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Therapy-related acute myeloid leukemia in Non-Hodgkin lymphoma survivors: Risk, survival outcomes and prognostic factor analysis

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ORIGINAL RESEARCH REPORT

Therapy-related Acute Myeloid Leukemia in Non-Hodgkin Lymphoma Survivors: Risk, Survival Outcomes and Prognostic Factor Analysis

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Abstract

Background: **Therapy-related acute myeloid leukemia (tAML) is a serious complication in patients with Non-Hodgkin lymphoma (NHL) exposed to chemotherapy or radiation. This extensive database study aims to quantify the risk of tAML in NHL and determine the impact of tAML on the overall survival (OS) of patients with NHL.**

Materials and methods: **Patients diagnosed with NHL and de novo AML from 2009 to 2018 were identified from the Surveillance, Epidemiology, and End Results database. Multiple primary standardized incidence ratio (SIR) sessions of the SEER*Stat software were used to calculate SIR and the absolute excess risk of tAML. Overall survival (OS) was evaluated using Kaplan−Meier curves and compared using log-rank tests. Multivariate analysis was used to study the role of each covariate on OS in patients with tAML.**

Results: **The SIR of tAML was 4.89 (95% CI 4.41−5.41), with a higher incidence of tAML observed for age <60 years, NHL prior to 2013 and within 5 years of diagnosis, and those who received chemotherapy. NHL patients with tAML had lower OS than those without tAML (5-year OS 59% vs. 13%, $p < 0.001$). Patients with tAML showed worse OS than de novo AML in univariate analysis (5-year OS 13% vs. 25%, $p = 0.001$) but not in multivariate analysis (HR 0.93, 95% CI 0.82−1.04, $p = 0.21$). Age ≥60 years and lack of chemotherapy were associated with poor OS in tAML subcategory.**

Conclusion: **Age, time since NHL diagnosis, and receipt of chemotherapy directly influence the risk of development of tAML in NHL survivors.**

Keywords: Non-Hodgkin lymphoma, Therapy-related myeloid neoplasm, Acute myeloid leukemia, Incidence, Overall survival, Prognosis

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1. Introduction

With newer advancements in cancer therapeutics and the prolonged life expectancy of patients with lymphoma, therapy-related acute myeloid leukemia (tAML) has emerged as a serious complication, especially with cytotoxic chemotherapy and radiation therapy [1]. Patients on alkylating agents, topoisomerase inhibitors, and radiation therapy can develop tAML with variable latency, progression, and response to therapy [2]. Besides direct DNA damage, chemotherapy may induce chromosomal translocation with the formation of fusion oncogene, create a pro-inflammatory milieu in bone marrow, or promote selective growth of treatment-resistant mutated stem cells. The leukemogenicity, cumulative dosing, and intensity of various chemotherapeutic agents result in the variable incidence of tAML in different cancers [3,4].

The development of a second primary malignancy in Non-Hodgkin lymphoma (NHL) survivors has been demonstrated in multiple studies [5,6]. However, only a limited number of population-based studies have investigated the risk of tAML in the background of NHL. Although Smith et al. showed that 23% of the patients with therapy-related myeloid neoplasm had preceding NHL, this was a single-center study with a selected cohort diagnosed before 2001 [7]. A Surveillance, Epidemiology, and End Results (SEER) database study from 1975 to 2008 showed 20% of the tAML cases to have developed in NHL survivors, but no large-scale study has been done since the turn of the decade to quantify tAML incidence and risks [1].

The primary objectives of our study were to quantify the risk of tAML in NHL and determine the impact of tAML on the overall survival (OS) of patients with NHL. Since tAML has been shown to differ from de novo AML in cytogenetics and OS, we also decided to compare OS and factors associated with OS between de novo AML and tAML in our study cohort.

2. Materials and methods

2.1. SEER registry and study population

We constructed our study cohort using the National Cancer Institute's SEER Program database. The SEER 18 database represents 27.8% of the US population and collects information on cancer incidence, patient demographics, staging, treatment data, and survival from locations and sources throughout the US.

We used the Lymphoid Neoplasm Recode 2021 revision to identify 312,576 patients diagnosed with NHL from 2009 through 2018. After excluding patients ≤18 years (N = 10,673), we included 301,903 patients with newly diagnosed NHL in the final analysis. We then created a cohort of NHL patients who developed tAML using the histological code ICD-O-3 9840/3, 9861/3, 9866/3, 9867/3, 9869/3, 9871/3-9874/3, 9895/3-9897/3, 9910/3, 9911/3 and 9920/3. Seven cases of APL were included in the tAML cohort. tAML was defined as histologically confirmed cases of AML that developed at least 1 year after the NHL diagnosis. A latency period of 12 months was chosen to avoid over-ascertainment bias, as done in prior studies [8,9]. In the tAML cohort, we also excluded patients who developed other malignancies between the diagnosis of NHL and tAML. To compare the survival outcomes between tAML and de novo AML, we further identified cases of de novo AML from the SEER 18 database within the same time duration using histological codes ICD-O-3 9840/3, 9861/3, 9865/3-9867/3, 9869/3, 9871/3-9874/3, 9895/3-9898/3, 9910/3, and 9911/3. After excluding patients <18 years, we included 23,360 cases of de novo AML in the final analysis (2480 of these patients were diagnosed with APL). The CONSORT diagram describes the cohort selection (Supplementary Figure 1).

2.2. Study variables

We extracted details on the following variables-age, sex, race, insurance status, marital status, receipt of chemotherapy and radiation therapy, year of diagnosis, the interval from diagnosis of NHL (for tAML), and survival months. Patient's age correlated with the age at diagnosis of NHL or de novo AML based on the study cohort. The race included blacks, whites, and others (American Indian, Alaskan Native, Asian and Pacific Islander). The SEER database categorizes the insurance status into four groups-uninsured, Medicaid, insured, and insurance status unknown. The insured population comprises those with Medicare, private insurance, or military or Veterans Affairs insurance. The year of diagnosis was divided into two 5-year cohorts: 2009-2013 and 2014-2018. Patients were followed from the date of diagnosis to the date of death or the last data collection point (December 2018). Our prior publication has additional details on the study variables [10].

2.3. Statistical analysis

We described the categorical variables as frequencies and percentages and the continuous

variables as mean or median. Using the Chi-square test, we compared the demographic and clinical characteristics of different groups (NHL with vs. without tAML and de novo AML vs. tAML). Multiple primary standardized incidence ratio (SIR) sessions of the SEER*Stat software (version 8.3.9) were utilized to calculate the SIR and absolute excess risk (AER) of tAML. We further stratified the tAML cohort based on age, sex, race, marital status, chemotherapy, interval from NHL diagnosis, and year of diagnosis to determine the association of these variables with an incidence of tAML. A multivariate Poisson regression model was applied to generate the 95% confidence intervals (CI) and p-values.

OS was evaluated using Kaplan–Meier curves and compared using log-rank tests. We plotted the curves to compare the survival outcomes between the NHL cohort who did vs. did not develop tAML and between de novo AML and tAML. We performed a multivariate cox proportional hazard regression analysis using the covariates mentioned above to compare the OS between de novo AML and tAML. We further conducted a separate multivariate cox regression analysis to study the role of each covariate on OS in patients with tAML. A hazard ratio (HR) with 95% CI was calculated for different groups based on covariates.

For the cubic spline graph, the cubic spline function of the NumPy library in Python was used to calculate the points of the curve using the desired data for the time range. A curve was graphed, joining all the initial and computed points. The data points from the original data are represented using bold dots on the graphs. The confidence interval of the graph was drawn using the principles of the bell curve for each of the calculated and initial points.

All statistical analyses were conducted using R software version 4.1.1. P-value <0.05 was considered statistically significant.

3. Results

3.1. Demographic and clinical characteristics of the NHL cohort

The median age of the NHL cohort who developed tAML was 64 years (age at the time of diagnosis of NHL), whereas the median age was 68 years for those who did not develop tAML. Seventy-one percent of the patients were above 60, 56% were males, 81% were whites, and 54% were married. Fifty percent of the patients received chemotherapy for NHL, and 52% were diagnosed after 2014.

3.2. tAML in NHL survivors

Out of 301,903 patients with NHL, 571 patients developed tAML during the 10-year period. We excluded 198 patients who developed other malignancies before the diagnosis of tAML and 73 patients with a latency period of less than a year. We included 373 patients with tAML in the final analysis.

NHL patients who developed tAML had a median age of 67 years at the time of diagnosis of tAML (median age at diagnosis of NHL in the same cohort was 64 years). Seventy-one percent were ≥60 years, 60% were males, and 85% were whites. Eighty-one percent of these patients had prior exposure to chemotherapy for NHL. Seventy-three percent were diagnosed after 2013, and 78% were diagnosed with tAML within 5 years of diagnosis of NHL (Table 1).

Table 1. Baseline characteristics of NHL patients with and without a diagnosis of tAML.

Characteristics	With tAML, N = 373 (%)	Without tAML, N = 301526 (%)	p-value
Age (years)[a]			
Median	64	68	
Mean	62.09	66.49	
Age groups			<0.001
<60 years	141 (37.80)	86539 (28.70)	
60–69 years	110 (29.49)	79270 (26.29)	
≥70 years	122 (32.71)	135720 (45.01)	
Gender			0.13
Male	225 (60.32)	170056 (56.40)	
Female	148 (39.68)	131470 (43.60)	
Race			0.01
Black	27 (7.24)	31251 (10.36)	
White	318 (85.25)	245932 (81.56)	
Others[b]	28 (7.51)	19660 (6.52)	
Unknown	0	4683 (1.55)	
Marital status			<0.01
Married	232 (62.20)	163208 (54.13)	
Single	52 (13.94)	43027 (14.27)	
Separated	59 (15.82)	65192 (21.62)	
Unmarried or Domestic Partner	0	927 (0.31)	
Unknown	30 (8.04)	29172 (9.67)	
Chemotherapy			<0.001
Yes	302 (80.97)	151034 (50.09)	
No/Unknown	71 (19.03)	150492 (49.91)	
Radiation therapy			0.68
Yes	44 (11.80)	38760 (12.85)	
No/Unknown	329 (88.20)	262766 (87.15)	
Year of diagnosis			<0.001
2009–2013	303 (81.23)	143998 (47.76)	
2014–2018	70 (18.77)	157528 (52.24)	
Interval from first primary cancer		N/A	–
12–59 months	291 (78.02)		
≥60 months	82 (21.98)		

[a] Age at diagnosis of NHL.
[b] Includes American Indian, Alaskan native, Asian and Pacific Islander.

3.2.1. Incidence of tAML in NHL survivors

The overall SIR of tAML in our cohort of NHL patients was 4.89 (95% CI 4.41–5.41), with an AER of 5.39 per 10,000 population. Patients <60 years (SIR 14.00, 95% CI 11.79–16.51) showed a greater risk of developing tAML compared to 60-69 years (SIR 4.87, 95% CI 4.00–5.86) and ≥70 years age group (SIR 2.80, 95% CI 2.32–3.34) ($p < 0.001$). There were no statistically significant differences in SIR based on race and marital status and only borderline significance based on gender ($p = 0.047$). The SIR of tAML in patients who received chemotherapy was higher compared to those who did not (SIR 8.44, 95% CI 7.51–9.44 vs. SIR 1.75, 95% CI 1.37–2.21, $p < 0.001$). We found a lower risk of tAML in 2014–2018 compared to 2009–2013 (SIR 3.97, 95% CI 3.10–5.02 vs SIR 5.16, 95% CI 4.60–5.78, $p = 0.01$). There was a higher risk of developing tAML within 5 years of NHL diagnosis compared to after 5 years (SIR 5.05, 95% CI 4.49–5.67 vs. SIR 4.39, 95% CI 3.49–5.45, $p = 0.002$) (Table 2). The incidence of tAML based on the age at diagnosis and year of diagnosis is shown in supplementary figures 2 and 3.

3.3. De novo AML vs tAML

While the median age for both groups at the time of diagnosis of AML was similar, a greater number of patients with tAML were ≥70 years compared to de novo AML (44% vs. 41%, $p = 0.001$). Compared to the de novo AML group, a relatively more significant proportion of tAML patients were diagnosed after 2014 (51.8% vs 73.19%, $p < 0.001$) (Table 3).

3.4. Survival outcomes

Within the NHL cohort, OS significantly declined with the diagnosis of tAML (median OS 90 months vs. 8 months, 5-year OS 59% vs. 13%, $p < 0.001$) (Fig. 1, supplementary Table 1).

OS was further compared between NHL survivors who developed tAML and de novo AML. OS was worse in patients with tAML than those with de novo AML on univariate analysis (median OS 8 months vs. 9 months, 5-year OS 13% vs. 25%, $p = 0.001$) (Fig. 2, supplementary Table 2). However, after adjusting for other covariates on multivariate analysis, a significant difference was not observed in OS between tAML and de novo AML (HR 0.93, 95% CI 0.82–1.04, $p = 0.21$) (Supplementary Table 3).

3.5. Prognostic factors for tAML

Multivariate cox proportional hazard analysis for patients with tAML substantiated older age as a poor prognostic factor (60-69 years: HR 1.53, 95% CI

Table 2. SIR and AER for diagnosis of tAML after NHL.

Characteristics	Patient, N	Observed	Expected	O/E	95% CI	AER	Person-years at risk	p value[a]
AML		373	76.3	4.89	4.41–4.51	5.39	550000.10	
Age								<0.001
<60 years	58870	141	10.07	14.00	11.79–16.51	5.9	222042.03	
60–69 years	46513	110	22.61	4.87	4.00–5.86	5.5	158872.84	
≥70 years	57883	122	43.62	2.80	2.32–3.34	4.6	169085.23	
Gender								0.047
Male	90915	225	49.39	4.56	3.98–5.19	5.81	302457.16	
Female	72351	148	26.91	5.50	4.65–6.46	4.89	247542.94	
Race								0.34
Black	17476	27	5.27	5.12	3.37–7.45	3.89	55827.74	
White	134705	318	67.57	4.71	4.20–5.25	5.47	457887.08	
Others[b]	11085	28	3.45	8.11	5.39–11.72	6.76	36285.29	
Marital status								0.60
Single	24911	52	7.25	7.17	5.36–9.40	5.40	82897.90	
Married	91675	232	45.59	5.09	4.46–5.79	5.91	315178.47	
Separated	30922	59	15.27	3.86	2.94–4.98	4.54	96229.66	
Chemotherapy								<0.0001
Yes	87177	302	35.8	8.44	7.51–9.44	9.27	287134.73	
No/Unknown	76089	71	40.5	1.75	1.37–2.21	1.16	262865.37	
Year of diagnosis								0.01
2009–2013	88362	303	58.67	5.16	4.60–5.78	5.81	420630.34	
2014–2018	74904	70	17.63	3.97	3.10–5.02	4.05	129369.76	
Interval from first primary cancer								0.002
12–59 months	163266	291	57.61	5.05	4.49–5.67	5.57	419370.49	
≥60 months	60456	82	18.69	4.39	3.49–5.45	4.85	130629.61	

[a] Includes American Indian, Alaskan native, Asian and Pacific Islander.
[b] Separated in marital status includes divorced, widowed, and separated.

Table 3. Baseline characteristics of patients with de novo AML and tAML.

Characteristics	De novo AML, N (%) N = 23360	tAML, N (%) N = 373	p-value
Age (years)[a]			
Median	66	67	
Mean	62.88	65.64	
Age groups			0.001
<60 years	8757 (37.49)	107 (28.69)	
60–69 years	5004 (21.42)	99 (26.54)	
≥70 years	9599 (41.09)	167 (44.77)	
Gender			0.016
Male	12605 (53.96)	225 (60.32)	
Female	10755 (46.04)	148 (39.68)	
Race			0.064
Black	2173 (9.30)	27 (7.24)	
White	18747 (80.25)	318 (85.25)	
Others[b]	2287 (9.79)	28 (7.51)	
Unknown	153 (0.65)	0	
Marital status			0.001
Married	12501 (53.51)	225 (59.37)	
Single	4401 (18.84)	50 (13.19)	
Separated	5208 (22.29)	67 (17.68)	
Unmarried or Domestic Partner	0	1 (0.26)	
Unknown	1250 (5.35)	36 (9.50)	
Chemotherapy			0.011
Yes	17124 (73.30)	251 (67.29)	
No/Unknown	6236 (26.70)	122 (32.71)	
Radiation therapy			0.21
Yes	919 (3.93)	20 (5.36)	
No/Unknown	22441 (96.07)	353 (94.64)	
Year of diagnosis			<0.001
2009–2013	11268 (48.24)	100 (26.81)	
2014–2018	12092 (51.76)	273 (73.19)	
Interval from first primary cancer			
12–59 months	n/a	291 (78.02)	
≥60 months		82 (21.98)	

*separated in marital status includes divorced, widowed, and separated.

[a] Age at diagnosis of de novo AML or tAML.

[b] Includes American Indian, Alaskan native, Asian and Pacific Islander.

1.08–2.15, p = 0.01; ≥70 years: HR 1.93, 95% CI 1.40–2.66, p < 0.001) compared to patients <60 years. Patients who did not receive chemotherapy for tAML treatment had poor OS compared to patients who received chemotherapy (HR 1.82, 95% CI 1.40–2.35, p < 0.001). There was no statistically significant difference in OS based on sex, race, marital status, radiation therapy, year of diagnosis, and interval from NHL diagnosis (Table 4).

4. Discussion

In this large-scale SEER database study, we found a 5-fold increased risk of tAML in survivors of NHL compared to the general population and a substantially higher risk in younger patients. Patients with NHL showed a greater predisposition for developing tAML after receiving chemotherapy, within the first five years of NHL diagnosis, and in years before 2013. Intriguingly, OS differed between tAML and de novo AML patients in the univariate analysis but not in the multivariate analysis. Patients with tAML who received supportive care only without chemotherapy had a worse OS.

The higher risk of tAML in younger NHL survivors in our study is consistent with the results from US and European registry-based studies [1,11]. Younger patients with better performance status and lesser comorbidities may survive long enough following NHL to develop tAML compared to the older adult population, or this may represent the inherent susceptibility of younger individuals to leukemogenecity of chemotherapy. The substantially higher risk of developing tAML within five years of primary cancer diagnosis aligns with published data [12]. A prior study on 306 patients with therapy-related myeloid neoplasms showed a latency duration of 68 months for the NHL cohort [7]. Different chemotherapy regimens, including alkylating agents and topoisomerase II inhibitors, can result in variable latency in diagnosing tAML. Prior studies have also shown that younger age and balanced rearrangement are associated with a shorter latency period.[4, 7] We would need further details on chemotherapy agents or cytogenetics of our study population to identify factors responsible for shorter latency. Notably, the higher SIR of tAML before 2013 may partly be due to the time period effect. More patients prior to 2013 will have lived long enough to develop tAML, whereas patients treated in the latter part of the decade have not been at risk long enough to develop tAML.

The lack of difference in the OS between tAML and de novo AML in our study is intriguing. Although patients with tAML are considered to have a worse complete remission rate and lower OS compared to de novo AML, prior studies have suggested that the presence of tAML by itself may not impart a poor prognosis [4,13,14]. Granfeldt et al. showed that after adjusting for karyotype status and comorbidities, patients >60 years with tAML had OS similar to de novo AML.[13] The poor prognosis in tAML may represent the interplay of advanced age and molecular characteristics rather than the sole presence of tAML [14]. However, older adults with tAML benefited from chemotherapy in our study. When possible, these patients should receive effective lower-intensity chemotherapy, such as a combination of venetoclax and hypomethylating agents, with additional investigational agents in a clinical trial.

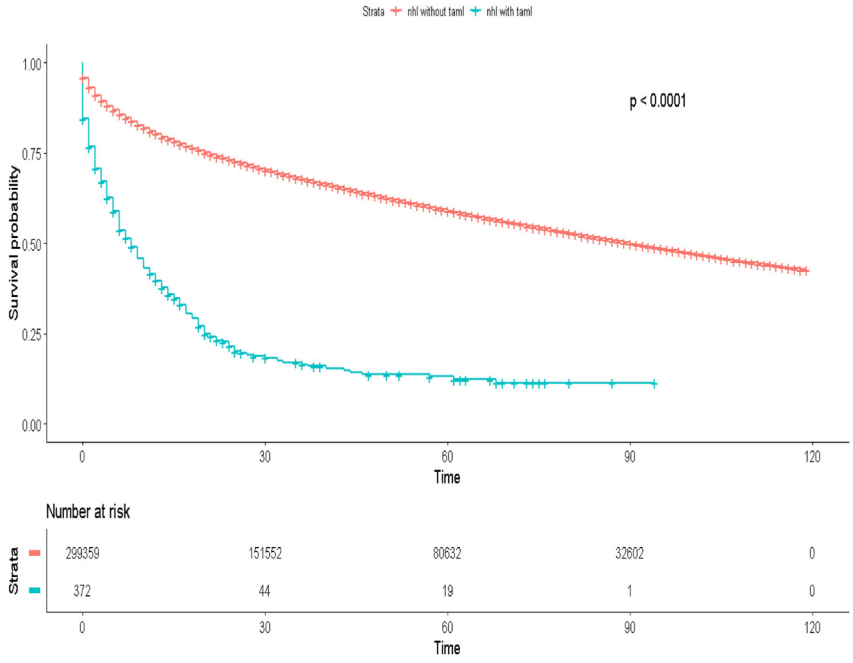

Fig. 1. Overall survival (Kaplan–Meier estimate) of the NHL cohort with and without tAML.

Although we could not explore further the relation between autologous stem cell transplant and risk of tAML due to lack of data on transplant in SEER, literature shows that the risk of therapy-related myeloid neoplasms is significantly higher and the latency period is shorter after stem cell transplant compared to conventional therapy [15].

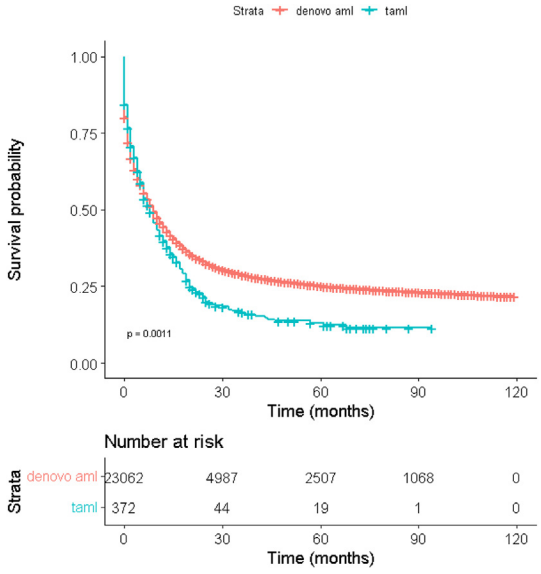

Fig. 2. Overall survival (Kaplan–Meier estimate) of patients with de novo AML and tAML.

Table 4. Multivariate cox proportional hazards analysis for tAML.

Characteristics	tAML, (HR, 95% CI)	p-value
Age		
<60 years	1	
60–69 years	1.53 (1.08,2.15)	0.01
≥70 years	1.93 (1.40,2.66)	<0.001
Gender		
Male	1	
Female	0.84 (0.64,1.09)	0.18
Race		
Black	1	
White	0.73 (0.47,1.14)	0.16
Others*	0.76 (0.40,1.41)	0.39
Marital status		
Married	1	
Single	0.87 (0.58,1.31)	0.51
Separated	1.35 (0.89,2.04)	0.15
Chemotherapy		
Yes	1	
No/Unknown	1.82 (1.40,2.35)	<0.001
Radiation therapy		
Yes	1	
No/Unknown	1.91 (0.93,3.94)	0.08
Year of diagnosis		
2009–2013	1	
2014–2018	1.12 (0.85,1.49)	0.39
Interval from first primary cancer		
12–59 months	1	
≥60 months	1.11 (0.81,1.52)	0.51

Metayer et al. showed the cumulative incidence rate of developing therapy-related myeloid neoplasms at 7 years in patients of NHL who undergo autologous transplant to be 3.9% (95% CI 2.6–5.2) [16].

The limitations of our retrospective study are the lack of data on chemotherapy regimens and cytogenetic and molecular characteristics. We did not have data on staging or subtypes of NHL, and the details on treatment strategies of NHL patients who did versus did not develop tAML were also unavailable in the SEER database. Data on therapy-related myelodysplastic syndrome could not be extracted from multiple primary SIR sessions of SEER and hence was not included in the analysis. However, our registry analysis represents one of the most extensive population-level studies in tAML. Identifying risk factors associated with the development of tAML in a large NHL-specific cohort is a significant advantage over prior studies. Our study presents real-world data from the last decade, including risks and outcomes based on more current management strategies.

5. Conclusion

Therapy-related AML appears to be an important complication in NHL survivors, with increased risk among younger patients, within the first 5 years of NHL diagnosis and chemotherapy recipients. Interestingly, our sizeable population-based study showed no difference in OS between tAML and de novo AML. Older age and no chemotherapy predispose to the dismal OS in tAML. Further studies are necessary to evaluate the role of cytogenetics in risk stratification and the choice of therapeutic options to maximize benefits and minimize adverse survival outcomes.

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Conflict of Interests

Vijaya Raj Bhatt reports participating in Safety Monitoring Committee for Protagonist, and receiving consulting fees from Genentech, Incyte, Servier Pharmaceuticals LLC, and Abbvie, research funding (institutional) from Abbvie, Pfizer, Incyte, Jazz, and National Marrow Donor Program, and drug support (institutional) from Oncoceutics for a trial. There are no conflicts of interest for any other authors.

Appendix.

Supplementary Table 1. Overall Survival in NHL cohort.

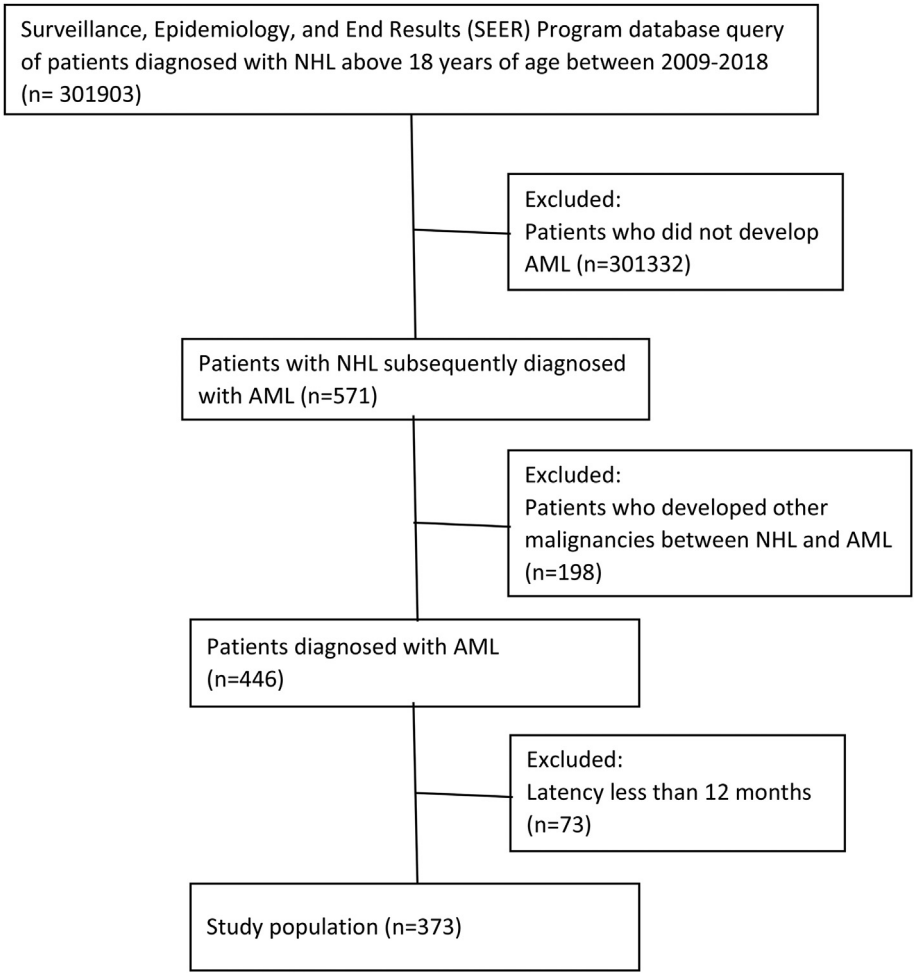
Survival (OS)	NHL without tAML	NHL with tAML
Median (in months)	90 (89,91)	8 (6,10)
1 year	0.80	0.40
5 year	0.59	0.13

Supplementary Table 2. Overall Survival in de novo and tAML.

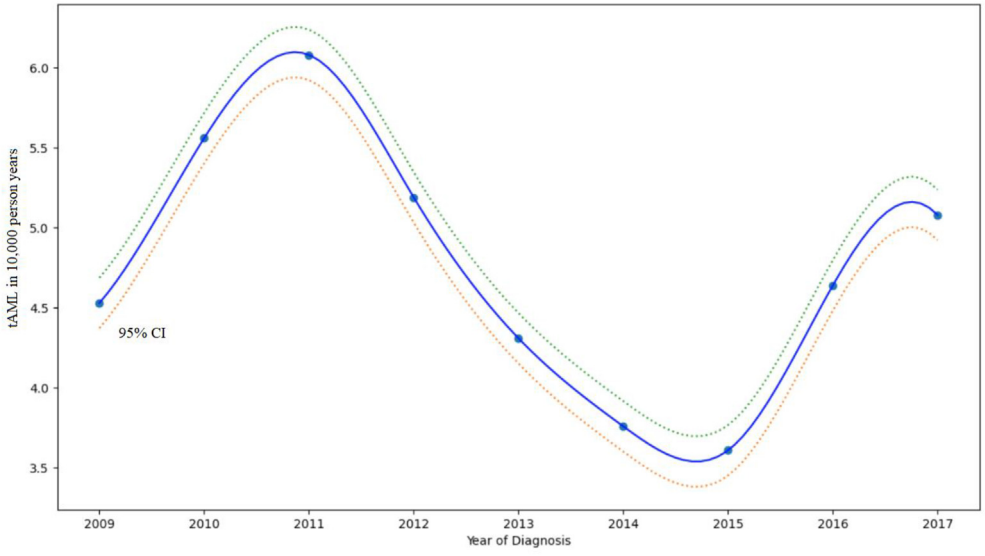
Survival (OS)	de novo AML	tAML
Median (in months)	9 (9,9)	8 (6,10)
1 year	0.44	0.40
5 year	0.25	0.13

Supplementary Table 3. Multivariate analysis for AML cohort (de novo + tAML).

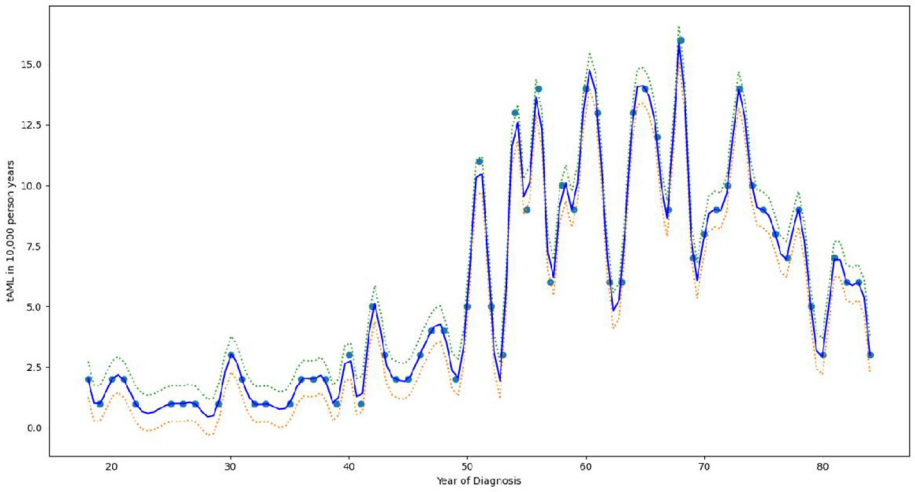
Characteristics	Hazard Ratio (HR), 95% CI	p-value
AML		
denovo AML	0.93 (0.82,1.04)	0.21
tAML		
Age		
<60 years	2.05 (1.91,2.10)	<0.001
60–69 years	3.11 (2.98,3.25)	<0.001
≥70 years		
Gender		
Male	0.91 (0.88,0.94)	<0.001
Female		
Race		
Black	0.92 (0.87,0.97)	0.003
White	0.89 (0.83,0.96)	0.002
Others*		
Marital status		
Married	1.05 (1.01,1.10)	0.023
Single	1.24 (1.19,1.29)	<0.001
Separated		
Chemotherapy		
Yes	2.83 (2.73,2.94)	<0.001
No/Unknown		
Radiation therapy		
Yes	1.36 (1.23,1.50)	<0.001
No/Unknown		
Year of diagnosis		
2009–2013	0.97 (0.94,1.01)	0.14
2014–2018		



Supplementary Fig. 1. CONSORT Diagram.



Supplementary Fig. 2. Restricted cubic spline graph showing the relationship between the year of diagnosis of NHL and the incidence of tAML.



Supplementary Fig. 3. Restricted cubic spline graph showing the relationship between the age at diagnosis of NHL and the incidence of tAML.

References

[1] Morton LM, Dores GM, Tucker MA, et al. Evolving risk of therapy-related acute myeloid leukemia following cancer chemotherapy among adults in the United States, 1975-2008. Blood 2013 Apr 11;121(15):2996–3004.

[2] McNerney ME, Godley LA, le Beau MM. Therapy-related myeloid neoplasms: when genetics and environment collide. Nat Rev Cancer 2017 Sep 24;17(9):513–27.

[3] Morton LM, Dores GM, Schonfeld SJ, et al. Association of Chemotherapy for Solid Tumors with Development of Therapy-Related Myelodysplastic Syndrome or Acute Myeloid Leukemia in the Modern Era. JAMA Oncol 2019 Mar 1;5(3):318–25.

[4] Kayser S, Döhner K, Krauter J, et al. The impact of therapy-related acute myeloid leukemia (AML) on outcome in 2853 adult patients with newly diagnosed AML. Blood 2011 Feb 17;117(7):2137–45.

[5] Travis LB, Curtis RE, Glimelius B, et al. Second cancers among long-term survivors of non-Hodgkin's lymphoma. J Natl Cancer Inst 1993 Jan 1;85(23):1932–7.

[6] Lorenzo Bermejo J, Pukkala E, Johannesen TB, Sundquist J, Hemminki K. Age-time risk patterns of solid cancers in 60 901 non-Hodgkin lymphoma survivors from Finland, Norway and Sweden. Br J Haematol 2014 Mar;164(5):675–83.

[7] Smith SM, le Beau MM, Huo D, et al. Clinical-cytogenetic associations in 306 patients with therapy-related myelodysplasia and myeloid leukemia: the University of Chicago series. Blood 2003 Jul 1;102(1):43–52.

[8] Bhatt VR, Giri S, Verma V, et al. Secondary acute myeloid leukemia in survivors of Hodgkin lymphoma. Future Oncol 2016 Jul;12(13):1565–75.

[9] Morton LM, Dores GM, Schonfeld SJ, et al. Association of Chemotherapy for Solid Tumors With Development of Therapy-Related Myelodysplastic Syndrome or Acute Myeloid Leukemia in the Modern Era. JAMA Oncol 2019 Mar 1;5(3):318–25.

[10] Joshi U, Khanal S, Bhetuwal U, Bhattarai A, Dhakal P, Bhatt VR. Impact of insurance on overall survival in acute lymphoblastic leukemia: a SEER database study. Clin Lymphoma Myeloma Leuk 2022 Jan.

[11] Moser EC, Noordijk EM, van Leeuwen FE, et al. Risk of second cancer after treatment of aggressive non-Hodgkin's lymphoma; an EORTC cohort study. Haematologica 2006 Nov;91(11):1481–8.

[12] Schoch C, Kern W, Schnittger S, Hiddemann W, Haferlach T. Karyotype is an independent prognostic parameter in therapy-related acute myeloid leukemia (t-AML): an analysis of 93 patients with t-AML in comparison to 1091 patients with de novo AML. Leukemia 2004 Jan 1;18(1):120–5.

[13] Østgård LSG, Medeiros BC, Sengeløv H, et al. Epidemiology and Clinical Significance of Secondary and Therapy-Related Acute Myeloid Leukemia: A National Population-Based Cohort Study. J Clin Oncol 2015 Nov 1;33(31):3641–9.

[14] Kern W, Haferlach T, Schnittger S, Hiddemann W, Schoch C. Prognosis in Therapy-Related Acute Myeloid Leukemia and Impact of Karyotype. J Clin Oncol 2004 Jun 15;22(12):2510–1.

[15] Bhatia S. Therapy-related myelodysplasia and acute myeloid leukemia. In: Seminars in oncology. vol. 40. WB Saunders; 2013 Dec 1. p. 666–75. No. 6.

[16] Metayer C, Curtis RE, Vose J, et al. Myelodysplastic syndrome and acute myeloid leukemia after autotransplantation for lymphoma: a multicenter case-control study. Blood J Am Soc Hematol 2003 Mar 1;101(5):2015–23.