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Emerging trends and disparities in mortality due to coexisting non-Hodgkin's lymphoma and respiratory infections

A U.S. nationwide retrospective analysis from 1999 to 2020

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Abstract

Non-Hodgkin lymphoma (NHL) patients are highly susceptible to respiratory infections due to immunosuppression from both the disease and its treatments. Understanding mortality trends and disparities in this population is crucial for improving care and reducing the burden of coexisting conditions. This study analyzed death certificates from the Center of Disease Control Wide-Ranging Online Data for Epidemiologic Research database for individuals aged ≥ 25 years who died between 1999 and 2020 with both NHL and respiratory infections. Age-adjusted mortality rates (AAMRs) and annual percent change were computed by year, gender, age group, race/ethnicity, geographic region, and urbanization status. From 1999 to 2020, 66,986 deaths were related to coexisting NHL and respiratory infections. AAMR decreased from 17.1 to 14.6 per 1,000,000 individuals. A significant decline in AAMR occurred between 1999 and 2018, followed by a significant rise from 2018 to 2020. Men had nearly double the AAMR compared to women. Older adults had the highest AAMRs, followed by middle-aged adults and young adults. Among racial and ethnic groups, non-Hispanic (NH) White individuals had the highest AAMR, followed by NH American Indian or Alaska Natives, Hispanic or Latino, NH Asian or Pacific Islanders, and NH Black or African American populations. Non-metropolitan areas had a higher AAMR than metropolitan areas. The overall AAMR decreased from 1999 to 2020, but a significant rise was observed in recent years. Mortality disparities were notable among men, older adults, NH White individuals, and residents of non-metropolitan areas, underscoring the need for targeted interventions to address these disparities.

Abbreviations: AAMR = age-adjusted mortality rates, CDC WONDER = Center of Disease Control Wide-Ranging Online Data for Epidemiologic Research, ISM = infection-specific mortality, NH = non-Hispanic, NHL = non-Hodgkin lymphoma.

Keywords: disparities, gender trends, mortality, non-Hodgkin lymphoma, racial trends, respiratory infections

1. Introduction

Non-Hodgkin lymphoma (NHL) is the most common lymphoma in adults, with approximately 70,000 new cases diagnosed annually in the USA.[1] It represents a heterogeneous group of hematologic cancers that arise from lymphocytes, with the majority originating from B cells, and a smaller fraction involving T cells or natural killer cells.[2]

While NHL itself is a major cause of morbidity and mortality, patients with NHL are also at heightened risk for respiratory tract infections, which significantly impact survival outcomes. Respiratory infections, caused by bacterial, fungal, and viral pathogens, are common among patients with hematologic malignancies, including NHL. These infections predominantly affect hospitalized patients with acute leukemia or those undergoing allogeneic stem cell transplantation, who often face prolonged neutropenia from aggressive chemotherapy, leading to hospital-acquired respiratory tract infections.[3] Additionally, patients with lymphoproliferative disorders, such as NHL, often experience immune impairments due to humoral

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The datasets generated during and/or analyzed during the current study are publicly available.

Ethical approval was not required for this study design, as all data were obtained from publicly available sources.

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immunodeficiency, either at diagnosis or following treatment, which further increases their susceptibility to viral, fungal, and bacterial infections.[4]

The immunosuppressive nature of NHL, compounded by the effects of chemotherapy and biological therapies, predisposes patients to opportunistic infections, particularly of the respiratory tract. Studies have shown that respiratory infections, especially pneumonia, are common causes of death in NHL patients, alongside the cancer itself, secondary malignancies, and cardiovascular disease.[5] Recent retrospective cohort studies indicate that pulmonary infections are the primary cause of death in 7.7% of patients with NHL.[6] This risk is exacerbated by immune system alterations and prolonged antigenic stimulation, mechanisms integral to NHL pathogenesis, which leave patients vulnerable to infections.[7]

NHL survivors, particularly those treated for childhood NHL, face elevated risks of death from pulmonary infections due to compromised cell-mediated immunity and the use of immunosuppressive treatments. Pulmonary complications, including infections caused by opportunistic pathogens, have been reported in up to 40% of elderly NHL patients receiving standard chemotherapy, such as the R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen, with severe respiratory complications occurring in approximately 10% of cases.[8] Despite the availability of advanced treatment options for NHL (ranging from rituximab-based therapies to CAR T-cell treatments and stem cell transplants) the management of respiratory infections remains a critical challenge in this patient population.[9]

The interactions between NHL and respiratory infections, particularly in terms of mortality, remain underexplored, emphasizing the need for a deeper understanding of the trends and disparities in mortality due to coexisting NHL and respiratory infections. The objective of this study is to evaluate the trends in mortality associated with coexisting NHL and respiratory infections among adults in the United States from 1999 to 2020, with a focus on identifying gender, ethnoracial, and regional disparities.

2. Methods

2.1. Study setting and population

We extracted mortality data from the Center of Disease Control Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER) database[10] and examined mortality rates among adults diagnosed with both NHL and respiratory infections from 1999 to 2020. Specifically, the Multiple Cause-of-Death Public Use Record database was used to identify cases where NHL and respiratory infections were listed as contributing causes on U.S. death certificates.[11] This methodology has been employed in several prior studies using CDC WONDER data.[12,13] Cases of NHL and respiratory infections were identified using the International Classification of Diseases, 10th Revision (ICD-10) codes: C82-C85 for NHL and J09-J18, J20-J22, U04, J40-J47 for respiratory infections.[14] As this study used de-identified public-use data from government sources, it was exempt from institutional review board approval, in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[15]

2.2. Data abstraction

Our demographic variables included population size, age distribution, gender composition, racial/ethnic background, geographic location, and urbanization level, spanning the years 1999 to 2020. The locations of death encompassed medical facilities, decedents' homes, hospices/nursing homes, long-term care facilities, and unspecified locations. Racial and ethnic groups were categorized as Hispanic (Latino), non-Hispanic (NH) White, NH Black, NH American Indian/Alaskan Native, and NH Asian. These classifications are consistent with previous CDC WONDER database analyses and align with the U.S. Office of Budget and Management Guidelines as reflected on death certificates.[11]

To segment the patients by age, we used 10-year intervals, defining young adults as 25 to 44 years, middle-aged adults as 45 to 64 years, and older adults as 65 to 85+ years. These age groupings reflect criteria used in prior CDC WONDER studies.[16] Geographic stratification followed the Urban-Rural Classification Scheme from the National Center for Health Statistics, categorizing counties into urban (large metropolitan areas with populations over 1 million), medium/small metropolitan areas (populations between 50,000 and 999,999), and rural/non-metropolitan areas (populations under 50,000). We also divided the U.S. into 4 major regions (Northeast, Midwest, South, and West) according to U.S. Census Bureau classifications.[17]

2.3. Statistical analysis

We analyzed patterns related to gender, race, age, urbanization, and census regions by calculating both crude and age-adjusted mortality rates (AAMR) per 1,000,000 population, using the 2000 U.S. population as the baseline for AAMR standardization.[18] Temporal changes in mortality rates were assessed using the Joinpoint Regression Program (Version 5.0.2, National Cancer Institute),[19] applying log-linear regression models to evaluate trends over time. Joinpoint regression was employed to identify inflection points in AAMR trends for NHL and respiratory infections from 1999 to 2020, as per established guidelines. For datasets with 17 to 21 time points, the standard is to detect up to 3 inflection points. However, given the 22-year duration of our study, we configured the software to identify up to 4 joinpoints where significant shifts in trends occurred. Fewer joinpoints could be detected if fewer points sufficiently captured the trend variability. The Grid Search method (2, 2, 0), permutation test, and parametric approach were used to calculate annual percent change (APC) and 95% confidence intervals (CIs). An APC was considered to be increasing or decreasing if the slope of the mortality trend significantly differed from 0, as determined by two-tailed t tests. Statistical significance was set at $P \leq .05$.

3. Results

Between 1999 and 2020, there were 66,986 deaths related to coexisting NHL and respiratory infections (Table S1, Supplemental Digital Content, https://links.lww.com/MD/P475). The place of death was recorded for 65,205 cases: 63% occurred in medical facilities, 17.7% in decedents' homes, 12.5% in nursing homes or long-term care facilities, and 4.2% in hospices (Table S2, Supplemental Digital Content, https://links.lww.com/MD/P475).

3.1. Demographic trends in mortality

The overall AAMR related to coexisting NHL and respiratory infections was 17.1 in 1999 and slightly decreased to 14.6 in 2020 per 1000,000 individuals. A significant decline occurred from 1999 to 2018 (APC: -1.83; 95% CI: -2.13 to -1.57; $P < .001$), followed by a significant increase from 2018 to 2020 (APC: 9.32; 95% CI: 4.04 to 12.09; $P = .002$) (Fig. 1, Tables S3 and S4, Supplemental Digital Content, https://links.lww.com/MD/P475).

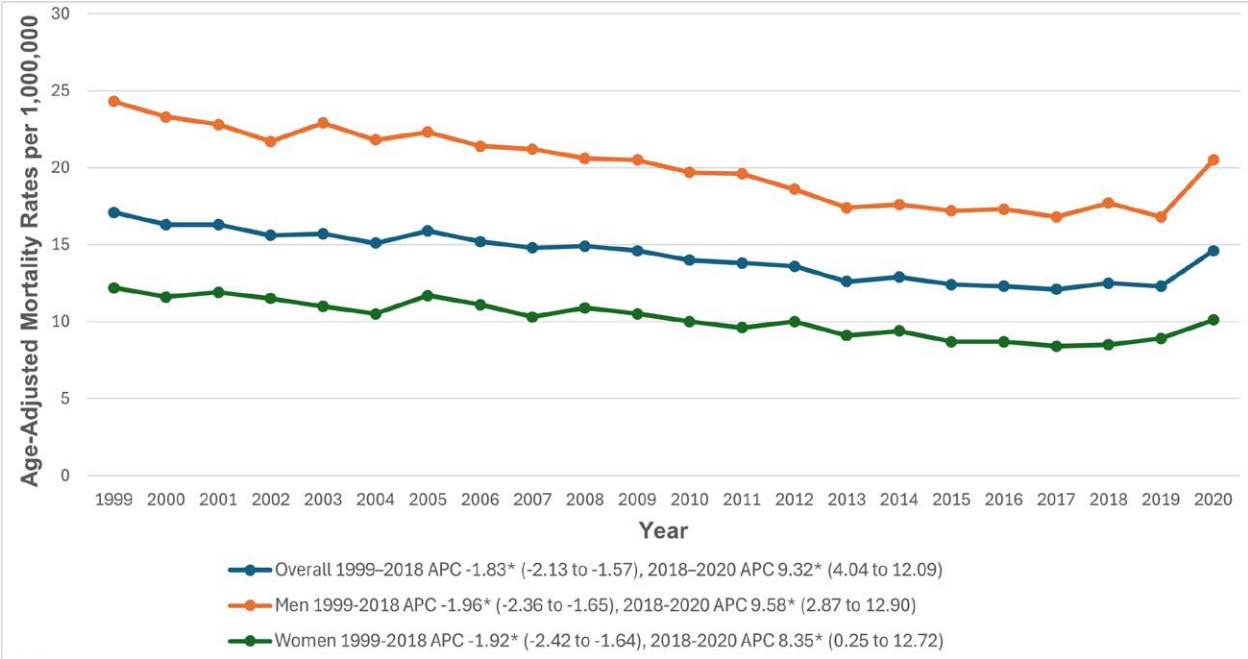

Figure 1. Overall and gender-stratified non-Hodgkin lymphoma and respiratory infections-related age-adjusted mortality rates per 1,000,000 in adults in the United States, 1999 to 2020. * The annual percentage change (APC) is significantly different from 0 at $\alpha = 0.05$. AAMR = age-adjusted mortality rate.

3.2. Gender stratification

During the study period, men consistently had an average AAMR nearly twice as high as women (19.8 vs 10.1). Both men and women experienced significant AAMR declines from 1999 to 2018 (men APC -1.96; 95% CI: -2.36 to -1.65; $P < .001$; women APC -1.92; 95% CI: -2.42 to -1.64; $P = .006$). This was followed by a significant increase from 2018 to 2020 (men APC 9.58; 95% CI: 2.87 to 12.90; $P = .005$; women APC 8.35; 95% CI: 0.25 to 12.72; $P = .046$) (Fig. 1, Tables S3 and S4, Supplemental Digital Content, https://links.lww.com/MD/P475).

3.3. Stratification by age groups

Older adults had the highest AAMRs (59.5), followed by middle-aged adults (6.2) and young adults (0.8). Among young adults, AAMR declined significantly from 1999 to 2003 (APC: -11.94; 95% CI: -24.12 to -4.57; $P < .001$), then remained stable until 2020. In middle-aged adults, AAMR decreased significantly from 1999 to 2017 (APC: -2.23; 95% CI: -2.97 to -1.74; $P = .001$), followed by a significant upward trend until 2020 (APC: 7.13; 95% CI: 0.91 to 15.96; $P = .022$). Older adults experienced a significant decline from 1999 to 2018 (APC: -1.73; 95% CI: -2.28 to -1.40; $P = .007$), followed by a significant increase until 2020 (APC: 7.98; 95% CI: 0.17 to 11.51; $P = .045$) (Fig. 2, Tables S3 and S5, Supplemental Digital Content, https://links.lww.com/MD/P475).

3.4. Racial stratification

AAMRs were highest among NH White individuals (15.3), followed by NH American Indian or Alaska Natives (10.7), Hispanic or Latino (9.9), NH Asian or Pacific Islanders (8.8), and NH Black or African Americans (8.5). Trend analysis for NH American Indian or Alaska Native individuals was not possible due to the low number of deaths. In NH Black individuals, AAMR remained stable throughout the study (APC: -1.06; 95% CI: -1.98 to 0.00; $P = .051$). NH White individuals experienced a significant decrease from 1999 to 2018 (APC: -1.61; 95% CI: -2.05 to -1.35; $P = .004$), followed by a significant rise from 2018 to 2020 (APC: 8.44; 95% CI: 0.97 to 11.89; $P = .031$). In NH Asian or Pacific Islanders, AAMR remained stable from 1999 to 2018 (APC: -2.53; 95% CI: -11.43 to 22.06; $P = .108$), followed by a non-significant rise through 2020 (APC: 11.78; 95% CI: -2.91 to 22.69; $P = .307$). Among the Hispanic population, AAMR declined significantly from 1999 to 2018 (APC: -2.54; 95% CI: -4.76 to -1.41; $P = .016$), followed by a steep increase from 2018 to 2020 (APC: 20.24; 95% CI: 0.25 to 31.39; $P = .044$) (Fig. 3, Tables S3 and S6, Supplemental Digital Content, https://links.lww.com/MD/P475).

3.5. State-wise distribution

AAMR values varied significantly by state, ranging from 8.9 in the District of Columbia to 21.2 in Vermont. States in the top 90th percentile (Oklahoma, West Virginia, Kentucky, South Dakota, Nebraska, Rhode Island, Vermont) had AAMRs nearly twice as high as those in the bottom 10th percentile (District of Columbia, Louisiana, Georgia, Arizona, Nevada, Virginia, Florida) (Fig. 4, Table S7, Supplemental Digital Content, https://links.lww.com/MD/P475).

3.6. Census region

AAMRs were highest in the Midwest (15.8), followed by the Western (14.8), Northeastern (13.5), and Southern regions (13.0). In the Northeastern region, AAMR decreased significantly from 1999 to 2020 (APC: -1.92; 95% CI: -2.46 to -1.58; $P = .005$), followed by a significant rise until 2020 (APC: 8.02; 95% CI: 0.12 to 12.67; $P = .044$). Significant declines were seen in the Midwestern (APC: -2.15; 95% CI: -3.28 to -1.63; $P = .008$) and Southern regions (APC: -1.55; 95% CI: -2.02 to -1.19; $P < .001$) from 1999 to 2017, followed by a non-significant increase in the Midwest (APC: 5.93; 95% CI: -0.49 to 13.89; $P = .077$), and a significant increase in Southern region (APC: 6.58; 95% CI: 2.40 to 12.90; $P = .007$). In the Western region, AAMR significantly decreased from 1999 to 2020 (APC: -1.76; 95% CI: -2.25 to -1.25; $P < .001$) (Fig. 5, Tables S3 and S8, Supplemental Digital Content, https://links.lww.com/MD/P475).

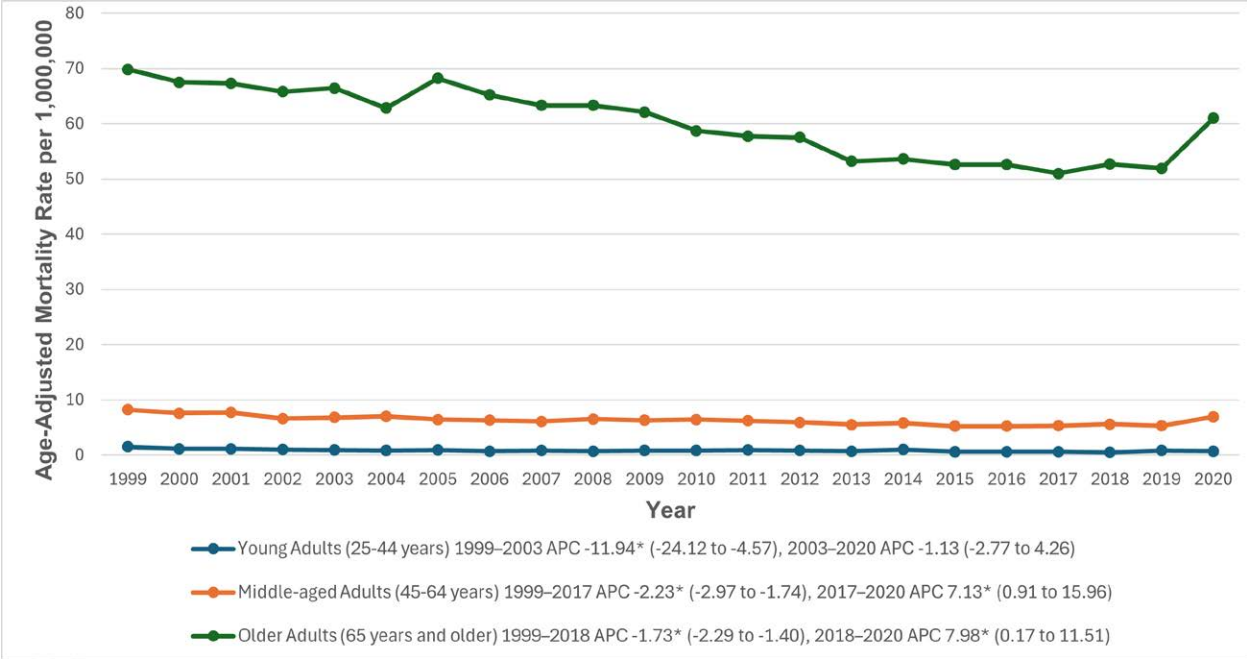

Figure 2. Non-Hodgkin lymphoma and respiratory infections-related age-adjusted mortality rates per 1,000,000, stratified by age groups in adults in the United States, 1999 to 2020. * The annual percentage change (APC) is significantly different from 0 at $\alpha = 0.05$. AAMR = age-adjusted mortality rate.

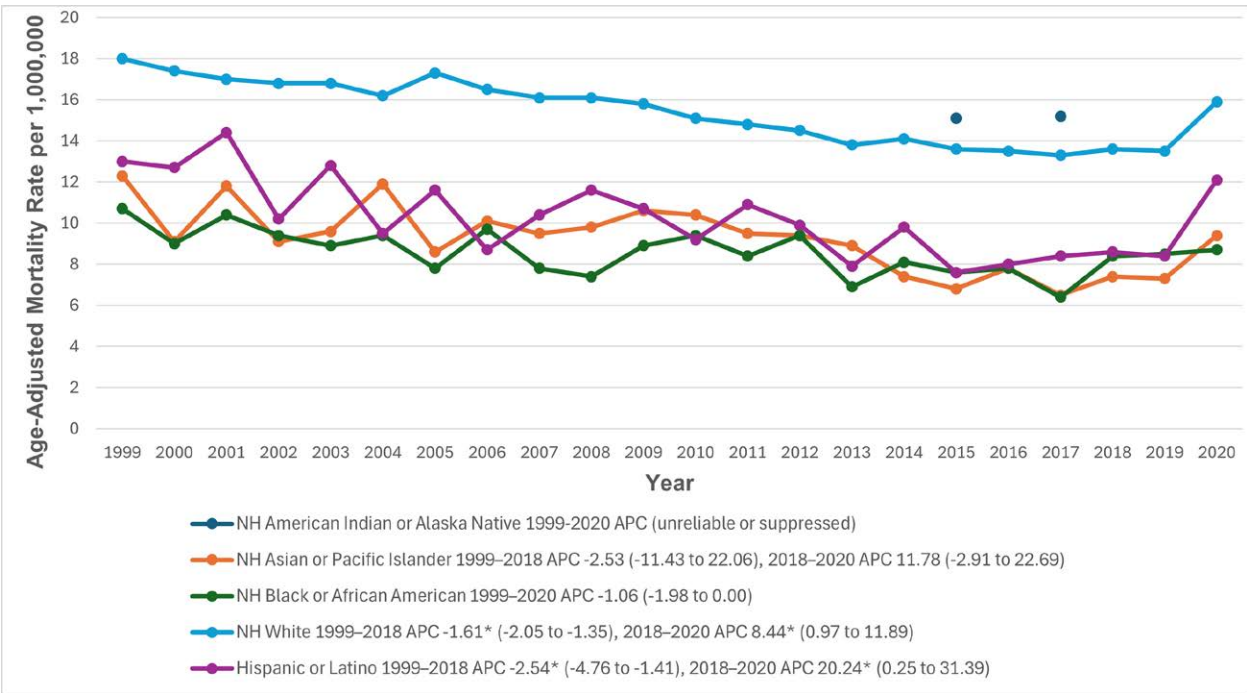

Figure 3. Non-Hodgkin lymphoma and respiratory infections-related age-adjusted mortality rates per 1,000,000, stratified by race in adults in the United States, 1999 to 2020. * The annual percentage change (APC) is significantly different from 0 at $\alpha = 0.05$. AAMR = age-adjusted mortality rate.

3.7. Urbanization

Non-metropolitan areas had a higher average AAMR than metropolitan areas (16.5 vs 13.6). Both regions saw significant AAMR declines from 1999 to 2018 (metropolitan APC: -1.93; 95% CI: -2.78 to -1.58; $P = .016$; non-metropolitan APC: -1.23; 95% CI: -1.99 to -0.85; $P = .010$). However, from 2018 to 2020, metropolitan areas showed a non-significant increase (APC: 7.68; 95% CI: -1.16 to 11.58; $P = .114$), while non-metropolitan areas experienced a significant increase (APC: 10.09; 95% CI: 0.24 to 14.52; $P = .040$) (Fig. 6, Tables S3 and S9, Supplemental Digital Content, https://links.lww.com/MD/P475).

4. Discussion

The study provides mortality trends related to coexisting NHL and respiratory infections. Overall, AAMR decreased from 17.1 in 1999 to 14.6 in 2020, with a significant decline

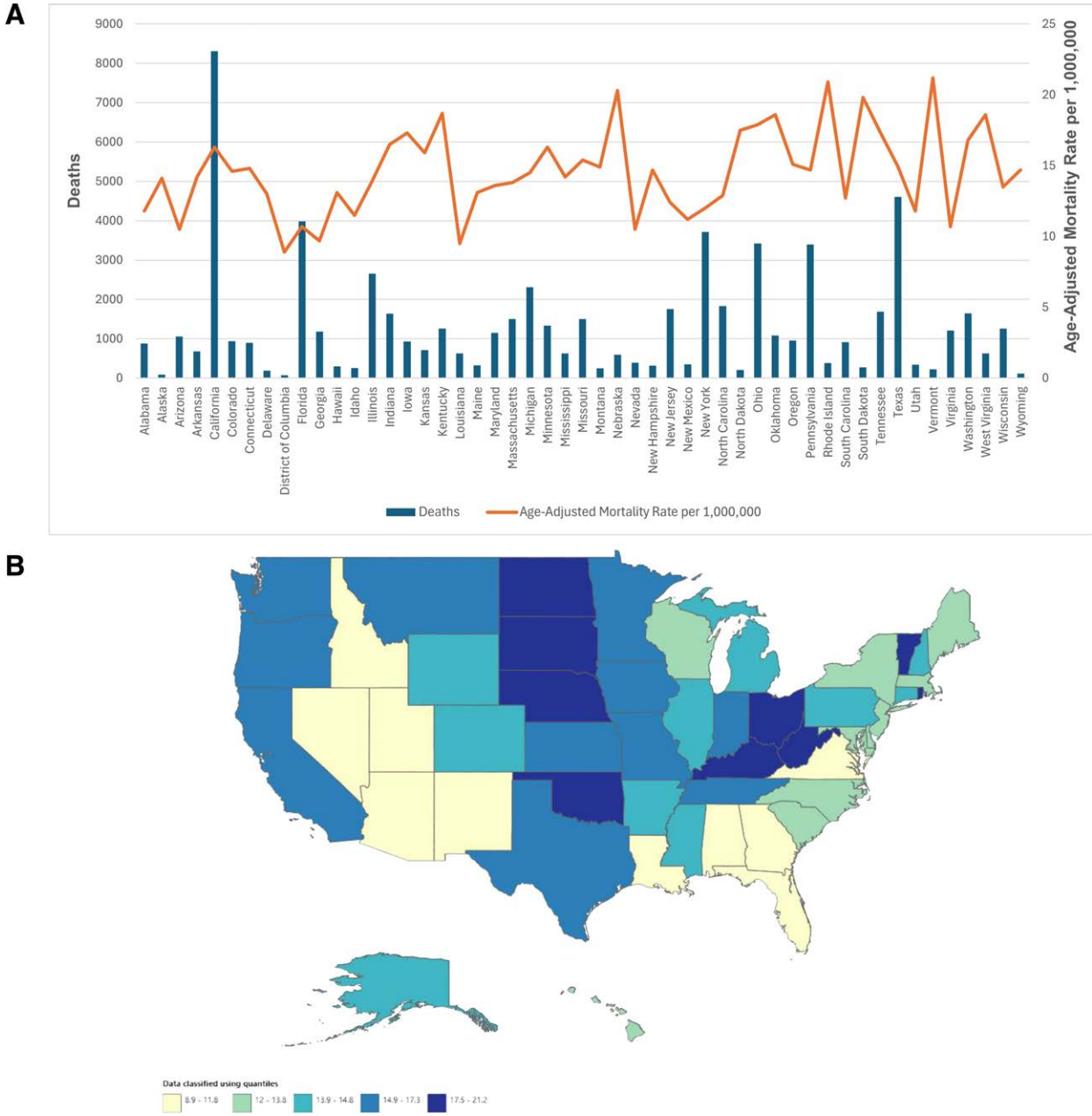

Figure 4. (A and B) Non-Hodgkin lymphoma and respiratory infections-related age-adjusted mortality rates per 1,000,000, stratified by state in adults in the United States, 1999 to 2020.

between 1999 and 2018 (APC: -1.83), followed by a sharp rise from 2018 to 2020 (APC: 9.32). Gender disparities were substantial, with men consistently having nearly double the AAMR (19.8) compared to women (10.1). Both genders saw declines until 2018, after which mortality rates rose. Older adults had the highest AAMR (59.5), followed by middle-aged (6.2) and young adults (0.8). Racial disparities showed that NH Whites had the highest AAMR (15.3), with a notable post-2018 increase in Hispanic individuals (APC: 20.24). Geographic trends revealed higher AAMR in the Midwest (15.8), particularly in states like Vermont (21.2), and in non-metropolitan areas (16.5) compared to urban regions (13.6), with both seeing a significant increase in mortality after 2018.

A recent study showed that since the introduction of rituximab in Japan and the United States, the disease burden, as measured by NHL mortality rates, has decreased across a broad range of individuals.[20] Additionally, recent advances in targeted therapies, such as pembrolizumab and venetoclax, have improved outcomes at various stages of the disease.[21] Key contributors to this decline in the overall AAMR include a heightened emphasis on vaccinations, particularly pneumococcal and influenza vaccines, widely recommended for hematologic cancer patients, especially those over 65, to prevent respiratory infections.[22] These vaccines have played a pivotal role in reducing infection-related deaths in this vulnerable group. Additionally, antibiotic stewardship and strict infection control measures have curbed the spread of drug-resistant bacteria, further lowering infection-specific mortality (ISM).[22] International guidelines and tailored prevention measures have been instrumental in this effort. The post-2018 rise in deaths might be attributed to increased pulmonary infections from COVID-19. In patients with hematologic malignancies, the immune response to SARS-CoV-2 is significantly reduced, with about one-third of those hospitalized with the virus succumbing to it.[23]

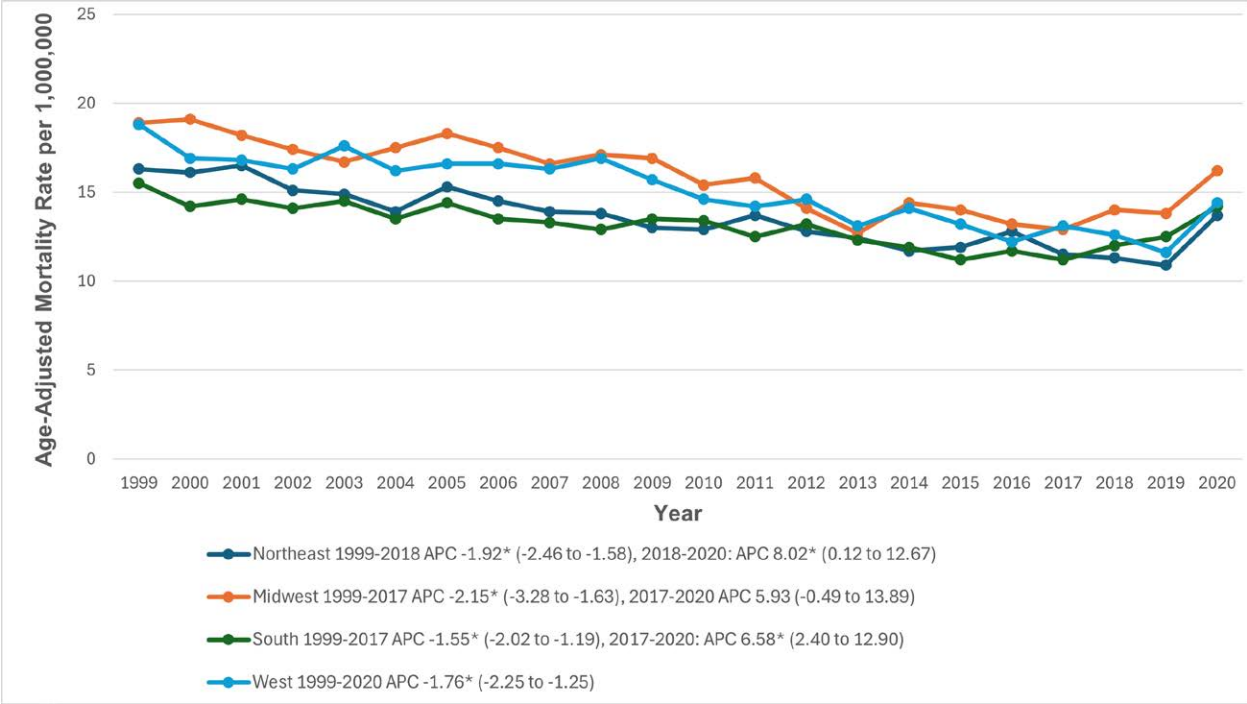

Figure 5. Non-Hodgkin lymphoma and respiratory infections-related age-adjusted mortality rates per 1,000,000, stratified by census regions in adults in the United States, 1999 to 2020. * The annual percentage change (APC) is significantly different from 0 at $\alpha = 0.05$. AAMR = age-adjusted mortality rate.

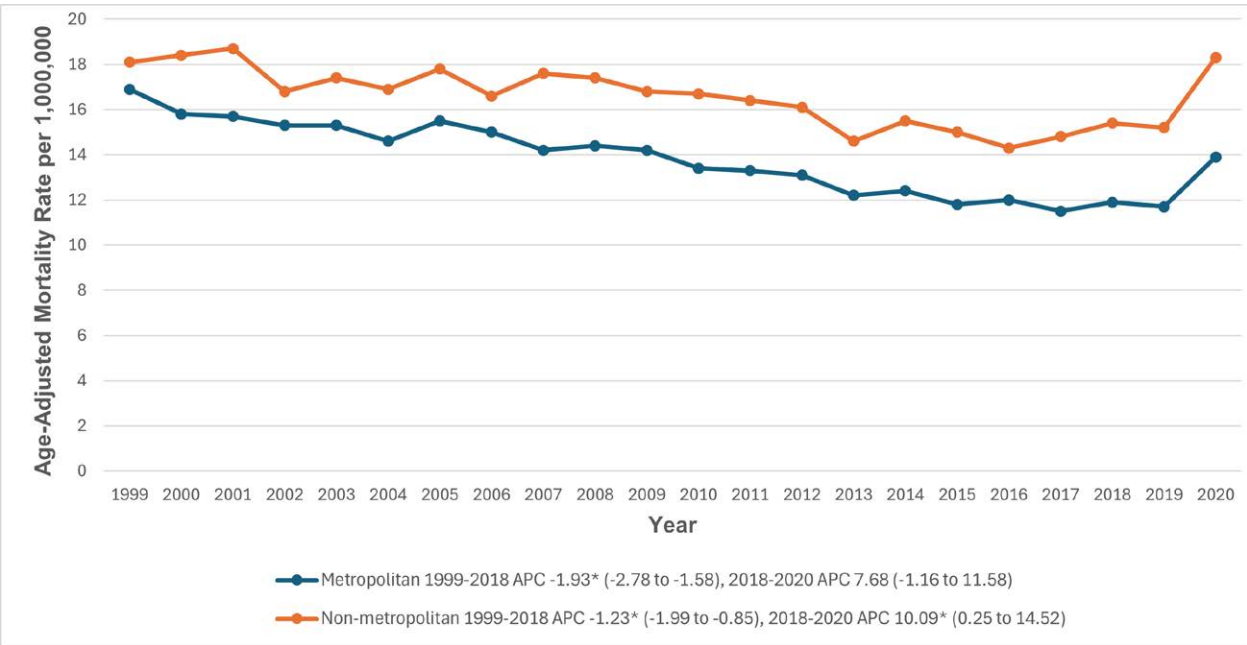

Figure 6. Non-Hodgkin lymphoma and respiratory infections-related age-adjusted mortality rates per 1,000,000 in adults in the metropolitan and non-metropolitan areas in the United States, 1999 to 2020. * The annual percentage change (APC) is significantly different from 0 at $\alpha = 0.05$. AAMR = age-adjusted mortality rate.

NHL is the sixth leading cause of cancer death, with an estimated 19,900 deaths in the US in 2020, accounting for 3.3% of all cancer deaths, according to a recent study. Moreover, half of the diagnoses were made in people older than 65 years.[24] Age plays a crucial role in ISM among patients with hematologic malignancies, particularly NHL, with ISM rates rising significantly in those over 65 years.[22] Various biological reasons, conflicting mortality risks, toxic side effects of treatment, reluctance to aggressively treat elderly patients, and end-of-life wishes may all contribute to poorer outcomes in older patients.[25] Globally, approximately half a million new NHL cases were diagnosed in 2018, with men facing a higher lifetime risk than women.[26] In a study by Yin X, males were found to have more than 3 times the ISM rate compared to females, a trend that mirrors overall mortality rates in hematologic malignancies such as NHL, multiple myeloma, and Hodgkin lymphoma. Contributing factors include

a stronger immune response in females, lifestyle differences such as higher smoking rates in men, and variations in drug metabolism and hormonal regulation. These results confirm our findings, highlighting the high AAMR in older adults and the male population. Demographic trends show that Asians/Pacific Islanders, Native Americans, and Blacks in the US have the lowest NHL risk. In contrast, Whites and NHs have the highest,[24] explaining the higher mortality rates observed in NH Whites. However, Hispanics have a higher prevalence of aggressive NHL subtypes, such as diffuse large B-cell lymphoma, Burkitt lymphoma, and NK/T-cell lymphoma, which are rapidly progressing and harder to treat.[27] These aggressive subtypes likely explain the recent increase in NHL-related deaths among Hispanics. Occupational exposure increases the risk of NHL, as many jobs involve contact with toxins and tobacco, both of which are associated with various NHL subtypes.[28] Additionally, lower mortality rates in large states and urban areas may be attributed to better access to healthcare and the financial resources needed for costly treatments, helping to explain the higher mortality observed in non-metropolitan regions.

Clinical studies have consistently shown that pulmonary complications are common in NHL patients undergoing chemotherapy, with respiratory tract infections being the leading cause of morbidity and mortality significantly in those receiving autologous bone marrow transplants.[29,30] Acute respiratory failure is particularly associated with a lower survival rate in NHL patients.[31] However, BLBC, the most prevalent NHL subtype, is linked to a notably high risk of respiratory complications. Diagnosing these infections (ranging from bacterial pneumonia to fungal infections, *pneumocystis jirovecii*, and respiratory viruses) relies on understanding the immune status, clinical presentation, and radiological findings such as pulmonary nodules or ground-glass opacities in the lung parenchyma.[29] In rapidly deteriorating cases, empirical treatment often begins before confirmation through bronchoscopy, CT-guided biopsy, or other diagnostic tools.[29] Pulmonary infections are a significant cause of morbidity and mortality among diffuse large B-cell lymphoma patients receiving chemotherapy, with around 21.8% developing pneumonia, particularly those with an underlying history of respiratory disease, high tumor burden, or direct lung involvement.[32] Key risk factors for pneumonia include a low lymphocyte-to-monocyte ratio, hypoalbuminemia, and severe myelosuppression, with granulocytopenia being a strong predictor. Bacterial lung infections are frequent in NHL patients and can progress rapidly to severe illness. Elevated cytokine levels, particularly IL-6 and IL-8, are useful markers for predicting respiratory infections, with IL-6 being more sensitive than procalcitonin or C-reactive protein in detecting bacterial infections.[30] IL-6 levels are also helpful in differentiating between pulmonary infection and bacteremia, making cytokine monitoring essential for managing respiratory infections in NHL patients.[30] The use of granulocyte colony-stimulating factor has been shown to lower infection risk by reducing granulocytopenia.[32]

The study highlights a critical need for action to address disparities in NHL-related mortality, particularly in rural areas and among vulnerable populations. Expanding the accessibility of advanced therapies to smaller cities and impoverished regions is essential to ensure equitable healthcare delivery. By reducing exposure to occupational pollutants linked to NHL,[33] enhancing the availability of treatments in underdeveloped areas, and making these treatments more affordable, we can effectively work towards reducing death rates. Moreover, targeted interventions should focus on high-risk groups, such as older adults, men, and those in non-urban areas, who have shown a concerning upward trend in mortality rates in recent years. Public health efforts to improve healthcare infrastructure in rural regions and promote environmental safety could significantly contribute to reversing this alarming trend.

4.1. Limitations

The limitations of the study include that it used death certificate data from the CDC WONDER database, which may have errors or missing details on the underlying causes of death, mainly when there were several concurrent medical problems. The study lacked clinical data that could have affected death rates, such as specifics on treatment plans, the severity of respiratory infections, or the particular forms of NHL. Throughout the study period, confounding variables, including improvements in treatment choices, modifications to healthcare access, or changes in population health behaviors, may not have been considered in the observed trends in mortality rates. The results may not apply to groups not in the United States, those with other healthcare systems, or those with different demographics. The study's grouping of racial and ethnic categories may have obscured variations in health outcomes and access to care within groups. Although the study classified regions according to their level of urbanization, it did not examine certain socioeconomic aspects that might contribute to the explanation of variations in death rates. Even if trends were examined using joinpoint regression, this approach may still overlook subtle variations in mortality trends or significant shifts at intervals the analysis could not record. Within more constrained age ranges, the selected age groups can miss significant differences in mortality patterns.

5. Conclusion

This study highlights significant trends in mortality related to coexisting NHL and respiratory infections, showing a significant decline following the introduction of rituximab and targeted therapies but a sharp rise from 2018 to 2020, largely due to respiratory infections and complications from COVID-19. Older adults, men, and NH Whites remain disproportionately affected, with notably higher mortality rates in rural and non-metropolitan areas. Geographic and demographic disparities underscore the need for targeted public health interventions to improve healthcare access, enhance vaccination and infection control measures, and address occupational hazards linked to NHL. A critical aspect of enhancing NHL outcomes involves reducing risk factors associated with pulmonary infections. Expanding the availability of advanced therapies and improving environmental safety in vulnerable regions are essential steps in reversing the recent increase in NHL-related deaths. Tailored approaches for high-risk populations, particularly those with hematologic malignancies and respiratory complications, will be crucial in mitigating future mortality rates.

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