Received: 16 April 2024 | Revised: 7 June 2024 | Accepted: 19 June 2024

DOI: 10.1002/pbc.31182

Pediatric Blood & Cancer | SIOP International Society of Paediatric Oncology | aspho The American Society of Pediatric Hematology/Oncology | WILEY

RESEARCH ARTICLE

Non-Hodgkin lymphoma presenting with spinal cord compression: A population-based analysis of the NHL-BFM study group

Amambay Riquelme[1] | **Jana Werner**[1] | **Martin Zimmermann**[2] | **Hannah von Mersi**[3] | **Edita Kabíčková**[4] | **Francesco Ceppi**[5] | **Jan Foerster**[1] | **Jasmin Finger**[6] | **Stephanie Müller**[6] | **Andishe Attarbaschi**[3,7] | **Birgit Burkhardt**[6] | **Wilhelm Woessmann**[1]

[1]Pediatric Hematology and Oncology and NHL-BFM Study Centre, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany

[2]Department of Pediatric Hematology and Oncology, Children's Hospital, Hannover Medical School, Hannover, Germany

[3]Department of Pediatric Hematology and Oncology, St. Anna Children's Hospital, Medical University of Vienna, Vienna, Austria

[4]Pediatric Hematology and Oncology, Charles University and University Hospital Motol, Prague, Czech Republic

[5]Pediatric Hematology-Oncology Unit, Division of Pediatrics, Department Woman-Mother-Child, University Hospital of Lausanne and University of Lausanne, Lausanne, Switzerland

[6]Pediatric Hematology and Oncology and NHL-BFM Study Centre, University Hospital Muenster, Muenster, Germany

[7]St. Anna Children's Cancer Research Institute, Vienna, Austria

Correspondence
Wilhelm Woessmann, University Medical Centre Hamburg-Eppendorf, Pediatric Hematology and Oncology and NHL-BFM Study Centre, Building 045, Martinistr. 52, 20246 Hamburg, Germany.
Email: w.woessmann@uke.de

Funding information
Deutsche Kinderkrebsstiftung

Abstract

Background: Spinal cord compression is a rare presentation of non-Hodgkin lymphoma (NHL) in children. We aimed to describe the prevalence, histological subtypes, clinical presentation, therapy, and outcome of those children in a population-based cohort. The chemotherapy regimen remained comparable over time.

Methods: We retrospectively identified all children and adolescents with paresis as initial manifestations of the NHL between January 1990 and December 2020 from the NHL-BFM database. Characteristics, therapy, and outcome data were gathered from the database and patient files.

Results: Fifty-seven of 4779 children (1.2%) presented with initial paresis due to spinal cord compression. The median age was 10.3 years (range, 3.1-18.0 years), and 33% were female. Initial symptoms were paresis/weakness (n = 50, 88%), back pain (n = 33, 58%), paresthesia (n = 23, 40%), and bladder dysfunction and/or

Abbreviations: ALCL, anaplastic large cell lymphoma; B-AL, Burkitt leukemia; BL, Burkitt lymphoma; B-NHL, B-cell non-Hodgkin lymphoma; CI-R, cumulative incidence of relapse; CNS, central nervous system; CSF, cerebrospinal fluid; DLBCL, diffuse large B-cell lymphoma; EFS, event-free survival probability; IPNHLSS, international Pediatric Non-Hodgkin Lymphoma Staging System; LBL, lymphoblastic lymphoma; LDH, lactate dehydrogenase; n.a., not assessed; NHL, non-Hodgkin Lymphoma; NHL-BFM study group, NHL-Berlin-Frankfurt-Muenster study group; OS, overall survival probability; pB-LBL, precursor B-lymphoblastic lymphoma; SE, standard error; T-LBL, T-cell lymphoblastic lymphoma.

Amambay Riquelme and Jana Werner contributed equally.

constipation ($n = 22$, 39%), persisting for a median of 14 days before diagnosis. Subtype distribution was mature B-NHL (n = 41, 72%), precursor B-lymphoblastic lymphoma (LBL) (n = 12, 21%), anaplastic large cell lymphoma (ALCL) (n = 3, 5%), and T-LBL (n = 1, 2%). Initial emergency therapy included surgery (70%) and/or chemotherapy/steroids (63%). Five-year event-free survival and overall survival (80% ± 5% and 82% ± 5%, respectively) were comparable with all other NHL patients. Neurological symptoms persisted in approximately one-third of surviving patients at the last follow-up.

Conclusion: 1.2% of pediatric NHL patients presented with paresis from spinal cord compression mainly due to B-cell lymphomas. Neurological sequelae were observed in one-third of surviving patients.

KEYWORDS
back pain, children, non-Hodgkin Lymphoma, paresis, spinal cord compression

1 | INTRODUCTION

Patients with non-Hodgkin lymphoma (NHL) rarely present with symptoms of spinal cord compression by an epidural manifestation. Previous case reports and single-center studies have reported spinal cord compression by lymphoma to be prevalent in 1.1% to 4.4% of NHL patients.[1–3] Reported initial symptoms were back pain, (para-)paresis, paresthesia, and bladder dysfunction or constipation.[1–4] Initial emergency treatment included surgery, radiotherapy, and chemotherapy. The largest single-center analysis that included children diagnosed over a 40-year period found event-free survival (EFS) to be approximately 50%.[1]

We aimed to analyze the frequency, initial presentation, histological subtype, treatment, and outcome of children presenting with spinal cord compression by lymphoma in a population-based cohort collected over 30 years. Patients were treated according to contemporary chemotherapy protocols in the NHL-BFM (NHL-Berlin-Frankfurt-Muenster) study group.

2 | PATIENTS AND METHODS

2.1 | Patients

Patients with newly diagnosed NHL registered in studies or registries of the NHL-BFM study group (Austria, Czech Republic, Germany, and Switzerland) between January 1990 and December 2020 were screened for "paresis" as reported initial observation. Clinical characteristics, histological subtypes, therapy, and outcome of the patients with lymphoma localization in the (para-)spinal region with spinal cord compression were extracted from the NHL-BFM databases and individual patient files. Patients with cranial nerve palsy were not included in the analysis. All patients or their parents or legal guardians gave informed consent for the transfer of their data to the NHL-BFM study center.

2.2 | Diagnosis

The patients underwent central histology or cytology review at the time of initial diagnosis. NHL diagnoses were classified according to the contemporary WHO classification.[5–7] Staging bone marrow smears and cerebrospinal fluid (CSF) cytospins were centrally reviewed. Initial staging and adequate therapy were monitored by the NHL-BFM study center. Patients were staged according to the St. Jude's staging system or the International Pediatric Non-Hodgkin Lymphoma Staging System (IPNHLSS).[8,9] Epidural and paraspinal tumors were defined as at least stage III disease. Actual CNS disease was defined by morphologically identifiable blast(s) in CSF [irrespective of cell count in mature B-NHL and anaplastic large-cell lymphoma (ALCL); ≥5 cells/μl in LBL]; cerebral/medullary infiltrates on cranial/spinal MRI; or cranial nerve palsy that cannot be explained by an extradural lesion.[10–16]

2.3 | Therapy

All patients were included in and treated according to the consecutive NHL-BFM studies NHL-BFM-90, -95, ALCL99, EUROLB-02, and B-NHL-BFM-04, or registered to the NHL-BFM Registry 2012.[10–16]

Patients with lymphoblastic lymphoma (LBL) were treated with the NHL-BFM regimen for precursor cell neoplasms that consists of induction, consolidation, re-intensification, and maintenance up to two years of therapy comparable to the regimen for acute lymphoblastic leukemia.[11,14,15] Patients with mature B-cell-NHL or ALCL received risk-stratified two to six courses of block-type chemotherapy as previously reported.[10,12,13,16,17] Since 2007, some patients

with mature B-NHL were treated in addition with rituximab in the rituximab-window study or outside of a study.[18]

2.4 | Statistical analysis

Frequencies of clinical characteristics were compared using chi-squared tests.

EFS was calculated from the date of diagnosis to the last follow-up or first event (relapse, secondary malignancy, or death from any cause). Overall survival (OS) was calculated from the date of diagnosis to death from any cause or last follow-up.

Probabilities of survival were estimated using the Kaplan-Meier method with standard errors (SEs) according to Greenwood and compared using the log-rank test.[19] Cumulative incidence functions of relapse were constructed by the method of Kalbfleisch and Prentice.[20] Functions were compared with Gray's test.[21] Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

3 | RESULTS

From January 1990 to December 2020, 4779 children and adolescents were newly diagnosed with NHL in the NHL-BFM study group. Of these patients, 57 (1.2%) presented with paresis due to spinal cord compression by the NHL. Patient characteristics are shown in Table 1.

Histological subtypes associated with spinal cord compression were almost exclusively precursor B- or mature B-cell NHL, resulting in a significantly different distribution of histopathological subtypes compared with the other patients (Table 1).

In accordance with the St. Jude's staging system and the IPNHLSS, paraspinal, or epidural tumors were classified at least as stage III. Children with symptomatic spinal cord compression presented in higher stages compared with all other pediatric NHL patients. Bone marrow and CNS involvement were significantly more frequent in children with initial paresis and therefore classified as stage IV more often than all other pediatric NHL patients (Table 1). The characteristics of patients with stage III/IV disease with or without spinal cord compression are compared in Supporting Information Table S1.

The initial neurological symptoms of patients with spinal cord compression by lymphoma are shown in Table 2. The median time from the reported onset of symptoms to diagnosis (available for all but one patient) was 14 days (range, 0 days to 9 months). Patients were commonly diagnosed within the first or the second week after symptom onset, 30% (n = 17) and 28% (n = 16), respectively. Nine patients (16%) were diagnosed between 15 and 30 days. The remaining 14 patients (25%) were diagnosed 30 days or more, with a maximum of 9 months, after symptom onset. Half of these 14 patients were diagnosed with DLBCL or mature B-NHL NOS, and only one patient with BL, whereas more than 60% of patients with a diagnosis within 30 days after symptom onset had a BL/B-AL. This finding is compatible with the differential growth pattern of these entities.

TABLE 1 Characteristics of children and adolescents with NHL presenting with initial paresis due to spinal cord compression compared with all pediatric NHL patients.

	All other		Initial paresis		
	N	%	*N*	%	*p*
All	4779		57		
Sex					0.31
Male	3472	73	38	67	
Female	1297	27	19	33	
Age					0.81
<10 years	2353	49	29	51	
≥10 years	2426	51	28	49	
Subtype					<0.0001
pB-LBL	222	5	12	21	
T-LBL	712	15	1	2	
BL/B-AL	1969	41	28	49	
DLBCL	609	13	11	19	
PMBL	142	3	–	–	
ALCL	516	11	3	5	
other	609	13	2[a]	4	
Initial stage[b]					<0.0001
Stage I	428	9	–	–	
Stage II	853	18	–	–	
Stage III	2238	47	21	37	
Stage IV	561	12	25	44	
B-AL	414	9	10	18	
n.a.	285	6	1[c]	2	
LDH (U/L)					0.53
LDH < 500	2737	57	30	53	
LDH 500 ≤ 1000	742	16	10	18	
LDH ≥ 1000	824	17	13	23	
n.a.	476	10	4	7	
CNS					<0.0001
Negative	4083	85	21	37	
Positive	357	8	28	49	
n.a.	335	7	8	14	
Bone marrow					0.0003
No	3883	81	35	61	
Yes	823	17	20	35	
n.a.	73	2	2	4	
Mediastinum					0.001
No	3300	69	51	90	
Yes	1411	30	6	10	
n.a.	68	1	–	–	
Abdominal involvement					0.61
No	2020	42	26	46	
Yes	2759	58	31	54	

(Continues)

TABLE 1 (Continued)

	All other		Initial paresis		
	N	%	*N*	%	*p*
Peripheral nodes					0.014
No	3115	65	48	84	
Yes	1610	34	9	16	
n.a.	54	1	–	–	

Abbreviations: ALCL, anaplastic large cell lymphoma; B-AL, Burkitt leukemia; BL, Burkitt lymphoma; CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; IPNHLSS, International Pediatric Non-Hodgkin Lymphoma Staging System; LDH, lactate dehydrogenase; n.a., not assessed; pB-LBL, precursor B-cell lymphoblastic lymphoma; PMBL, primary mediastinal B-cell lymphoma; T-LBL, T-cell lymphoblastic lymphoma.

[a]1 mature B-NHL nos, 1 ALK$^+$ LBCL.

[b]According to St. Jude's staging system or IPNHLSS.

[c]Missing initial lumbar puncture.

TABLE 2 Neurological symptoms of the 57 patients with spinal cord compression due to NHL (multiple possible).

Symptom	*N*	%
Back pain	33	58
Paresis	50	88
Upper extremity	4	7
Lower extremity	46	81
Upper + lower extremity	3	5
Bladder dysfunction/constipation	22	39
Paresthesia	23	40
n.a.	1	2

Abbreviation: n.a. not assessed.

Spinal cord compression was identified by spinal MRI in 52 of 57 cases, CT in 2 cases, and lumbar myelography in 1 case. In two patients, the imaging method employed was not known.

The most common intraspinal localizations of the lymphoma were thoracic (82%, $n = 47$) and lumbar (46%, $n = 26$). The lymphoma affected the cervical and sacral spine each in 16% ($n = 9$). In 46% ($n = 26$) of patients, the lymphoma comprised up to three vertebrae, in 42% ($n = 24$) between four and seven vertebrae, and in 9% ($n = 5$) more than seven. For two patients, the information was not available. Within the spinal region, 72% ($n = 41$) of NHL manifestations were unilocular, and 28% ($n = 16$) were multilocular, presenting as non-contiguous tumor detectable in more than one anatomic region of the (para-)spinal area.

Overall, emergency treatment varied between patients but not substantially over time. Forty patients (70%) received emergency surgery with myelon decompression and 36 patients (63%) received dexamethasone and/or chemotherapy. Twenty-two patients received emergency surgery and dexamethasone and/or chemotherapy. Only one child was irradiated, and two children did not start treatment immediately. The type of surgery for myelon decompression was documented in 36 of the 40 patients who underwent emergency surgery

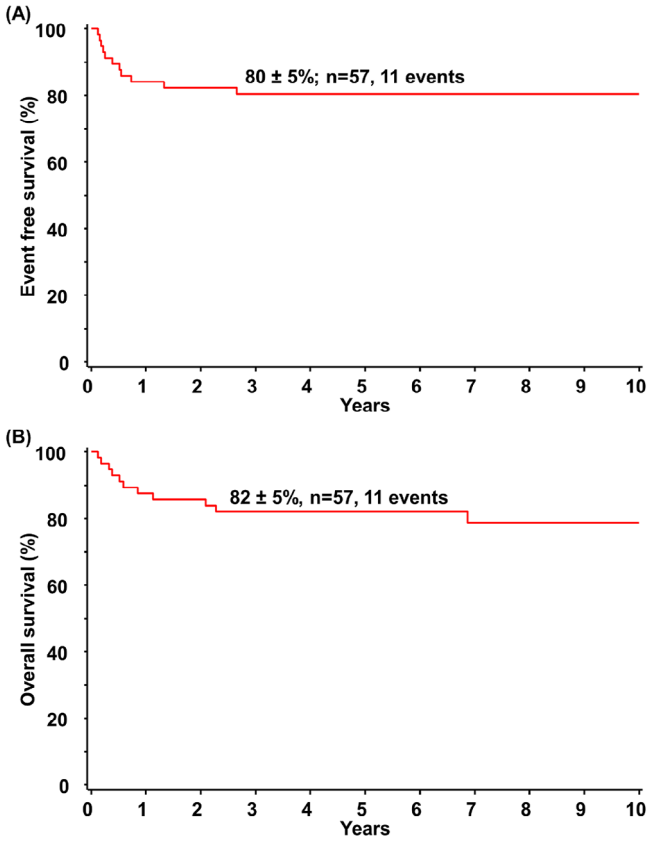

FIGURE 1 (A) EFS and (B) OS at 5 years of NHL patients with initial spinal cord compression due to NHL.

and varied from laminectomy ($n = 18$), hemilaminectomy ($n = 8$), laminotomy ($n = 9$) to laminoplasty ($n = 1$). In 29 of the 40 patients who underwent emergency surgery, the paraspinal tumor was resected (total resection $n = 28$, subtotal resection $n = 1$).

All 13 children with LBL received BFM-type chemotherapy for precursor cell neoplasms including re-induction. One child died of therapy, and no relapses were observed among these patients.

Forty-one children with mature B-NHL were stratified according to resection status, stage, CNS involvement, and lactate dehydrogenase (LDH) into risk and therapy groups R4 ($n = 24$), as well as R3 ($n = 13$) and R2 ($n = 4$), since parameningeal extension or spinal cord compression is not defined as CNS involvement in the BFM strategy.[13] Seven children progressed ($n = 1$) or relapsed ($n = 6$). Of note, none of the four patients who received R2 therapy (4 courses with intermediate dose MTX) relapsed.

Five-year EFS and OS of patients with initial spinal cord compression are shown in Figure 1. EFS, OS, and the cumulative incidence of relapse (CI-R) were not statistically different from all other children with NHL (EFS: 80% ± 5% and 83% ± 0.6%, $p = 0.66$; OS 82 ± 5 and 89% ± 0.5%, $p = 0.053$; CI-R: 11% ± 4% and 12% ± 0.5%, $p = 0.8$, respectively). Outcome parameters were not significantly different when restricting the comparison of EFS, OS, and CI-R to all other patients with stage III/IV disease (EFS: 82% ± 0.8%; OS: 88% ± 0.6%; CI-R: 13% ± 0.7%).

All seven children with initial spinal cord compression and relapse or progression died of disease. Two children died of therapy, one from a second malignancy, and one child with Fontane circulation due to a pseudomonas sepsis one month after the end of treatment.

After completion of therapy, more than half of the surviving, non-relapsed patients did not report functional impairment and showed a normal neurological examination (54%, $n = 25$). Of these patients without neurological sequelae, 32% ($n = 8$) had surgery only as emergency treatment, 44% ($n = 11$) had surgery and received cortisone or chemotherapy, 16% ($n = 4$) had chemotherapy only, and in one patient the therapy was not started immediately. 30% ($n = 14$) of the surviving, non-relapsed patients experienced persistent neurological symptoms after the completion of therapy, ranging from mild paresis to complete tetraparesis. The recorded individual persistent symptoms of the 14 patients are listed in the supplementary data (Supporting Information Table S2). These patients with neurological sequelae had received different emergency treatments: 29% ($n = 4$) had surgery only, 29% ($n = 4$) had surgery and received cortisone or chemotherapy, and 36% ($n = 5$) received chemotherapy only. One patient did not receive immediate treatment until one week after the biopsy. Data on the neurological outcome were not available for 15% of the patients ($n = 7$).

4 | DISCUSSION

In our population-based retrospective cohort of nearly 5000 children and adolescents with NHL, 57 children presented with initial paresis due to spinal cord compression by lymphoma. This cohort allowed for an analysis of the initial presentation, histological subtypes, treatment, and outcome of these patients.

The reported prevalence of 1.2% in this cohort confirms the previously reported prevalence of initial spinal cord compression by lymphoma in 1%-2% of all newly diagnosed NHL.[1–3]

Most clinical characteristics, such as age and sex, were similar between patients with initial spinal cord compression and all other pediatric NHL patients. However, the distribution of histopathological subtypes differed with more than 90% precursor and mature B-NHL among patients with initial spinal cord compression. This might in part reflect the higher frequency of bone involvement in precursor B-cell LBL (pB-LBL), diffuse large B-cell lymphoma (DLBCL), and Burkitt lymphoma/leukemia (BL/B-AL) compared with T-LBL as 21% of the children who presented with spinal cord compression also had vertebral involvement.[22–25] Dho et al. reported a B-cell phenotype in 10 of 12 (83%) cases of spinal cord compression by childhood NHL[4] and Kurucu et al. in 10 of 11 (91%) with known immunophenotype.[1]

In our cohort of children with initial spinal cord compression, only one patient had a T-LBL, which explains the low frequency of mediastinal involvement in these children. Since all paramenigeal/intraspinal localizations define stage III in the St. Jude's staging system and IPNHLSS, no child had low-stage disease.[8,9] In addition, the majority of children with initial spinal cord compression had widespread disease documented by the high frequency of BM and CNS involvement as well as high LDH. As expected, several children could not receive an initial lumbar puncture, so the CNS status could not be defined in eight children without intracerebral mass or meningeal involvement on imaging. However, a few children with mature B-NHL had low LDH and no CNS involvement defined by St. Jude/IPNHLSS, so they were treated in risk group R2 with limited chemotherapy. Remarkably, none of these four patients relapsed.

The time to diagnosis after symptom onset varied widely, from a few days to many months. This is consistent with reported pediatric malignancies presenting with spinal cord compression and might be accounted for by the differential growth pattern of the lymphoma subtypes.[1–3,26] It is noteworthy that a rather unspecific symptom such as back pain was sometimes the first and leading symptom, preceding neurological deficits by weeks and sometimes months, both in our cohort and in the literature.[2,4] This observation highlights the need for awareness of this rare presentation of NHL.

Our cohort of patients with initial spinal cord compression had comparable outcomes to all pediatric NHL patients. In contrast to our findings, Kurucu et al. reported a 3-year EFS and OS of 51% and 62%, respectively, in a single-center analysis of 15 pediatric patients with paraspinal/spinal epidural lymphoma collected between 1980 and 2018.[1] Furthermore, in their literature review of 84 pediatric patients with primary paraspinal/spinal epidural lymphoma, long-term follow-up was reported for 64 patients, of whom 66% were alive without disease at a median of 65 (14 to 227) months.[1] The reasons for the reported poorer outcome of the patients in comparison with our cohort can only be hypothesized. First, the cases reviewed were diagnosed over a long and earlier period of time, from the 1970s to the 2000s, during which diagnostic methods, classifications, and treatment strategies evolved. Second, patient selection and small numbers might have led to differences in single-center analyses, and reported treatment strategies for both spinal cord compression by lymphoma and the NHL varied between hospitals.

More than half of the 64 patients with follow-up had a complete neurological recovery in the cases reviewed by Kurucu et al., 17% had a partial recovery and 27% had no recovery.[1] This is comparable to our findings of about one-third of the surviving patients having some neurological deficiencies ranging from mild to severe such as tetraparesis. A systematic analysis of the neurological outcome and associated parameters in our cohort was not possible due to our retrospective multicenter analysis with sometimes limited information on the last neurological status. Nevertheless, our analysis underscores that a substantial proportion of patients with initial paresis due to NHL have neurological sequelae and require long-term care.

Further evidence on neurological outcome after spinal cord compression due to malignancy in children comes from other malignancies. In a systematic review of 28 studies that analyzed neuroblastoma with intraspinal extension, a median of 50% of patients had long-term neurological motor deficits.[27] As might be expected, several studies describe a correlation of the severity of the neurological deficit at diagnosis with the neurological outcome.[4,27] The evidence for an association between time from symptom onset to diagnosis and neurological outcome is less clear. Three studies report a significantly better

outcome with a shorter time from symptom onset to diagnosis, while two studies found no association between these two parameters.[27,28]

However, symptoms suspicious for spinal cord compression should be investigated promptly.

The optimal treatment strategy for patients with spinal cord compression due to NHL remains controversial. Although neurosurgery can provide decompression immediately, it can lead to significant acute and late complications like spinal deformity and instability.[4,29–31] Historically, treatment of spinal cord compression by childhood malignancies included urgent decompressive surgery and radiotherapy.[1,4,27] Once it was shown that chemotherapy can have a rapid and effective decompressive effect, it has been used in addition to surgery or radiotherapy but also as an option on its own.[32] Although emergency radiation has largely been abandoned for NHL, the available retrospective analyses — mainly case reports and case series — were not able to show a clear superiority of surgery or chemotherapy.[1–4,33] Our analysis is also limited in this regard not only due to the retrospective nature but also because information on treatment and neurological outcome was sometimes limited by inaccurate, incomplete, or missing data in patient files. No emergency treatment strategy — surgery, chemotherapy, or a combination of both — showed clear superiority regarding the neurological outcome. The challenge remains to identify the optimal strategy for each patient. The choice of treatment should consider individual patient factors such as the severity and progression of the symptoms, whether diagnosis can be established from another localization, and the overall health of the patient.

In conclusion, 1.2% of children and adolescents with NHL initially presented with signs of spinal cord compression, mainly due to B-cell lymphomas. The most frequent initial symptoms of paresis/limb weakness and back pain should prompt imaging by spinal MRI. Chemotherapy and surgery both were effective emergency treatments. With concurrent treatment approaches, EFS, OS, and relapse incidence of patients with initial spinal cord compression were comparable to all NHL patients. One-third of surviving patients had persistent neurological symptoms after the completion of therapy and require long-term care.

AUTHOR CONTRIBUTIONS

Wilhelm Woessmann and **Birgit Burkhardt**: Designed the work. **Amambay Riquelme, Jana Werner, Martin Zimmermann, Jan Foerster,** and **Wilhelm Woessmann**: Collected and analyzed the data. **Martin Zimmermann**: Performed the statistical analyses. **Amambay Riquelme, Jana Werner,** and **Wilhelm Woessmann**: Wrote the manuscript. **Hannah von Mersi, Edita Kabíčková, Francesco Ceppi, Jasmin Finger, Stephanie Müller, Birgit Burkhardt,** and **Andishe Attarbaschi**: Contributed and analyzed patient data.

ACKNOWLEDGMENTS

We thank all documentation specialists and colleagues from local centers of the NHL-BFM study group who provided data for the study. This work was supported by grants from the "Deutsche Kinderkrebsstiftung" to Birgit Burkhardt and Wilhelm Woessmann.

Open access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Anonymized data can be provided by the corresponding author upon request.

ORCID

Jana Werner https://orcid.org/0009-0002-6399-6960
Andishe Attarbaschi https://orcid.org/0000-0002-9285-6898

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Riquelme A, Werner J, Zimmermann M, et al. Non-Hodgkin lymphoma presenting with spinal cord compression: A population-based analysis of the NHL-BFM study group. *Pediatr Blood Cancer*. 2024;71:e31182. https://doi.org/10.1002/pbc.31182