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Risk and outcome of acute myeloid leukaemia among survivors of primary diffuse large B-cell lymphoma: a retrospective observational study based on SEER database

Yu Du,[1] Ying Wang,[2] Qinlu Li,[2] Xiaona Chang,[3] Heng Zhang,[2] Min Xiao,[2] Shugang Xing [2]

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[1]Department of Radiology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
[2]Department of Haematology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
[3]Department of Pathology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Correspondence to
Dr Shugang Xing;
xingsg@tjh.tjmu.edu.cn

ABSTRACT

Objectives Survivors of diffuse large B-cell lymphoma (DLBCL) are at an increased risk of developing second primary malignancies. However, the risk of secondary acute myeloid leukaemia (sAML) has not been previously described in detail, and the outcomes of patients with sAML are also undiscovered compared with their de novo counterparts (de novo acute myeloid leukaemia, dnAML).

Design This study is a retrospective database study.

Setting and participants A total of 70 280 patients with primary DLBCL, diagnosed between 2000 and 2016, were identified from the Surveillance, Epidemiology, and End Results (SEER) database. Another cohort with dnAML matching with sAML was also obtained from SEER database.

Results The standardised incidence ratio was 6.23 (95% CI: 5.50 to 7.03) for sAML among survivors of DLBCL. The estimated cumulative incidence of sAML was 0.61% 15 years after the diagnosis of DLBCL. Patients aged 60–74 years were more likely to have sAML than those <60 years (subdistribution HR (sHR)=1.417; 95% CI: 1.087 to 1.850), whereas patients aged ≥75 years were less likely to have sAML (sHR=0.648; 95% CI: 0.452 to 0.930). Patients with advanced-stage DLBCL were more prone to sAML than those with early-stage disease (sHR=1.307; 95% CI: 1.012 to 1.690). There was a significant difference of survival between patients with dnAML and those with sAML (HR=1.25; 95% CI: 1.01 to 1.53).

Conclusions The risk of developing sAML after DLBCL is substantial. Patients aged 60–74 years and with advanced-stage are more prone to sAML. And, compared with their dnAML counterparts, patients with sAML have a worse prognosis.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Surveillance, Epidemiology, and End Results database is a large database of US patients, but the detailed information regarding disease treatments is not mentioned.
⇒ Competing risk model was performed to eliminate the effect of death, which would lead to a bias for the incidence of secondary acute myeloid leukaemia (sAML).
⇒ Case–control matching analysis was performed to eliminate the effect of confounding variables between sAML group and de novo acute myeloid leukaemia group.

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common and aggressive type of lymphoma.[1] The combination of rituximab with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) chemotherapy has improved the overall survival (OS) of patients with DLBCL by at least 20%.[2] However, with the increasing survival of patients after DLBCL, the risk of second primary malignancies (SPMs) has also increased, and their management has become an emerging challenge. Currently, SPMs are an important cause of death among survivors of DLBCL.[3 4]

One of the main secondary malignancies following DLBCL is acute myeloid leukaemia (AML). For years, more cases of AML have been reported in survivors of DLBCL than in the general population.[5 6] Although the underlying factors and biological mechanisms of AML following DLBCL need to be better clarified, the factors about treatment, including the use of rituximab, have been thought to be the main cause of the increased risk.[7–9] The management of patients with secondary AML (sAML) may be challenging because of cumulative toxicity from the treatment of primary DLBCL. Previous exposure to treatment-related factors, including radiotherapy and systemic chemotherapy, has limited the treatment options for secondary neoplasms and further alters their outcomes.[10–13] Hence, we asked if the outcome of sAML was poorer than

that of de novo AML (dnAML). Meanwhile, considering the difficulty in the management of patients with sAML, a search for the predictive factors for the occurrence of sAML will be meaningful. As far as we know, information available regarding the incidence and prognosis of sAML following DLBCL is limited.

Here, we used sequential cancer data available from the large and high-quality, population-based National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) programme to describe the pattern of incidence, investigate the predictive factors for the occurrence of sAML and compare the outcomes of patients with sAML with their de novo counterparts.

MATERIALS AND METHODS

Data source and sample

The SEER programme's research data for 17 registries (excluding Alaska) were used to assess the incidence and explore the hazard factors of sAML in survivors of primary DLBCL diagnosed between 2000 and 2016.[14] DLBCL cases were identified according to the Lymphoma Subtype Recode/WHO 2008, which is updated for haematopoietic conditions and coded based on the 3rd edition of the International Classification of Disease for Oncology (ICD-O-3) morphology codes (DLBCL: 9678–9680, 9684, 9688, 9712, 9735 and 9737–9738) and the WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues (2008).[15] We excluded cases which were coded as autopsy or death-certificate-only, where DLBCL was not the first primary cancer, and those with unknown age or race. To exclude patients with synchronous DLBCL and AML, cases diagnosed with AML within the first 2 months of being diagnosed with DLBCL were not included in this study, as well as those with <2 months of follow-up. The process of cases selection was shown in figure 1. At last, a total of 70 280 patients with primary DLBCL were identified, and by the end of the follow-up, 264 of them had developed sAML. For each case, age, gender, year of diagnosis, Ann Arbor stage, survival status, follow-up time, interval time between the diagnosis of DLBCL and sAML and some other information were extracted from SEER. And, the Ann Arbor stage at diagnosis of DLBCL was classified into two: stage I and II disease as early stage, and stage III and IV disease as advanced stage.

In order to explore whether there was a difference in survival outcome between patients with sAML and patients with dnAML, we first listed the detailed characteristics of all patients with sAML (two cases with unknown survival time were excluded). We then obtained cases list of dnAML from the SEER database using the same histological subtype as for cases of sAML, but the AML was the first malignancy for a given individual.[14] Finally, a total of 30 835 patients were identified from SEER database in 2000–2016.

Statistical analysis

Kolmogorov-Smirnov normality test was performed to examine the distributions of continuous numerical variables. Variables that did not conform to a normal distribution were described by median and range, and comparison was done with the Wilcoxon rank-sum non-parametric test. Otherwise, data are expressed by means and SDs, and t-test or variance analysis was used for the comparison. Differences in proportions across the groups were compared with the χ^2 test. The calculation of the standardised incidence ratio (SIR) and 95% CI for sAML in patients with DLBCL was performed using SEER*stat software. And, the calculation of person-years for DLBCL survivors was also performed by SEER*stat.

The analyses of cumulative incidence of sAML were completed using competing risk analysis, in which death

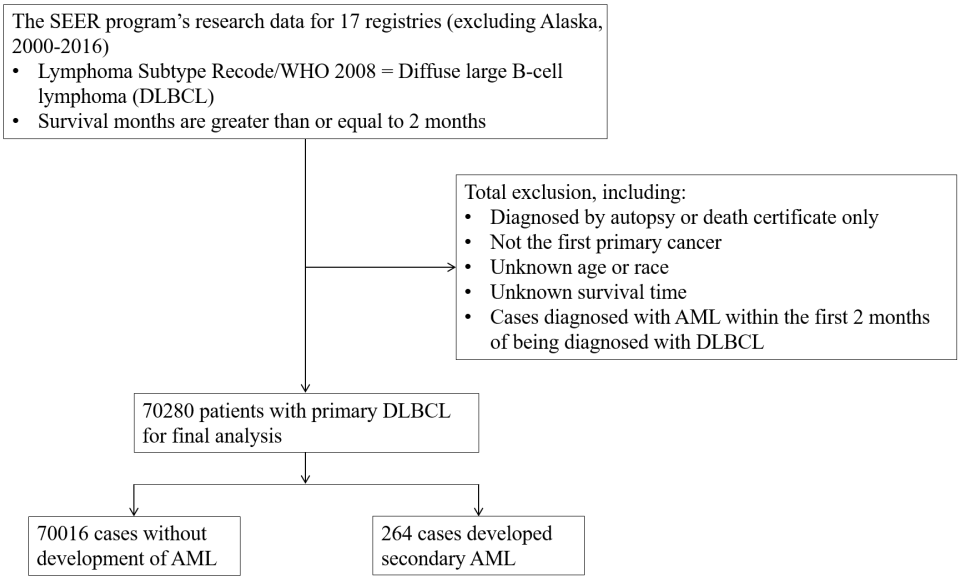

Figure 1 The process of cases selection. AML, acute myeloid leukaemia; DLBCL, diffuse large B-cell lymphoma; SEER, Surveillance, Epidemiology, and End Results.

from any cause was considered the sole competing risk. The differences in cumulative incidence among the groups were compared using Gray's test. Furthermore, to explore the risk factors for sAML, a regression analysis using the semiparametric proportional hazards model proposed by Fine and Gray was performed.[16] Using these models, the semiparametric HRs and their 95% CIs for risk factors were estimated.

To compare the survival outcome of patients with sAML and patients with dnAML, we performed a case–control matching analysis. Based on age (±2 years), calendar year of diagnosis (±2 years), sex and race, we matched sAML with patients with dnAML at a 1:1 ratio. Case matching was completely random and the variables (survival status and cause of death) that might affect the matching result were with no awareness. Because the SEER database does not have detailed information about the treatment, matching for therapy was impossible. We used a shared-frailty Cox model to interpret the 1:1 matched design. Meanwhile, the factors, age, sex, race and number of years of diagnosis were adjusted for the model. For AML with previous DLBCL versus dnAML, the HR and its 95% CI was calculated.

R software (V.3.6.3) with 'cmprsk' and 'survival' packages, STATA (V.14.0; Stata Corporation, College Station, Texas, USA), and SEER*stat software (V.8.3.6, NCI, NIH, Bethesda, Maryland, USA) were used to perform these analyses. In this study, we treated a two-sided p value<0.05 to be a statistically significant difference.

Patient and public involvement

No patients or public were involved in this study.

RESULTS

In this study, we identified a total of 70 280 patients with primary DLBCL, and the median follow-up is 90 months (range: 2–203 months), contributing to a total follow-up of 334 516 person-years. By the end of the follow-up, 264 of these cases were diagnosed with sAML. The median interval between the diagnosis of DLBCL and sAML was 44 months (range: 3–178 months). The characteristics of

Table 1 Characteristics of 2-month survivors of DLBCL reported to the SEER programme (2000–2016)

Characteristics	All n=70 280	No sAML n=70 016	With sAML n=264	P
Follow-up (range), month	90 (2–203)	90 (2–203)	157 (3–198)	
Age (range), years	64 (0–106)	64 (0–106)	63.5 (12–88)	0.197
Age group, years				<0.001
< 60	28 289 (40.3%)	28 186 (40.3%)	103 (39.0%)	
60–74	23 796 (33.9%)	23 677 (33.8%)	119 (45.1%)	
75+	18 195 (25.9%)	18 153 (25.9%)	42 (15.9%)	
Sex				0.165
Male	38 409 (54.7%)	38 253 (54.6%)	156 (59.1%)	
Female	31 871 (45.3%)	31 763 (45.4%)	108 (40.9%)	
Race				0.490
Black	5499 (7.8%)	5483 (7.8%)	16 (6.1%)	
White	58 661 (83.5%)	58 434 (83.5%)	227 (86.0%)	
Other	6120 (8.7%)	6099 (8.7%)	21 (8.0%)	
Primary site				0.015
Nodal	46 241 (65.8%)	46 048 (65.8%)	193 (73.1%)	
Extranodal	24 039 (34.2%)	23 968 (34.2%)	71 (26.9%)	
Ann Arbor stage				0.001
Stage I	18 535 (26.4%)	18 470 (26.4%)	65 (24.6%)	
Stage II	13 717 (19.5%)	13 672 (19.5%)	45 (17.0%)	
Stage III	10 726 (15.3%)	10 672 (15.2%)	54 (20.5%)	
Stage IV	20 026 (28.5%)	19 937 (28.5%)	89 (33.7%)	
Unknown	7276 (10.4%)	7265 (10.4%)	11 (4.2%)	
Years of diagnosis				<0.001
2000–2005	23 047 (32.8%)	22 933 (32.8%)	114 (43.2%)	
2006–2011	25 196 (35.9%)	25 084 (35.8%)	112 (42.4%)	
2012–2016	22 037 (31.4%)	21 999 (31.4%)	38 (14.4%)	

DLBCL, diffuse large B-cell lymphoma; sAML, secondary acute myeloid leukaemia; SEER, Surveillance, Epidemiology, and End Results.

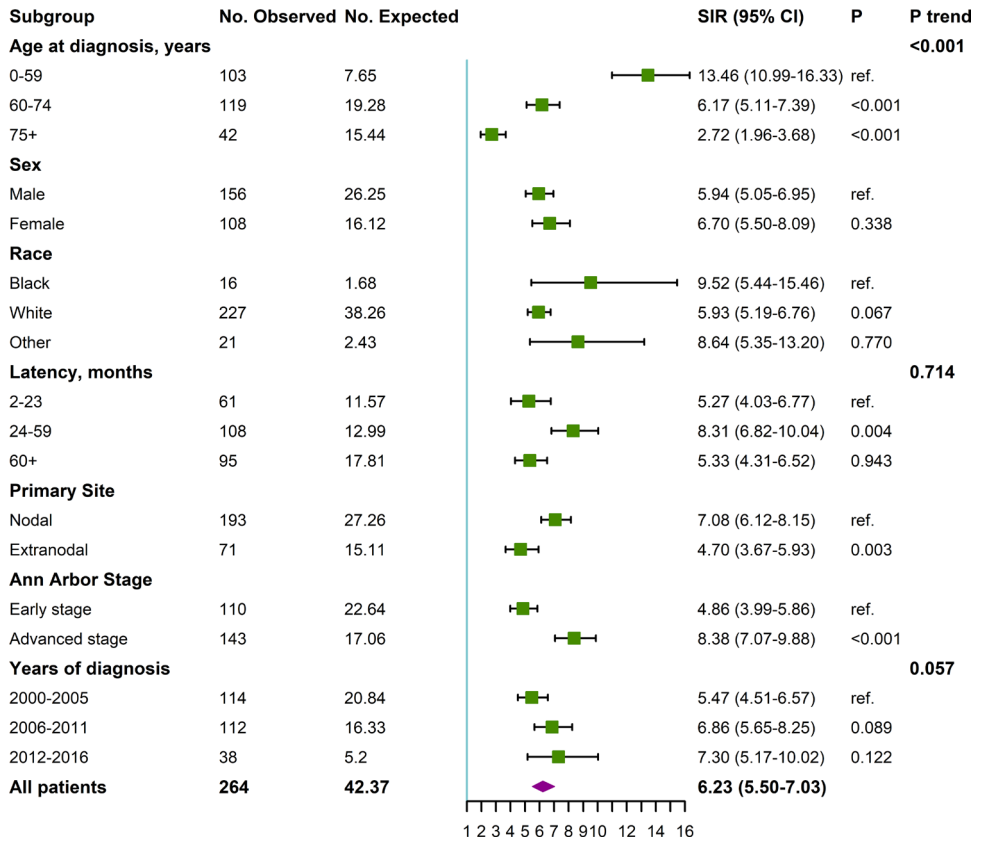

Figure 2 The SIR forest plot for patients with secondary acute myeloid leukaemia among survivors of diffuse large B-cell lymphoma. ref, reference; SIR, standardised incidence ratio.

the entire cohort of patients with DLBCL who have or have not developed sAML are shown in table 1.

The SIR for sAML overall was 6.23 (95% CI: 5.50 to 7.03), indicating an elevated incidence compared with that for the general population of the USA. The forest plot for the SIRs is shown in figure 2. The SIR was 13.46 (95% CI: 10.99 to 16.33) in patients aged <60 years, 6.17 (95% CI: 5.11 to 7.39) in patients aged 60–74 years and 2.72 (95% CI: 1.96 to 3.68) in patients aged ≥75 years; thus, it decreased with increasing age (p for trend <0.001). The nodal DLBCL had a higher SIR for sAML than extranodal DLBCL. As for the Ann Arbor stage of DLBCL, the SIR was less for the early-stage as compared with that for advanced-stage disease. Patients with a latency of 24–59 months had a higher SIR than those with other latencies. For the groups of sex, race and years of diagnosis, no heterogeneity or trend for SIRs was observed.

Further, when competing causes of deaths were considered, the cumulative incidence of sAML was 0.30% (95% CI: 0.26% to 0.35%), 0.53% (95% CI: 0.46% to 0.60%) and 0.61% (95% CI: 0.53% to 0.70%) at 5, 10 and 15 years after the diagnosis of DLBCL, respectively. Moreover, we found that the cumulative incidence of sAML was closely related to the patients' age at the diagnosis of DLBCL (p<0.001), the primary site (p=0.010) and the Ann Arbor stage of DLBCL (p=0.007). The cumulative incidence at 10 years after DLBCL diagnosis was 0.51% (95% CI: 0.41% to 0.62%) in patients aged <60 years, 0.74% (95% CI: 0.61% to 0.89%) in patients aged 60–74 years and 0.29% (95% CI: 0.21% to 0.39%) in patients aged ≥75 years. For extranodal DLBCL, the cumulative incidence in patients at 10 years was 0.40% (95% CI: 0.31% to 0.51%); it was 0.59% (95% CI: 0.51% to 0.69%) for DLBCL occurring in the lymph node. As regards the Ann Arbor stage of DLBCL, the cumulative incidence in patients at 10 years was 0.43% (95% CI: 0.35% to 0.52%) and 0.66% (95% CI: 0.55% to 0.79%) for the early and advanced stages, respectively (figure 3).

Furthermore, according to the semiparametric proportional hazards model, we investigated the risk factors for sAML occurrence. The results are presented in table 2. Univariate analyses showed that patients' age, primary site and Ann Arbor stage of DLBCL were statistically significant risk factors (p<0.05). These three variables were selected for the final multivariate analysis, which showed that the patients' age at diagnosis and the Ann Arbor stage of DLBCL were independent predictors of the occurrence of sAML. Patients aged 60–74 years were more likely to have sAML than those aged <60 years. However, patients aged ≥75 years were less likely to have sAML than patients aged <60 years. Patients with advanced-stage DLBCL were more prone to sAML than those with early-stage disease.

The table 3 listed the characteristics of patients with sAML and their dnAML counterparts. The median survival time for patients with sAML and dnAML was 7

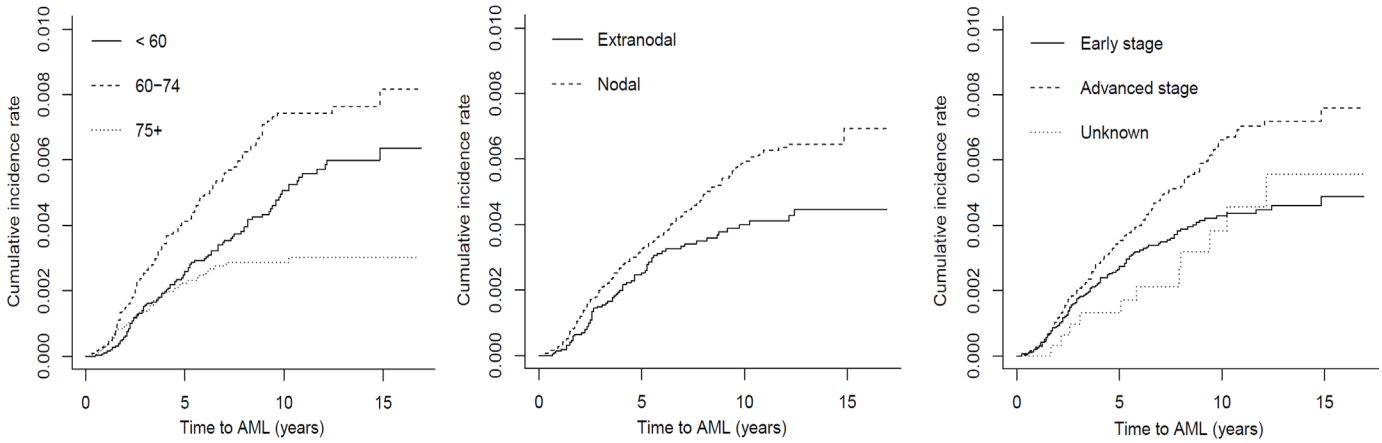

Figure 3 Cumulative incidence of secondary acute myeloid leukaemia among survivors of diffuse large B-cell lymphoma. AML, acute myeloid leukaemia.

months (95% CI: 6 to 9 months) and 13 months (95% CI: 10 to 17 months), respectively (figure 4). The Cox model showed that patients with sAML had a higher risk of death and a shorter OS than their dnAML counterparts (HR=1.25; 95% CI: 1.01 to 1.53; p=0.038). Of all the causes of death, AML is the most common in patients with both sAML and dnAML. However, we found that death from DLBCL was still a main component of overall mortality for patients who subsequently developed sAML (table 4).

DISCUSSION

As far as we know, this is the largest population-based study of sAML in patients with DLBCL. In this study, we observed an increased incidence of sAML among survivors of DLBCL and demonstrated substantial heterogeneity in the occurrence of sAML by age at diagnosis, primary site and Ann Arbor stage of DLBCL. Specifically, we identified that the age at diagnosis and stage of DLBCL were independent risk factors for sAML. We also observed that sAML had a shorter OS than dnAML, and that death from DLBCL was a main component of overall mortality for patients who subsequently developed sAML.

Table 2 Univariate and multivariate analyses for predictive factors of developing sAML

	Univariate			Multivariate		
Factors	**sHR**	**95% CI**	**P**	**sHR**	**95% CI**	**P**
Age, years						
<60	ref.			ref.		
60–74	1.421	1.092 to 1.850	0.009	1.417	1.087 to 1.850	0.010
75+	0.635	0.443 to 0.908	0.013	0.648	0.452 to 0.930	0.018
Sex						
Male	ref.					
Female	0.827	0.647 to 1.060	0.130			
Race						
White	ref.					
Black	0.764	0.460 to 1.270	0.300			
Other	0.947	0.605 to 1.480	0.810			
Primary site						
Nodal	ref.			ref.		
Extranodal	0.703	0.536 to 0.923	0.011	0.770	0.583 to 1.020	0.065
Ann Arbor stage						
Early stage	ref.			ref.		
Advanced stage	1.423	1.110 to 1.830	0.005	1.307	1.012 to 1.690	0.040
Unknown	0.808	0.434 to 1.500	0.500	0.807	0.431 to 1.510	0.500

ref, reference; sAML, secondary acute myeloid leukaemia; sHR, subdistribution HR.

Table 3 The baseline characteristics of patients with sAML and the matched cases with dnAML

Characteristics	sAML n=262	dnAML n=262
Age (range), years	68.0 (15.0–95.0)	67.5 (15.0–93.0)
Age group, years		
<60	67 (25.6%)	71 (27.1%)
60–74	121 (46.2%)	120 (45.8%)
75+	74 (28.2%)	71 (27.1%)
Sex		
Male	155 (59.2%)	155 (59.2%)
Female	107 (40.8%)	107 (40.8%)
Race		
Black	16 (6.1%)	16 (6.1%)
White	225 (85.9%)	225 (85.9%)
Other	21 (8.0%)	21 (8.0%)
Year of diagnosis		
Median (range)	2011 (2001–2016)	2010 (2000–2016)

dnAML, de novo acute myeloid leukaemia; sAML, secondary acute myeloid leukaemia.

In a population-based study, the SIR of sAML was 4.29 for patients with DLBCL, indicating a higher incidence of sAML in patients with DLBCL than that in the general population,[17] which is consistent with our results. Another large study combined data from 25 089 patients with DLBCL from California and reported 75 cases of sAML.[7] This was 4.39 (pre-rituximab) or 8.70 (post-rituximab)

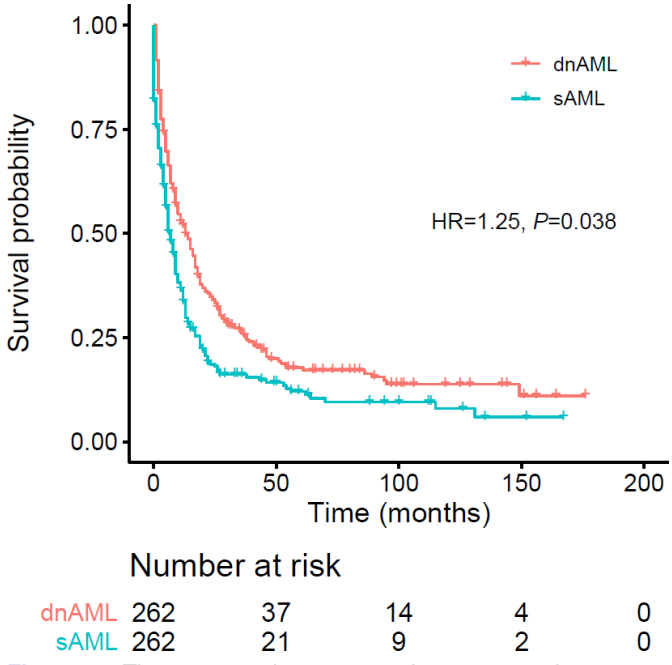

Figure 4 The comparative outcome between survivors of diffuse large B-cell lymphoma who developed sAML and matching patients with dnAML. dnAML, de novo acute myeloid leukaemia; sAML, secondary acute myeloid leukaemia.

Table 4 Causes of death in patients with sAML and matched dnAML

Causes of death	sAML (n)	dnAML (n)
Number of deaths	218	210
AML	105	144
DLBCL	66	0
Other cancers	18	21
Other haematopoietic and lymphoid tumours	12	17
Solid tumour	6	4
Cardiovascular and cerebrovascular	5	6
Infection	4	6
Other	20	28
NA	0	5

AML, acute myeloid leukaemia; dnAML, de novo acute myeloid leukaemia; NA, not available; NHL, non-Hodgkin's lymphoma; sAML, secondary acute myeloid leukaemia.

times the number of expected cases from the general population, indicating an increased risk, which was similar to that reported herein.

In this study, we confirmed that the SIR of sAML decreased with an increase in age at diagnosis. However, when competing causes of death were considered, patients aged 60–74 years had the highest cumulative probability of sAML at 10 years of follow-up. This result is consistent with that reported in the papers, which show that sAML tends to occur more commonly in older patients.[18–20] However, this study also showed that patients aged ≥75 years had a lower cumulative incidence than younger patients. Since high-dose chemoradiotherapy has been associated with an elevated risk of sAML,[21] and the elderly are usually not given intensive chemotherapy or radiotherapy due to the comorbidity and functional status, which may lower the risk of sAML.[22]

The link of AML risk with the stage at diagnosis of DLBCL has been not well clarified for DLBCL. A large population-based study indicated that patients with advanced-stage DLBCL were more likely to develop haematological SPMs, and that the most common histology of haematological SPM was AML.[6] In this study, we also found that patients with advanced-stage DLBCL had a higher SIR than those with early-stage DLBCL (p<0.001). Considering the competing causes of death, we found that the cumulative probability of sAML for patients with advanced-stage DLBCL was higher than that for patients with early-stage at 10 years of follow-up. Furthermore, the advanced-stage DLBCL was identified as an independent risk factor for sAML in our study.

In an experimental research with the analysis of gene expression profiling, a number of genes were differentially expressed in patients with early-stage DLBCL compared with those with advanced-stage DLBCL.[23] Another study suggested that increased late relapses in the early-stage DLBCL compared with advanced-stage DLBCL may be

caused by biological differences.[24] However, a report of patients with advanced-stage DLBCL also recognised the risk of late relapse.[25] These reports indicate that early-stage DLBCL has a unique biology compared with advanced-stage DLBCL, which may explain the difference in incidence of sAML partly. On the other hand, according to National Comprehensive Cancer Network guideline, patients with early-stage DLBCL usually receive fewer cycles chemotherapy and is treated with local radiotherapy more often than advanced disease.[26] The difference in treatment may also lead to a lower incidence of sAML for patients with early-stage DLBCL.

Our study found that patients with primary sites in the lymph nodes had a higher SIR and cumulative probability than those with extranodal disease. However, according to the semiparametric proportional hazards model, multivariate analysis showed that the primary sites of DLBCL were not independent risk factors for the progress of sAML. As reported in the literature, patients with early-stage DLBCL are more likely to have extranodal disease.[27] This study also showed similar results (data not shown). Given this finding, it is possible that early-stage DLBCL, which is mainly located in extranodal sites, lowers the SIR or cumulative probability.

In the present study, we compared the survival outcomes of patients with sAML and their dnAML counterparts. The results show that the prognosis is worse for patients diagnosed with sAML after surviving DLBCL than those diagnosed with dnAML in matched cases. Previously studies have indicated that the prior therapy of DLBCL shows a detrimental effect, which has been verified in patients who have developed malignant mesotheliomas, bladder cancer and kidney cancer.[28–30] The successful treatment of second cancer in patients who survive DLBCL has been affected by many factors, such as limitations on the dose and site of radiotherapy, a poor tolerance to chemotherapy, and impaired physiologic reserve. Another intriguing factor may result from the intrinsically worse biology of sAML, which require more in-depth research.

Since this is a retrospective observational study based on SEER database, there are some limitations for this study. First, we are limited by the extent of the data for some covariates of interest. And, one of the primary limitations is that we cannot obtain the detailed information regarding disease treatments. Therefore, it is impossible to establish a correlation between DLBCL treatment and the development of sAML. In addition, the therapeutic modalities that could be used to treat patients with sAML are also not mentioned in the database, which limits the exploration of prognosis. Second, the diagnostic standard and classification are not uniform, such as the diagnosis of AML and the classification of DLBCL, which may impact on the conclusions. Third, we have to exclude some cases with unknown characteristics, and this may lead to a bias of the result. However, there are several novel findings shown in this study. These findings may be helpful in future prospective trials for patients with DLBCL.

In conclusion, the current findings suggest that the incidence of AML increases significantly among survivors of DLBCL. Furthermore, we showed that age and Ann Arbor stage of DLBCL at diagnosis are independent risk factors for sAML. We also found that patients with sAML had shorter OS than their dnAML counterparts. These findings will be beneficial for the management of patients with newly diagnosed DLBCL.

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Contributors YD: conceptualisation and design, collection and assembly of the data, formal analysis and interpretation, visualisation, writing-original draft and writing-review and editing. YW: collection and assembly of the data, data curation, visualisation, writing-original draft and writing-review and editing. QL: data curation and analysis, writing-review and editing. XC: methodology, supervision and writing-review. HZ: supervision and writing-review. MX: conceptualisation, methodology, validation, data curation and writing-review and editing. SX: guarantor, conceptualisation, methodology, validation, formal analysis, data curation, supervision, writing-original draft, writing-review and editing.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study used the SEER research database, which is approved by the NIH Ethics Program.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. Data used in this study are available from the Surveillance, Epidemiology, and End Results (SEER) database (https://seer.cancer.gov).

ORCID iD

Shugang Xing http://orcid.org/0000-0002-2676-2893

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