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Letter to the Editor: Risk factors for second acute myeloid leukemia/myelodysplastic syndrome among survivors of non-Hodgkin lymphoma

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Non-Hodgkin lymphoma (NHL) survivors are at increased risk for developing acute myeloid leukemia/myelodysplastic syndrome (AML/MDS), a rare but often fatal complication of chemotherapy.[1] Previous studies have demonstrated particularly elevated risks associated with fludarabine and, to a lesser extent, cyclophosphamide, likely due to the direct genotoxic effects of these agents.[1] Several studies have suggested that immune dysfunction also may contribute to AML/MDS risk in the general population, with increased risks associated with certain autoimmune disease and infections.[2-5] However, no previous study has considered whether these conditions may also be risk factors for AML/MDS among NHL survivors.

To investigate the potential contribution of autoimmune diseases and infections as well as treatments to AML/MDS after NHL, we used the SEER-Medicare database linkage to assemble a cohort of 33,922 Medicare enrollees who were diagnosed with first primary NHL during 2000-2009 at ages 66-83 years. Follow-up began one year after NHL diagnosis and continued until diagnosis of second primary malignancy, age 85 years, death, loss to follow-up, or end of study (December 31, 2009), whichever came first. Survivors were required to

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have continuous fee-for-service Medicare Parts A and B coverage ≥12 months before NHL diagnosis through ≥12 months following NHL diagnosis for ascertainment of treatment and medical conditions. Patients who survived <1 year after NHL diagnosis (N=1,157) or had Medicare claims for HIV (N=171), solid organ transplantation (N=107), or hematopoietic stem cell transplantation (N=226) were excluded from the analysis.

Information on NHL treatments, autoimmune diseases, and infections was derived from Medicare claims (see Supplementary Tables 1-3 for more details). For analyses of infused chemotherapy, we focused on combinations of the most commonly used specific chemotherapy agents (cyclophosphamide, rituximab, and fludarabine), as well as granulocyte colony-stimulating factor (G-CSF). Data on radiotherapy consisted of whether patients did or did not receive radiotherapy. Occurrences of autoimmune diseases and infections were defined as having ≥1 Medicare claim, considering diagnoses occurring prior to NHL diagnosis separately from those occurring after NHL. Claims for autoimmune conditions and infections occurring before the start of the study or prior to age 65 years were not captured. Analyses considered individual conditions and infections with ≥10 exposed AML/MDS cases, diagnosed either before or after NHL. Due to the rarity of many diagnoses, we grouped diagnoses based on the tissue and organ systems involved and, for autoimmune conditions only, according to whether they activate B- or T-cells (see Table 2 footnotes and Supplementary Tables 2-3).[6-9]

Multivariate Cox proportional hazards regression was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) to assess the association between specific risk factors and risk of AML/MDS after NHL (see model details in Table 2 footnote). In secondary analyses, we considered risks separately for AML and MDS (Supplementary Tables 4-6). All analyses were conducted using SAS 9.3 (Cary, NC).

Most (90.7%) of the 33,922 NHL survivors were white, and median age at diagnosis was 75 years (Table 1). A total of 150 second AML/MDS (70 AML, 80 MDS) were diagnosed during 172,994 total person-years of follow-up (mean person-years at risk=5.1; median interval from NHL to AML/MDS=3.2 years). AML/MDS risks were higher among males than females. Lower risks were observed among survivors of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) than all other NHL subtypes, although these differences were significant only for DLBCL. These risk patterns were more pronounced for AML than MDS (Supplementary Table 4).

Compared with individuals who did not receive any infused chemotherapy, AML/MDS risk was significantly elevated among NHL survivors who received any fludarabine-containing chemotherapy (HR=4.48, 95%CI=2.77-7.23) and non-significantly increased among those who received cyclophosphamide (HR=1.35, 95%CI 0.80-2.27) or rituximab without fludarabine or cyclophosphamide (HR=1.79, 95%CI=0.94-3.43; Table 2). These risk patterns were generally consistent for AML and MDS, though the fludarabine-related risk was higher for MDS (HR=5.94, 95%CI=3.10-11.37) whereas the rituximab-related risk was higher for AML (HR=2.38, 95%CI=1.02-5.56; Supplementary Tables 5-6). Substantially elevated risks of AML/MDS have been reported among patients receiving fludarabine, a purine analog most frequently used to treat CLL/SLL, possibly due to the genotoxic effects

in addition to the loss of immunosurveillance in these patients.[10–13] Using Medicare claims data to ascertain treatments precluded us from considering risks by dose. Additionally, our risk estimates are likely conservative because Medicare claims for oral chemotherapy agents were not available, thus individuals who received oral agents only were included in our referent group.

We also observed significantly increased risk of AML/MDS among NHL survivors who received G-CSF (HR=1.71, 95%CI=1.17-2.51; Table 2). This finding is consistent with previous studies and may reflect individuals who received the highest doses or most intensive chemotherapeutic regimens, or may reflect a direct stimulation effect on white blood cells.[14] We observed no evidence of an association between radiotherapy and AML/MDS risk (HR=0.78, 95%CI=0.50-1.22; Table 2).

In multivariate models adjusting for NHL treatment, we observed increased risk of AML/MDS among NHL survivors with a range of autoimmune conditions and infections (Table 2). Risks were increased 1.5- to 2.0-fold for autoimmune diseases occurring prior to NHL diagnosis for nearly all conditions we evaluated. In contrast, fewer associations were observed for diagnoses of autoimmune diseases occurring after NHL, with the exception of pernicious anemia (HR=2.59, 95%CI=1.69-3.99) and asthma (HR=2.41, 95%CI=1.47-3.93). Infections also were broadly associated with risks for subsequent AML/MDS, with significantly elevated risks observed for diagnoses occurring both before and after NHL (Table 2). Upper airway respiratory infections were associated with increased second AML/MDS risk (before NHL HR=1.64, 95%CI=1.11-2.40; after NHL HR=1.96, 95%CI=1.22-3.15), with the highest associations for sinusitis after NHL (HR=2.43, 95%CI=1.59-3.72). Increased AML/MDS risks were observed with various other infections occurring after NHL, particularly pneumonia (HR=1.87, 95%CI=1.27-2.77), cystitis/pyelonephritis urinary tract infections (UTI) (HR=1.85, 95%CI=1.20-2.86), prostatitis (HR=2.61, 95%CI=1.35-5.05), and gastroenteritis (HR=1.85, 95%CI=1.15-2.98). In contrast, AML/MDS was strikingly increased among individuals with claims for herpes zoster only prior to NHL diagnosis (HR=1.93, 95%CI=1.20-3.15).

Our observation that various autoimmune conditions and infections are associated with increased risk of subsequent AML/MDS among NHL survivors emphasizes their underlying immune dysfunction, and our findings are generally consistent with previous research on these risk factors conducted in the general population.[2–5] In our study, increased AML/MDS risks were observed for several autoimmune conditions. Our results of significantly increased AML/MDS risks with pernicious anemia diagnosed before and after NHL agree with previous results showing an association between this condition and AML/MDS among persons in the general population.[4–5] Significantly increased risks of AML/MDS associated with localized scleroderma and Graves' disease in our study of NHL survivors were not seen in a prior investigations of autoimmune diseases in the general population.[5] In a new finding, asthma diagnosed after NHL increased AML/MDS risks. Asthma initiates similar chronic inflammatory pathways of cytokine activity found in other autoimmune conditions and may manifest the immune disruption that precedes the development of AML/MDS.[15] The exact mechanisms by which autoimmune conditions may influence AML/MDS risk is unknown. Possible explanations may include immunosuppression resulting from treatment for some

autoimmune diseases,[2, 4, 5] immunosuppression from the underlying NHL disease and its therapy, or alternatively, autoimmune diseases might have a more direct effect by damaging hematopoietic stem cells.[2, 4, 5]

The potential importance of immune dysfunction in the etiology of AML/MDS after NHL is further supported by observed associations for various infections. In general, the associations between infections and AML/MDS in our NHL study were similar to those reported in previous studies in the general population,[3,4] particularly for those infections diagnosed after NHL. We found significant elevations in risk of AML/MDS among patients diagnosed with various respiratory infections, specifically sinusitis and pneumonia, skin infections (cellulitis, herpes zoster), cystitis/pyelonephritis UTI, and gastroenteritis that were similar to significant excesses of AML/MDS linked to these infections found in community population studies.[3,4] It is not clear how infections can increase the risk for AML/MDS, but the biological mechanism may involve an underlying immune dysfunction that could predispose NHL survivors to AML/MDS.[3,4]

Due to the nature of Medicare claims data, we were unable to ascertain infections and autoimmune diseases diagnosed prior to entry into Medicare or mild infections for which patients did not seek medical care. Second cancers can be underreported due to survivors leaving the SEER registry areas; however, our risk estimates should not be affected since this underreporting is unlikely to be related to the risk factors we assessed in our study.

In this large, population-based study of NHL survivors, we show for the first time that AML/MDS risk may be related to diagnoses of immune-related medical conditions in addition to chemotherapy for NHL. These findings support a potential role for immune dysfunction in addition to direct DNA damage in the development of AML/MDS after NHL. Further research is needed to better understand the immune-related biological mechanisms that contribute to AML/MDS after NHL.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Selected characteristics and risk of AML/MDS among 33,922 1-year survivors of first primary NHL

	Total NHL (N=33,922) N (%)	AML/MDS cases* (N=150) N (%)	HR †	95% CI
Age at NHL diagnosis (years)				
66-69	7,096 (20.9)	37(24.7)		
70-74	9,653 (28.5)	55 (36.7)		
75-79	9,770 (28.8)	48 (32.0)		
80-83	7,403 (21.8)	10 (6.7)		
Year of NHL diagnosis				
2000-2004	17,026 (50.2)	108 (72.0)		
2005-2009	16,896 (49.8)	42 (28.0)		
Sex				
Male	16,731 (49.3)	87 (58.0)	1.00	Referent
Female	17,191 (50.7)	63 (42.0)	0.65	0.47-0.91
Race				
White	30,751 (90.7)	138 (92.0)	1.00	Referent
Other/unknown	3,171 (9.3)	12 (8.0)	0.86	0.47-1.56
Charlson comorbidity index ‡				
No comorbidities	8,494 (25.0)	45 (30.0)	1.00	Referent
1 comorbidity	8,284 (24.4)	31 (20.7)	0.66	0.42-1.04
2+ comorbidities	17,041 (50.2)	72 (48.0)	0.76	0.52-1.12
Socioeconomic status §				
Lowest quintile	7,572 (22.3)	29 (19.3)	1.00	Referent
2nd lowest quintile	7,462 (22.0)	38 (25.3)	1.29	0.79-2.10
Middle quintile	7,548 (22.3)	33 (22.0)	1.07	0.65-1.77
2nd highest quintile	7,032 (20.7)	33 (22.0)	1.09	0.66-1.81
Highest quintile	4,003 (11.8)	14 (9.3)	0.80	0.42-1.52
Missing	305 (0.9)	<10 ~	2.33	0.71-7.70
NHL subtype **				
CLL/SLL	10,441 (30.8)	35 (23.3)	1.00	Referent
DLBCL	7,802 (23.0)	39 (26.0)	1.67	1.05-2.63
FL	5,643 (16.6)	30 (20.0)	1.62	0.99-2.64
MZL	3,068 (9.0)	12 (8.0)	1.31	0.68-2.54
Other	6,968 (20.5)	34 (22.7)	1.65	1.03-2.65

Abbreviations: acute myeloid leukemia/myelodysplastic syndrome (AML/MDS); chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); diffuse large B-cell lymphoma (DLBCL); follicular lymphoma (FL); International Classification of Diseases for Oncology, 3rd edition (ICD-O-3); marginal zone lymphoma (MZL); non-Hodgkin lymphoma (NHL); Surveillance, Epidemiology and End Results (SEER).

~ Counts and percentages are not reported for less than 10 AML/MDS cases to protect patient confidentiality.

* AML/MDS cases were identified through SEER ICD-O-3 morphology codes (AML: 9840, 9861, 9865-9867, 9869, 9871-9874, 9895-9898, 9910-9911, 9920, 9945-9946, and 9975; MDS: 9980, 9982-9987, and 9989) and a sequence code of 2.

[†] HR (95% CI) derived from a multivariate model including sex, race, Charlson Index comorbidities, socioeconomic status, NHL subtype, and follow-up time (time-dependent covariate) and stratified by calendar year. Age was used as the time scale.

[‡] Excludes 103 individuals (0.3% of the total population) with missing information on comorbidities.

[§] Socioeconomic status derived from census tract variables, does not represent individual status.

[**] First primary NHL subtype defined by ICD-O-3 morphology codes recorded in SEER as DLBCL (9678-9680, 9684 [B-cell]), FL (9690-9691, 9695, 9698), CLL/SLL (9670, 9823), MZL (9689, 9699) and other NHL (9590-9596, 9671, 9673, 9675, 9684 [non B-cell], 9687, 9700-9702, 9705, 9708-9709, 9714-9719, 9727-9729, 9827 [primary site=420-421, 424]).

Table 2

Risk of AML/MDS after first primary NHL in relation to NHL treatments, autoimmune conditions, and infections

	Prior to NHL diagnosis				After NHL diagnosis*			
		AML/MDS				AML/MDS		
Medical factors †	**Total NHL N (%)**	**cases N (%)**	**HR ‡**	**95% CI**	**Total NHL N (%)**	**cases N (%)**	**HR ‡**	**95% CI**
NHL treatment								
Infused chemotherapy §								
None recorded					14,280 (42.1)	36 (24.0)	1.00	Referent
Any fludarabine					3,699 (10.9)	44 (29.3)	4.48	2.77-7.23
Cyclophosphamide (±rituximab)					12,054 (35.5)	57 (38.0)	1.35	0.80-2.27
Rituximab (without fludarabine or cyclophosphamide)					3,802 (11.2)	13 (8.7)	1.79	0.94-3.43
Granulocyte colony-stimulating factor								
No					27,952 (82.4)	95 (63.3)	1.00	Referent
Yes					5,970 (17.6)	55 (36.7)	1.71	1.17-2.51
Radiotherapy								
No					26,558 (78.3)	122 (81.3)	1.00	Referent
Yes					7,364 (21.7)	28 (18.7)	0.78	0.50-1.22
Autommune conditions, by cell type affected #								
B-cell activating conditions	6,820 (20.1)	35 (23.3)	1.75	1.16-2.64	8,517 (25.1)	55 (36.7)	2.20	1.42-3.41
T-cell activating conditions	15,037 (44.3)	70 (46.7)	1.78	1.20-2.63	15,928 (47.0)	73 (48.7)	1.72	1.08-2.75
Autoimmune conditions, by organ system								
Systemic/connective tissue	5,334 (15.7)	28 (18.7)	1.57	1.02-2.42	4,755 (14.0)	28 (18.7)	1.19	0.62-2.31
Rheumatoid arthritis	3,268 (9.6)	15 (10.0)	1.27	0.74-2.20	2,671 (7.9)	16 (10.7)	1.48	0.68-3.20
Cardiovascular	3,797 (11.2)	20 (13.3)	1.62	0.99-2.65	5,607 (16.5)	21 (14.0)	1.12	0.64-1.97
Chronic rheumatic heart disease	3,344 (9.9)	17 (11.3)	1.56	0.93-2.63	5,180 (15.3)	18 (12.0)	1.02	0.56-1.87
Endocrine	2,791 (8.2)	16 (10.7)	1.63	0.95-2.78	2,860 (8.4)	<10 ˜	0.68	0.27-1.67
Graves' disease	2,344 (6.9)	16 (10.7)	1.95	1.14-3.34	1,986 (5.9)	<10˜	0.41	0.10-1.66
Skin	6,333 (18.7)	35 (23.3)	1.52	1.02-2.26	5,433 (16.0)	24 (16.0)	1.12	0.61-2.06
Localized scleroderma	4,920 (14.5)	30 (20.0)	1.66	1.09-2.52	4,183 (12.3)	20 (13.3)	1.20	0.64-2.27
Gastrointestinal	4,078(12.0)	22 (14.7)	1.80	1.12-2.90	6,495 (19.1)	44 (29.3)	2.63	1.74-3.99
Pernicious anemia	3,158 (9.3)	19 (12.7)	2.06	1.25-3.42	5,507 (16.2)	39 (26.0)	2.59	1.69-3.99
Nervous system	240 (0.7)	<10˜	2.02	0.49-8.30	388 (1.1)	<10˜	1.41	0.20-10.24
Asthma	5,221 (15.4)	17 (11.3)	1.05	0.62-1.79	5,585 (16.5)	31 (20.7)	2.41	1.47-3.93
Infections, by organ system								
Respiratory - upper airway	15,043 (44.3)	72 (48.0)	1.64	1.11-2.40	12,749 (37.6)	77 (51.3)	1.96	1.22-3.15
Otitis media	3,969 (11.7)	22 (14.7)	1.37	0.86-2.18	2,941 (8.7)	13 (8.7)	1.11	0.54-2.30
Pharyngitis	5,508 (16.2)	28 (18.7)	1.34	0.88-2.04	4,441 (13.1)	26 (17.3)	1.38	0.80-2.37
Sinusitis	10,752 (31.7)	45 (30.0)	1.26	0.86-1.85	8,963 (26.4)	61 (40.7)	2.43	1.59-3.72
Respiratory - lower airway	15,069 (44.4)	70 (46.7)	1.57	1.05-2.34	17,408 (51.3)	82 (54.7)	1.50	0.94-2.38

	Prior to NHL diagnosis				After NHL diagnosis*			
		AML/MDS				AML/MDS		
Medical factors †	Total NHL N (%)	cases N (%)	HR ‡	95% CI	Total NHL N (%)	cases N (%)	HR ‡	95% CI
Acute bronchitis	11,553 (34.1)	54 (36.0)	1.32	0.91-1.90	10,038 (29.6)	49 (32.7)	1.25	0.76-2.03
Influenza	1,846 (5.4)	10 (6.7)	1.33	0.69-2.56	1,278 (3.8)	<10~	1.58	0.69-3.65
Pneumonia	6,670 (19.7)	28 (18.7)	1.38	0.88-2.17	12,635 (37.2)	59 (39.3)	1.87	1.27-2.77
Skin	5,354 (15.8)	31 (20.7)	1.62	1.07-2.46	7,259 (21.4)	29 (19.3)	0.93	0.56-1.54
Cellulitis	2,948 (8.7)	13 (8.7)	1.26	0.70-2.24	3,943 (11.6)	18 (12.0)	1.58	0.93-2.70
Herpes zoster	2,753 (8.1)	20 (13.3)	1.93	1.20-3.15	4,022 (11.9)	15 (10.0)	0.87	0.48-1.60
Urinary tract	16,449 (48.5)	71 (47.3)	1.46	0.98-2.18	18,427 (54.3)	91 (60.7)	1.85	1.16-2.93
Cystitis/pyelonephritis, UTI	14,970 (44.1)	59 (39.3)	1.31	0.88-1.94	17,629 (52.0)	81 (54.0)	1.85	1.20-2.86
Prostatitis **	3,817 (22.8)	27 (31.0)	1.85	1.13-3.02	2,430 (17.7)	25 (28.7)	2.61	1.35-5.05
Gastrohepatic	5,410 (15.9)	28 (18.7)	1.48	0.96-2.28	5,624 (16.6)	31 (20.7)	1.75	1.09-2.82
Gastroenteritis	5,178 (15.3)	27 (18.0)	1.50	0.97-2.33	5,202 (15.3)	31 (20.7)	1.85	1.15-2.98

Abbreviations: acute myeloid leukemia/myelodysplastic syndrome (AML/MDS); confidence interval (CI); hazard ratio (HR); non-Hodgkin lymphoma (NHL); urinary tract infections (UTI).

~ Counts and percentages are not reported for less than 10 AML/MDS cases to protect patient confidentiality.

* New claims occuring after NHL but prior to second cancer, death, end of study, or loss to follow-up, with no claims prior to NHL; diagnoses were evaluated as time-dependent covariates in the Cox model, described further below.

† Detailed information on ascertainment of NHL treatments, autoimmune conditions, and infections is provided in Supplementary Tables 1-3.

‡ HR (95% CI)were adjusted for sex, race, Charlson Index comorbidities, socioeconomic status, and follow-up time (time-dependent covariate), and stratified by calendar year and NHL subtype. Age was used as the time scale. Time-dependent covariates were used to indicate receipt of specific NHL treatments during follow-up based on timing of initiation of therapy, with individuals with no infused chemotherapy claims comprising the referent group. For analyses of autoimmune conditions and infections, models were additionally adjusted for NHL treatments and individuals with no history of the condition of interest comprised the referent group.

§ Excludes 87 individuals (0.3% of the total population) who received other infused chemotherapeutic agents (did not receive rituximab, fludarabine, cyclophosphamide, or G-CSF), as detailed in Supplementary Table 1.

B-cell activating conditions include rheumatoid arthritis, Sjogren's syndrome, discoid lupus erythematosus, reactive arthritis, Felty's syndrome, chronic thryoiditis, systemic/discoid lupus erythematosus, pernicious anemia, and myasthenia gravis. T-cell activating conditions include ankylosing spondylitis, dermatomyositis, polymyalgia rheumatica, sarcoidosis, systemic sclerosis, rheumatic fever, chronic rheumatic heart disease, giant cell arteritis, systemic vasculitis, Addison's disease, Graves' disease, primary biliary cirrhosis, alopecia areata, localized scleroderma, dermatitis herpetiformis, psoriasis, celiac disease, Crohn's disease, ulcerative colitis, amyotrophic sclerosis, multiple sclerosis, and asthma. Hematologic autoimmune conditions (e.g., autoimmune hemolytic anemia, thrombocytopenia) were excluded from consideration because of difficulty distinguishing these diagnoses from manifestations of chemotherapy toxicity.