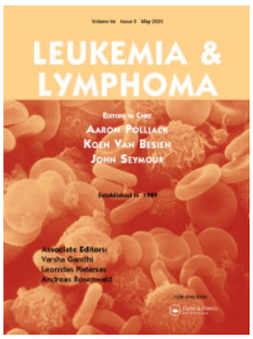

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The journey of patients with diffuse large B-cell lymphoma: from symptoms to diagnosis

Prokop Vodicka[a], Michal Masar[a], Katerina Benesova[a], Jan Koren[a], Pavel Klener[a], Kamila Polgarova[a], Jan Galko[b], Radek Jaksa[b], Vit Campr[c], Jitka Dlouha[a,d], Sarka Hrabetova[a,d], Petra Blahovcova[a,d], Magdalena Klanova[a] and Marek Trneny[a]

[a]First Department of Medicine, First Faculty of Medicine, Charles University and General Hospital, Prague, Czech Republic; [b]Institute of Pathology, First Faculty of Medicine, Charles University and General Hospital, Prague, Czech Republic; [c]Department of Pathology and Molecular Medicine, Second Faculty of Medicine, Charles University and Motol University Hospital, Prague, Czech Republic; [d]Datacentre, Czech Lymphoma Study Group, Prague, Czech Republic

ABSTRACT

Symptoms of lymphomas include peripheral lymphadenopathy, B-symptoms, and other organ-specific symptoms; however, data on initial symptoms incidence in diffuse large B-cell lymphoma (DLBCL) remain limited. We aimed to investigate real-world patterns of initial DLBCL symptoms, correlating them with baseline characteristics and symptom onset-to-diagnosis interval. Patients with DLBCL diagnosed between 2010 and 2021 receiving R-CHOP were screened. 706 individuals with reported initial symptoms were analyzed. 682 (97%) patients had documented symptoms; remaining 24 patients (3%) had incidental findings discovered during examinations for unrelated reasons. Abdominal/gastrointestinal complaints were the most prevalent symptoms (26%), followed by peripheral lymphadenopathy (22%), and B-symptoms (13%). The median symptom-to-diagnosis interval was 10 weeks. Peripheral lymphadenopathy and testicular tumors correlated with low-risk characteristics, with testicular DLBCL featuring a shorter symptom-to-diagnosis interval. Limb pain/swelling and back pain were associated with high-risk characteristics and prolonged symptom-to-diagnosis interval. This analysis enhances our understanding of DLBCL symptomatology, aiding in timely recognition and management.

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KEYWORDS
Non-Hodgkin lymphoma; extranodal lymphoma; diffuse large B-cell lymphoma; symptoms; time to diagnosis

Introduction

Symptoms of hematologic malignancies vary across diagnoses, and the proportions of patients diagnosed incidentally, without reported symptoms, also differ [1,2]. Common symptoms of lymphomas typically encompass peripheral lymphadenopathy, B-symptoms (i.e. drenching night sweats, unexplained fever above 38 °C, and/or unintended weight loss of greater than 10% of body weight in the six preceding months), gastrointestinal (GIT) issues, and other manifestations correlating with involved lymph node sites or affected organs [3–7]. Despite the prevalence of these symptoms, there is a notable lack of comprehensive data on the incidence and types of initial lymphoma symptoms.

It has been previously reported that the time from diagnosis (i.e. biopsy) to treatment initiation correlates with outcomes in aggressive lymphomas [8], and is also considered to be an important bias in clinical trials. However, no study has systematically explored the impact of different lymphoma symptoms on the duration between the onset of clinical manifestations and the subsequent diagnosis.

The primary objective of this analysis was to delineate a real-world pattern of initial symptoms specifically associated with diffuse large B-cell lymphoma (DLBCL). These symptoms prompted patients to seek medical attention, initiating the diagnostic process that led to the diagnosis of DLBCL. The aim was also to correlate these findings with baseline characteristics. Additionally, we examined the correlation between various types of symptoms and the time elapsed from the first manifestation of DLBCL to the final diagnosis.

CONTACT Marek Trneny trneny@cesnet.cz First Department of Medicine, First Faculty of Medicine, Charles University and General Hospital, U Nemocnice 499/2, Prague 2, 128 08, Czech Republic

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Methods

Consecutive patients diagnosed with *de novo* systemic DLBCL, not otherwise specified (NOS), or high-grade B-cell non-Hodgkin lymphomas (B-NHL), NOS, who were subsequently treated at the First Department of Medicine, Charles University and General Hospital in Prague, Czech Republic, were screened for this study ($n = 1714$). Their data were prospectively collected in the Czech non-Hodgkin lymphoma registry 'NiHiL' (NCT03199066). The diagnoses of DLBCL or high-grade B-NHL were made according to the World Health Organization classification of tumors [9]. Pathological analyses were conducted at Czech reference centers for haematopathology, and all findings were confirmed by expert hematopathologists. Data on fluorescence *in situ* hybridization and/or next-generation sequencing to identify high-grade B-NHL with gene rearrangements were not systematically collected in this study; these patients were analyzed as part of a single cohort alongside DLBCL patients. Patients with central nervous system infiltration by DLBCL at diagnosis, as well as with primary mediastinal B-cell lymphoma were excluded from this study.

A total of 981 patients with a date of diagnosis between 1 January 2010 and 31 December 2021 were identified in the NiHiL registry as potentially eligible for the study. Among these, 726 patients (74%) who received at least one cycle of the first-line full-dose chemoimmunotherapeutic regimen R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) were screened for initial symptoms. Remaining patients ($n = 255$) receiving any regimen other than full-dose R-CHOP were excluded. Twenty patients (3%) lacked data on initial symptoms and were consequently excluded. The analysis focused on the remaining 706 patients, of whom 682 (97%) had documented initial symptoms or findings that prompted them to seek medical attention. The remaining 24 patients (3%) had incidental findings discovered during unrelated examinations, initiating the diagnostic process that eventually led to the DLBCL diagnosis.

The types of initial symptoms in the 682 symptomatic patients were retrieved from the medical documentation and grouped into broader categories. Additionally, the interval between the onset of initial symptoms and the date of biopsy (i.e. diagnosis) was recorded for each patient.

The data prospectively collected in the NiHiL registry were thoroughly verified in the medical records of each participant, including age, gender, clinical stage based on the Ann Arbor staging system, number of extranodal sites, performance status according to the Eastern Cooperative Oncology Group (PS ECOG) [10], serum levels of lactate dehydrogenase (LDH), International Prognostic Index (IPI) [11], presence of B-symptoms at the time of diagnosis, tumor size, and the immunophenotype of DLBCL.

Categorical variables were presented as numbers and percentages, while continuous variables were described using median and interquartile range (IQR). Differences between categorical variables were assessed using Pearson's χ^2 test or Fisher's Exact Test, and the Mann–Whitney U test was applied to compare medians of continuous variables. A p value <0.05 was considered statistically significant, and a 95% confidence interval was applied. All analyses were performed using R Statistical Software (v4.3.3; R Core Team 2024).

Results

Initial symptoms

Out of 706 analyzed patients, a total of 682 individuals (97%) were symptomatic, while remaining 24 patients (3%) were asymptomatic – with their DLBCL diagnosis established during examination for unrelated reasons. Among the 682 symptomatic patients, a majority of patients ($n = 602$; 88%) reported a single initial symptom, and 80 patients (12%) reported two or more symptoms, resulting in a total of 809 analyzed symptoms (Figure 1).

Among the 809 initial symptoms, the most commonly reported symptom category was abdominal and/or GIT issues, accounting for 26% ($n = 209$) of symptoms, followed by peripheral lymphadenopathy (22%, $n = 177$; most commonly of head and/or neck region in 106 cases), B-symptoms (13%, $n = 104$; most frequently unintended weight loss in 67 cases), craniofacial symptoms (10%, $n = 83$), back pain (8%, $n = 62$), limb pain/swelling (7%, $n = 53$), respiratory symptoms (6%, $n = 45$), testicular tumor (4%, $n = 34$), chest symptoms (2%, $n = 20$), urologic or gynaecological symptoms (1%, $n = 11$), and skin symptoms (1%, $n = 11$; for detailed description of symptoms and categories see Supplementary Table 1).

From the total of 80 patients reporting two or more symptoms, the most common combination included B-symptoms together with abdominal/GIT symptoms in 45% of cases ($n = 36$), followed by the combination of B-symptoms with peripheral lymphadenopathy (13%, $n = 10$) or respiratory symptoms (9%, $n = 7$).

Incidental findings discovered during unrelated examinations that ultimately led to the DLBCL diagnosis in the 24 (3%) asymptomatic patients were most

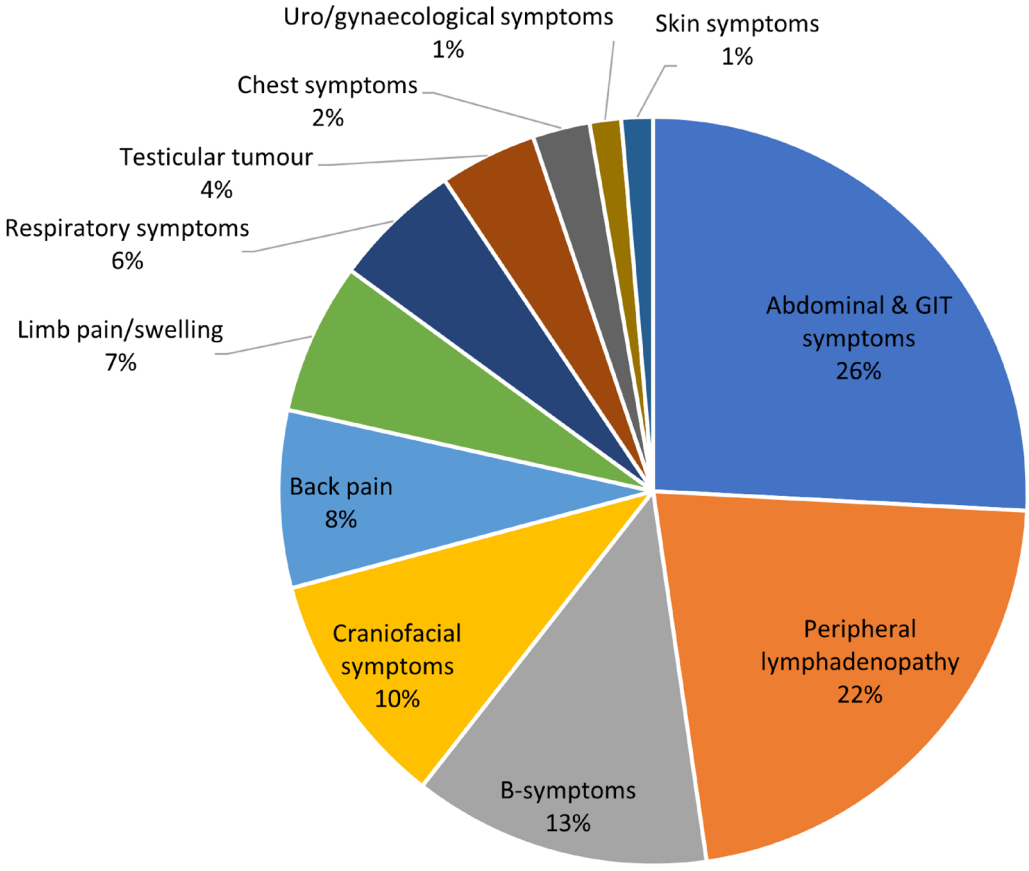

Figure 1. Initial symptoms ($n=809$) reported by patients with diffuse large B-cell lymphoma.

frequently detected through imaging methods (79%, $n=19$; for details see Supplementary Table 2).

Baseline characteristics and initial symptom-to-diagnosis interval

For further analyses, one leading initial symptom was selected for each patient. The 706 patients included in this analysis were diagnosed with median age 64 years (IQR 52–70 years), male gender in 55% ($n=387$), advanced clinical stage in 67% ($n=471$), two or more involved extranodal sites in 42% ($n=295$), PS ECOG ≥2 in 26% ($n=182$), elevated LDH in 63% ($n=448$), IPI 3–5 in 54% ($n=379$), bulky disease ≥7.5 cm in 47% ($n=295$ out of 622), and non-germinal center immunophenotype in 47% ($n=204$ out of 437; Table 1). The incidence of B-symptoms increased from 12% ($n=87$) as a first leading manifestation of DLBCL to 45% ($n=315$) at the time of diagnosis.

Median symptom-to-diagnosis interval was 10 weeks (IQR 5–19 weeks), or 66 days (IQR 33–126 days). Patients with an IPI score 0–2 had shorter symptom-to-diagnosis interval (median 9 weeks) when compared to those with an IPI score 3–5 (median 11 weeks; $p=0.005$). No significant difference in this interval was observed between patients aged up to 65 years ($n=380$) and those over 65 years ($n=302$) with a median of 10 weeks in both subgroups. Patients with a testicular tumor had a significantly shorter symptom-to-diagnosis interval (median 5 weeks; $p<0.001$; Table 2 and Figure 2). Prolonged symptom-to-diagnosis interval was associated with limbs pain/swelling (median 17 weeks; $p=0.002$), and with B-symptoms (median 13 weeks; $p=0.042$).

Symptoms associated with low- and high-risk features of DLBCL

Patients presenting initially with peripheral lymphadenopathy as a leading symptom exhibited a significantly lower number of involved extranodal sites at the time of diagnosis (≥2; 25 vs. 42%; $p=0.007$), along with a better PS ECOG (≥2; 9 vs. 26%; $p<0.001$), and a lower incidence of B-symptoms (31 vs. 45%; $p=0.041$). Similarly, patients with a testicular tumor demonstrated a better PS ECOG (≥2; 3 vs. 26%; $p=0.012$) and a lower incidence of B-symptoms (6 vs. 45%; $p=0.001$).

Limb pain/swelling was associated with a worse PS ECOG (≥2; 47 vs. 26%; $p=0.017$) and elevated serum LDH (79 vs. 63%; $p=0.006$). Patients with back pain

Table 1. Baseline characteristics.

			Age			Gender male			Stage III–IV			No. EN sites ≥2			PS ECOG ≥2			LDH elevated			IPI 3–5			B-symptoms present			Bulky ≥7.5 cm†			Immunophenotype non-GC‡		
	n	%	Med.	IQR	*p*	*n*	%	*p*	*n*	%	*p*	*n*	%	*p*	*n*	%	*p*	*n*	%	*p*	*n*	%	*p*	*n*	%	*p*	*n*	%	*p*	*n*	%	*p*
No. of patients	706	100	64	52–70		387	55		471	67		295	42		182	26		448	63		379	54		315	45		295	47		204	47	
Abdominal/GIT S.	205	29	63	52–70	0.556	113	55	0.967	133	65	0.825	81	40	0.706	61	30	0.393	138	67	0.638	112	55	0.895	129	63	0.009*	100	58	0.146	56	46	0.891
Peripheral LAP	163	23	63	49–70	0.654	93	57	0.772	102	63	0.646	41	25	0.007*	14	9	<0.001*	87	53	0.235	65	40	0.062	51	31	0.041*	56	36	0.103	46	48	0.895
B-symptoms	87	12	65	55–71	0.363	49	56	0.886	72	83	0.205	35	40	0.039*	15	18	0.223	68	78	0.227	62	71	0.111	87	100	<0.001*	42	52	0.660	28	56	0.468
Craniofacial S.	83	12	63	51–69	0.491	44	53	0.776	39	47	0.083	29	35	0.429	15	18	0.223	47	57	0.554	30	36	0.074	17	20	0.004*	16	22	0.007*	22	40	0.561
Back pain	61	9	64	49–71	0.708	34	56	0.940	55	90	0.122	39	64	0.048*	31	51	0.004*	44	72	0.535	49	80	0.045*	33	54	0.394	34	64	0.189	18	44	0.835
Limb pain/swelling	53	8	64	54–74	0.676	19	36	0.119	43	81	0.359	30	57	0.202	25	47	0.017*	42	79	0.006*	38	72	0.191	21	40	0.656	29	58	0.409	8	29	0.227
Respiratory S.	43	6	68	61–73	0.021*	21	49	0.673	36	84	0.330	23	53	0.355	16	37	0.226	33	77	0.426	30	70	0.286	27	63	0.178	26	65	0.227	15	58	0.527
Testicular tumor	33	5	62	53–69	0.510	33	100	0.166	13	39	0.109	9	27	0.261	1	3	0.012*	11	33	0.064	9	27	0.071	2	6	0.001*	5	22	0.109	17	81	0.098
Chest S.	20	3	64	37–70	0.421	5	25	0.111	12	60	0.774	11	55	0.470	3	15	0.380	15	75	0.629	11	55	0.949	10	50	0.772	8	44	0.880	9	60	0.559
Uro/gynaecological S.	11	2	71	55–74	0.206	2	18	0.133	10	91	0.481	8	73	0.233	4	36	0.558	9	82	0.574	9	82	0.349	6	55	0.694	5	56	0.778	5	71	0.469
Skin S.	11	2	60	47–74	0.885	10	91	0.247	8	73	0.854	8	73	0.233	3	27	0.932	7	64	0.995	8	73	0.516	4	36	0.727	7	64	0.546	4	67	0.582
Incidental findings	24	3	65.5	55–75	0.158	9	38	0.335	18	75	0.712	12	50	0.618	2	8	0.109	16	67	0.881	14	58	0.808	4	17	0.060	8	40	0.688	7	41	0.784

EN: extranodal; GIT: gastrointestinal; IPI: International Prognostic Index; IQR: interquartile range; LAP: lymphadenopathy; LDH: lactate dehydrogenase; med.: median; non-GC: non-germinal center immunophenotype; S.: symptoms.
*significant; †available in 622 patients; ‡available in 437 patients.

also presented with a worse PS ECOG (51 vs. 26%; $p=0.004$), an increased incidence of involved extranodal sites (≥2; 64 vs. 42%; $p=0.048$), and a higher risk IPI (3–5; 80 vs. 54%; $p=0.045$).

Patients with an IPI score of 0–2 were more likely to present initially with peripheral lymphadenopathy (30 vs. 17% in those with an IPI score of 3–5; $p=0.001$) and testicular tumor (7 vs. 2%; $p=0.007$). Conversely, patients with an IPI score of 3–5 more frequently presented with B-symptoms (16 vs. 8%; $p=0.001$), back pain (13 vs. 4%; $p<0.001$), and limb pain/swelling (10 vs. 5%; $p=0.011$).

Discussion

DLBCL is a heterogeneous disease characterized by variable clinical manifestations, molecular backgrounds, and prognoses [12–14]. Typically, literature reports suggest that DLBCL patients present with painless enlarged lymph nodes, and approximately one-third develop extranodal involvement [3–7,15]. However, these reports often rely on staging imaging methods, such as PET/CT scans, at the time of diagnosis, rather than patients' self-reports at the onset of symptoms. To the best of our knowledge, no study has systematically described the initial symptoms or complaints of DLBCL patients that prompted them to seek medical attention, ultimately leading to the diagnosis during further examination.

While peripheral lymphadenopathy is conventionally regarded as a typical manifestation of lymphomas, it accounted for only 22% of reported symptoms in this analysis. These individuals presented with more favorable baseline characteristics, and a slightly shorter time from symptom onset to diagnosis. This may be attributed to physicians' awareness of potential serious conditions associated with such symptoms and the

Table 2. Initial symptom-to-diagnosis (i.e. biopsy) intervals (weeks).

	n	Med.	IQR	95% CI	*p*
No. of included patients	706	10	5–19	13–15	
Abdominal/GIT symptoms	205	12	5–20	13–17	0.552
Peripheral lymphadenopathy	163	9	5–15	11–16	0.249
B-symptoms	87	13	8–20	13–18	0.042*
Craniofacial symptoms	83	9	4–17	11–17	0.531
Back pain	61	10	6–17	10–15	0.693
Limb pain/swelling	53	17	6–30	16–26	0.002*
Respiratory symptoms	43	11	7–18	11–17	0.190
Testicular tumor	33	5	2–11	4–13	<0.001*
Chest symptoms	20	9.5	7–26	10–22	0.331
Uro/gynaecological symptoms	11	13	5–19	8–20	0.573
Skin symptoms	11	13	5–30	8–28	0.408
Incidental findings	24	7.5	5–16	4–25	0.122

CI: confidence interval; GIT: gastrointestinal; IQR: interquartile range; med.: median.
*Significant.

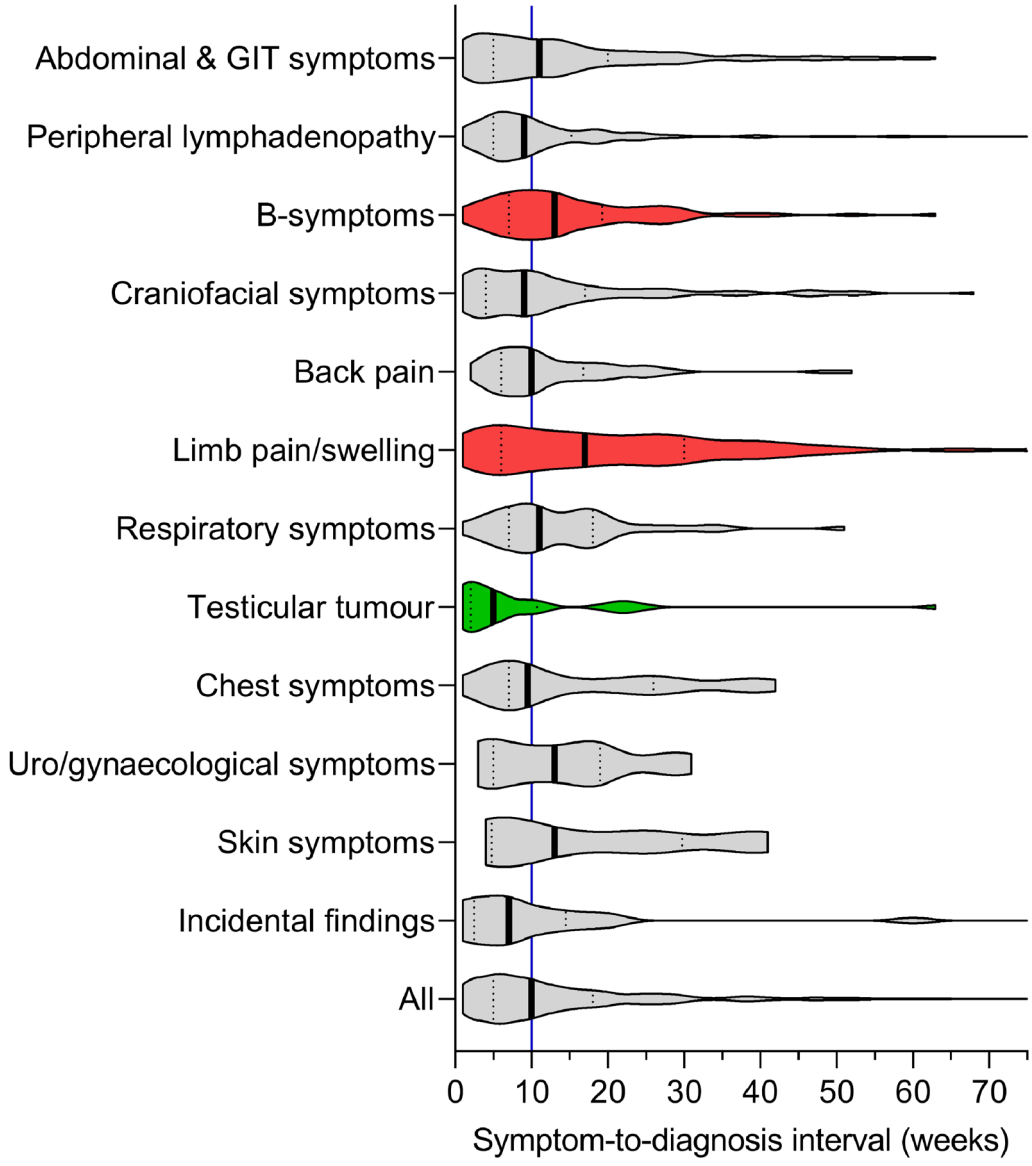

Figure 2. Violin plot showing the initial symptom-to-diagnosis interval with a median of 10 weeks in the entire patient cohort (depicted by blue line). B-symptoms (median 13 weeks, $p = 0.042$) and limb pain/swelling (median 17 weeks, $p = 0.002$) were associated with a significantly prolonged interval (red), while patients with testicular tumor had a significantly shorter interval to diagnosis (median 5 weeks, $p < 0.001$, green).

ready availability of diagnostic material for biopsy. These results align with previously published data showing that nodal DLBCL have more favorable prognosis in comparison to extranodal DLBCL [6,7].

The most commonly reported initial complaints among DLBCL patients were abdominal or GIT symptoms in 26% of cases, primarily involving abdominal pain. This analysis did not focus on further determining DLBCL involvement, i.e. whether symptoms arose from subdiaphragmatic lymph node enlargement or involvement of GIT organs. However, the incidence of extranodal involvement in these individuals was not increased compared to the whole DLBCL cohort. Therefore, this symptomatology was presumably not associated with higher-risk features of the lymphoma.

B-symptoms were reported in 12% of patients as an initial leading complaint, with an unintended weight loss being the most common symptom. At the time of diagnosis, B-symptoms were detected in 45% of patients, indicating a fourfold increase during time from symptom onset to the diagnosis of DLBCL. These patients had worse PS ECOG compared to other patients, as well as a prolonged time to the diagnosis of DLBCL. We assume that this fact is due to the non-specific nature of these symptoms.

Limb pain/swelling was associated with high-risk DLBCL features. These patients mostly presented with

lower limb involvement, resulting in worse PS ECOG compared to others. It is evident that the lower limb involvement leads to a worse PS ECOG; thus, these individuals might be excluded from clinical trials that usually require favorable PS ECOG only because of this criterion, while this condition does not reflect their general functional status and comorbidities. These individuals had the longest interval from symptom occurrence to the diagnosis of DLBCL (median 17 vs. 10 weeks in the whole cohort) presumably due to the broad differential diagnosis of such symptoms.

Another symptom associated with worse initial characteristics was back pain. Although the interval to diagnosis was not prolonged, these individuals presented with an increased incidence of extranodal involvement, worse PS ECOG, and especially a higher IPI.

Testicular lymphomas represented only a minority of all DLBCL patients in this analysis, as well is in the general DLBCL population [16]. The time from symptom occurrence to the diagnosis was the shortest among all other cases (median 5 weeks), likely due to its easily recognizable location. The patients presented with shorter time to diagnosis, and favorable baseline characteristics.

Of note, we observed only 3% of patients who had an incidental finding of DLBCL. These patients sought medical attention for various reasons or underwent preventive medical checkups, with a result of tumor suspicion leading to further diagnostic work-up and a final diagnosis of DLBCL. The proportion of patients with incidental findings is surprisingly low compared to other hematologic malignancies like multiple myeloma (15% of asymptomatic cases) or chronic lymphocytic leukemia (80%) [1,2].

Although current trends in DLBCL research mainly focus on the molecular characteristics of DLBCL subtypes and personalized treatment of these entities, there is still an unmet clinical need to properly describe the first symptoms of this disease to accelerate the diagnostic process of DLBCL. The strength of our study lies in the large dataset of real-world DLBCL patients with a detailed description of initial symptoms prospectively collected from their medical documentation as well as the Czech registry of non-Hodgkin lymphomas. This might help hematologists and other physicians consider the differential diagnosis of DLBCL in patients with various symptoms, as this disease can involve any lymph node sites or organs. On the other hand, the weakness of our study lies in missing survival data as well as molecular-genetic data of DLBCL involving certain extranodal sites. Such an analysis, however, exceeds the primary endpoints of this clinical analysis.

In conclusion, we described a real-world pattern of initial symptoms of DLBCL, with abdominal/GIT complaints being the most common initial symptoms of this disease, followed by peripheral lymphadenopathy. DLBCL initially presenting as a testicular tumor and peripheral lymphadenopathy was associated with favorable baseline characteristics, while DLBCL with initial limb pain/swelling, back pain, and B-symptoms exhibited high-risk DLBCL features.

Ethical approval

Ethics approval was obtained from the local ethics committee and approved by the competent national authority. The study was conducted in accordance with the rules of Good Clinical Practice. Written informed consent was obtained from each patient before enrollment.

Author contributions

PV and MT conceived and designed the study. All authors collected, analyzed, and interpreted the data and had full access to it. Pathological findings were reviewed by JG, RJ, and VC at Czech reference centers for hematopathology. PV and MT contributed to the final data analysis and the writing of the manuscript. All authors critically reviewed and approved the final version of the manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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ORCID

Prokop Vodicka http://orcid.org/0000-0002-7848-1268

Data availability statement

The datasets analyzed in this study are available from the corresponding author upon reasonable request. The corresponding author had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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