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Examination of clinical outcomes in patients with autoimmune disease and diffuse large B cell lymphoma

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Examination of clinical outcomes in patients with autoimmune disease and diffuse large B cell lymphoma

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M.D., Emory University, 2010

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An abstract of
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ABSTRACT

Examination of clinical outcomes in patients with autoimmune disease and diffuse large B cell lymphoma

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Jean Louise Koff, M.D.

Background: Severe immune dysregulation as seen in autoimmune (AI) disease is known to act as a significant risk factor for diffuse large B cell lymphoma (DLBCL), but little is known about the demographics or clinical outcomes of DLBCL that arises in the setting of AI disease.

Patients and Methods: We used the Surveillance, Epidemiology, and End Results (SEER) database for patients diagnosed 2002-2009 linked to their Medicare claims data through 2011 to characterize presentation, treatment, and survival patterns in DLBCL patients, including those with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), and other B cell-mediated AI diseases. Kaplan-Meier curves and Cox proportional hazards models were generated to examine the effect of concurrent AI disease diagnosis on overall survival (OS) and lymphoma-related survival (LRS). Multivariable logistic regression models were employed to investigate the relationships between patient characteristics and discrete survival endpoints.

Results: Patients with DLBCL and AI disease were more commonly female, but patients with DLBCL and RA, SLE, SS, or other B cell AI diseases did not differ from other DLBCL patients in any other baseline presenting features and received similar first-line treatments. Patients with concomitant RA and DLBCL had decreased LRS compared to patients without AI disease (hazard ratio 1.52, 95% confidence interval 1.03– 2.22). There was also a trend towards decreased LRS in patients with SLE and DLBCL compared to all other groups, but this difference was not statistically significant in this cohort.

Conclusions: In this retrospective claims-based cohort of older patients with DLBCL, concomitant AI disease was uncommon and was more likely to occur in female DLBCL patients, which likely reflects the higher incidence of AI disease in women. The possibility of lower LRS for RA and SLE patients should be explored in future studies.

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INTRODUCTION

The association between autoimmune (AI) disease and increased incidence of lymphoma has long been described. However, until lately, examination of whether specific lymphoma subtypes arise in the setting of certain autoimmune disorders has been limited by inadequate sample sizes, given the relative rarity of each disease subtype. Several recent large case-control studies revealed that autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and Sjögren's syndrome (SS) represent major risk factors for diffuse large B cell lymphoma (DLBCL), the most common subtype of non-Hodgkin lymphoma (NHL) in the Western world. (1-3) DLBCL is characterized by clinical heterogeneity: although about half of patients will be cured with standard frontline chemoimmunotherapy, others will relapse and often succumb to the disease despite salvage treatments.(4, 5) Investigating the mechanisms by which autoimmunity contributes to DLBCL development and outcomes could yield unique insights into the complex events that underlie lymphomagenesis and disparities in survival.

Given that the processes of inflammation and chronic self-antigen stimulation that define AI diseases represent specific pathways that could promote lymphoma development, it is possible that AI-associated lymphomas comprise a distinct subset within DLBCL exhibiting characteristic clinical and biologic behavior. However, little is known about the demographics or clinical outcomes of DLBCL that arises in the setting of AI disease. We examined the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database to determine the frequency of common B cell AI diseases

among older patients with DLBCL and characterize the patterns of presentation, treatment, and survival for DLBCL patients with concomitant AI disease.

BACKGROUND

While data from population-based cancer registries has helped to characterize the epidemiology of NHL as a single entity, identification of risk factors for the more than 40 individual NHL subtypes, each defined by distinct biologic and clinical features, has been difficult due to their relative rarity. In order to perform a comprehensive analysis of risk factors contributing to specific NHL subtypes, the International Lymphoma Epidemiology Consortium (InterLymph) was formed in 2001. By pooling large numbers of cases and controls across studies, the InterLymph group has been able to provide well-powered comparisons of factors such as medical and family history, lifestyle, and occupation as they relate to risk of developing certain lymphoma subtypes. In multivariable analysis of 4,667 DLBCL cases and 22,639 controls, B cell-activating AI disease (including autoimmune hemolytic anemia, Hashimoto's thyroiditis/hypothyroidism, myasthenia gravis, pernicious anemia, RA, SS, and SLE) emerged as a major risk factor for DLBCL development, with an odds ratio (OR) of 2.45 (95% confidence interval [CI] 1.91-3.16). More specifically, personal history of SS conferred an OR of 8.77 (95% CI 3.94-19.5), and history of SLE an OR of 2.49 (95% CI 1.42-4.37). (6)

Conversely, much work has been done to characterize the incidence of NHL subtypes in large cohort studies of patients with autoimmune disease. In general, SS is known to carry the highest risk of lymphoma, with estimates of relative risk (RR) ranging from 4 to 40 times that of the general population. (7, 8) The majority of these are mucosa-associated lymphoid tissue (MALT) lymphomas, but DLBCL cases made up about 15% of SS-associated NHL in a 584-patient cohort. (9) A 2005 cohort study

involving 9,547 patients with SLE showed that of the cases in which NHL was diagnosed, aggressive subtypes predominated, with DLBCL accounting for over half of cases for which subtype was available. (10) There is significant heterogeneity in studies of NHL risk in RA, which preempted the InterLymph group from performing a focused analysis of lymphoma subtype risk in this patient population. (6) However, in a large Swedish study that included >74,000 RA patients, increased risk of NHL in general and DLBCL in particular (48% of cases) was seen in patients with higher indices of inflammatory activity. (11)

The question of whether lymphoma risk in SLE and RA stems in fact from immunosuppressive therapy used to treat those disorders rather than the autoimmune disease itself remains controversial. In the case of RA, a systematic review of the literature revealed no significant association of either methotrexate or azathioprine with NHL risk.(12) The review's author notes that inconsistencies between the studies examined may in part stem from smaller studies' lack of statistical power to detect the relatively rare event of lymphoma. Notably, larger studies showed a relatively smaller risk of lymphoma associated with methotrexate, whereas risk estimates for azathioprine were heterogeneous.

There is some suggestion that use of tumor necrosis factor-alpha (TNFα) inhibitors may increase lymphoma risk, but this association is far from clear-cut. A 2006 meta-analysis investigating the effect of the monoclonal antibodies infliximab and adalimumab on lymphoma risk based on randomized clinical trial data found a summary OR of 3.3. (13) However, interpretation of that result is limited by inclusion of heterogeneous studies with short follow-up periods (1-4 years), and lack of data

regarding etanercept, a soluble receptor TNFα inhibitor. A prospective French study investigating risk of lymphoma in patients with any inflammatory disease treated with anti-TNF therapy found that the two- to three-fold increased risk of lymphoma seen in this population was similar to that expected in patients with such disorders. (14) Interestingly, that study found that risk of lymphoma was increased with use of infliximab and adalimumab compared to etanercept. Further confounding this issue is the fact that patients with increased disease severity are more likely to receive toxic medications, making it very difficult to distinguish whether disease activity or specific medications contribute most to lymphoma risk. However, as alluded to above, there is some evidence that DLBCL risk specifically correlates with increased disease activity in RA. (11) In SLE, a large case-cohort analysis evaluating 75 lymphoma cases against almost 5000 cancer-free controls failed to show significant association between either disease activity or specific therapy, including cyclophosphamide, methotrexate, azathioprine, mycophenolate mofetil and hydroxychloroquine, and increased lymphoma risk. (15) In fact, many of the lymphoma patients had not been exposed to any of those medications prior to onset of malignancy.

Given that DLBCL and certain AI disorders are both characterized by pathologic B cell proliferation, agents that target these cells are of special interest in patients with DLBCL arising in the setting of AI disease. At present, the chemoimmunotherapeutic regimen known as R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) remains the standard of care in first-line treatment of DLBCL. However, as we learn more about the distinct molecular pathways that underlie the disease's clinical heterogeneity, there is mounting evidence that this regimen may be modified to better

target certain DLBCL subsets characterized by inferior treatment responses and survival outcomes. For instance, phase III trials stratified by cell-of-origin subtype are currently underway to evaluate the addition to RCHOP of oral agents such as lenalidomide that show preferential activity in the activated B cell-like (ABC) subtype. (16) Moreover, several studies show that intensifying frontline therapy with a regimen such as dose-adjusted R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin) or HyperCVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, methotrexate, cytarabine and dexamethasone) results in improved outcomes for patients with lymphomas harboring poor-risk chromosomal translocations. (17) It is possible that DLBCLs that arise in the setting of AI disease may represent a disease subset with characteristic pathogenesis and prognosis. Whether and how AI disease influences lymphoma outcomes, let alone DLBCL outcomes, are questions that remain understudied. For example, although preliminary data suggested that DLBCL patients with RA have inferior survival compared to patients with *de novo* DLBCL, (18) other studies have not borne out the same. (19) It is interesting to note that several immunosuppressive drugs such as cyclophosphamide and methotrexate represent cornerstones in the treatment of both lymphoma and certain AI disorders such as RA and SLE. Indeed, several studies show that treatment of AI-related lymphoma with R-CHOP resulted in remission not only of the malignancy but also of the autoimmune condition.(20, 21) Investigating whether patients with AI-associated DLBCL experience disparate outcomes compared to patients with *de novo* DLBCL could help guide prospective trials of targeted treatment approaches in this unique subgroup.

METHODS

Research Aim

Utilizing large clinical databases, evaluate clinical outcomes in patients with DLBCL arising in the setting of autoimmune disease (AI-DLBCL) compared to those with *de novo* DLBCL.

Hypothesis

Patients with AI-DLBCL exhibit inferior overall survival and lymphoma-related survival after front-line therapy compared to patients with *de novo* DLBCL.

Data Source

We used the National Cancer Institute (NCI) SEER database for patients diagnosed 2002-2009 linked to their Medicare claims data through 2011 to conduct a retrospective cohort study and characterize presentation, treatment, and survival patterns in patients with DLBCL, including those with RA, SLE, SS, and other B cell-mediated autoimmune diseases as defined by InterLymph criteria (autoimmune hemolytic anemia, Hashimoto's thyroiditis/hypothyroidism, myasthenia gravis and pernicious anemia (22)). The SEER program reports data on cancer incidence and survival collected from U.S. registries, covering about 28% of the population as of 2016.(23) Collected data include patient demographics, tumor pathology, stage of disease, primary site of tumor, first-line treatment, and dates of diagnosis and death.

Linking SEER with Medicare claims data allows for the identification of concomitant health conditions and specific treatments received by elderly cancer patients. Among individuals older than 65, 97% are Medicare-eligible, and 93% of those listed in SEER are linked to the Medicare enrollment file.(24) Since this database does not include patient identifiers, our study did not require approval from an Institutional Review Board; however, a data use agreement was signed prior to initiation of the study.

Eligibility Criteria

Patients were considered eligible for analysis if diagnosed with DLBCL between 1/1/2002 and 12/31/2009, had linked Medicaid claims available up to 2011, and were aged ≥66 at diagnosis. The minimum required age was 66 in order to ensure that patients had been enrolled in Medicare for ≥12 months prior to diagnosis. Cases were identified using the World Health Organization (WHO) International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) histology codes 9680 and 9684.(25) The following ICD, 9th Revision, Clinical Modification (ICD-9 CM) codes were used to identify presence of concomitant AI disease: SLE: 710.0; RA: 714.0 – 714.3; autoimmune hemolytic anemia: 283.0; myasthenia gravis: 358.00, 358.01; pernicious anemia: 281.0; SS: 710.2. Exclusion criteria are shown in Figure 1.

Patient Characteristics

Patients were stratified into groups by AI disease (none coded, SLE, SS, RA or other B cell-activating AI disease) as identified in Medicare claims. Self-reported race

was categorized as Caucasian, African-American, or "other"; using SEER data, the "other" category includes individuals of Asian, Native American, Pacific Islander, or Alaskan Native ancestry.(26) The SEER-Medicare database uses census tract information (e.g., percentage of residents living in poverty and percentage with only a high school education) from the 2000 U.S. Census as a surrogate for socioeconomic status, as described in other SEER-Medicare studies.(27-29) Other demographic variables analyzed in this study included sex, marital status, and type of geographical area (less urban/rural, urban, or metropolitan).

In terms of disease status, patients were classified with regard to the following: Ann Arbor stage (I/II, III/IV, or unknown), primary disease site (nodal vs. extranodal), presence of B symptoms, performance status, NCI Comorbidity Index score (0, 1, or ≥2), and year of diagnosis. Performance status was classified as poor if a patient had claims for any of the following: hospice, home health agency, skilled nursing facility, oxygen, or wheelchair/related supplies. Such claims-based measures of performance status have been used in other cancer studies.(30-33) NCI Comorbidity Index scores were calculated using the Deyo adaptation of the Charlson Comorbidity Index (CCI) to identify the 15 non-cancer comorbidities included in the CCI from Medicare claims.(34, 35)

Treatment and Mortality Classification

We determined initial management strategies based on Medicare claims made within 6 months of diagnosis; if no treatment was documented within this time frame, management was categorized as "observation." The SEER-Medicare dataset does not

include information regarding the receipt of oral medications without an intravenous equivalent. Thus, patients with claims for cyclophosphamide, doxorubicin, and vincristine were categorized as receiving CHOP, and those with claims for cyclophosphamide and vincristine were classified as receiving CVP. Patients with those same claims who also received rituximab were classified as receiving R-CHOP and R-CVP, respectively.

We utilized SEER date and cause of death to determine mortality classification. Since SEER only reports diagnosis by month and year, date of diagnosis for our survival analyses was designated as the 15th day of the reported month. Patients were followed until death, enrollment in a health maintenance organization (HMO), or last date of available Medicare claims. We examined two different survival endpoints: overall survival (OS) measured from date of diagnosis until death censored at last follow-up, and lymphoma-related survival (LRS), measured from date of diagnosis until death from lymphoma censored at death from other causes or last follow-up.

Statistical Analysis

Patients without concomitant AI disease were compared to patients with SLE, SS, RA, or any B cell-mediated AI disease using chi-squared tests. Kaplan-Meier curves were constructed to examine the effect of concurrent AI disease diagnosis on OS and LRS. Cox proportional hazards models were adjusted for the following demographic and clinical variables: sex, race, marital status, percent in census tract living in poverty, percent in census tract with only a high school education, type of geographical area,

stage, primary site of disease, presence of B symptoms, NCI comorbidity index score, performance status, treatment regimen, and year of diagnosis. We tested the global proportional hazards assumption with the Wald test, and proportional hazards assumptions for individual covariates were tested by assessing Schoenfeld residuals. No violations were detected.

To investigate the relationships between patient characteristics and discrete survival endpoints known to have prognostic significance in DLBCL (1-year OS, 1-year LRS, 2-year OS, and 2-year LRS), multivariable logistic regression models were employed with calculation of OR with 95% confidence intervals. These regression models were adjusted for the same variables described above. We used the Hosmer-Lemeshow test to assess goodness of fit of the logistic regression model. Sensitivity analyses were performed using propensity score methods to adjust for imbalances in observable covariates between treatment groups. We set $\alpha=0.05$ to determine statistical significance, and all p-values were two-sided. Data were analyzed using SAS 9.4 (Cary, NC) and Stata 13 (StataCorp LP, TX).

RESULTS

We identified a total of 5,926 patients with DLBCL, of whom 270 had B cell-mediated AI disease. Patient characteristics are summarized in Table 1. Of note, the SEER-Medicare data use agreement stipulates that patient data with $n < 11$ may not be directly reported or be derivable with more precision than "$n < 11$", which limits presentation of baseline characteristics for patients with concurrent DLBCL and either RA ($n = 155$), SLE ($n = 25$), or SS ($n = 18$). With the exception that patients with concomitant DLBCL and AI disease were more commonly female, patients with DLBCL and RA, SLE, SS, or other B cell AI diseases had similar baseline presenting features as other DLBCL patients and received similar first-line treatments. More specifically, there were no statistically significant differences in receipt of either anthracycline-containing regimens (74% in all patients, 78% in RA, 80% in SLE, 83% in SS) or rituximab (63% in all patients, 66% in RA, 60% in SLE, 72% in SS). Among treatment regimens excluded from analysis (i.e., regimens other than chemotherapy with R-CHOP, R-CVP, CHOP, or CVP), 40% had missing data for agents used, 7% contained both rituximab and an anthracycline, 24% included rituximab but no anthracycline, 3% included an anthracycline without rituximab, 7% contained neither rituximab nor an anthracycline, and 19% of patients received radiation alone; these treatment regimens were not significantly different between groups of patients based on AI disease status. Total number of chemotherapy cycles received did not vary significantly by AI disease status, with 54% of all patients receiving ≥ 4 cycles, compared to 58% of RA, 68% of SLE, and 60% of SS patients. Similarly, 31% of all patients received ≥ 6 cycles, compared to 38% of RA, 45% of SLE, and 33% of SS patients.

Median OS in patients with AI disease did not differ significantly from that seen in patients without AI disease: 6.34 (95% confidence interval [CI]:4.55-8.60) years for RA patients, 3.23 (95% CI: 2.14-11.97) for SLE patients, 5.51 (95% CI: 2.42-not reached) for SS patients, and 5.97 (95% CI: 4.45-7.78) for patients with any B cell-mediated AI disease, compared to 6.96 (95% CI: 6.69-7.37) years for patients without AI disease. Table 2 depicts results of our Cox regression analysis assessing OS by disease stage and AI disease status; no difference in survival was found between DLBCL patients with and without concomitant AI disease. Interestingly, patients with RA and DLBCL had an increased risk of lymphoma-related death (hazard ratio [HR] 1.52 with CI 1.03 – 2.22; $p = 0.034$) in our Cox proportional hazards model (Table 3). There was also a trend towards decreased LRS in patients with SLE and DLBCL compared to all other groups, but this difference was not found to be statistically significant in this cohort (Table 3 and Figure 2). Median LRS was not reached for any group. When DLBCL patients with any B cell-mediated AI disease were compared to patients without AI disease, there was a trend towards decreased OS (HR 1.20 with CI 0.94 – 1.52), but this also failed to meet statistical significance (Figure 3).

Because there were few differences in baseline characteristics between groups, traditional multivariable regression models are reported rather than propensity-matched models. As shown in Tables 4-7, AI disease status did not impact the following discrete survival endpoints per our logistic regression analysis: 1-year OS, 1-year LRS, 2-year OS, and 2-year LRS. Not unexpectedly, presence of B symptoms, advanced stage, and poor performance status were associated with inferior survival for all four endpoints. NCI comorbidity status >1 was also associated with inferior survival in all models except for

2-year LRS. Similar to previous studies, female sex and a marital status of married were favorable prognostic factors for 2-year OS and 2-year LRS. Race was not found to be a statistically significant prognostic factor except in the 1-year LRS model, in which African-Americans had inferior outcomes compared to Caucasians (OR 0.63 with CI 0.40 – 0.99; p = 0.044; Table 5).

DISCUSSION

In our retrospective claims-based cohort of older DLBCL patients, concomitant AI disease was uncommon and was more likely to occur in female DLBCL patients, which likely reflects the higher incidence of AI disease in women. We found that patients with concomitant RA and DLBCL had decreased lymphoma-related survival. The trend towards decreased survival in patients with SLE and DLBCL was not statistically significant, but this may have resulted due to a low number of patients in this group.

By virtue of the use of Medicare claims to capture data on AI diagnosis and cancer treatments, our analysis was limited to patients older than 65. Thus, we would expect to capture more cases of *de novo* and AI-associated DLBCL via analysis of datasets that include younger patients. In our separate analysis of AI disease as a comorbidity in 736 DLBCL patients in the Mayo/Iowa Molecular Epidemiology Resource (MER) cohort, we found a trend towards increased risk of death in patients with concomitant B cell-mediated AI diseases (HR=1.41, 95% CI 0.95 – 2.08).(36) Our group has previously shown that African-American DLBCL patients present at a younger age and with more aggressive disease compared to Caucasian patients;(37) data suggests that such a relationship may exist for patients with AI disease as well. For example, the median age of SLE patients at NHL diagnosis was 49 years in one study of 11 cases,(38) and 57 years in a 2005 study that included 42 cases;(10) a 2012 study of SS-associated NHL reported median age at DLBCL diagnosis of 66.5.(9) Although the current study did not show that AI-associated DLBCL was more likely to present in African-American patients, it is possible that African-American patients were under-represented in our dataset.(39) Since the state of Georgia is the only major southern SEER site, SEER may

miss populations with larger proportions of African-American individuals. Notably, the large Lymphoma Epidemiology of Outcomes cohort study is currently attempting to selectively recruit African-American and Hispanic patients with DLBCL in centers where these patients are likely to be diagnosed, in order to overcome limitations in analysis when such populations are under-represented. To examine factors that might explain the racial disparity in NHL incidence patterns, Koshiol and colleagues assessed immune-related conditions and risk of developing NHL among 7,999 Caucasian and 1,497 African-American hospitalized veterans. The authors found that patients with autoimmune disease were generally more likely to develop NHL, but that risks associated with autoimmune conditions were similar by race.(40) However, women and healthier individuals who only received outpatient care (as could be the case for patients with DLBCL) were under-represented in this population, which likely biased these results. Given that certain AI disorders like SLE are prevalent in African-American women and show similar patterns of earlier age at diagnosis and increased disease severity among African-American patients,(41-43) there may be biologic factors such as host genetics and prolonged exposure to inflammatory milieu that result in earlier diagnosis of DLBCL compared to the general population. However, this hypothesis has yet to be explored and will require populations that include younger patients and women.

Decreased lymphoma-related survival in DLBCL patients with concomitant RA and a trend towards decreased LRS in patients with SLE suggest that these patients may indeed suffer inferior outcomes compared to DLBCL patients without AI disease. DLBCL subtype as distinguished by gene expression profiling has been shown to be an important factor in prognosis, with activated B cell-like (ABC) subtype exhibiting

inferior survival outcomes compared to germinal center B cell-like (GCB) DLBCL.(44-46) There is evidence that patients with autoimmune-associated DLBCL are more likely to harbor the more aggressive ABC subtype; for instance, a Swedish study found that 70% of DLBCL cases arising in a large cohort of RA patients exhibited a non-GCB phenotype.(47) Unfortunately, information on DLBCL subtype is not available in the SEER-Medicare database, limiting our assessment of a possible interaction with AI disease in impacting lymphoma outcomes.

Our analysis was also limited by the fact that a record of patients' oral medications is not available in the SEER-Medicare dataset. Although data on chemotherapeutic regimens for first-line treatment of DLBCL was largely extractable, most immunosuppressive therapies for AI disorders remained unavailable for our analysis. As described above, the question of whether NHL risk and outcomes for patients with systemic AI diseases such as SLE and RA stems from immunosuppressive therapy used to treat those disorders rather than disease activity itself remains controversial. Clearly, more work is needed to tease out the complicated relationships between autoimmunity, immunosuppressive therapy and risk of lymphoma development. Furthermore, no published studies have yet addressed the relationships between AI disease severity, duration, and treatment, and lymphoma outcomes. To our knowledge, our study is the first to examine the outcomes of DLBCL patients with AI disease in a large population-based cohort treated with contemporary regimens and suggests that most elderly patients with DLBCL and AI disease have similar outcomes to the general population of DLBCL patients.

Future Directions

While it may be difficult to capture enough AI-associated DLBCLs in any one dataset to demonstrate statistically significant survival disparities, the unique pathophysiology of such cases may lend insight into molecular abnormalities that portend poor prognosis in both AI- and non-AI-associated DLBCL. AI disease and DLBCL are both characterized by B cells that fail to respond to physiologic regulatory cues: in AI disease, B cells become pathologically activated and produce autoantibodies; in lymphoma, B cells acquire oncogenic genetic "hits" that cause malignant transformation and unchecked proliferation. Genome-wide association studies (GWAS) have identified variants in genes that both affect the inflammatory milieu and confer increased DLBCL risk, including cytokines such as IL10.(48, 49) In addition, B cell receptor (BCR) signaling represents a pathway that is dysregulated in both DLBCL and AI disease. While some DLBCLs harbor mutations in BCR pathway members that result in constitutive BCR signaling, binding of the BCR to a cognate antigen, as occurs during autoreactivity for AI diseases, represents an alternative activation mechanism for this survival pathway. Disruption of pathways engaged in cross-talk with BCR-mediated signaling can lead to abnormal survival and activation of autoreactive B cells,(50) thereby facilitating AI disease development and highlighting a key intersection between autoimmunity and lymphoma. It is possible that AI-associated lymphomas achieve constitutive BCR signaling through chronic antigen stimulation rather than from the mutations in BCR pathway members seen in some ABC-DLBCL.(51) Given the link between chronic antigen stimulation and dysregulated BCR signaling, the shift toward increased circulating activated B cell subsets in AI diseases may represent a crucial factor

underlying increased lymphoma risk in these patients.(52) In addition, lymphomas arising in the setting of AI disease may harbor distinct genetic abnormalities that reveal mechanistic pathways, but analysis of this disease subset remains relatively unexplored.

Linking epidemiologic and genetic findings, Wang *et al*. found that NHL risk across major subtypes increased in individuals with B cell-mediated AI conditions who harbored G308A variants in the gene encoding TNFα.(53) This suggests a common pathway for AI disorders and lymphoma that promotes a chronic inflammatory state through increased TNFα expression and resultant nuclear factor-kappaB (NF-κB) activation. Another recent GWAS from our collaborators in InterLymph found that a single nucleotide variant in the gene coding for CD40, a surface receptor on B cells that mediates B cell activation, antibody isotype switching, and memory B cell development when bound by ligand, increased risk of both SLE (OR 1.40, 95% CI 1.20–1.56, $p=1.4 \times 10^{-6}$)(54) and DLBCL (OR per risk allele=1.09, 95% CI 1.02–1.16, p=0.013).(55) Intriguingly, constitutive CD40 signaling in B cells selectively activates the noncanonical NF-κB pathway and promotes lymphomagenesis in mouse models, with tumors showing an activated B cell phenotype.(56) My prior work examined the relationships between signaling of the p100 (noncanonical) and p105 (canonical) NF-κB subunits, DLBCL subtypes, and the coding genome by integrating gene expression analysis, parallel whole-exome sequencing, flow cytometry, and immunofluorescence methods.(57) This work identified distinct roles for p100 and p105 signaling in regulating B cell activation; a noncanonical gene expression signature was associated with an activated B cell phenotype in DLBCL and non-malignant B cells. Characterization of somatic abnormalities in AI-associated lymphoma tumors using a similar approach could lend

further insights into mechanisms of pathogenesis, but such analysis has heretofore been limited by relative rarity of appropriate specimens from patients with AI disease and lymphoma.

AI-associated lymphoma remains an understudied disease and understanding its pathophysiology may provide insight into the clinical behavior of *de novo* DLBCL. In my ongoing research, I will study SLE-associated DLBCL as a pathogenetic model to investigate the complex interplay between immune dysregulation and genetic alterations in influencing DLBCL subtype and clinical outcome. I will leverage existing collaborations with leaders in lymphoma epidemiology, high-throughput sequencing, and rheumatology to characterize the circulating B cell profile and conduct sequencing in DLBCL cases identified from large clinical databases. As part of my integrative approach, I have adapted Dr. Ignacio Sanz' novel flow cytometric methodology (58-60) to examine B cell profiles in lymphoma. Given the compounding effects of B cell-mediated AI disease and genetic variants in increasing lymphoma risk, it is possible that these factors may also impact lymphoma outcomes, but assessing the impact of B cell profiles on outcomes has yet to be applied in the setting of lymphoma. By characterizing B cell repertoire, genetic abnormalities, and clinical outcomes in lymphomas associated with immune dysregulation, I hope to provide novel insights into the impact of etiologic differences on survival and identify targets for further molecular study through the first-ever linkage of SLE and lymphoma cohorts. In the future, I aim to integrate understanding of lymphoma etiology gained from epidemiologic and genetic analyses to identify biomarkers that can guide treatment decisions and posit new therapeutic targets for lymphoma patients.

Conclusions

Our results serve as an initial characterization of AI-associated DLBCL in older patients. The possibility of lower lymphoma-related survival for patients with RA and SLE should be explored in future studies, especially those including younger patients, to capture larger numbers of patients with AI-associated DLBCL and further define the characteristics of this group.

REFERENCES

1. Sant M, Allemani C, Tereanu C, De Angelis R, Capocaccia R, Visser O, et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. Blood. 2010;116(19):3724-34.

2. Morton LM, Wang SS, Devesa SS, Hartge P, Weisenburger DD, Linet MS. Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. Blood. 2006;107(1):265-76.

3. Cerhan JR, Kricker A, Paltiel O, Flowers CR, Wang SS, Monnereau A, et al. Medical history, lifestyle, family history, and occupational risk factors for diffuse large B-cell lymphoma: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. J Natl Cancer Inst Monogr. 2014;2014(48):15-25.

4. Flowers CR, Armitage JO. A decade of progress in lymphoma: advances and continuing challenges. Clinical lymphoma, myeloma & leukemia. 2010;10(6):414-23.

5. Sinha R, Nastoupil L, Flowers CR. Treatment Strategies for Patients with Diffuse Large B-Cell Lymphoma: Past, Present, and Future. Blood and lymphatic cancer : targets and therapy. 2012;2012(2):87-98.

6. Ekstrom Smedby K, Vajdic CM, Falster M, Engels EA, Martinez-Maza O, Turner J, et al. Autoimmune disorders and risk of non-Hodgkin lymphoma subtypes: a pooled analysis within the InterLymph Consortium. Blood. 2008;111(8):4029-38.

7. Zintzaras E, Voulgarelis M, Moutsopoulos HM. The risk of lymphoma development in autoimmune diseases: a meta-analysis. Archives of internal medicine. 2005;165(20):2337-44.

8. Lazarus MN, Robinson D, Mak V, Moller H, Isenberg DA. Incidence of cancer in a cohort of patients with primary Sjogren's syndrome. Rheumatology (Oxford, England). 2006;45(8):1012-5.

9. Voulgarelis M, Ziakas PD, Papageorgiou A, Baimpa E, Tzioufas AG, Moutsopoulos HM. Prognosis and outcome of non-Hodgkin lymphoma in primary Sjogren syndrome. Medicine. 2012;91(1):1-9.

10. Bernatsky S, Ramsey-Goldman R, Rajan R, Boivin JF, Joseph L, Lachance S, et al. Non-Hodgkin's lymphoma in systemic lupus erythematosus. Annals of the rheumatic diseases. 2005;64(10):1507-9.

11. Baecklund E, Iliadou A, Askling J, Ekbom A, Backlin C, Granath F, et al. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. Arthritis and rheumatism. 2006;54(3):692-701.

12. Kaiser R. Incidence of lymphoma in patients with rheumatoid arthritis: a systematic review of the literature. Clinical lymphoma & myeloma. 2008;8(2):87-93.

13. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. Jama. 2006;295(19):2275-85.

14. Mariette X, Tubach F, Bagheri H, Bardet M, Berthelot JM, Gaudin P, et al. Lymphoma in patients treated with anti-TNF: results of the 3-year prospective French RATIO registry. Annals of the rheumatic diseases. 2010;69(2):400-8.

15. Bernatsky S, Ramsey-Goldman R, Joseph L, Boivin JF, Costenbader KH, Urowitz MB, et al. Lymphoma risk in systemic lupus: effects of disease activity versus treatment. Annals of the rheumatic diseases. 2014;73(1):138-42.

16. Nowakowski GS, LaPlant B, Macon WR, Reeder CB, Foran JM, Nelson GD, et al. Lenalidomide combined with R-CHOP overcomes negative prognostic impact of non-germinal center B-cell phenotype in newly diagnosed diffuse large B-Cell lymphoma: a phase II study. J Clin Oncol. 2015;33(3):251-7.

17. Petrich AM, Gandhi M, Jovanovic B, Castillo JJ, Rajguru S, Yang DT, et al. Impact of induction regimen and stem cell transplantation on outcomes in double-hit lymphoma: a multicenter retrospective analysis. Blood. 2014;124(15):2354-61.

18. Baecklund E, Sundstrom C, Ekbom A, Catrina AI, Biberfeld P, Feltelius N, et al. Lymphoma subtypes in patients with rheumatoid arthritis: increased proportion of diffuse large B cell lymphoma. Arthritis and rheumatism. 2003;48(6):1543-50.

19. Mikuls TR, Endo JO, Puumala SE, Aoun PA, Black NA, O'Dell JR, et al. Prospective study of survival outcomes in Non-Hodgkin's lymphoma patients with rheumatoid arthritis. J Clin Oncol. 2006;24(10):1597-602.

20. Voulgarelis M, Giannouli S, Tzioufas AG, Moutsopoulos HM. Long term remission of Sjogren's syndrome associated aggressive B cell non-Hodgkin's lymphomas following combined B cell depletion therapy and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone). Annals of the rheumatic diseases. 2006;65(8):1033-7.

21. Voulgarelis M, Giannouli S, Anagnostou D, Tzioufas AG. Combined therapy with rituximab plus cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP) for

Sjogren's syndrome-associated B-cell aggressive non-Hodgkin's lymphomas. Rheumatology (Oxford, England). 2004;43(8):1050-3.

22. Wang SS, Vajdic CM, Linet MS, Slager SL, Voutsinas J, Nieters A, et al. Associations of non-Hodgkin Lymphoma (NHL) risk with autoimmune conditions according to putative NHL loci. Am J Epidemiol. 2015;181(6):406-21.

23. Branch. NCIUSCS. Overview of the SEER Program 2016 [Available from: https://seer.cancer.gov/about/overview.html.

24. Branch. NCIUSCS. SEER-Medicare linked database 2016 [Available from: https://healthcaredelivery.cancer.gov/seermedicare/.

25. Fritz AG. International classification of diseases for oncology : ICD-O. Third edition, First revision. ed. Geneva: World Health Organization; 2013. viii, 242 pages p.

26. Adamo M, Dickie L, Ruhl J. SEER Program Coding and Staging Manual 2016: National Cancer Institute; 2016.

27. Wang M, Burau KD, Fang S, Wang H, Du XL. Ethnic variations in diagnosis, treatment, socioeconomic status, and survival in a large population-based cohort of elderly patients with non-Hodgkin lymphoma. Cancer. 2008;113(11):3231-41.

28. Griffiths R, Gleeson M, Knopf K, Danese M. Racial differences in treatment and survival in older patients with diffuse large B-cell lymphoma (DLBCL). BMC cancer. 2010;10:625.

29. Satram-Hoang S, Reyes C, Hoang KQ, Momin F, Skettino S. Treatment practice in the elderly patient with chronic lymphocytic leukemia-analysis of the combined SEER and Medicare database. Annals of hematology. 2014;93(8):1335-44.

30. Davidoff AJ, Tang M, Seal B, Edelman MJ. Chemotherapy and survival benefit in elderly patients with advanced non-small-cell lung cancer. J Clin Oncol. 2010;28(13):2191-7.

31. Davidoff AJ, Zuckerman IH, Pandya N, Hendrick F, Ke X, Hurria A, et al. A novel approach to improve health status measurement in observational claims-based studies of cancer treatment and outcomes. Journal of geriatric oncology. 2013;4(2):157-65.

32. Griffiths R, Mikhael J, Gleeson M, Danese M, Dreyling M. Addition of rituximab to chemotherapy alone as first-line therapy improves overall survival in elderly patients with mantle cell lymphoma. Blood. 2011;118(18):4808-16.

33. Griffiths RI, Gleeson ML, Mikhael J, Dreyling MH, Danese MD. Comparative effectiveness and cost of adding rituximab to first-line chemotherapy for elderly patients diagnosed with diffuse large B-cell lymphoma. Cancer. 2012;118(24):6079-88.

34. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. Journal of clinical epidemiology. 1992;45(6):613-9.

35. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of chronic diseases. 1987;40(5):373-83.

36. Kleinstern G, Maurer MJ, Liebow M, Habermann TM, Koff JL, Allmer C, et al. Autoimmune Diseases and Prognosis across Lymphoma Subtypes. American Society of Hematology annual meeting; Atlanta, GA2017.

37. Flowers CR, Shenoy PJ, Borate U, Bumpers K, Douglas-Holland T, King N, et al. Examining racial differences in diffuse large B-cell lymphoma presentation and survival. Leuk Lymphoma. 2013;54(2):268-76.

38. King JK, Costenbader KH. Characteristics of patients with systemic lupus erythematosus (SLE) and non-Hodgkin's lymphoma (NHL). Clinical Rheumatology. 2007;26(9):1491-4.

39. Shenoy PJ, Malik N, Nooka A, Sinha R, Ward KC, Brawley OW, et al. Racial differences in the presentation and outcomes of diffuse large B-cell lymphoma in the United States. Cancer. 2011;117(11):2530-40.

40. Koshiol J, Lam TK, Gridley G, Check D, Brown LM, Landgren O. Racial differences in chronic immune stimulatory conditions and risk of non-Hodgkin's lymphoma in veterans from the United States. J Clin Oncol. 2011;29(4):378-85.

41. Petri M. Epidemiology of systemic lupus erythematosus. Best practice & research Clinical rheumatology. 2002;16(5):847-58.

42. Danchenko N, Satia JA, Anthony MS. Epidemiology of systemic lupus erythematosus: a comparison of worldwide disease burden. Lupus. 2006;15(5):308-18.

43. Pons-Estel GJ, Alarcon GS, Scofield L, Reinlib L, Cooper GS. Understanding the epidemiology and progression of systemic lupus erythematosus. Seminars in arthritis and rheumatism. 2010;39(4):257-68.

44. Alizadeh AA, Eisen MB, Davis RE, Ma C, Lossos IS, Rosenwald A, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature. 2000;403(6769):503-11.

45. Fu K, Weisenburger DD, Choi WW, Perry KD, Smith LM, Shi X, et al. Addition of rituximab to standard chemotherapy improves the survival of both the germinal center B-cell-like and non-germinal center B-cell-like subtypes of diffuse large B-cell lymphoma. J Clin Oncol. 2008;26(28):4587-94.

46. Rosenwald A, Wright G, Chan WC, Connors JM, Campo E, Fisher RI, et al. The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. N Engl J Med. 2002;346(25):1937-47.

47. Baecklund E, Backlin C, Iliadou A, Granath F, Ekbom A, Amini RM, et al. Characteristics of diffuse large B cell lymphomas in rheumatoid arthritis. Arthritis and rheumatism. 2006;54(12):3774-81.

48. Rothman N, Skibola CF, Wang SS, Morgan G, Lan Q, Smith MT, et al. Genetic variation in TNF and IL10 and risk of non-Hodgkin lymphoma: a report from the InterLymph Consortium. The Lancet Oncology. 2006;7(1):27-38.

49. Cao HY, Zou P, Zhou H. Genetic association of interleukin-10 promoter polymorphisms and susceptibility to diffuse large B-cell lymphoma: a meta-analysis. Gene. 2013;519(2):288-94.

50. Grimaldi CM, Hicks R, Diamond B. B cell selection and susceptibility to autoimmunity. J Immunol. 2005;174(4):1775-81.

51. Davis RE, Ngo VN, Lenz G, Tolar P, Young RM, Romesser PB, et al. Chronic active B-cell-receptor signalling in diffuse large B-cell lymphoma. Nature. 2010;463(7277):88-92.

52. Glass S, Phan A, Williams JN, Flowers CR, Koff JL. Integrating understanding of epidemiology and genomics in B-cell non-Hodgkin lymphoma as a pathway to novel management strategies. Discov Med. 2016;21(115):181-8.

53. Wang SS, Vajdic CM, Linet MS, Slager SL, Voutsinas J, Nieters A, et al. Associations of Non-Hodgkin Lymphoma (NHL) Risk With Autoimmune Conditions According to Putative NHL Loci. American Journal of Epidemiology. 2015.

54. Lee YH, Bae SC, Choi SJ, Ji JD, Song GG. Associations between the functional CD40 rs4810485 G/T polymorphism and susceptibility to rheumatoid arthritis and systemic lupus erythematosus: a meta-analysis. Lupus. 2015;24(11):1177-83.

55. Bernatsky S, Velasquez Garcia HA, Spinelli JJ, Gaffney P, Smedby KE, Ramsey-Goldman R, et al. Lupus-related single nucleotide polymorphisms and risk of diffuse large B-cell lymphoma. Lupus Sci Med. 2017;4(1):e000187.

56. Homig-Holzel C, Hojer C, Rastelli J, Casola S, Strobl LJ, Muller W, et al. Constitutive CD40 signaling in B cells selectively activates the noncanonical NF-kappaB pathway and promotes lymphomagenesis. The Journal of experimental medicine. 2008;205(6):1317-29.

57. Guo/Koff XK, J. L.* co-first authors, Moffitt AB, Cinar M, Ramachandiran S, Chen Z, Switchenko JM, et al. Molecular impact of selective NFKB1 and NFKB2 signaling on DLBCL phenotype. Oncogene. 2017;36(29):4224-32.

58. Kaminski DA, Wei C, Qian Y, Rosenberg AF, Sanz I. Advances in human B cell phenotypic profiling. Frontiers in immunology. 2012;3:302.

59. Tipton CM, Fucile CF, Darce J, Chida A, Ichikawa T, Gregoretti I, et al. Diversity, cellular origin and autoreactivity of antibody-secreting cell expansions in acute Systemic Lupus Erythematosus. Nature immunology. 2015;16(7):755-65.

60. Richardson C, Chida AS, Adlowitz D, Silver L, Fox E, Jenks SA, et al. Molecular Basis of 9G4 B Cell Autoreactivity in Human Systemic Lupus Erythematosus. The Journal of Immunology Author Choice. 2013;191(10):4926-39.

TABLES AND FIGURES

Table 1. Demographic and disease characteristics of diffuse large B cell lymphoma patients with and without autoimmune disease in the Surveillance, Epidemiology, and End Results (SEER)-Medicare database, 2002-2009.

	All patients N (%)	B cell AI disease N (%)
Total Patients	5924	270
Median age (IQR)	75 (71-80)	75 (71-79)
Sex		
Male	2811 (47)	79 (29)
Female	3113 (53)	191 (71)
Race		
Caucasian	5341 (90)	243 (90)
African American	185 (3)	-
Others	398 (7)	-
Stage		
I/II	3224 (54)	147 (54)
III/IV	2290 (39)	107 (40)
Unknown	410 (7)	16 (6)
Nodality		
Nodal	3820 (64)	168 (62)
Extranodal	2104 (36)	102 (38)
Poor Performance Status		
Absent	4835 (82)	211 (78)
Present	1089 (18)	59 (22)
NCI Comorbidity Index		
0	3738 (63)	48 (18)
1	1422 (24)	119 (44)
>2	764 (13)	103 (38)
Frontline management		
CHOP	1025 (17)	47 (17)
R-CHOP	3346 (57)	157 (58)
CVP	122 (2)	-
R-CVP	345 (6)	-
No recorded chemotherapy	1086 (18)	42 (16)
Median OS for R-CHOP and CHOP patients (95% CI)	8.0 (7.7-8.4)	7.1 (5.0-8.7)

"-" denotes numbers for which $n < 11$ limits direct reporting per the SEER-Medicare data use agreement. Abbreviations: autoimmune (AI); interquartile range (IQR); National Cancer Institute (NCI); cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP); cyclophosphamide, vincristine, prednisone (CVP); rituximab (R-); overall survival (OS); confidence interval (CI).

Table 2. Cox regression analysis of overall survival by stage and autoimmune disease status in diffuse large B cell lymphoma patients treated with CHOP or R-CHOP, in the Surveillance, Epidemiology, and End Results (SEER)-Medicare database, 2002-2009.

	All stages HR (95% CI)	Stage I/II HR (95% CI)	Stage III/IV HR (95% CI)
None	Ref	Ref	Ref
RA (n=155)	0.86 (0.69, 1.08)	0.82 (0.60, 1.12)	0.83 (0.58, 1.19)
SLE (n=25)	1.17 (0.70, 1.95)	0.97 (0.40, 2.37)	1.22 (0.60, 2.48)
SS (n=18)	1.23 (0.68, 2.23)	1.07 (0.44, 2.63)	1.59 (0.65, 3.87)
Other B cell AI disease (n=72)	1.22 (0.90, 1.64)	1.21 (0.82, 1.79)	1.25 (0.77, 2.04)

Model adjusted for the following covariates: sex, race, marital status, % in census tract living in poverty, % with only a high school education, type of geographical area, stage, primary site of disease, B symptoms, NCI comorbidity index score, performance status, year of diagnosis. Abbreviations: hazard ratio (HR); confidence interval (CI); reference (Ref); rheumatoid arthritis (RA); systemic lupus erythematosus (SLE); Sjögren's syndrome (SS); autoimmune (AI); cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP); rituximab (R-).

Table 3. Cox proportional hazards model of overall survival (OS) and lymphoma-related survival (LRS) by autoimmune disease status in diffuse large B cell lymphoma patients treated with CHOP or R-CHOP, in the Surveillance, Epidemiology, and End Results (SEER)-Medicare database, 2002-2009.

	OS		LRS	
AI disease	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
None	Ref	-	Ref	-
RA	1.07 (0.825 – 1.38)	0.6173	1.52 (1.03 – 2.22)	*0.0335*
SLE	0.886 (0.470 – 1.67)	0.7075	1.75 (0.710 – 4.30)	0.2245
SS	1.51 (0.780 – 2.93)	0.2205	0 (0 – undefined)	0.9358

Model adjusted for the following covariates: sex, race, marital status, percent in census tract living in poverty, percent with only a high school education, type of geographical area, stage, primary site of disease, B symptoms, NCI comorbidity index score, performance status, year of diagnosis. Abbreviations: hazard ratio (HR); confidence interval (CI); reference (Ref); rheumatoid arthritis (RA); systemic lupus erythematosus (SLE); Sjögren's syndrome (SS); autoimmune (AI); cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP); rituximab (R-).

Table 4. Multivariable analysis with logistic regression of 1-year overall survival in diffuse large B cell lymphoma patients in the Surveillance, Epidemiology, and End Results (SEER)-Medicare database, 2002-2009.

Parameter	OR (95% CI)	p-value
Autoimmune disease		
None	Ref	-
SLE	0.745 (0.246 – 2.26)	0.602
RA	1.24 (0.732 – 2.09)	0.429
SS	1.03 (0.223 – 4.79)	0.967
Other B cell AI disease	0.596 (0.334 – 1.07)	0.0807
Other AI disease	1.06 (0.661 – 1.71)	0.801
B symptoms		
No	Ref	-
Yes	0.665 (0.503 – 0.879)	0.0041
Stage		
I/II	Ref	-
III/IV	0.635 (0.533 – 0.756)	<0.0001
NCI Comorbidity Index		
0	Ref	-
1	0.799 (0.657 – 0.971)	0.0238
>1	0.691 (0.544 – 0.876)	0.0023
Performance status		
Not poor	Ref	-
Poor	0.493 (0.410 – 0.592)	<0.0001

All patients received one of the following treatment regimens: cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP); cyclophosphamide, vincristine, and prednisone (CVP); rituximab-CHOP; or rituximab-CVP. Adjusted for the following covariates: sex, race, marital status, percent in census tract living in poverty, percent in census tract with only a high school education, type of geographical area, stage, primary site of disease, presence of B symptoms, NCI comorbidity index score, performance status, treatment received, and year of diagnosis. Variables with statistically significant odds ratios are shown

along with variable of interest (autoimmune disease). Abbreviations: odds ratio (OR); confidence interval (CI); reference (Ref); autoimmune (AI); systemic lupus erythematosus (SLE); rheumatoid arthritis (RA); Sjögren's syndrome (SS); National Cancer Institute (NCI).

Table 5. Multivariable analysis with logistic regression of 1-year lymphoma-related survival in diffuse large B cell lymphoma patients in the Surveillance, Epidemiology, and End Results (SEER)-Medicare database, 2002-2009.

Parameter	OR (95% CI)	p-value
Autoimmune disease		
None	Ref	-
SLE	0.541 (0.146 – 2.01)	0.358
RA	1.15 (0.620 – 2.12)	0.663
SS	1.59 (0.199 – 12.6)	0.664
Other B cell AI disease	0.730 (0.362 – 1.47)	0.380
Other AI disease	1.28 (0.698 – 2.35)	0.425
Race		
Caucasian	Ref	-
African-American	0.627 (0.398 – 0.988)	0.0443
Other	1.02 (0.667 – 1.55)	0.935
B symptoms		
No	Ref	-
Yes	0.619 (0.432 – 0.885)	0.0086
Stage		
I/II	Ref	-
III/IV	0.649 (0.527 – 0.800)	<0.0001
NCI Comorbidity Index		
0	Ref	-
1	0.803 (0.635 – 1.02)	0.0664
>1	0.735 (0.548 – 0.987)	0.0406
Performance status		
Not poor	Ref	-
Poor	0.494 (0.396 – 0.617)	<0.0001

All patients received one of the following treatment regimens: cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP); cyclophosphamide, vincristine, and prednisone (CVP); rituximab-CHOP; or rituximab-CVP. Adjusted for the following covariates: sex, race, marital status, percent in census tract living in poverty, percent in census tract with only a high school education, type of geographical area, stage, primary site of disease, presence of B symptoms, NCI comorbidity index score, performance status, treatment received, and year of diagnosis. Variables with statistically significant odds ratios are shown along with variable of interest (autoimmune disease). Abbreviations: odds ratio (OR); confidence interval (CI); reference (Ref); autoimmune (AI); systemic lupus erythematosus (SLE); rheumatoid arthritis (RA); Sjögren's syndrome (SS); National Cancer Institute (NCI).

Table 6. Multivariable analysis with logistic regression of 2-year overall survival in diffuse large B cell lymphoma patients in the Surveillance, Epidemiology, and End Results (SEER)-Medicare database, 2002-2009.

Parameter	OR (95% CI)	p-value
Autoimmune disease		
None	Ref	-
SLE	0.800 (0.317 – 2.02)	0.638
RA	1.32 (0.870 – 2.00)	0.192
SS	2.23 (0.481 – 10.3)	0.306
Other B cell AI disease	0.632 (0.385 – 1.04)	0.0704
Other AI disease	1.21 (0.823 – 1.79)	0.328
Sex		
Male	Ref	-
Female	1.28 (1.11 – 1.47)	0.0004
Marital status		
Single/Divorced	Ref	-
Married	1.29 (1.05 – 1.57)	0.0141
Widowed	0.925 (0.745 – 1.15)	0.484
B symptoms		
No	Ref	-
Yes	0.716 (0.571 – 0.899)	0.0041
Stage		
I/II	Ref	-
III/IV	0.636 (0.555 – 0.730)	<0.0001
NCI Comorbidity Index		
0	Ref	-
1	0.799 (0.685 – 0.931)	0.0042
>1	0.689 (0.568 – 0.836)	0.0002
Performance status		
Not poor	Ref	-

Poor	0.522 (0.448 – 0.608)	<0.0001

All patients received one of the following treatment regimens: cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP); cyclophosphamide, vincristine, and prednisone (CVP); rituximab-CHOP; or rituximab-CVP. Adjusted for the following covariates: sex, race, marital status, percent in census tract living in poverty, percent in census tract with only a high school education, type of geographical area, stage, primary site of disease, presence of B symptoms, NCI comorbidity index score, performance status, treatment received, and year of diagnosis. Variables with statistically significant odds ratios are shown along with variable of interest (autoimmune disease). Abbreviations: odds ratio (OR); confidence interval (CI); reference (Ref); autoimmune (AI); systemic lupus erythematosus (SLE); rheumatoid arthritis (RA); Sjögren's syndrome (SS); National Cancer Institute (NCI).

Table 7. Multivariable analysis with logistic regression of 2-year lymphoma-related survival in diffuse large B cell lymphoma patients in the Surveillance, Epidemiology, and End Results (SEER)-Medicare database, 2002-2009.

Parameter	OR (95% CI)	p-value
Autoimmune disease		
None	Ref	-
SLE	0.418 (0.142 – 1.24)	0.115
RA	1.14 (0.696 – 1.85)	0.611
SS	3.11 (0.394 – 24.6)	0.282
Other B cell AI disease	0.697 (0.395 – 1.23)	0.212
Other AI disease	1.19 (1.01– 1.40)	0.516
Sex		
Male	Ref	-
Female	1.19 (1.01 – 1.40)	0.040
Marital status		
Single/Divorced	Ref	-
Married	1.29 (1.02 – 1.64)	0.0331
Widowed	1.02 (0.791 – 1.32)	0.875
B symptoms		
No	Ref	-
Yes	0.684 (0.515 – 0.910)	0.0091
Stage		
I/II	Ref	-
III/IV	0.634 (0.539 – 0.745)	<0.0001
Performance status		
Not poor	Ref	-
Poor	0.533 (0.444 – 0.639)	<0.0001

All patients received one of the following treatment regimens: cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP); cyclophosphamide, vincristine, and prednisone (CVP); rituximab-CHOP; or rituximab-CVP. Adjusted for the following covariates: sex, race, marital status, percent in census tract

living in poverty, percent in census tract with only a high school education, type of geographical area, stage, primary site of disease, presence of B symptoms, NCI comorbidity index score, performance status, treatment received, and year of diagnosis. Variables with statistically significant odds ratios are shown along with variable of interest (autoimmune disease). Abbreviations: odds ratio (OR); confidence interval (CI); reference (Ref); autoimmune (AI); systemic lupus erythematosus (SLE); rheumatoid arthritis (RA); Sjögren's syndrome (SS); National Cancer Institute (NCI).

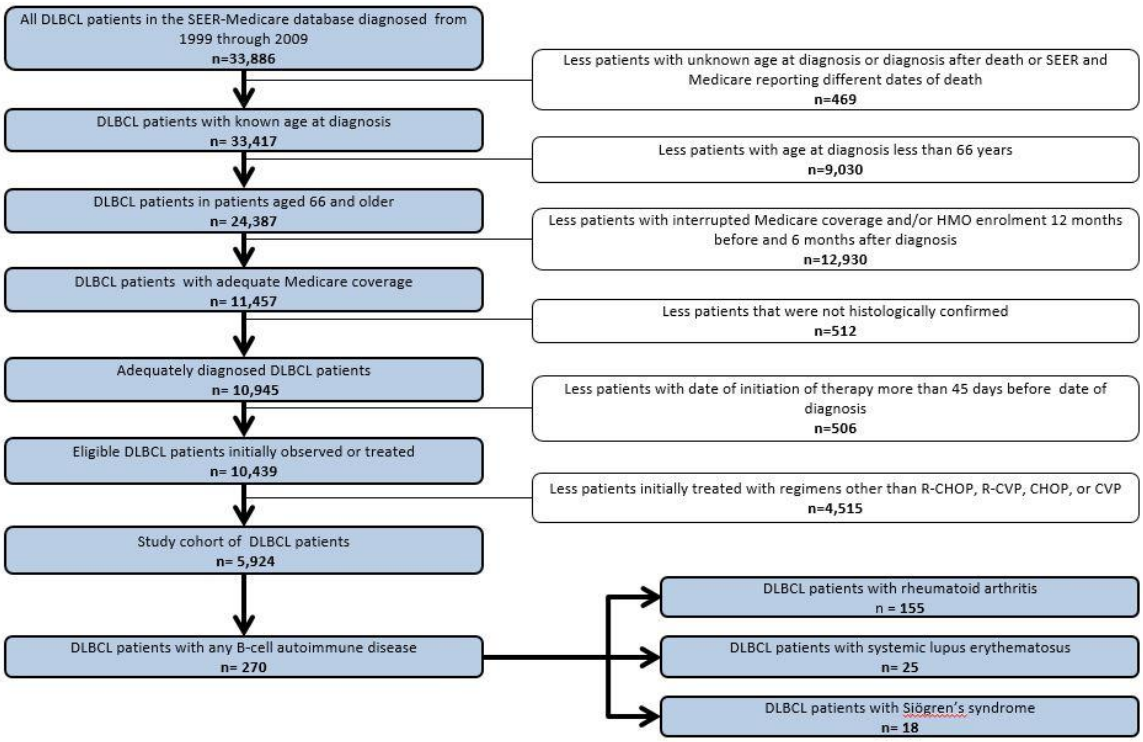

Figure 1. Selection of the study cohort. Abbreviations: diffuse large B cell lymphoma (DLBCL); Surveillance, Epidemiology, and End Results (SEER); cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP); cyclophosphamide, vincristine, prednisone (CVP); rituximab (R-); health maintenance organization (HMO).

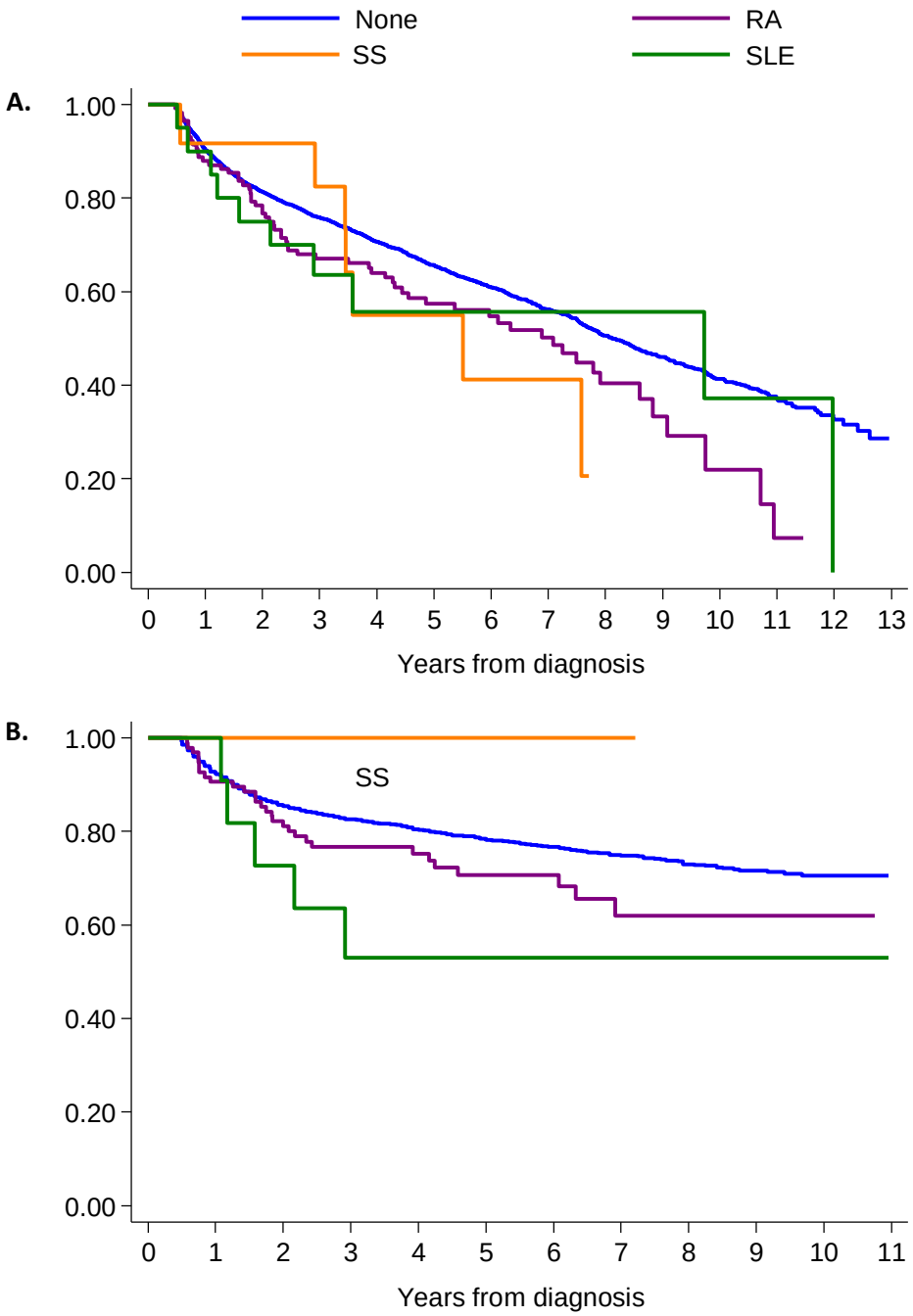

Figure 2. Survival by autoimmune status of diffuse large B cell (DLBCL) patients treated with CHOP or R-CHOP in the Surveillance, Epidemiology, and End Results (SEER)-Medicare database, 2002-2009. **A.** Kaplan-Meier curve of overall survival (OS) in DLBCL patients treated with CHOP or R-CHOP, by autoimmune status. **B.** Kaplan-Meier curve of lymphoma-related survival (LRS) in DLBCL patients treated with CHOP

or R-CHOP, by autoimmune status. Abbreviations: rheumatoid arthritis (RA); systemic lupus erythematosus (SLE); Sjögren's syndrome (SS); cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP); rituximab (R-).

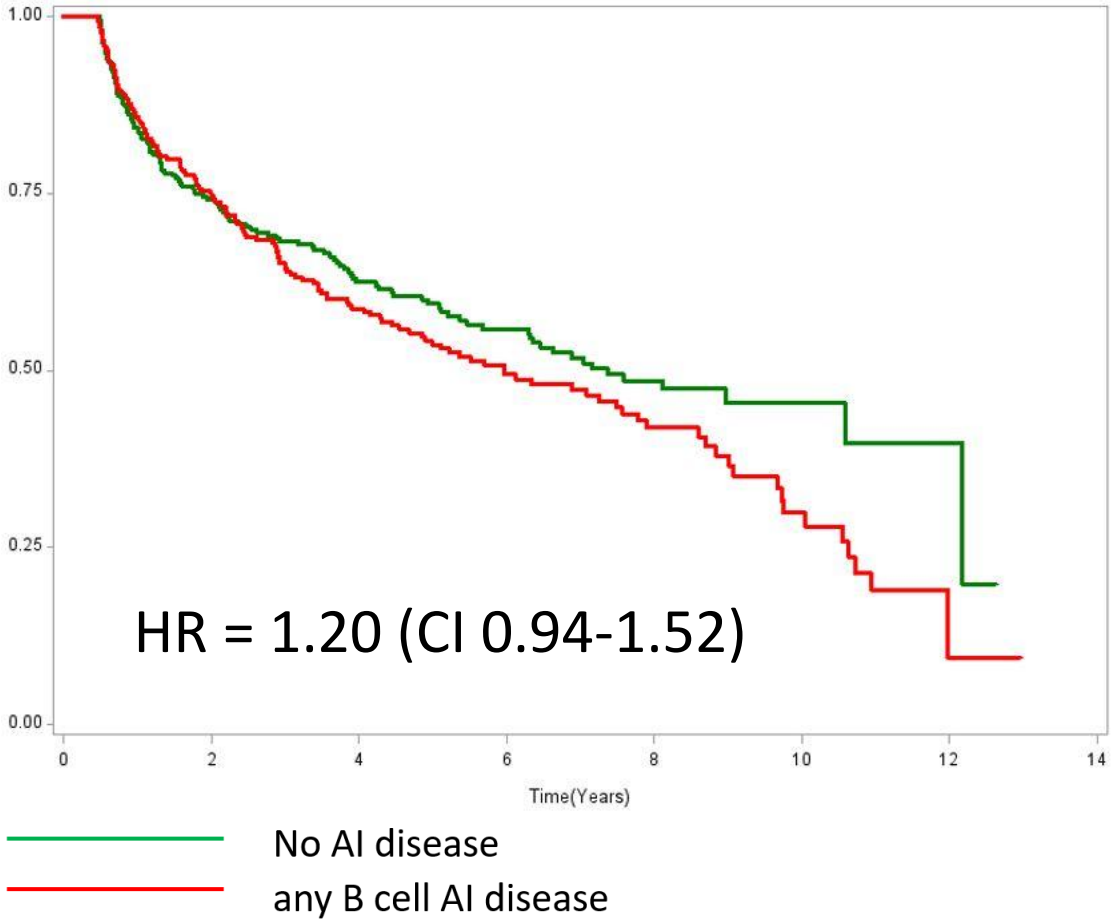

Figure 3. Overall survival by autoimmune status of performance status-matched DLBCL patients treated with CHOP or R-CHOP. Abbreviations: autoimmune (AI); confidence interval (CI); hazard ratio (HR).