concurrent patients with Hodgkin lymphoma (HL) and diffuse large B-cell lymphoma (DLBCL) population who had no evidence of AC.

### Response to treatment

Response to treatment was assessed as proposed by the most recent system, known as the Lugano classification, which applies to both HL and NHL.<sup>6</sup> Overall survival was calculated from the lymphoma diagnosis

to the last follow-up visit or death. Progression-free survival was estimated as the interval between the date of diagnosis and the estimated date of progression or death or end of follow-up.

## Statistical analyses

Kaplan–Meier plots and log-rank tests were performed to visualize and compare survival curves. The median follow-up was calculated using the Schemper and Smith method. Pearson's  $\chi^2$  test was used to analyze the independence of categorical variables. Appropriate corrections were used where needed: the Yates's correction for continuity or Fisher's exact test. In general, if any of the expected frequencies of the  $2 \times 2$  table was below 15, Yates's correction was used, but when it was below 5, the Fisher's exact test was used.

P-values  $<0.05$  were considered significant. The Shapiro–Wilk test was used to confirm where the continuous variables had a normal distribution. Depending on the variable distribution, they were presented as mean  $\pm$  standard deviation ( $M \pm SD$ ). A normal probability plot of continuous variables (age at diagnosis) is provided in Fig. 1. All statistical analyses were performed in MedCalc (MedCalc Software Ltd, Ostend, Belgium).

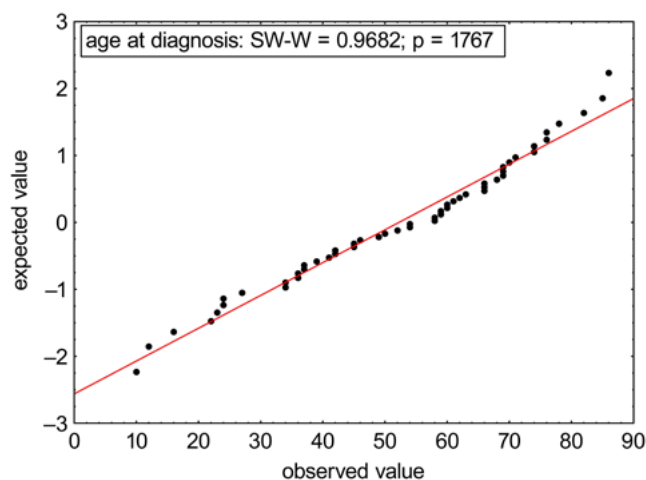


Fig. 1. Normal probability plot of age at diagnosis

## Results

### Patients

We identified 51 patients diagnosed with AC and lymphoma in 5 PLRG centers. Of these, 23 (45%) were women, and the mean age at lymphoma diagnosis was 52 years (95% confidence interval (95% CI):  $46.7\text{--}57.7 \pm 19.7$ ). Thirty-five patients were diagnosed with AIHA, 15 with ITP and 1 patient with both AIHA and ITP. The most common diagnosis of lymphoma was DLBCL (15 patients) and HL (12 patients), followed by indolent lymphoma, including marginal zone lymphoma, follicular lymphoma, mantle

cell lymphoma (19 patients) and T cell lymphoma (5 patients). Thirty-one patients (61%) were in stage IV according to the Ann Arbor classification at the time of diagnosis (23 AIHA and 8 ITP, 66% and 53%, respectively), although most patients were in a good clinical stage (Eastern Cooperative Oncology Group (ECOG)-0 in 16 patients, ECOG-1 in 26 patients, 31% and 51%, respectively). Thirty-four patients (68%) had B cell symptoms (27 AIHA and 7 ITP, 77% and 47%, respectively), and 36 patients (71%) had extranodal lymphoma at the time of diagnosis (26 AIHA and 10 ITP, 74% and 67%, respectively). Interestingly, in the AIHA group, 14/34 patients (41%) had bone marrow involvement. A high prognostic index was found in 26 out of 49 patients (53%), which was adequate for their specific type of lymphoma (20 AIHA and 6 ITP, 57% and 40%, respectively). The detailed patient characteristics are provided in Table 1.

We then made the comparison between the AIHA and ITP group with all parameters according to patient characteristics (age, sex, ECOG, B symptoms, nodal and extranodal lymphoma), comorbidities, risk factors (Ann Arbor classification, prognostic index, type of lymphoma), morphology, biochemistry and response to the treatment, observing some major differences. It was seen that in the AIHA group (27/34, 79%), significantly more patients had B symptoms than in the ITP group (7/15, 47%) ( $\chi^2 = 3.90$ ,  $p = 0.049$ ,  $\chi^2$  test with Yates's correction). In the AIHA group, LDH during the lymphoma diagnosis was significantly higher than in the ITP group ( $p = 0.002$ ). Interestingly, patients with AIHA had disease localized in the spleen less often than in the ITP group (2.9% compared to 25.0%,  $p = 0.029$ , Fisher's exact test). Moreover, the AIHA group had AC diagnosed without disease progression more frequently than in ITP ( $p = 0.039$ ). While not a significant result, when comparing the AIHA group to ITP, we observed less type 2 diabetes ( $p = 0.186$ , Fisher's exact test), while asthma ( $p = 0.295$ , Fisher's exact test) was more frequently observed. The data also suggested that in the AIHA group, bone marrow tended to be more frequently involved in the lymphoma ( $p = 0.203$ , Fisher's exact test). The treatment analysis showed that patients with AIHA had radiotherapy less often in relapsed and refractory disease ( $p = 0.263$ , Fisher's exact test). Moreover, intravenous immunoglobulin (IVIG) and splenectomy were used more frequently in the ITP group as a salvage treatment ( $p = 0.235$  and  $p = 0.294$  respectively; Fisher's exact test). All data are shown in Table 2.

### Treatment

The median observation time of our cohort was 78.9 months (95% CI: 61.4–143.2 months), and 49 out of 51 patients received treatment for lymphoma. A variety of different protocols was used for first-line therapy, including 47 patients (96%) treated with chemotherapy and 27 patients (55%) with immunotherapy, while 8 patients (16%) required radiotherapy. Of these, 20 patients (39%),

**Table 1.** Patient characteristics

AC		AIHA	ITP	Total
Number of patients		35	16	51
Sex	female	15 (43%)	8 (50%)	23 (45%)
	male	20 (57%)	8 (50%)	28 (55%)
At lymphoma diagnosis				
Age of diagnosis [years], median (range)		59 (18–89)		
Lymphoma type	DLBCL	10 (26%)	5 (31%)	15 (31%)
	HL	6 (17%)	6 (39%)	12 (24%)
	indolent B-cell	16 (46%)	3 (18%)	19 (27%)
	T-cell	3 (11%)	2 (12%)	4 (8%)
Ann Arbor	I	3 (9%)	3 (20%)	6 (12%)
	II	2 (6%)	1 (7%)	3 (6%)
	III	6 (18%)	3 (20%)	9 (18%)
	IV	23 (67%)	8 (53%)	31 (64%)
Performance status according to ECOG	0	13 (37%)	3 (19%)	17 (32%)
	1	18 (51%)	8 (54%)	26 (52%)
	2	3 (9%)	4 (27%)	7 (14%)
	3	1 (3%)	0 (0%)	1 (2%)
Comorbidities	yes	24 (66%)	10 (67%)	34 (68%)
	no	12 (34%)	5 (33%)	17 (32%)
B symptoms	yes	27 (77%)	7 (47%)	34 (68%)
	no	8 (23%)	8 (53%)	17 (32%)
Extranodal disease	yes	26 (74%)	10 (63%)	36 (71%)
	no	9 (26%)	6 (37%)	15 (29%)
Bone marrow involvement	yes	14 (40%)	3 (19%)	17 (33%)
	no	21 (60%)	13 (81%)	34 (67%)
Prognostic index	low	3 (9%)	3 (20%)	6 (12%)
	intermediate	11 (32%)	6 (40%)	17 (35%)
	high	20 (59%)	6 (40%)	26 (53%)

AIHA – autoimmune hemolytic anemia; ITP – immune thrombocytopenia; AC – autoimmune cytopenia; DLBCL – diffuse large B-cell lymphoma; ECOG – Eastern Cooperative Oncology Group; HL – Hodgkin lymphoma.

**Table 2.** Comparison between the AIHA and ITP groups (symptoms in bold were more frequent)

AC	AIHA	ITP	p-value
B symptoms	<b>27/35 (77%)</b>	7/15 (47%)	0.049
Spleen involvement with lymphoma	1/35 (3%)	<b>4/16 (25%)</b>	0.029
Elevated LDH	<b>30/35 (86%)</b>	4/16 (25%)	0.002
Immunotherapy at relapse	4/13 (31%)	<b>4/5 (80%)</b>	0.088
AC diagnosis with lymphoma progression	<b>3/13 (23%)</b>	0/5 (0%)	0.039
Diabetes	3/35 (9%)	<b>4/16 (25%)</b>	0.186
Asthma	<b>4/35 (11%)</b>	0/16 (0%)	0.295
Bone marrow involvement with lymphoma	<b>14/35 (40%)</b>	3/16 (19%)	0.203
Radiotherapy at relapse	0/35 (0%)	<b>1/5 (20%)</b>	0.263
AC treatment with IVIG	1/35 (3%)	<b>4/16 (25%)</b>	0.235
AC treatment with splenectomy	1/35 (3%)	<b>3/16 (19%)</b>	0.294

AIHA – autoimmune hemolytic anemia; ITP – immune thrombocytopenia; LDH – lactate dehydrogenase; IVIG – intravenous immunoglobulin; AC – autoimmune cytopenia.

i.e., 15 in AIHA group (44%), and 5 in ITP group (33%), were refractory or relapsed and needed salvage therapy. Finally, 5 patients (10%) had an autologous HSCT, and 2 patients (4%) underwent allogeneic HSCT (Table 3).

Among 49 patients eligible for response assessment, 25 (15 AIHA; 10 ITP) (51%) had complete response (CR) and 6 (3 AIHA; 3 ITP) (12%) had partial response (PR). Moreover,

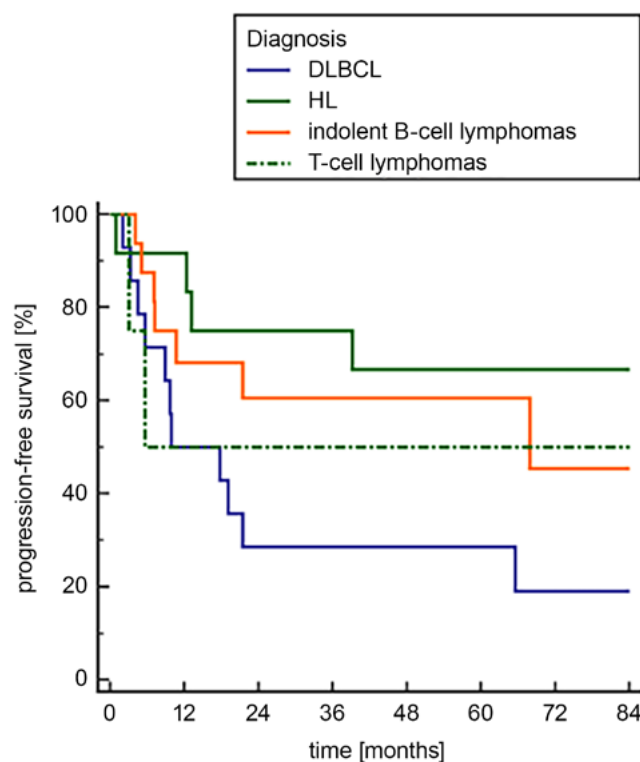
19 patients (39%) had no response or had disease progression after first-line treatment (Table 3). We also observed 20 deaths (38%), with 15 related to lymphoma progression, 2 to hemophagocytic syndrome, 2 to AIHA progression, and 1 to ITP progression.

The diagnosis of AC in a majority of patients was made together with with lymphoma diagnosis or progression

**Table 3.** Response to treatment

AC		AIHA	ITP	Total
Lymphoma treatment		33/35 (94%)	16/16 (100%)	49/51 (96%)
chemotherapy		32/35 (91%)	15/16 (94%)	47/51 (92%)
immunotherapy		20/35 (57%)	7/16 (44%)	27/51 (53%)
radiotherapy		5/35 (14%)	3/16 (19%)	8/51 (16%)
Response to treatment	CR	15/35 (43%)	10/16 (62%)	25/51 (49%)
	PR	3/35 (9%)	3/16 (19%)	6/51 (12%)
	PD	17/35 (49%)	3/16 (19%)	20/51 (39%)
Treatment in relapsed disease		14/35 (40%)	5/16 (31%)	19/51 (37%)
chemotherapy		13/14 (93%)	5/5 (100%)	18/19 (95%)
immunotherapy		4/14 (29%)	4/5 (80%)	8/19 (42%)
radiotherapy		0/14 (0%)	1/5 (20%)	1/19 (5%)
autoHSCT		4/35 (11%)	1/16 (6%)	5/51 (10%)
alloHSCT		1/35 (3%)	1/16 (6%)	2/51 (4%)
AC treatment		35/35 (100%)	12/16 (75%)	47/51 (92%)
1 line		0/35 (0%)	2/16 (13%)	2/51 (4%)
2 lines		15/35 (43%)	5/16 (31%)	20/51 (39%)
>3 lines		20/35 (57%)	5/16 (31%)	27/51 (53%)
Deaths		15/35 (43%)	5/16 (31%)	20/51 (39%)

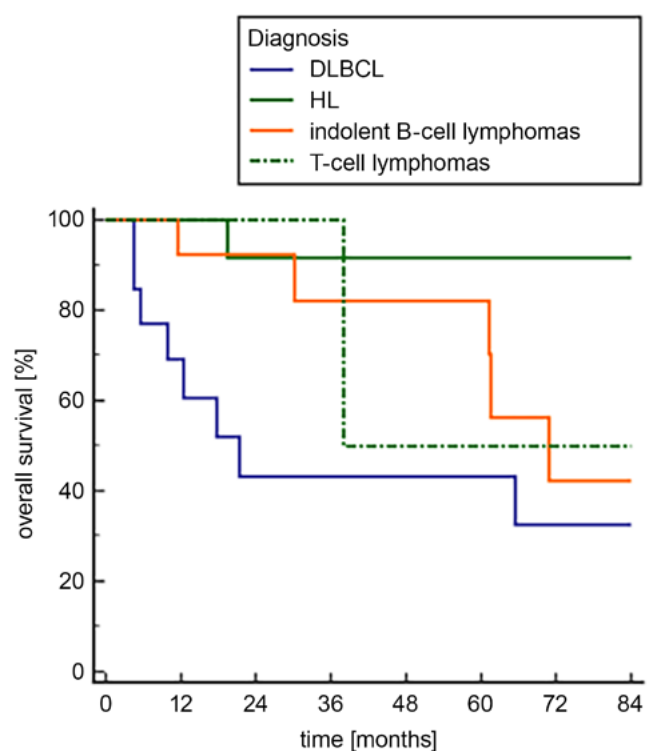
AIHA – autoimmune hemolytic anemia; ITP – immune thrombocytopenia; AC – autoimmune cytopenia; CR – complete response; PR – partial response; PD – progressive disease; autoHSCT – autologous hematopoietic stem cell transplantation; alloHSCT – allogeneic hematopoietic stem cell transplantation.



**Fig. 2.** Progression-free survival (PFS) in the studied groups of patients. Patients with DLBCL had a trend into poorer PFS compared to the other diagnosis groups, but the difference did not yield statistical significance (log-rank p-value = 0.063)

DLBCL – diffuse large B-cell lymphoma; HL – Hodgkin lymphoma.

(35 out of 51 patients, 68%). A further 8 patients (16%) had their AC diagnosis before lymphoma, and 8 patients (16%) had AC after lymphoma diagnosis without disease progression. Out of 35 patients with a diagnosis of AIHA, all received treatment, with 8 patients (23%) receiving 1 line

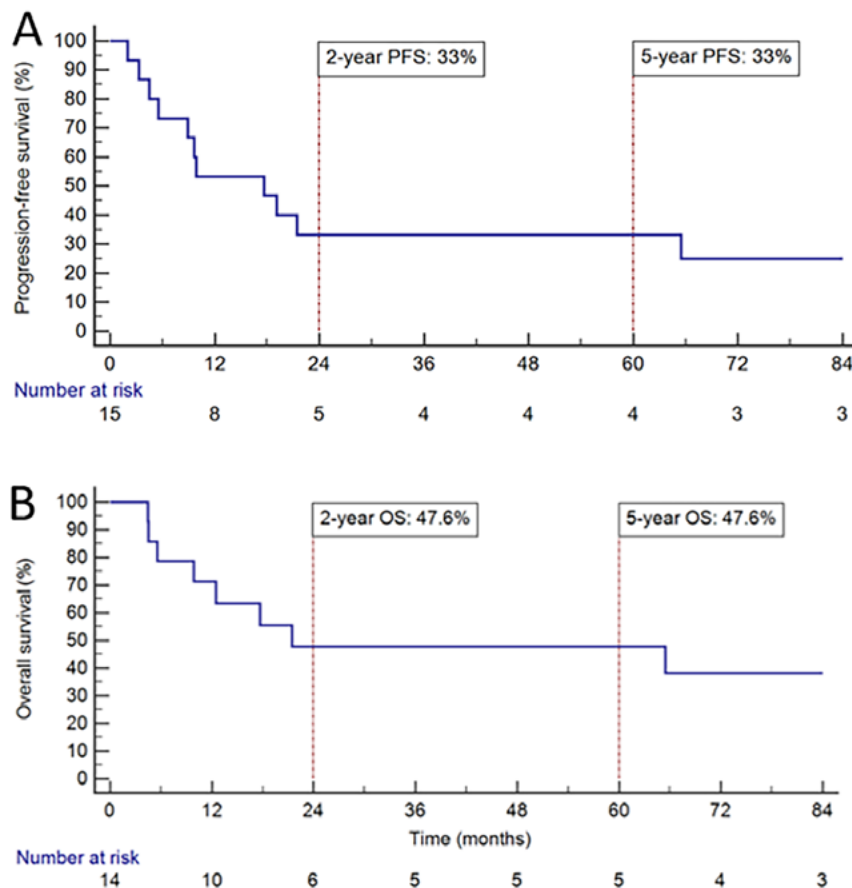


**Fig. 3.** Overall survival (OS) in the studied groups of patients. Patients with Hodgkin lymphoma (HL) had a significantly better outcome in terms of OS (median not reached) compared to other groups: DLBCL (median OS: 1.8 years), indolent B-cell lymphoma (median OS: 5.9 years) and T-cell lymphoma (median OS: 3.2 years). Log-rank p-value = 0.008

DLBCL – diffuse large B-cell lymphoma.

of treatment, 6 (17%) had 2 lines of treatment and 21 (60%) had 3 or more lines of treatment. Out of 16 patients with ITP diagnosis, 2 were not treated at all (12.5%), 5 (31%) had 1 line of treatment, 7 (44%) had 2 lines of therapy and 2 (12.5%) had 3 or more lines.





**Fig. 4.** Progression-free survival (PFS) (A) and overall survival (OS) (B) in the diffuse large B-cell lymphoma (DLBCL) group. The median PFS was 17.7 months (95% confidence interval (95% CI): 8.9–65.5), with a 2-year PFS rate of 33% and a 5-year PFS rate of 33%. The median OS for this group was 21.4 months (95% CI: 9.9–65.5) with a 2-year OS rate of 47.6% and a 5-year OS rate of 47.6%.

## Survival analysis

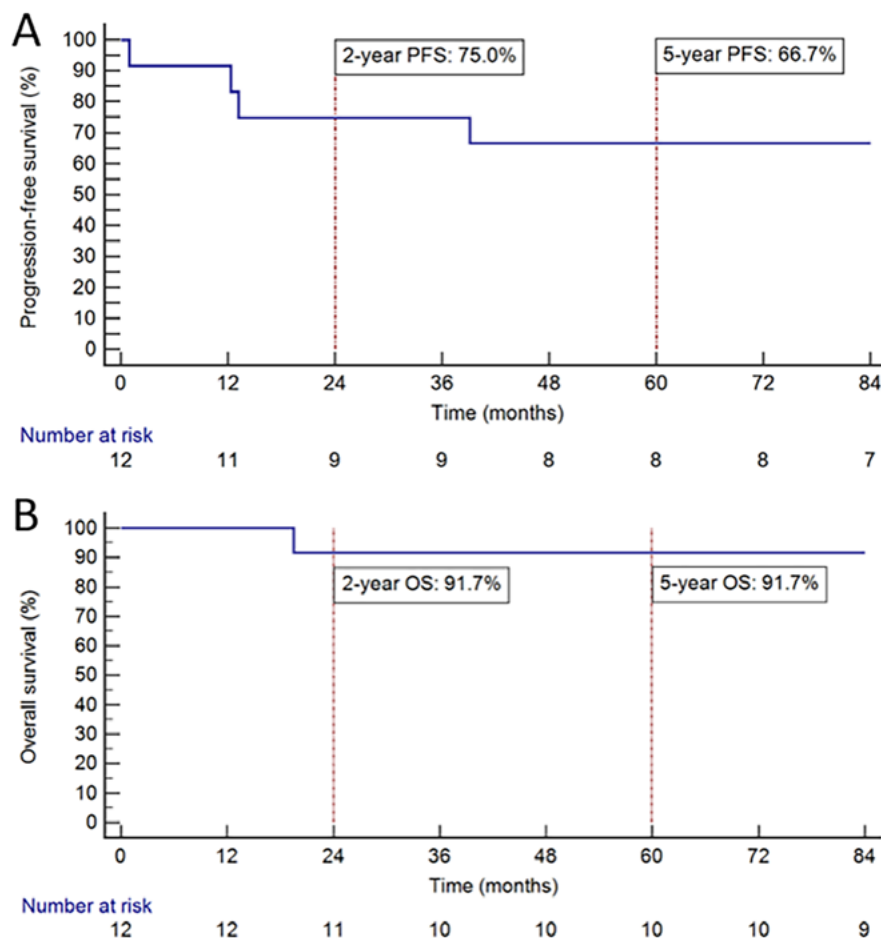
The data on survival was available for 50 patients, and the median observation time in our cohort was 78.9 months (95% CI: 61.4–143.2 months). The median PFS in the whole cohort was 65.5 months (95% CI: 13.2–288.4), although there was a trend towards a lower PFS in DLBCL patients compared to the other groups (log-rank  $p$ -value = 0.063) (Fig. 2). The median OS of the whole study group was 27.2 years (95% CI: 65.5–325.9 months), and patients with HL had a significantly better outcome in terms of OS (median not reached) compared to other groups: DLBCL (median OS: 1.8 years), indolent B-cell lymphoma (median OS: 5.9 years) and T cell lymphoma (median OS: 3.2 years). Log-rank  $p$ -value was 0.008 (Fig. 3).

For the DLBCL group (survival data available for 15 patients), median PFS was 17.7 months (95% CI: 8.9–65.5), with a 2-year PFS rate of 33% and 5-year PFS rate of 33% (Fig. 4A). Median OS for this group was 21.4 months (95% CI: 9.9–65.5) with a 2-year OS rate of 47.6% and a 5-year OS rate of 47.6% (Fig. 4B). For the HL group, the median PFS was not reached, with a 2-year PFS rate of 75.0% and a 5-year PFS rate of 66.7% (Fig. 5A). Moreover, the median OS was not reached, with a 2-year OS rate of 91.7% and a 5-year OS rate of 91.7% (Fig. 5B). Moreover, patients with DLBCL had both shorter PFS (log-rank  $p$  = 0.0115) and OS ( $p$  = 0.003) when compared to patients with HL.

## Discussion

Despite the long recognition of the coexistence of lymphoma and AC, the exact characteristics of patients with AC and lymphoma remain poorly defined. In our multi-center study, we investigated a large cohort of Polish patients, and we analyzed their clinical and prognostic profiles. To the best of our knowledge, this study is the largest to report AC-associated lymphoma. Previously, the largest cohort reported so far was Hu et al., with 28 patients with B cell and T cell lymphoma.<sup>7</sup> In their study group, 24 patients were diagnosed with AIHA and 6 with ITP. Similar to our study with 51 patients, the majority were DLBCL (10 out of 28; 36%), followed by HL and B cell indolent lymphoma (less than 30%).

Our study revealed a distinct pattern of a worse prognostic profile, with 61% of investigated patients in an advanced stage of the disease (66% AIHA; 53% ITP), i.e., at stage IV according to the Ann Arbor classification for lymphoma diagnosis. The IPI adequate for different types of lymphoma diagnosis was high in 57% of AIHA patients and 40% of those with ITP. Moreover, 68% of patients had B symptoms (77% AIHA; 47% ITP) and 71% had extranodal disease (74% AIHA; 67% ITP), both known to be poor prognostic factors for DLBCL patients. It was interesting that 41% of AIHA patients had bone marrow involvement. The extranodal involvement of lymphoma observed



**Fig. 5.** Progression-free survival (PFS) (A) and overall survival (OS) (B) in the Hodgkin lymphoma (HL) group. The median PFS was not reached with a 2-year PFS rate of 75.0% and a 5-year PFS rate of 66.7%. Median OS was not reached with a 2-year OS rate of 91.7% and a 5-year OS rate of 91.7%.

in patients who also had an AC diagnosis was consistent with findings published by Hu et al.<sup>7</sup> Similar to our results, in work by Pinczes et al. examining 16 patients with HL and AC, the authors observed advanced disease features such as stage III/IV, bone marrow involvement and B symptoms.<sup>8</sup> The same observation was published by Dimou et al., who reported a remarkable predominance of advanced-stage lymphoma.<sup>9</sup> All these results are consistent with our data in a larger group.

Although the number of AC cases was small, we found statistically significant differences between the AIHA and ITP groups. We observed that B symptoms, elevated LDH and AC diagnosis connected with lymphoma progression were statistically more likely in AIHA compared to ITP patients and may be associated with worse clinical outcome in the AIHA group. Conversely, spleen involvement with lymphoma was more often found in ITP patients. We have also seen a trend that AIHA patients were diagnosed with asthma more often and had bone marrow involvement with lymphoma during the diagnosis. Moreover, the ITP group seemed to be more often diabetic and was treated with radiotherapy following relapse. However, to conduct a more accurate analysis between these 2 groups, a larger number of patients is necessary.

Lechner and Chen observed that out of 39 lymphoma patients with AC, 13 relapsed or were refractory to first-line treatment.<sup>2</sup> This was similar to our PLRG database, in which we were able to identify 39% of relapsed and refractory disease (44% in AIHA and 33% in the ITP group). In the relapsed and refractory group, 5 patients undergo autologous HSCT (10%) and 2 allogeneic HSCT (4%). Historically, most patients are cured with anthracycline-containing immunochemotherapy, and approx. 1 in 4 experience primary refractory disease or relapse (25–30%).<sup>10</sup> Similar data were published by the Hemato-Oncology Latin America Observational Registry Study (HOLA), in which out of 578 DLBCL patients, 29% had relapsed or refractory AC.<sup>11</sup> Furthermore, response to first-line treatment in our group was poor, with CR in 51% and PR in 12%. Moreover, 20 patients died (38%), mainly due to disease progression. In other studies with higher subject numbers, 20–30% of patients with NHL and 15% with HL will not be able to achieve a CR with standard induction.<sup>12,13</sup> Our experience suggests that the coexistence of AC and lymphoma is associated with more aggressive clinical behavior, inferior outcomes and increased risk of death. However, our study numbers were too low to draw a definitive conclusion.

In the present study, we found that the median PFS was 17.7 months in the DLBCL group, a much lower result

compared to data from other studies. In the HOLA study, the median PFS was 7.7 years.<sup>11</sup> Moreover, our 5-year PFS was much worse, with 33% in our study compared to 56.2% in the HOLA study. Moreover, 2- and 5-year OS for our DLBCL group were both 47.6%; again, a much lower result compared to other large cohort studies. In data from an article published by Mauer et al. in the SEAL database, 2-year OS was 87% and 5-year OS was 80%.<sup>14</sup> We observed that in our patients with the concurrence of AC and lymphoma, not only efficacy but also OS was lower with AC than without. The possible explanation is that the development of AC affects the survival of lymphoma patients, especially in the DLBCL group.

Finally, we observed the trend of decreased PFS in DLBCL patients ( $p = 0.063$ ) compared to other lymphoma groups. Moreover, patients with HL had significantly better outcomes in OS compared to all the other lymphoma groups. These results are consistent with the prognosis of HL and DLBCL in patients without AC. It may demonstrate that AC worsens the prognosis of all lymphoma subtypes, not only DLBCL. Still, the most important prognostic factor for OS and PFS is the histopathological type of lymphoma.

## Limitations

The main limitation of this study is its retrospective nature, but evaluation of characteristics and outcomes of lymphoma-associated AC is not possible prospectively. Another limitation may be a relatively small sample size. However, the rarity of the diagnosis precludes the possibility of gathering a large group of patients, even if performed mutationally. According to our knowledge, we pooled one of the biggest study groups so far. Nevertheless, we believe that the inclusion of all patients from all age groups and different lymphoma subtypes represents a real group and provides clinically useful information. Thus, it may be the main strength of this analysis.

## Conclusions

Lymphoma patients with AC are more likely to present advanced stages of the disease and seem to have worse outcomes and responses to treatment. This association can be a significant prognostic factor, especially for the DLBCL group, both for PFS and OS. Moreover, AIHA patients have a stronger trend towards increased mortality. Patients who present with any kind of AC should always be assessed for relapse of refractory disease. Large prospective studies are needed to confirm our preliminary findings.

## Data availability

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

## Consent for publication

Not applicable.

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