CORRESPONDENCE OPEN

Check for updates

Survival of patients with classical Hodgkin lymphoma in Finland: a national population-based analysis

Blood Cancer Journal (2024)14:139 ; https://doi.org/10.1038/s41408-024-01125-4

Dear Editor,

Classical Hodgkin lymphoma (cHL) is a B-cell derived malignancy that is characterized by a bimodal incidence peak in the 20–30 and 60–75 years age groups [1]. Curative treatment for cHL has been feasible since the 1960s, after the introduction of mantle-field irradiation [2, 3] and combination chemotherapy protocols, including mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) and MOPP–doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) [4]. Data collected by IARC NORDCAN indicated that the 5-year age-standardized relative survival rates improved from 51.7% and 55.8% in 1971–1975 to 88.2 and 90% in 2016–2020 for males and females, respectively [5]. However, age of the patient at diagnosis consistently affects survival significantly. Furthermore, improvement in therapy efficacy has come at the expense of severe long-term toxicities. The less toxic ABVD regimen [6] with a shorter duration [7] has substituted the MOPP–ABVD backbone to mitigate side effects while maintaining disease control. Advances in radiotherapy (RT) planning and delivery have enabled local control maintenance while minimizing exposure to surrounding tissues [8]. Considering these continuous adjustments to therapeutic regimens, the up-to-date reporting of survival and late effects within patients with cHL of different age cohorts remains highly relevant.

Our retrospective cHL registry study utilized existing nationwide data (Fig. S1) available from six Finnish electronic healthcare registries, including the Finnish Cancer Registry (FCR), the National Institute of Health and Welfare, the Social Insurance Institution of Finland, the Finnish Centre for Pensions, Statistics Finland, and Digital and Population Data Services Agency (DPA). The analysis cohort included patients with record of HL based on FCR database (ICD-10: C81*), excluding those with nodular lymphocyte-predominant HL (ICD-O-3 morphology code 9659/3) from January 1, 2000, to December 31, 2019 ($n = 2510$). An age, sex, and region-matched control cohort in a 1:1 ratio was determined using DPA records, and eligible control participants included individuals without lymphoma diagnosis (C81–C85) from January 1, 2000, and December 31, 2019, and who were alive at the index of the corresponding case. Tables S1 and S2 present the baseline characteristics of the participants. Table S3 presents the methods. The end of follow-up (FU) was defined as death, end of study, or loss to FU. The mean FU time were 9.7 and 8.3 years in the younger and older patients (9.9 and 8.3 years for respective control cohorts), respectively.

Consistent with other reports [9], we observed excellent 5-, 10-, and 20-year survival rates of 96.6% (95% confidence interval [CI]: 95.6–97.4%), 94.6% (95% CI: 93.1–95.7%), and 90.9% (95% CI: 88.4–92.8%) in younger patients with cHL (Fig. 1A) and 99.7% (95% CI: 99.3–99.9%), 99.2% (95% CI: 98.5–99.6%), and 97.3% (95% CI: 95.2–98.4%) in the younger control cohort, respectively. Importantly, in concordance with data from the United States [10] and other Nordic countries [11], we observed a temporal improvement in overall survival (OS) and a reduction in the overall risk of mortality in younger patients from the 2000–2009 to 2010–2019 treatment era ($p = 0.0033$) (Fig. 1C, Table S4). The 2010–2019 era was also associated with a lower mortality risk than the 2000–2010 era in the Cox multivariable analysis (hazard ratio [HR]: 0.41, 95% CI: 0.22–0.74, $p < 0.01$) (Table S5). The reasons for the improved survival could not be thoroughly described because the hospital medical records of the administered therapy protocols were not retrieved for this study. However, this finding may be attributed to more effective salvage treatments, such as brentuximab vedotin or immune checkpoint inhibitors, because no major changes have occurred in the first-line treatment of cHL since 2000 [12]. General healthcare improvement is an unlikely explanation because the survival of the control cohort remained similar between the two eras of interest (Fig. S2).

Despite the excellent survival rates, we revealed a consistently higher overall mortality risk in younger patients with cHL in comparison to controls. The Cox multivariable analysis (Table S6) revealed that the HRs for death in patients with cHL in comparison to controls was 12.13 (95% CI: 4.37–33.67, $p < 0.001$) at 0–5 years after diagnosis and 2.24 (95% CI: 0.96–5.19, $p = 0.06$) even at 10 years after diagnosis. We categorized the causes of death into cHL, other lymphomas, solid malignancies, myeloid malignancies, cardiovascular diseases (CVDs), and others for the cause-specific analysis of mortality (Table 1). Of the 87 deaths in younger patients during the FU study, cHL was the cause of death in 53 (60.9%) (Table S7). Cumulative cHL-specific mortality increased to 3.7% by the 10-year FU and leveled off thereafter (Table 1). Mortality caused by other reasons accumulated during the later years of FU but remained surprisingly low. For example, the cumulative risk of mortality from CVD was only 0.9% (0.1% in controls) and that from solid cancers was 1.6% (1.1%) at 20 years. The rates are comparable to those from a recent Danish study from the same era [13]. Similar results between countries are not unexpected considering the joint Nordic treatment guidelines for cHL. Thus, mortality from secondary toxicities may have a decreasing tendency among younger patients with cHL treated from 2000 onward, given the caveat of short FU.

Alarmingly, however, our study revealed a rapidly and steadily increasing cumulative incidence of CVDs and solid malignancies from 5 years onward without a plateau in the younger cHL cohort, which contrasts with the low mortality rates (Table 1, Supplementary Fig. S3). The cumulative incidence of solid malignancies at 10- and 20-year FU was

Received: 7 May 2024 Revised: 11 August 2024 Accepted: 12 August 2024
Published online: 20 August 2024

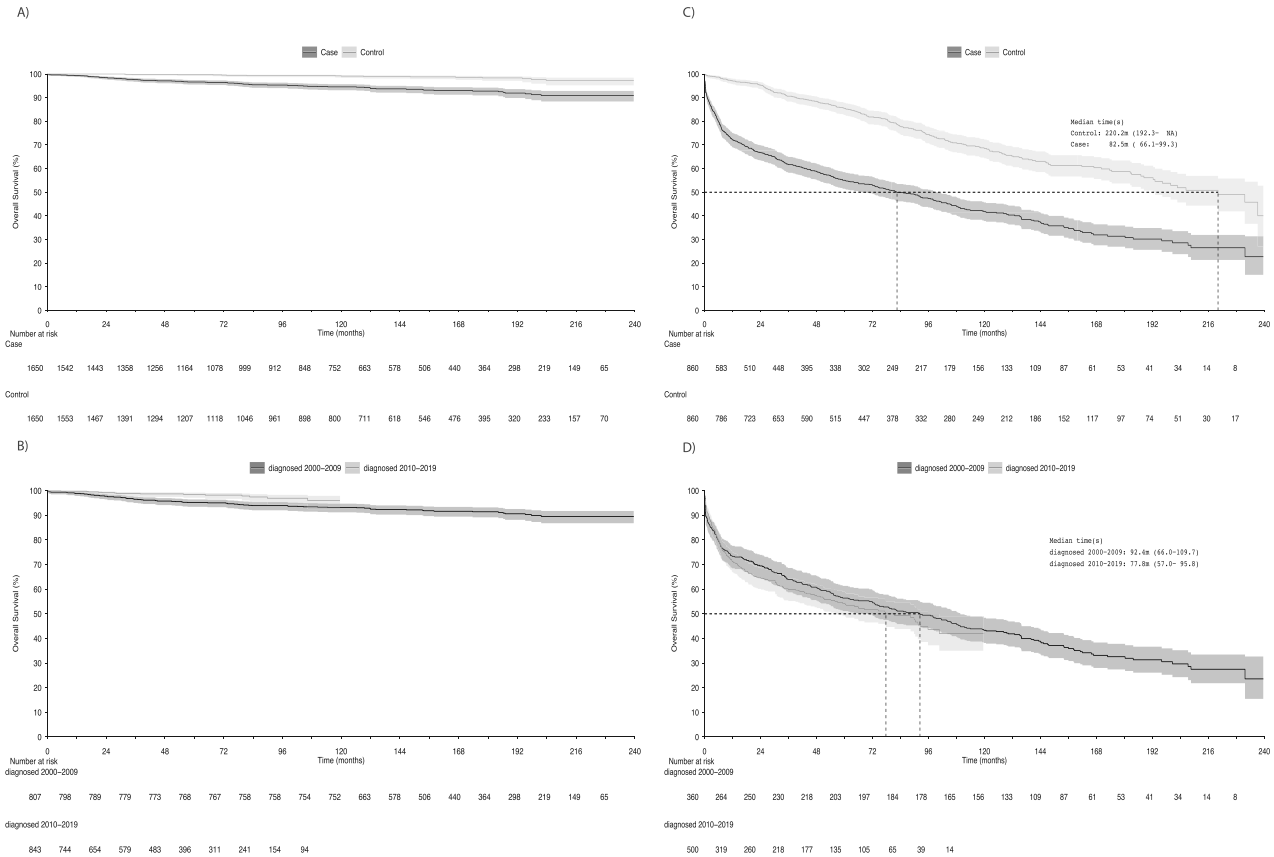

Fig. 1 Overall survival of cHL patients. A Younger patients with cHL and their controls, **B** Younger patients by the diagnosis year period of 2000–2009 or 2010–2019, **C** Older patients with cHL and their controls, **D** Older patients by the diagnosis year period.

7.7% and 13.8%, in patients with cHL and 1.0% and 3.6% in controls, respectively. Similarly, the cumulative incidence of CVDs at 10- and 20-year FU was 7.0% (3.9%) and 17.4% (9.6%), respectively. The numbers are in the same range or only slightly lower than those for patients treated before 2000 [14]. The high incidence, together with low death rates, could be attributed to improved patient monitoring, enabling early therapy interventions for treatment-induced CVDs, and a curative approach for early-stage secondary cancers [15]. Nevertheless, there is a risk that extended FU would turn the high incidence of CVDs in our study into increased late mortality. Notably, the incidence of myeloid malignancies of 1.0% (0.2%) at 20 years of FU remained moderate in our study, indicating successful conversion away from highly mutagenic protocols.

We observed significantly poorer survival rates of 55.1% (95% CI: 51.5–58.5%), 41.8% (95% CI: 37.8–45.7%), and 22.7% (95% CI: 15.1–31.3%) in older patients and 85.5% (95% CI: 82.7–87.9%), 68.5% (95% CI: 64.4–72.3%), and 40.1% (95% CI: 27.0–52.7%) in older controls at 5, 10, and 20 years of FU, respectively, in contrast to younger patients. Poor survival was mostly attributed to high cHL-specific mortality in older patients with cHL during early FU (21.7% during the first year, Table 1). No temporal improvement in OS or reduction in the overall risk of mortality was observed from 2000–2010 to 2010–2019, unlike in younger patients (Fig. 1D and Table S4). However, the median age of patients treated in the latter period (Table S2) was higher than in the former period (68.1 vs. 65.8 years), which may have countervailed the possible OS improvement. We did not observe any excess morbidity or mortality from other malignancies or CVD in the older patient cohort (Table 1). In particular, the 20-year cumulative mortality from solid malignancies was 7.0% and from CVDs was 9.5%, which were lower than in the control (11.4% and 17.0%, respectively, Table 1). This is most likely explained by the healthy survivor effect, i.e., the enrichment of fit and less morbidity among long-term survivors.

The strengths of our study include a population-based approach using real-life data, excellent coverage and reliability from national registries used for the study. This study has limitations, including a short FU time, which restricts the comprehensive characterization of late toxicities and mortality. Additionally, we have no access to detailed information on patients' treatment or therapy intend, and missing or inaccurate data are possible because of differences in recording practices. Moreover, due to technical reasons, no lymphomas were allowed in the FU in control groups which may have a marginal biasing effect between the study groups.

In conclusion, the prognosis of patients aged <50 years is excellent and is still improving with the current therapeutic modalities. However, the high incidence of secondary solid cancers and CVDs remains a concern. Considering the long lifetime expectancy of these patients, our results emphasize the importance of close monitoring of secondary complications and evaluations for therapeutic de-escalation. The survival of patients aged >50 years is poor because of high mortality associated with

Table 1. Cumulative incidence (%) of other malignancies and CVDs and mortality (%) by cause of death in younger and older age cohorts.

Younger cohort		Follow-up time (years)					Older cohort		Follow-up time (years)				
		1	5	10	15	20			1	5	10	15	20
Cum. incidence Solid malignancy	*cHL*	2.6	4.9	7.7	9.7	13.8	Cum. incidence Solid malignancy	*cHL*	3.6	8.7	14.0	17.2	17.2
	Control	0.1	0.4	1.0	1.9	3.6		*Control*	2.0	9.8	16.7	20.4	24.5
Cum. incidence Myeloid malignancy	*cHL*	0.2	0.5	0.7	1.0	1.0	Cum. incidence Myeloid malignancy	*cHL*	0.2	1.0	1.2	1.5	1.5
	Control	0.0	0.1	0.2	0.2	0.2		*Control*	0.1	0.7	0.9	0.9	1.9
Cum. incidence CVD	*cHL*	0.9	3.5	7.0	12.1	17.4	Cum. incidence CVD	*cHL*	5.3	13.7	20.5	28.2	33.2
	Control	0.3	1.6	3.9	5.9	9.6		*Control*	4.8	18.2	32.2	40.9	48.1
OS rate (%)	*cHL*	99.3	96.6	94.6	92.8	90.9	OS rate (%)	*cHL*	72.1	55.1	41.8	31.4	22.7
	Control	100	99.7	99.2	98.4	97.3		*Control*	97.1	85.5	68.5	58.7	40.1
Cum. mortality cHL	*cHL*	0.5	2.6	3.7	4.2	4.2	Cum. mortality cHL	*cHL*	21.7	30.9	33.8	34.7	34.7
	Control	0.0	0.0	0.0	0.0	0.0		*Control*	0.0	0.0	0.0	0.0	0.0
Cum. mortality Other lymphoma[a]	*cHL*	0.0	0.1	0.1	0.1	0.1	Cum. mortality Other lymphoma[a]	*cHL*	0.7	2.2	4.2	4.2	4.2
	Control	0.0	0.0	0.0	0.0	0.0		*Control*	0.0	0.0	0.0	0.0	0.0
Cum. mortality Solid malignancy	*cHL*	0.0	0.0	0.1	0.6	1.6	Cum. mortality Solid malignancy	*cHL*	0.2	1.6	4.3	6.4	7.0
	Control	0.0	0.0	0.2	0.4	1.1		*Control*	0.6	2.9	6.5	8.2	11.4
Cum. mortality Myeloid malignancy	*cHL*	0.0	0.0	0.1	0.3	0.3	Cum. mortality Myeloid malignancy	*cHL*	0.0	0.1	0.4	0.7	0.7
	Control	0.0	0.0	0.0	0.0	0.0		*Control*	0.0	0.3	0.5	0.5	0.5
Cum. mortality CVD	*cHL*	0.0	0.2	0.4	0.5	0.9	Cum. mortality CVD	*cHL*	2.2	4.5	6.6	9.5	9.5
	Control	0.0	0.0	0.1	0.1	0.1		*Control*	1.4	4.9	9.3	12.8	17.0
Cum. mortality Other[b]	*cHL*	0.2	0.4	1.0	1.3	1.9	Cum. mortality Other[b]	*cHL*	3.0	5.6	8.9	13.1	21.2
	Control	0.0	0.3	0.5	1.1	1.6		*Control*	0.8	6.4	15.3	19.8	31.0

Cum cumulative, *OS* overall survival, *CVD* cardiovascular disease, *cHL* classical Hodgkin lymphoma.
Other lymphoma: ICD-10: C82-C85.
Solid malignancy: ICD-10: C00-80.
Other myeloid malignancy: ICD-10: C92, D46, D47.
CVD: ICD-10: I10-25, I34-37, I42-43, I46, I50.
[a]For controls, any lymphoma diagnosis (C81-85) was an exclusion criteria.
[b]Other: Any other cause of death.

either lymphoma or complications of conventional therapy. Evidently, more tolerable therapeutic modalities are required in older patients with cHL.

Noora Hannuksela[1]✉, Anu Partanen[2], Anna Anttalainen[3], Liisa Ukkola-Vuoti[3], Iiro Toppila[3], Johanna Vikkula[3], Katja Marin[4], Hanne Kuitunen[5], Tatu Miettinen[6], Outi Kuittinen[1,4,7] and Aino Rönkä[1,4,7]

[1]Oncology, Faculty of Health Medicine, School of Medicine, Institute of Clinical Medicine, University of Eastern Finland, Kuopio, Finland. [2]Department of Medicine, Kuopio University Hospital, Wellbeing Services County of Northern Savo, Kuopio, Finland. [3]Medaffcon Oy, Espoo, Finland. [4]Department of Oncology, Kuopio University Hospital, Kuopio, Finland. [5]Cancer Center, Oulu University Hospital, Oulu, Finland. [6]Takeda Oy, Helsinki, Finland. [7]These authors contributed equally: Outi Kuittinen, Aino Rönkä.
✉email: nhannuks@student.uef.fi

DATA AVAILABILITY

This study is based on secondary use of healthcare register data. Data can be acquired with data permission by following the guidance and application process of the registries.

REFERENCES

1. Shenoy P, Maggioncalda A, Malik N, Flowers CR. Incidence patterns and outcomes for Hodgkin lymphoma patients in the United States. Adv Hematol. 2011;2011:725219.
2. Behringer K, Diehl V. Twenty-five years clinical trials of the German Hodgkin Study Group (GHSG). Eur J Haematol. 2005;75:21–5.
3. Koontz BF, Kirkpatrick JP, Clough RW, Prosnitz RG, Gockerman JP, Moore JO, et al. Combined-modality therapy versus radiotherapy alone for treatment of early-stage Hodgkin's disease: cure balanced against complications. J Clin Oncol. 2006;24:605–11.
4. Santoro A, Bonadonna G, Valagussa P, Zucali R, Viviani S, Villani F, et al. Long-term results of combined chemotherapy-radiotherapy approach in Hodgkin's disease: superiority of ABVD plus radiotherapy versus MOPP plus radiotherapy. J Clin Oncol. 1987;5:27–37.
5. 5-year age-standardised relative survival (%), Males and Females. In: International Agency for Research on Cancer, NORDCAN. World Health Organization. 2023. https://nordcan.iarc.fr/en/dataviz/survival?cancers=370&sexes=1_2. Accessed 9 June 2023.
6. Canellos GP, Anderson JR, Propert KJ, Nissen N, Cooper MR, Henderson ES, et al. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. N. Engl J Med. 1992;327:1478–84.
7. Engert A, Plütschow A, Eich HT, Lohri A, Dörken B, Borchmann P, et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. N Engl J Med. 2010;363:640–52.
8. Yahalom J. Don't throw out the baby with the bathwater: on optimizing cure and reducing toxicity in Hodgkin's lymphoma. J Clin Oncol. 2006;24:544–8.

9. Pulte D, Gondos A, Brenner H. Trends in survival after diagnosis with hematologic malignancy in adolescence or young adulthood in the United States, 1981-2005. Cancer. 2009;115:4973–79.
10. Pulte D, Jansen L, Brenner H. Changes in long-term survival after diagnosis with common hematologic malignancies in the early 21st century. Blood Cancer J. 2020;10:56.
11. Hemminki K, Hemminki J, Försti A, Sud A. Survival in hematological malignancies in the Nordic countries through a half century with correlation to treatment. Leukemia. 2023;37:854–63.
12. Desai SH, Spinner M, Evens AM, Syrokova A, Bachanova V, Goyal G, et al. Overall survival in classic Hodgkin lymphoma pts who progress after autologous stem cell transplant in the era of novel agents. Blood Adv. 2023;7:7295–303.
13. Rossetti S, Juul SJ, Eriksson F, Warming PE, Glinge C, El-Galaly TC, et al. Long-term cause-specific mortality in adolescent and young adult Hodgkin lymphoma patients treated with contemporary regimens-A nationwide Danish cohort study. Br J Haematol. 2024;00:1–9.
14. van Eggermond AM, Schaapveld M, Lugtenburg PJ, Krol ADG, de Boer JP, Zijlstra JM, et al. Risk of multiple primary malignancies following treatment of Hodgkin lymphoma. Blood. 2014;124:319–27.
15. Wong FL, Lee JM, Leisenring WM, Neglia JP. Efficacy and cost-effectiveness of breast cancer (BC) screening in female survivors of childhood Hodgkin lymphoma (HL). JCO. 2021;39:6593–93.

ACKNOWLEDGEMENTS

This study was funded by a grant from Takeda Oy.

AUTHOR CONTRIBUTIONS

AA, LU-V, IT, and JV coordinated the data collection. AA, LU-V, IT, JV, NH, AP, AR, and OK conducted the data analyses and AA, LU-V, IT, and JV provided expert insight into the statistical analyses. NH, AR, AP, and OK wrote the manuscript. NH, AR, AP, OK, AA, LU-V, IT, KM, HK, and JV critically reviewed the manuscript. All the authors read and approved the final manuscript.

COMPETING INTERESTS

AR reports personal fees for speaking at symposia or financial support for attending conferences from Amgen, Bristol-Myers Squibb, Merck, Novartis, Pfizer, Daichii Sankyo and Roche. AP reports honoraria from Behring and Abbvie and has participated in Scientific Advisory Board meetings organized by Abbvie, Janssen-Cilag, Novartis, Pfizer and Takeda. None of the financial support was related to the present study. TM has been contractor by Takeda Oy during the study time. LU-V, IT, JV, and AA are employed by Medaffcon Oy. The rest of the authors declared no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41408-024-01125-4.

Correspondence and requests for materials should be addressed to Noora Hannuksela.