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RESEARCH ARTICLE

Comprehensive analysis of constitutional mismatch repair deficiency-associated non-Hodgkin lymphomas in a global cohort

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Abstract

Background: Constitutional mismatch repair deficiency syndrome (CMMRD) is a rare childhood cancer predisposition syndrome associated with a broad spectrum of malignancies, including non-Hodgkin lymphomas (NHL). Most patients die due to cancer before the age of 20 years. Limited data exist on CMMRD-associated lymphomas and their outcome.

Methods: We conducted a retrospective study including all CMMRD-associated NHL patients registered before 2020 in the European and North American databases or reported by members of the European Intergroup for Childhood Non-Hodgkin Lymphoma (EICNHL). Events considered to define event-free survival included relapse/progression, second malignancy (SML), or death, whichever occurred first.

Findings: The analysis included 74 patients, with 20 having multiple metachronous NHL. The median age at diagnosis was 9.4 years. Previous malignancies were reported in 36% of the patients, café au lait spots in 96%, and consanguinity in 54%. The initial lymphoma subtypes were 53 T-cell lymphoblastic lymphomas (T-LBL), four

Abbreviations: BFM, Berlin–Frankfurt–Munich; BL, Burkitt lymphoma; B-LBL, B-lymphoblastic lymphoma; B-NHL, B-cell non-Hodgkin lymphoma; C4CMMRD, Care for CMMRD; CI, confidence interval; CMMRD, constitutional mismatch repair deficiency syndrome; CR, complete remission; DLBCL, diffuse large B-cell lymphoma; DNA, deoxyribonucleic acid; EFS, event-free survival; EICNHL, European Intergroup for Childhood Non-Hodgkin Lymphoma; IRRDC, International Replication Repair Deficiency Consortium; MMR, mismatch repair; NHL, non-Hodgkin lymphoma; OS, overall survival; PV, pathogenic variant; SCT, stem cell transplantation; SML, second malignancy; TCR, T-cell receptor rearrangement; T-LBL, T-cell lymphoblastic lymphoma; TTP, time to progression; UK, United Kingdom.

Uri Tabori and Laurence Brugieres contributed equally to the study.

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B-lymphoblastic lymphomas, and 17 mature B-cell non-Hodgkin lymphoma (B-NHL). All patients were treated with curative intent, with current chemotherapy regimens adapted to their subtype. The median follow-up was 8.7 years. After the first lymphoma, the 5-year event-free and overall survival rates were, respectively, 23.5% [95% confidence interval (CI): 14.9–35.1] and 61.5% [95% CI: 49.6–72.1]. The 5-year cumulative risk of progression/relapse, SML or death as a first event was 20.8%, 52.9%, and 2.7%.

Interpretation: Standard treatments for sporadic NHL are effective in most CMMRD-associated NHL cases, but multiple malignancies, including lymphomas, impair prognosis. Future strategies should evaluate the potential of less genotoxic therapies, including immunotherapy, in preventing SMLs while maintaining effective control of NHL.

KEYWORDS

CMMRD, genetic predisposition, lymphoblastic lymphomas, lymphomas, second malignancy

1 | INTRODUCTION

Heterozygous pathogenic variants (PV) in deoxyribonucleic acid (DNA) mismatch repair (MMR) genes cause Lynch syndrome, increasing the risk of gastrointestinal, gynecologic, and urologic cancers in adulthood. Conversely, biallelic germline PV in these genes lead to constitutional mismatch repair deficiency syndrome (CMMRD, OMIM#276300), a rare autosomal recessive cancer predisposition syndrome first described in 1999.¹ Patients with CMMRD face a significantly elevated risk of developing various neoplasms, including hematological, brain, and gastrointestinal cancers during childhood, adolescence, and early adulthood.^{2,3} Many also display non-neoplastic features such as café au lait macules or cerebral developmental venous anomalies.² Before surveillance programs were introduced,^{4,5} most patients succumbed to cancer before the age of 20.^{2,6} Based on the frequency of PV in MMR genes in a large North American and Australian registry, the incidence of CMMRD has been estimated to be around 1:1,000,000 in children of unrelated parents, but is expected to be higher in populations with a high degree of consanguinity.⁴

Given the role of MMR proteins in DNA damage recognition and apoptosis signaling upon drug-induced DNA damage, there are concerns about the efficacy and safety of chemotherapy in patients with MMR deficiency. Pre-clinical data suggest that MMR deficiency is associated with a degree of chemoresistance, in particular for methylating agents and thiopurines.^{7–9,10} Additionally, the accumulation of unrepaired mutations in cells escaping apoptosis after exposition to these agents may increase the risk of chemotherapy-related secondary malignancies.⁹ There are limited clinical data available to support this hypothesis thus so far. This poses a significant challenge for CMMRD-associated non-Hodgkin lymphomas (NHL) where treatment exclusively relies on chemotherapy, including thiopurine maintenance in lymphoblastic lymphoma treatment, a common tumor in individuals with CMMRD.

To study response to treatment and outcomes of patients with CMMRD-associated NHL and to evaluate the need for specific treatment approaches for these patients, we established a collaboration between the European Intergroup for Childhood NHL (EICNHL) and two international consortia, the “Care for CMMRD” (C4CMMRD) consortium in Europe^{2,11} and the International Replication Repair Deficiency Consortium (IRRDC) based in Canada.³ Here, we present a comprehensive series of patients with CMMRD-associated lymphomas collected through this international collaboration.

2 | PATIENTS AND METHODS

This was an observational and retrospective study, encompassing all patients diagnosed with histologically proven NHL and CMMRD before 2020 and registered in the C4CMMRD or IRDCC databases, or reported by members of the EICNHL group. There was no limit for age at diagnosis.

CMMRD diagnosis was based on criteria established by international consensus.^{2,3} Details of genetic results were reviewed by members of each consortium whenever data were available. MMR gene variants were classified according to InSIGHT (International Society for Gastrointestinal Hereditary Tumor) classification guidelines (v2.4).

Both databases were approved by institutional research ethics board: Approval no. 20681 from the French INSERM (Institut national de la Santé et de la Recherche Médicale) (C4CMMRD database) and SickKids Research Ethics Board no. 1000048813 (IRRDC).

Patients were diagnosed in the context of clinical care through a standard genetic pathway, and their data reported by EICNHL members either came from a national database for childhood NHL or were obtained through direct contact with physicians in the context of national network of cancer centers. Consent for data collection was

obtained for all patients, their parents, and/or guardians in compliance with country-specific legislation.

2.1 | Data collection

Data were extracted from CMMRD consortia databases or obtained from treating physicians for patients in the EICNHL study group. Clinical data, such as personal and familial history of cancer, café au lait spots, consanguinity, lymphoma subtype, treatment type, and outcomes, were extracted from C4CMMRD and IRDCC databases. Additional data regarding staging at diagnosis, response to treatment, and unusual side effects were obtained through standard data forms from treating physicians whenever available.

Given the high risk of multiple malignancies in these patients, we established specific criteria to distinguish late relapses from new lymphomas with the same histology, given the limited availability of molecular analyses for tumor samples in most cases. Lymphomas diagnosed 3 years or more after the previous one were categorized as new lymphomas rather than relapses. This classification, stemming from discussions with EICNHL pediatric lymphoma experts, is particularly relevant due to the brief time to relapse in pediatric NHL, around 12 months for T-lymphoblastic lymphoma and 9 months for mature B-cell lymphoma.¹²

2.2 | Statistics

Overall survival (OS) and event-free survival (EFS) were estimated using the Kaplan–Meier method. We defined OS as the time from the first lymphoma diagnosis to death due to any cause and EFS as the time from the first lymphoma diagnosis to the first progression of the same lymphoma, the occurrence of a second malignancy (SML) or death. Cumulative incidences of first lymphoma progression (including progression concomitant to SML) of SML, and of death as first event (i.e., without previous progression or SML) were estimated within the framework of competing risk analysis. For progressions, the rate at 3 years was provided as all lymphoma events after 3 years were classified as SML.

Time to progression (TTP) was also estimated and defined as the time from the first lymphoma diagnosis to any progression (ignoring SML). Patients were censored at death or last follow-up without previous progression. TTP was estimated using the Kaplan–Meier method.

All *p*-values were two-sided. We conducted analyses with SAS (version 9.4) and R software for competing risk analyses.

3 | RESULTS

3.1 | Demographics and general characteristics

Overall, 81 patients from 18 countries were reported by the three study groups: 36 from C4CMMRD, 18 from the IRRDC, and 27 accrued through EICNHL network (Table S1). Seven cases were excluded: five

TABLE 1 Characteristics of CMMRD-associated lymphomas.

Patients' characteristics (74 patients)			
Age at diagnosis of the first NHL	7.9 years (IQR: 5–12.1)		
Sex			
Male	45 (61%)		
Female	29 (39%)		
Previous malignancy	27 (36%)		
Gene involved (missing data: 2 patients)			
<i>MLH1</i>	4 (5%)		
<i>MSH2</i>	5 (7%)		
<i>MSH6</i>	24 (33%)		
<i>PMS2</i>	39 (54%)		
Consanguinity (missing data: 25 patients)	27/50 (54%)		
Familial history of cancer (missing data: 29 patients)	32/45 (71%)		
Characteristics of the first NHL			
Period of treatment of the first NHL	1983–2020: only 5 before 1997		
Histologic subtypes			
T-LBL	53 (72%)		
Pre-B-LBL	4 (5%)		
B-cell lymphoma including	17 (23%)		
Burkitt lymphoma	6		
DLBCL	10		
Other B-NHL	1		
	T-LBL	B-LBL	B-NHL
Stage according to Jude's classification (missing data: 7 patients)			
I–II	0	0	3
III	45	0	11
IV	5	3	0

Abbreviations: B-LBL, B-lymphoblastic lymphoma; B-NHL, B-cell non-Hodgkin lymphoma; CMMRD, constitutional mismatch repair deficiency syndrome; DLBCL, diffuse large B-cell lymphoma; IQR, interquartile range; NHL, non-Hodgkin lymphoma; Pre-B-LBL, precursor B-lymphoblastic lymphoma; T-LBL, T-cell lymphoblastic lymphoma.

due to dual registration in consortium databases, and two due to insufficient data.

Total 74 patients, treated for their first lymphoma between 1983 and 2020, were included in the analysis (Table 1). One-third of these cases had already been reported as small patient series^{13–16} or as case reports.^{1,17–22}

The median age at diagnosis of the first lymphoma was 7.9 years, with only five patients diagnosed before the age of 2.

3.2 | Familial history and genetic background

The 74 patients included in this study came from 70 families, including four families with two siblings with lymphoma. A familial history of

cancers belonging either to Lynch syndrome or CMMRD was reported in 32 cases among 45 (71%) with available family history, including malignancies in siblings for 12 patients. Consanguinity was reported in 27 out of the 50 (54%) cases with available information.

Lymphoma was the first malignancy in 47 patients (64%), while 27 (36%) had already been treated for one or more previous malignancies, 22 for brain tumor, five for colorectal carcinoma, B-cell acute lymphoblastic leukemia (B-ALL), neuroblastoma, sarcoma, and salivary gland carcinoma (one each).

Café au lait macules were reported in 58 out of 60 (96%) patients with available cutaneous phenotype information.

For all 69 cases with minimal data available to calculate the C4CMMRD score² (Table S2), the score was above 3 at the time of the first lymphoma diagnosis.

Regarding germline variants, *PMS2* was involved in 39 (54%) patients, *MSH6* in 24 (33%), *MLH1* in four (5%), and *MSH2* in five (7%) (data missing for two patients). Homozygous variants were found in 36 patients and compound heterozygous variants in 27 patients (data missing for 11 patients). The classification of MMR variants was centrally reviewed in 51/74 patients.

3.3 | Histological subtypes, clinical characteristics, treatment, and outcome

The histologic subtypes of the first lymphomas are as follows: 53 T-cell lymphoblastic lymphomas (T-LBL), four precursor B-lymphoblastic lymphomas (B-LBL), and 17 mature B-cell non-Hodgkin lymphoma (B-NHL) including six Burkitt lymphomas (BL), 10 diffuse large B-cell lymphomas (DLBCL), and one unclassified high-grade B-NHL (Table 1). Data on initial staging of first NHL were available for 67 patients, with the majority presenting at St. Jude²³ stage 3 ($n = 56$) or 4 ($n = 8$).

3.4 | Multiple lymphomas

At the time of analysis, 20 patients had experienced multiple lymphomas, with 14 having two NHL and six with three NHL (Table 2). The median interval between each NHL was 4.3 years (range: 1.1–20), 4.5 years (range: 3.2–20.5) for NHL of the same lineage and 2.6 (range: 1.1–10) for NHL of a different lineage. Among the 11 patients with a second lymphoma of similar histology, two T-LBL patients underwent molecular analysis, which confirmed the presence of a different T-cell receptor (TCR) rearrangement compared to their first NHL.

3.5 | Treatment and outcome

All patients received curative-intent treatment for the first lymphoma with contemporary pediatric chemotherapy regimens tailored to the histology subtype (Table 3).²⁴ The median follow-up was 8.7 years (interquartile range: 5.7–17.8 years).

Regarding lymphoblastic lymphoma as first NHL, 57 patients were treated including 53 T-LBL and four B-LBL. Most patients with T-LBL received a Berlin–Frankfurt–Munich (BFM)-derived protocol designed for lymphoblastic lymphoma such as EUROLB-02²⁵ ($n = 37$), or a regimen designed for acute lymphoblastic leukemia²⁴ ($n = 13$) (Table 3). A complete response (CR) was achieved in 46 patients (87%), with nine experiencing a relapse at a median time of 20.8 months from initial diagnosis (range: 7.9–30.9). The sites of relapse included the mediastinum in seven cases (with central nervous system [CNS] involvement in two of these), isolated CNS involvement in two patients, and the testis in one patient (Table S2). Seven patients never achieved CR and died, including three patients who died during the first week of treatment, two from a complication and one from a concomitant SML. Overall, 15/53 patients had an event directly linked to the lymphoma. The 3-year rate of progression-free survival (PFS) was 70.43% [95% confidence interval (CI): 56.15–81.59] (Figure 1A). The 5-year OS and EFS rates were 58.6% [95% CI: 44.4–71.6] and 20.6% [95% CI: 11.2–34.8], respectively (Figure 1B,C), with a 5-year cumulative incidence of progression, SMLs, and death as first event of 25.6% (standard deviation [SD] 6.3%), 50.0% (SD 7.6%), and 3.8% (SD 2.6%), respectively (Figure 1D).

All four patients with B-LBL were treated with a BFM-derived protocol, and all achieved CR with no further relapse.

Regarding mature B-NHL as first lymphoma, data on treatment were available for 16/17 patients, all of whom treated with standard protocols designed for pediatric B-NHL: LMB-based protocols ($n = 14$), BFM based-protocol ($n = 1$), and R-CHOP (rituximab–cyclophosphamide–doxorubicin–vincristine–prednisone; $n = 1$). A CR was obtained in 15/17 cases. The two cases that did not achieve CR were DLBCL. The 3-year rate of progression-free patients was 87.84% [95% CI: 64.72–96.61] (Figure 1).

Five-year OS and EFS rates were 64.7% [95% CI: 41.3–82.7] and 23.5% [95% CI: 9.6–47.3], respectively, with a 5-year cumulative incidence of progression and SMLs as first event of 11.8% (SD 8.1%) and 64.7% (SD 12.4%), respectively.

All patients with second lymphomas received curative-intent treatment, 15 with regimens designed for NHL front-line treatment and five with regimens designed for relapses including allogeneic ($n = 3$) or autologous hematopoietic stem cell transplantation (SCT; $n = 2$) after remission. Among these 20 patients, one died of toxicity, one had early progression and one relapsed. Among the six patients who presented with a third lymphoma, one experienced progression without previous CR, and one a relapse (Table 4).

3.6 | Treatment tolerance

Four fatal adverse events (AE) were reported, three as first event with cause of death as follows: acute respiratory failure due to mediastinal compression at initial diagnosis ($n = 1$), tumor lysis syndrome ($n = 1$), unexplained death several years post allogeneic SCT ($n = 1$), and one after a second NHL (invasive aspergillosis). Seven severe AE were reported: bleeding due to CMMRD-related brain cavernoma

TABLE 2 Multiple lymphomas: Histologic subtypes and time interval between diagnosis of each NHL.

Histologic subtype of 1st NHL	Interval between 1st and 2nd NHL (years)	Histologic subtype of 2nd NHL	Interval between 2nd and 3rd NHL (years)	Histologic subtype of 3rd NHL
T-LBL	11.0	Burkitt	2.5	T-LBL
T-LBL	12.8	T-LBL		
T-LBL	12.8	DLBCL		
T-LBL	3.2	T-LBL		
T-LBL	4.18	T-LBL		
T-LBL	4.3	T-LBL		
T-LBL	4.4	T-LBL	4.3	T-LBL
T-LBL	4.5	T-LBL		
T-LBL	7.3	T-NHL		
T-LBL	9.8	T-LBL		
T-LBL	4.0	T-NHL		
DLBCL	3.8	DLBCL	2.3	T-LBL
DLBCL	2.2	T-LBL	2.6	PTCL
DLBCL	2.5	T-LBL		
DLBCL	2.9	T-LBL		
Burkitt	1.1	T-LBL	5.2	T-LBL
Burkitt	1.2	T-LBL	10.3	T-LBL
Burkitt	3.2	T-LBL		
Burkitt	7.9	B-NHL		
B-NHL	20.5	DLBCL		

Abbreviations: B-NHL, B-cell non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; NHL, non-Hodgkin lymphoma; PTCL, peripheral T-cell lymphoma; T-LBL, T-cell lymphoblastic lymphoma; T-NHL, T-cell non-Hodgkin lymphoma.

TABLE 3 Treatment and outcome after the first NHL according to the lymphoma subtype.

	T-LBL	B-LBL	Mature B-cell lymphoma		
			Burkitt	DLBCL	Other
Number of patients	53	4	6	10	1
Treatment	EURO-LB02 or NHLBFM 30 EURO-LB LB + allo-SCT 1 LMT96 5 EORTC ALL regimen 3 UK ALL regimen 4 COG ALL regimen 6 Other 4	EUROLB 02 4	FAB/LMB 96 5 BNHBFM04 + ritux 1	FAB/LMB 96 6 Inter-B-RITUX2010 2 8 RCHOP 1 Missing 1	LMB96 + maintenance 1
Complete remission rate	87%	100%	100%	83%	100%
Events					
- Relapse/Progression	15	0	0	2	0
- Second malignancy	27	3	6	8	1
- Treatment-related death as 1st event	3	0	0	0	0
3-Year progression-free survival	70.43% [56.15–81.59]	100%	87.84% [64.72–96.61]		
5-Year overall survival	58.6% [44.4%–71.6%]	100%	64.7% [41.3%–82.7%]		

Abbreviations: ALL, acute lymphoblastic leukemia; allo-SCT, allogeneic stem cell transplantation; B-LBL, B-lymphoblastic lymphoma; COG, Children's Oncology Group; DLBCL, diffuse large B-cell lymphoma; NHL, non-Hodgkin lymphoma; T-LBL, T-cell lymphoblastic lymphoma.

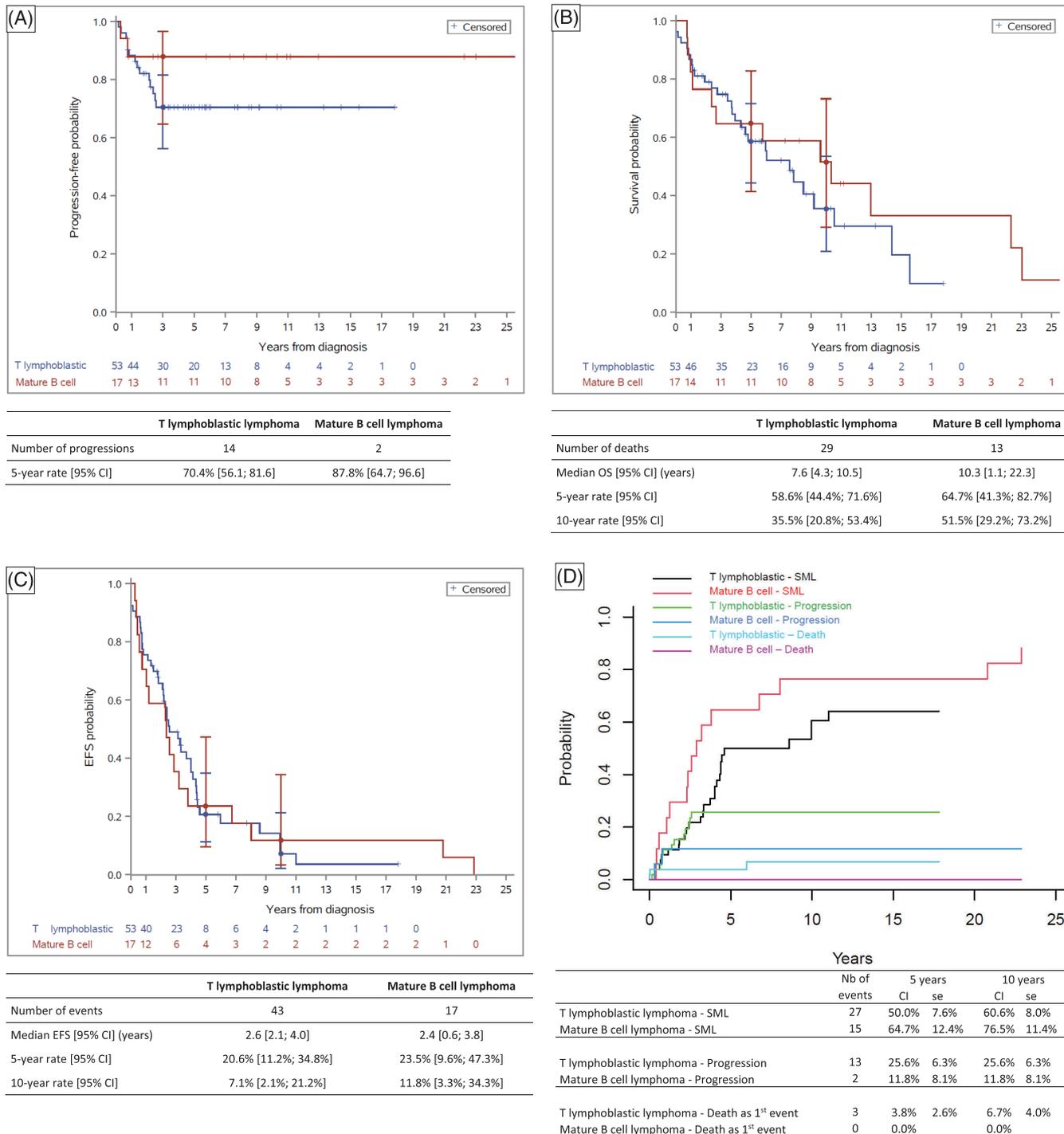


FIGURE 1 (A) Time to progression since diagnosis of first non-Hodgkin lymphoma (NHL), by type of lymphoma. (B) Overall survival since diagnosis of first NHL by type of lymphoma. (C) Event-free survival since diagnosis of first NHL by type of lymphoma. (D) Cumulative incidence of second malignancy, progression, and death as first events after the diagnosis of first NHL according to the type of lymphoma.

during thrombopenia ($n = 1$), invasive aspergillosis during induction chemotherapy ($n = 3$), asparaginase-related pancreatitis ($n = 2$) and leukoencephalopathy in one patient with previous brain radiotherapy. Five patients had autologous or allogeneic hematologic SCT without any specific safety concerns, except possibly for the unexplained death-related mentioned earlier.

3.7 | Second malignancies

Forty-six patients developed a total of 75 malignancies after their initial diagnosis of NHL. These comprised 26 new NHL, 23 cancers of the Lynch syndrome spectrum, and 20 brain tumors, including 17 high-grade gliomas and three medulloblastoma/PNET (primitive

TABLE 4 Responses to treatment and outcome of CMMRD-associated NHL.

	1st NHL (N = 74)	2nd NHL (N = 20)	3rd NHL (N = 6)	Total (N = 100)
Response to treatment				
CR	64	16	4	84 (82%)
No CR	10	4	2	16
Evolution after treatment				
Relapse/progressions	15	2	2	19

Abbreviations: CMMRD, constitutional mismatch repair deficiency syndrome; CR, complete remission; NHL, non-Hodgkin lymphoma.

neuro-ectodermic tumor). Additionally, there were six cases of other tumor types, including neuroblastoma, osteosarcoma, myelodysplastic syndrome, acute myeloblastic leukemia, precursor B-cell acute leukemia, and thyroid carcinoma. The median interval between the first NHL diagnosis and the first SML was 4.4 years (range: 0–9). The 5- and 10-year cumulative incidences of SML were 52.9% (SD 6.2%) and 65.7% (SD 6.3%), respectively (Figure 2A).

3.8 | Event-free survival and overall survival

Sixty-three patients experienced events. The first event was SML for 45 patients, relapse/progression of the first lymphoma for 14 patients, relapse concomitant to a SML for one patient, and death as first event for three patients. For the whole cohort, the 3-year cumulative incidence of relapse/progression after the first lymphoma was 20.8% (SD 4.8%) (Figure 2), with no significant difference in the 3-year rate of non-progression between patients with or without a previous malignancy.

Overall, 44/74 patients died. Median survival after the first lymphoma diagnosis was 8.5 years [95% CI: 4.8–10.5 years]. Deaths were attributed to first NHL progression in 13 cases (including two cases with a concomitant SML), SMLs in 26 cases, AE in three cases, and remained unknown in two.

The EFS and OS rates were 23.5% [95% CI: 14.9–35.1] and 61.5% [95% CI: 49.6–72.1], respectively, at 5 years and 9.0% [95% CI: 3.7–19.9] and 40.2% [95% CI: 27.6–54.2], respectively, at 10 years (Figure 2C).

4 | DISCUSSION

This extensive international collaboration, involving both oncogeneticists and pediatric lymphoma oncologists, allowed us to assess the therapeutic response, treatment tolerance, and outcomes of patients with CMMRD-associated NHL. Although a high proportion of patients have achieved remission of their lymphoma with standard therapy, their long-term survival remains poor primarily due to the high risk of SMLs, notably subsequent NHL, Lynch spectrum-associated cancers, and brain tumors.

The median age at diagnosis of the first NHL was 7.9 years, slightly older than previously described for CMMRD-associated NHL.² Only three patients were older than 18 years at the time of diagnosis of the first lymphoma, even though there was no upper age limit of inclusion in this study. The distribution of NHL subtypes is distinctive, with a marked predominance of T lymphoblastic lymphoma accounting for 72% of the lymphomas in this series, whereas they represent only 20%–25% of all childhood NHL.¹² Mature B-cell NHL are rarer, but can occur in the context of CMMRD.

The notable prevalence of T-cell malignancies in CMMRD warrants further examination. While most childhood lymphoid malignancies stem from B cells and typically involve the activation of oncogenic genes through fusion events, lymphoblastic lymphomas, in contrast, arise from T cells. These T cells undergo a phase of rapid proliferation and differentiation within the thymus, primarily driven by the somatic rearrangement of TCR genes. In the presence of MMR deficiency, this intricate process is vulnerable to the accumulation of mutations and the subsequent risk of malignant transformation. This may also account for the rarity of T-cell malignancies in adults with CMMRD or Lynch syndrome, as thymic T-cell training is significantly reduced in adulthood.

Identifying eight patients with CMMRD in a cohort of 88 Dutch T-LBL diagnosed between 2007 and 2020, Kroeze et al. estimated that the prevalence of CMMRD among pediatric T-LBL could be as high as 10%.¹⁶ This high prevalence necessitates consideration for systematic CMMRD screening in T-LBL. All newly diagnosed pediatric NHL patients should be screened for CMMRD using C4CMMRD scoring point criteria (Table S1).² All patients reaching 3 points should benefit from genetic testing for CMMRD. An ongoing study aiming to detect constitutional microsatellite instability in blood DNA,²⁶ a hallmark of CMMRD, in patients included in the European trial for T-LBL (LBL 2018, NCT04043494) will allow a more accurate evaluation of the prevalence of CMMRD in this population.

An important concern regarding CMMRD-associated lymphoma is the efficacy of chemotherapy in these patients compared to those with sporadic lymphomas. MMR inactivation has been shown to confer resistance to various cancer drugs, potentially through mechanisms like impaired drug-induced DNA damage recognition. This is particularly relevant for drugs involving nucleobase methylation (such as temozolomide) or integration of chemically modified nucleotides like 6-thioguanine or 6-mercaptopurine. Additionally, MMR deficiency can contribute to reduced chemotherapy-induced apoptosis and increased genomic instability resulting in the accumulation of additional genetic alterations.^{9–11}

CMMRD cell resistance to temozolomide has been established as an indicator for identifying patients with bi-allelic MMR PV, forming the basis of a diagnostic test.⁷ While resistance to thiopurines is noteworthy, it did not exhibit the same discriminatory strength to warrant inclusion in this functional test.⁷ Currently, no clinical data are available to assess the impact of this in-vitro reduced activity on the response to treatment and outcomes in CMMRD-associated lymphoma patients. In T-LBL, where long-term maintenance with 6-mercaptopurine is a part of

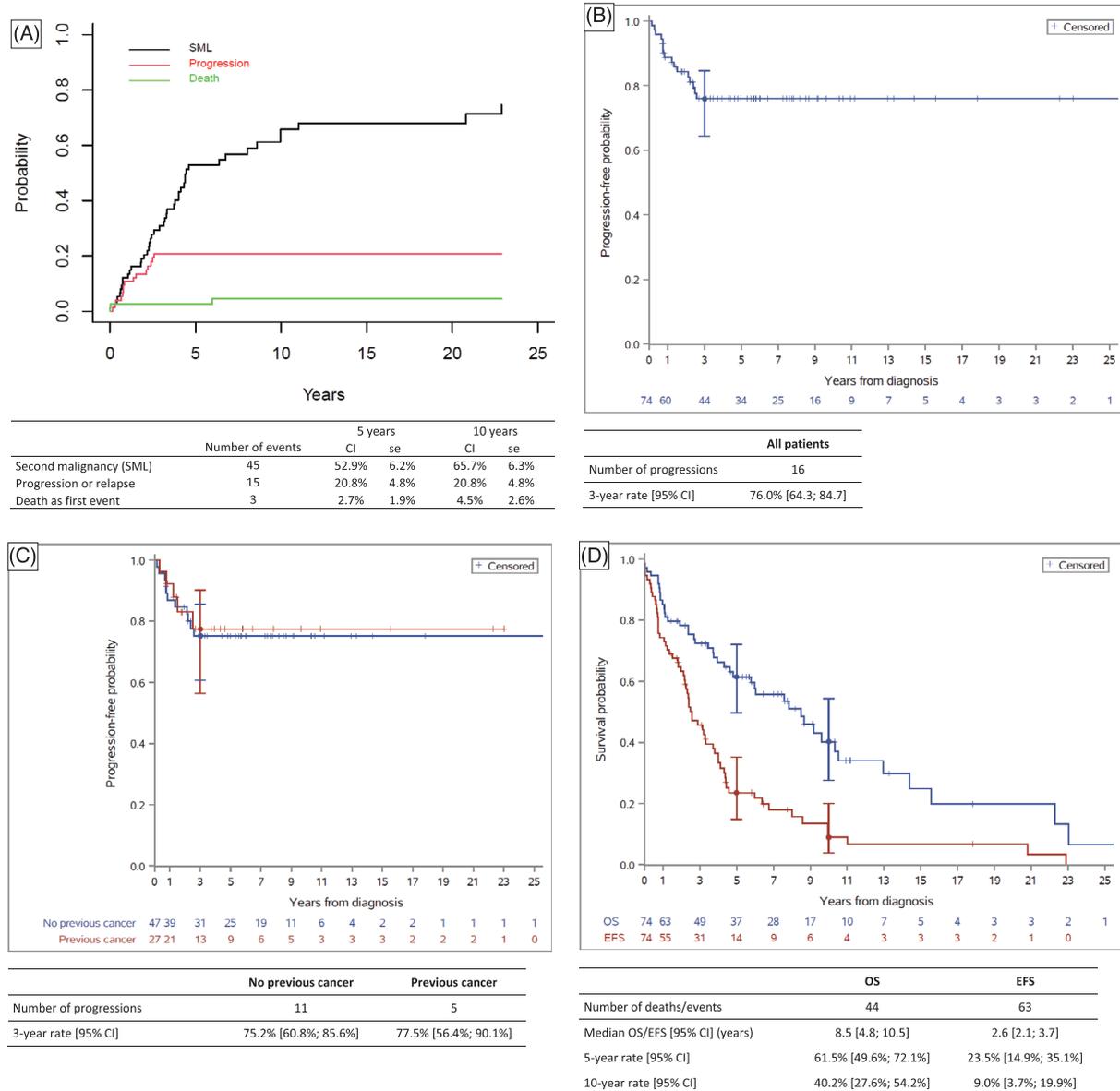


FIGURE 2 (A) Cumulative incidences of second malignancy, progression, and death as first event since diagnosis of first non-Hodgkin lymphoma (NHL), in all patients. (B) Time to progression since diagnosis of first NHL, in all patients. (C) Time to progression according to the presence of a previous cancer. (D) Overall survival and event-free survival since diagnosis of first NHL, in all patients.

the treatment, the 5-year cumulative incidence of tumor progression reported as 25.6% (SD 6%) in this series is somewhat higher than the 5-year incidence of non-response/relapse reported at 13% (SD 2%) in the EURO-LB02 protocol (NCT00275106) in 233 patients.²⁵ However, it is important to note that the present study covers patients treated over a 30-year period. The PFS is likely underestimated, because some events categorized as relapses may actually be second NHL of the same lineage. This is particularly relevant for patients whose relapses occur ≥ 2 years after the initial diagnosis, especially those presenting with mediastinal symptoms similar to newly diagnosed T-LBL. Supporting this, the time to relapse in this series (20.8 months) is longer than the typical relapse time seen in sporadic T-LBL cases (12 months) and the incidence of local relapses reaches 70% versus only 45% in sporadic T-LBL. Therefore, based on this analysis, there is currently insuffi-

cient clinical evidence to recommend modifications to the therapeutic strategy for CMMRD-associated T-LBL.

For B-cell lymphoma, where thiopurines are not typically part of current chemotherapy regimens, our data suggest that chemotherapy is equally effective as in sporadic B-NHL. The observed progression risk in this series is notably low and mirrors the failure rate described in sporadic mature B-NHL.²⁴

A noteworthy finding of this study is the substantial number of patients diagnosed with multiple consecutive lymphomas. It is important to note that our results might slightly overestimate this figure as we intentionally discriminated subsequent lymphomas from relapses, considering a delay over 3 years from the initial diagnosis. This differentiation led us to classify certain events previously reported as relapses as second lymphomas. However, we believe our definition is accurate,

as the response rate observed in these patients was much higher than expected in relapses of sporadic pediatric NHLs.²⁵ Additionally, the median time to relapse in our population (10.1 months) closely aligns with that of sporadic NHL (11 months). Nevertheless, when dealing with lymphoma progression in CMMRD patients, it is crucial to compare the genetic characteristics (clonality, mutational profile, fusion breakpoint in case of BL) of the initial lymphoma and the tumor at progression to determine the appropriate therapeutic strategy adapted for a second primary NHL or an NHL relapse. Notably, in this series regimens designed for front-line treatment were effective in most patients with multiple lymphomas.

CMMRD lymphomas have not previously been associated with poor chemotherapy tolerance. Unfortunately, for this retrospective study, we could only gather data on unexpected toxicities, not comprehensive treatment tolerance. The rates of treatment-related deaths and unexpected toxicity are in the expected range for lymphoblastic lymphoma,^{25,27} except for three cases of aspergillosis previously reported.¹⁶

Importantly, a significant portion of patients in this series developed SMLs after the initial lymphoma diagnosis. Assessing the role of chemotherapy in the pathogenesis of these multiple malignancies is challenging. DNA antimetabolites such as thiopurines have raised concerns about increasing the risk of SMLs in CMMRD patients due to the accumulation of unrepaired therapy-induced mismatches potentially leading to mutations in cancer driver genes.²⁸ However, patients with B-NHL treated without thiopurines have shown similar rates of SML as those treated for T-LBL.

The main limitation of our study is its retrospective nature, relying on registry data that were not originally intended to comprehensively assess the treatment efficacy for each CMMRD-associated tumor. Consequently, our analysis suffers from a significant amount of missing data. Nevertheless, this represents the largest series to date emphasizing the high incidence of multiple malignancies as a critical factor influencing the long-term prognosis of CMMRD patients with NHL. Furthermore, our data suggest that standard guidelines for sporadic NHL are effective in these patients. Nevertheless, exploring the role of chemotherapy in the pathogenesis of SMLs as well as the efficacy of non-genotoxic agents such as targeted agents or immunotherapy in this context is crucial. Checkpoint inhibitors have been shown to induce response in MMR-deficient tumors²⁹ and also to reduce the risk of SMLs in patients with apparently sporadic tumors.³⁰ Investing in these drugs in future trials with CMMRD tumors, including lymphomas, is essential.

AUTHOR CONTRIBUTIONS

LB, UT, CR, BB, AA, GAAB, and JL planned the study. The data collection was ensured by CR, VF, AA, HA, VB, GAAB, BB, CC, CD, CK, ME, SE, AG, YG, DJ, EK, JL, MD, DR, AT, AU, UT, VPA. Details of genetic results were reviewed by KW, CRP, MP, and SH. Statistical analysis was performed by AA. Data analysis was performed by CR and LB. Results from the study were discussed with all authors. The first draft of the manuscript was written by CR, VF, LB, and UT. All the authors contributed to data control and to the manuscript writing and revisions.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

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

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