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Trends in mortality from infection among patients with hematologic malignancies: differences according to hematologic malignancy subtype

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Abstract

Background: Infection is the most important cause of non-relapse mortality in hematologic malignancy patients, leading to increased costs and prolonged hospitalization times. However, comprehensive and comparable reports on infection-specific mortality (ISM) trends in hematologic malignancy patients are lacking.

Objectives: We aimed to provide updated ISM trends and factors associated with ISM among hematologic malignancy patients.

Design: This is a retrospective study.

Methods: Patients diagnosed with the five most common hematologic malignancies from 1983 to 2016 from the Surveillance, Epidemiology, and End Results database were included. Joinpoint regression was used to analyze mortality trends.

Results: ISM decreased beginning in 1983, 1988, and 1994, with yearly decreases of –2.1% for acute leukemia (AL), –1.3% for Hodgkin lymphoma (HL), and –14.3% for non-Hodgkin lymphoma (NHL). In contrast, ISM in patients with chronic leukemia (CL) and multiple myeloma (MM) increased dramatically beginning in 2000, with yearly increases of 2.8% and 3.3%, respectively. ISM rates were higher in males than in females across all hematologic malignancy subtypes. The mortality trends significantly differed according to race, age, sex, and stage, which could help in further etiological investigations. Moreover, male sex, older age at diagnosis, black race, and unmarried status were poor prognostic factors for ISM across all hematologic malignancy subtypes.

Conclusion: A promising downward trend in ISM in recent years occurred in patients with AL, HL, and NHL; however, ISM increased dramatically in patients with CL and MM. Our data suggest that risk assessment and careful infection monitoring are recommended for hematologic malignancy patients, particularly those with CL and MM.

Keywords: hematologic malignancies, infection-specific mortality, prognosis, SEER, trend

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Introduction

In 2012, hematological malignancies accounted for 6.9% of all incident cancer cases and 7.2% of all cancer-related deaths. Currently, the survival of patients with hematological malignancies is greatly improved due to recent developments in intensive chemotherapy protocols, hematopoietic stem cell transplantation, and radiation therapies. Immunosuppression and neutropenia due to these treatments enhance the incidence of infection, however. Fifty to eighty percent of hematological malignancy patients may develop infections during the disease course and treatment, accounting for a substantial portion of overall mortality in these patients.[1] Infection is not only the most important cause of nonrelapse mortality in patients

with hematologic malignancies but is also associated with higher costs of health care and a higher frequency and longer duration of hospitalization.[2,3] Infections usually lead to delays or dose reductions in chemotherapy protocols, which decrease the chance of therapeutic success. With respect to infections in hematological malignancy patients, pneumonia accounts for approximately 30% of hospital admissions,[4] while sepsis, another common infection, has an incidence of 66 per 1000 person-years among patients with hematological malignancies and 275 per 1000 person-years among patients with acute myeloid leukemia (AML).[5]

The improved understanding of immunosuppression with regard to particular hematological malignancies and therapies, the timely identification of clinical features, the development of advanced diagnostic testing methods, and improvements in nursing have greatly reduced infection-specific mortality (ISM) among patients with hematological malignancies. In addition, hematological malignancy patients who undergo stem cell transplants and aggressive treatments may receive antibacterial, antifungal, and antiviral prophylaxis to prevent infections and reduce ISM rates.[6,7] Early empiric antibiotic therapy has reduced the mortality of leukemia patients by nearly 50% since 1965.[8] Nevertheless, with the wide use of antibiotics and prophylactic agents in these patients, the resistance of many such infectious pathogens to the available agents has developed quickly, while the development of new antibiotics has advanced slowly in comparison.[9]

ISM trends, however, have not been extensively evaluated in hematological malignancy patients. It is unknown whether ISM rates have changed in recent decades and, if they have, which factors are related to that change. Therefore, our aim was to explore and compare the trends in ISM among different hematological malignancy patients stratified by age, race, sex, stage, geographical region, and marital status using the Surveillance, Epidemiology, and End Results (SEER) database from 1983 to 2016.

Materials and methods

Data sources

This is a retrospective study. The SEER database is the main source of cancer incidence data in the United States; it compiles and reports various data of patients with tumors, including demographic, morphological, primary tumor-site, treatment, and survival data. The database covers up to 28% of the population in the United States, including 67% of the Pacific/Hawaiian Islander, 50% of the Asian, 44% of the Alaskan/American Indian/Native, 38% of the Hispanic, and 26% of the black populations.

The SEER 9 registry was used to explore mortality trends.
The SEER 18 registry was used to evaluate possible factors associated with ISM.

Study population selection

Data on patients with the five major types of hematologic malignancies, namely, acute leukemia (AL), chronic leukemia (CL), Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), and multiple myeloma (MM), were collected to explore the factors related to and trends in ISM. Data on AL, CL, and MM between 1983 and 2016 were collected using the 2008 World Health Organization (WHO) classification system and International Classification of Diseases for Oncology (third edition) codes. For HL and NHL, the data were limited to the period from 1983 to 2015 because information about Ann Arbor staging was only available during that period. AL consists of two principal types, namely, acute lymphocytic leukemia (ALL) and AML. ALL histology codes included 9727-9729, 9826, 9835-9837, 9800-9801, and 9805, and AML histology codes included 9840, 9860-9861, 9865-9867, 9869, 9870-9874, 9891, 9895-9898, 9910-9911, 9920, 9930-9931, 9984, and 9987. CL consists of two principal types, namely, chronic lymphocytic leukemia (CLL) and chronic myeloid leukemia (CML). CLL histology codes included 9820, 9823, 9832-9833, and 9940, and CML histology codes included 9863 and 9875-9876. The MM histology code included 9732. HL histology codes included 9650-9655, 9659, and 9661-9667. For NHL, six common NHL subtypes were extracted, spanning the range from highly aggressive to indolent: diffuse large B-cell lymphoma (DLBCL), Burkitt's lymphoma (BL), mantle cell lymphoma (MCL), follicular lymphoma (FL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), and marginal zone lymphoma (MZL). DLBCL histology codes included 9678-80, 9684, 9688, 9712,

9735, and 9737-9738; the BL histology code included 9687; the MCL histology code included 9673; FL histology codes included 9690-91, 9695, and 9698; the CLL/SLL histology code included 9670; and MZL histology codes included 9699 and 9689.

We limited our analysis to AL, CL, MM, HL, and NHL as the primary or only malignancies. Patients diagnosed only by autopsy or death certificates and patients for whom the cause of death was unknown were excluded. Patients who survived less than a month were excluded as their survival time is recorded as 0 in the SEER database. In addition, MM patients younger than 40 years and CL patients younger than 15 years were excluded due to the small sample size.

Information regarding age at diagnosis, sex, Ann Arbor staging, race, marital status, geographic areas, radiation exposure, survival time, outcome and cause of death was extracted.

Cause of death data

Causes of death (CODs) were obtained from death certificates from the National Center for Health Statistics. The primary endpoint was ISM. According to the International Statistical Classification of Diseases and Related Health Problems–Tenth Edition (ICD-10), the composite variable 'ISM' consists of three common types of infection-related deaths, namely, sepsis, pneumonia, and other infectious and parasitic diseases, including HIV.

Statistical analysis

Annual age-standardized mortality rates were calculated by SEER*Stat software. The rates were adjusted to the 2000 standard population in the United States and expressed per 100,000 person-years. Joinpoint regression analysis software was used to analyze the ISM trends of each hematologic malignancy type via annual percentage changes (APCs) and 95% confidence intervals (95% CIs), which were used to evaluate rate changes. All statistical analyses were two-sided with a threshold of significance of $p < 0.05$. If no cases were reported in a certain year, the data were excluded from the Joinpoint analysis of mortality trends.

Univariable and multivariable Cox regression analyses were used to estimate the possible factors related to ISM within each hematologic malignancy type. Hazard ratios (HRs) and 95% CIs were calculated to evaluate the association.

Results

In total, 571,970 patients diagnosed with the 5 major types of hematologic malignancies were extracted from the SEER database from 1983 to 2016: 73,018 with AL, 99,930 with CL, 82,627 with MM, 45,898 with HL, and 270,497 with NHL. Of these patients, 13,744 (2.4%) died of infection, including 961, 2013, 1479, 884, and 8407 patients with AL, CL, MM, HL, and NHL, respectively.

The characteristics of the patients who died from infections are outlined in Table 1. The majority of deaths occurred in men (61.6% in AL; 61.25% in CL; 58.42% in MM; 76.13% in HL; and 72.27% in NHL), in white individuals (78.77% in AL; 87.68% in CL; 67% in MM; 71.04% in HL; and 80.27% in NHL), and in individuals living on the Pacific Coast (42.87% in AL; 39.2% in CL; 39.28% in MM; 46.27% in HL; and 52.42% in NHL). In the population of patients who died due to infections, those aged 40–64 years at diagnosis accounted for the largest proportion of patients with AL, HL, and NHL, while most patients with CL and MM were aged 65–79 years at diagnosis. Among HL and NHL patients who died due to infection, 56.45% and 42.75% had advanced stage (III/IV stage) disease, and 21.04% and 18.85% underwent radiation therapy, respectively.

Table 2 shows the results of Cox regression analyses stratified by hematologic malignancy subtype, which showed the independent prognostic effects of the patient characteristics for ISM. Across all hematologic malignancy subtypes, male sex, older age at diagnosis, black race, and unmarried status were negative prognostic factors for ISM. In addition, advanced stage was related to a higher risk of ISM in patients with HL and NHL.

AL cohort

Among patients with AL, the overall mortality due to infection decreased at a rate of −2.1% (95% CI = −2.8% to −1.3%) per year during the

Table 1. Distribution of infection-related deaths in patients with hematologic malignancies from the Surveillance, Epidemiology, and End Results (SEER) database, 1983–2016.

Characteristic	AL (%)	CL (%)	MM (%)	HL (%)	NHL (%)
Overall	961	2013	1479	884	8407
Age, years					
⩽14	95 (9.89)	–	–	13 (1.47)	14 (0.17)
15–39	185 (19.25)	73 (3.63)	–	316 (35.75)	1589 (18.9)
40–64	392 (40.79)	462 (22.95)	478 (32.32)	397 (44.91)	3449 (41.03)
65–79	208 (21.64)	835 (41.48)	650 (43.95)	115 (13.01)	2060 (24.5)
80+	81 (8.43)	643 (31.94)	351 (23.73)	43 (4.86)	1295 (15.4)
Sex					
Male	592 (61.6)	1233 (61.25)	864 (58.42)	673 (76.13)	6076 (72.27)
Female	369 (38.4)	780 (38.75)	615 (41.58)	211 (23.87)	2331 (27.73)
Race					
White	757 (78.77)	1765 (87.68)	991 (67)	628 (71.04)	6748 (80.27)
Black	124 (12.9)	172 (8.54)	395 (26.71)	223 (25.23)	1248 (14.84)
Other	78 (8.12)	70 (3.48)	91 (6.15)	31 (3.51)	393 (4.67)
Unknown	2 (0.21)	6 (0.3)	2 (0.14)	2 (0.23)	18 (0.21)
Marital status					
Married	450 (46.83)	991 (49.23)	709 (47.94)	260 (29.41)	2924 (34.78)
Unmarried	466 (48.49)	827 (41.08)	681 (46.04)	587 (66.4)	5005 (59.53)
Unknown	45 (4.68)	195 (9.69)	89 (6.02)	37 (4.19)	478 (5.69)
Geographic areas					
East	342 (35.59)	699 (34.72)	572 (38.67)	323 (36.54)	2639 (31.39)
Northern Plains	151 (15.71)	424 (21.06)	268 (18.12)	114 (12.9)	1030 (12.25)
Pacific Coast	412 (42.87)	789 (39.2)	581 (39.28)	409 (46.27)	4407 (52.42)
Southwest	56 (5.83)	101 (5.02)	58 (3.92)	38 (4.3)	331 (3.94)
Ann Arbor stage					
Early (I/II)	–	–	–	338 (38.24)	2750 (32.71)
Advanced (III/IV)	–	–	–	499 (56.45)	3594 (42.75)
Unknown	–	–	–	47 (5.32)	2063 (24.54)
Radiation					
Yes	–	–	–	186 (21.04)	1585 (18.85)
No/unknown	–	–	–	698 (78.96)	6822 (81.15)

AL, acute leukemia; CL, chronic leukemia; HL, Hodgkin lymphoma; MM, multiple myeloma; NHL, non-Hodgkin lymphoma.

Table 2. Multivariate analysis of the associations between patient characteristics and infection-specific mortality among patients with hematologic malignancies (1983–2016).

Variable	AL		CL		MM	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Age, years						
⩽14	1	Ref.	–	–	–	–
15–39	3.565 (2.769–4.588)	<0.001	1	Ref.	–	–
40–64	7.533 (5.878–9.654)	<0.001	1.074 (0.837–1.377)	0.575	1	Ref.
65–79	8.178 (6.25–10.701)	<0.001	2.683 (2.103–3.422)	<0.001	1.77 (1.569–1.997)	<0.001
80+	10.853 (7.908–14.895)	<0.001	7.781 (6.064–9.984)	<0.001	3.568 (3.083–4.129)	<0.001
Sex						
Male	1	Ref.	1	Ref.	1	Ref.
Female	0.721 (0.632–0.822)	<0.001	0.685 (0.623–0.753)	<0.001	0.63 (0.566–0.703)	<0.001
Race						
White	1	Ref.	1	Ref.	1	Ref.
Black	1.598 (1.315–1.942)	<0.001	1.457 (1.242–1.709)	<0.001	1.493 (1.322–1.686)	<0.001
Other	1.084 (0.853–1.377)	0.509	1.37 (1.074–1.748)	0.011	1.32 (1.059–1.644)	0.014
Unknown	0.389 (0.097–1.562)	0.183	0.231 (0.104–0.518)	<0.001	0.253 (0.063–1.014)	0.052
Marital status						
Married	1	Ref.	1	Ref.	1	Ref.
Unmarried	1.263 (1.09–1.462)	0.002	1.444 (1.308–1.595)	<0.001	1.671 (1.493–1.87)	<0.001
Unknown	1.272 (0.934–1.732)	0.127	0.893 (0.764–1.043)	0.152	1.026 (0.821–1.281)	0.824
Geographic areas						
East	1	Ref.	1	Ref.	1	Ref.
Northern Plains	1.093 (0.901–1.325)	0.367	1.017 (0.9–1.148)	0.791	1.145 (0.99–1.324)	0.069
Pacific Coast	0.862 (0.743–1)	0.051	0.809 (0.729–0.897)	<0.001	0.843 (0.748–0.95)	0.005
Southwest	0.886 (0.666–1.178)	0.404	0.732 (0.593–0.902)	0.004	0.777 (0.591–1.021)	0.07
Variable	**HL**		**NHL**			
	HR (95% CI)	***p***	**HR (95% CI)**	***p***		
Age, years						
⩽14	1	Ref.	1	Ref.		
15–39	3.131 (1.797–5.457)	<0.001	20.72 (12.241–35.072)	<0.001		
40–64	10.706 (6.135–18.682)	<0.001	12.211 (7.219–20.654)	<0.001		

(Continued)

Table 2. (Continued)

Variable	HL		NHL	
	HR (95% CI)	***p***	**HR (95% CI)**	***p***
65–79	16.167 (9.041–28.91)	<0.001	11.338 (6.695–19.199)	<0.001
80+	30.537 (16.287–57.253)	<0.001	21.917 (12.927–37.158)	<0.001
Sex				
Male	1	Ref.	1	Ref.
Female	0.365 (0.312–0.427)	<0.001	0.377 (0.359–0.396)	<0.001
Race				
White	1	Ref.	1	Ref.
Black	2.561 (2.183–3.005)	<0.001	1.98 (1.86–2.108)	<0.001
Other	1.061 (0.737–1.527)	0.749	0.875 (0.789–0.97)	0.011
Unknown	0.363 (0.09–1.461)	0.154	0.226 (0.142–0.359)	<0.001
Marital status				
Married	1	Ref.	1	Ref.
Unmarried	2.664 (2.283–3.108)	<0.001	3.037 (2.896–3.185)	<0.001
Unknown	1.772 (1.251–2.509)	0.001	1.43 (1.297–1.578)	<0.001
Geographic areas				
East	1	Ref.	1	Ref.
Northern Plains	0.762 (0.614–0.945)	0.013	0.896 (0.834–0.964)	0.003
Pacific Coast	1.021 (0.879–1.187)	0.782	1.201 (1.143–1.261)	<0.001
Southwest	0.761 (0.542–1.069)	0.115	0.835 (0.744–0.937)	0.002
Ann Arbor stage				
Early (I/II)	1	Ref.	1	Ref.
Advanced (III/IV)	2.14 (1.861–2.46)	<0.001	1.383 (1.315–1.454)	<0.001
Unknown	1.551 (1.14–2.11)	0.005	0.899 (0.847–0.953)	<0.001

AL, acute leukemia; CI, confidence interval; CL, chronic leukemia; HL, Hodgkin lymphoma; HR, hazard ratios; MM, multiple myeloma; NHL, non-Hodgkin lymphoma.

study period (Figure 1(a)). When sex-specific trends were explored, steady declines in ISM in both males [annual percent change (APC) = −2.4% (95% CI = −3.4% to −1.4%)] and females (APC = −1.7% (95% CI = −2.8% to −0.6%)) were observed (Figure 1(b)). When age-specific mortality was analyzed, a gradual increase in the ISM rate was observed with increasing age until the age group from 40 to 64 years, after which the ISM rate decreased. In addition, the ISM demonstrated a continuously decreasing trend over time in all age and race subgroups (Supplementary Figure S1 and Table 3).

CL cohort

Among patients with CL, the overall rate of ISM initially increased from 1983 to 1998 (APC = 2.1%

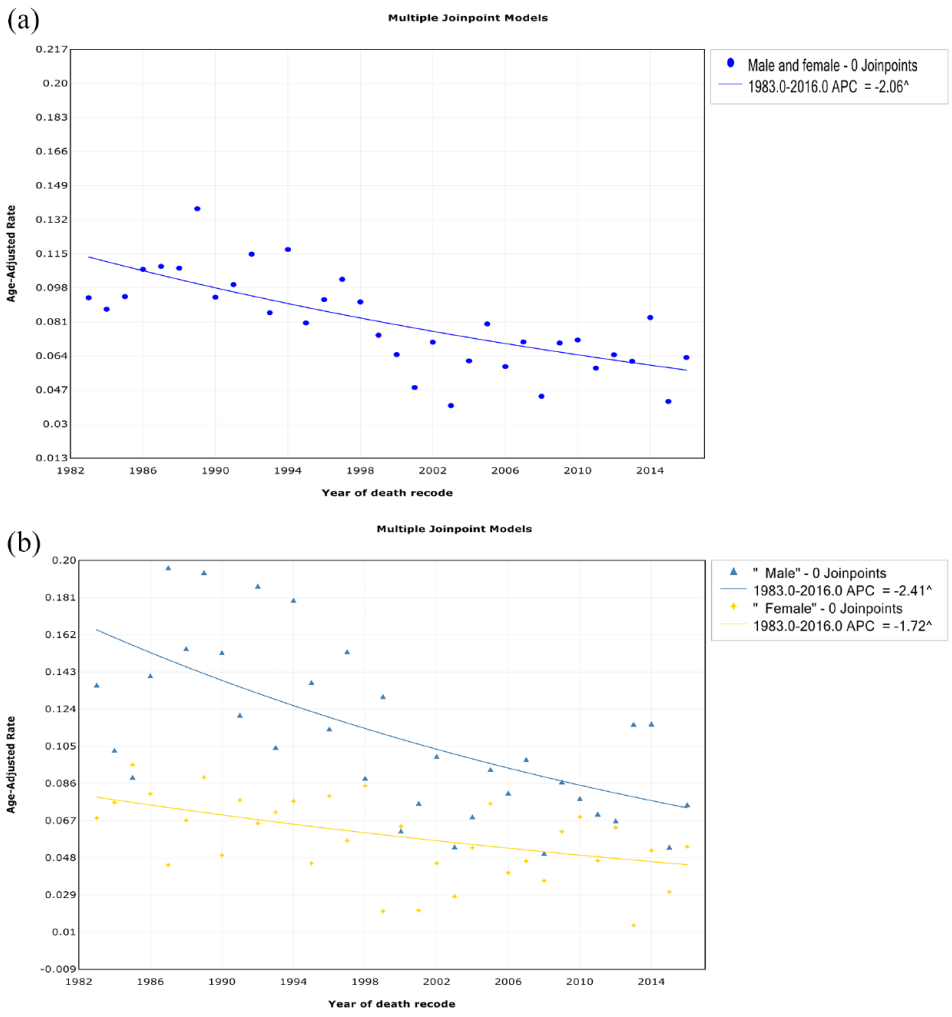

Figure 1. Trends in incidence-based mortality from infection for acute leukemia. (a) Overall incidence trends and (b) incidence trends according to sex.

(95% CI = 0.1% to 4.2%)) then decreased from 1998 to 2001 (APC = −26.1% (95% CI = −54.6% to 20.5%)), followed by a significant increase from 2001 to 2016 (APC = 2.8% (95% CI = 0.8% to 4.9%)) (Figure 2(a)). When sex-specific trends were explored, the mortality rate in male patients was more than two times that in female patients (Supplementary Table S1). Among male patients, the mortality rate stabilized from 1983 to 1998 (APC = 0.4% (95% CI = −1.6% to 2.3%)), then it decreased at a rate of −26.4% (95% CI = −55.3% to 21.2%) from 1998 to 2001, followed by an increase at a rate of 2.6% (95% CI = 0.5% to 4.7%) from 2001 to 2016 (Figure 2(b)). Among female patients, the ISM rate steadily decreased over the study period, although the reduction in the rate was not significant (APC = −1.2% (95% CI = −2.4% to 0.1%)). With regard to age-specific and race-specific mortality trends, the mortality rates among those aged 15–39 years and 40–64 years and nonwhite patients all steadily but nonsignificantly decreased over the study period (Supplementary Figure S2 and Table 3). Among those aged 65–79 years and 80+ years and white patients, the mortality rates initially increased and then decreased from 1998 to 2001, followed by a significant increase from 2001 to 2016.

MM cohort

Among patients with MM, the overall mortality rate due to infection initially increased from 1983 to 1997 (APC = 3% (95% CI = −0.1% to 6.1%)), then decreased from 1997 to 2000 (APC = −23.8%

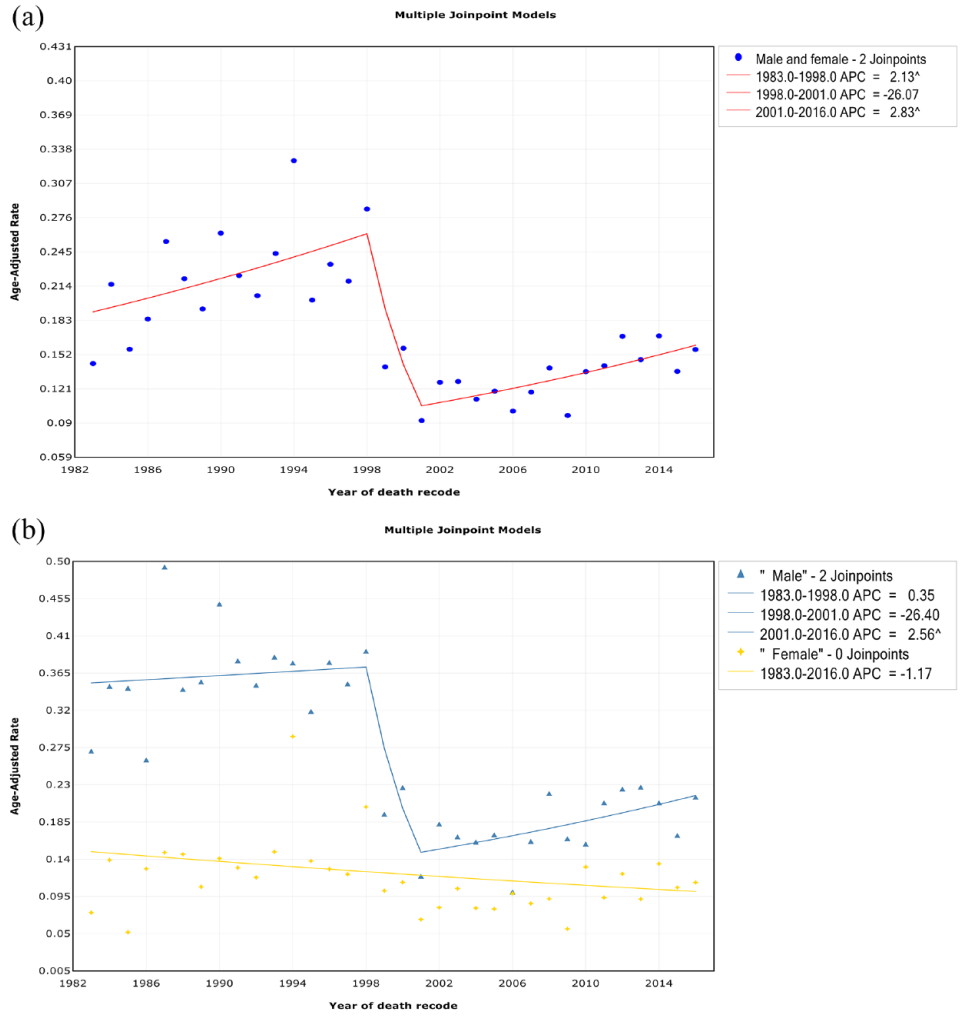

Figure 2. Trends in incidence-based mortality from infection for chronic leukemia. (a) Overall incidence-based mortality trends and (b) incidence-based mortality trends according to sex.

(95% CI = −61.2% to 49.6%)), followed by a significant increase from 2000 to 2016 (APC = 3.3% (95% CI = 1.0% to 5.7%)) (Figure 3(a)). When sex-specific trends were explored (Figure 3(b)), we found a steady decrease in the ISM rate in male patients (APC = −1.5% (95% CI = −2.8% to −0.2%)). In female patients, the ISM rate decreased from 1983 to 2010 (APC = −1.8% (95% CI = −3.3% to −0.4%)) and increased thereafter (APC = 11.5% (95% CI = −0.4% to 24.8%)). In terms of age-specific mortality, the ISM rates recently increased in all age subgroups (Supplementary Figure S3A). When race-specific trends were analyzed, there was no joinpoint in the trends in ISM rates in the nonwhite subgroups during the study period. In the white subgroup, the mortality rate initially increased and then decreased from 1997 to 2000, followed by a significant increase from 2000 to 2016 (Supplementary Figure S3B and Table 3).

HL cohort

Among the patients with HL, the overall mortality rate due to infection initially increased, then decreased with an APC of −1.3% (95% CI = −2.4% to −0.1%) starting in approximately 1988 (Figure S4A). When sex-specific trends were explored, the mortality rate in male patients was more than 3 times that in female patients (Supplementary Figure S4B and Table S1). The mortality rate in males showed a decreasing trend (APC = −0.7% (95% CI = −1.8% to 0.5%)), and the mortality rate in females showed an increasing trend (APC = 0.5%

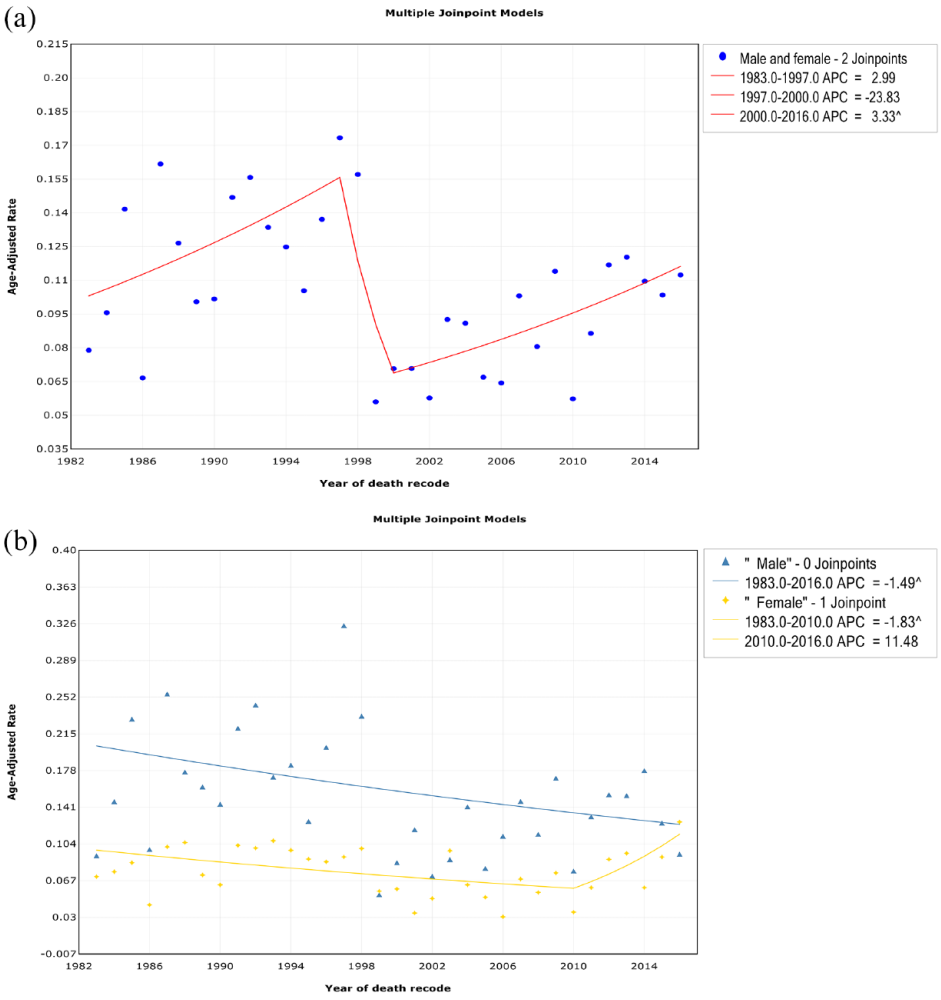

Figure 3. Trends in incidence-based mortality from infection for multiple myeloma. (a) Overall incidence-based mortality trends. (B) Incidence-based mortality trends according to sex.

(95% CI = −1.4% to 2.4%)), although they were both nonsignificant. In terms of age-specific and stage-specific trends, the ISM continuously decreased over time in all age and stage subgroups (Figure S5A and B), but the decrease was only significant in the groups aged 65–79 years and 80 + years. When race-specific trends were analyzed, there were no joinpoints in the mortality trends in the nonwhite subgroups during the study period. In the white subgroup, the mortality rate initially increased and then decreased at a rate of −2.3% (95% CI = −3.6% to −1%) from 1988 to 2015 (Figure S5C and Table 3).

NHL cohort

Among patients with NHL, the overall rate of ISM increased steeply from 1983 to 1990 (APC = 21.5% (95% CI = 15.7% to 27.7%)) and then more slowly from 1990 to 1994 (APC = 6.5% (95% CI = −4.6% to 18.8%)). Thereafter, it decreased steeply from 1994 to 1999 (APC = −14.3% (95% CI = −20.4% to −7.7%)) and then more slowly from 1999 to 2015 (APC = −0.8% (95% CI = −1.9% to 0.2%)) (Supplementary Figure S6A). When sex-specific trends were explored, the mortality rate in male patients was more than three times that in female patients (Supplementary Figure S6B). The male-specific trend in ISM had a pattern similar to that for overall mortality. In female patients, the ISM rate initially increased steeply (APC = 9.1% (95% CI = 4.8% to 13.5%)), decreased starting in approximately 1994 (APC = −6.1% (95% CI = −13.5% to 2%)), and then increased from 2001 to 2015 (APC = 1.6% (95% CI = −0.6% to 3.8%)). In terms of age-specific and stage-specific

Table 3. Trends in annual rates of death from infection among patients with hematologic malignancies by year.

Characteristic	AL		CL		MM	
	Calendar period	APC (95% CI)	Calendar period	APC (95% CI)	Calendar period	APC (95% CI)
Overall	1983–2016	−2.1* (−2.8 to −1.3)	1983–1998 1998–2001 2001–2016	2.1* (0.1 to 4.2) −26.1 (−54.6 to 20.5) 2.8* (0.8 to 4.9)	1983–1997 1997–2000 2000–2016	3 (−0.1 to 6.1) −23.8 (−61.2 to 49.6) 3.3* (1 to 5.7)
Sex						
Male	1983–2016	−2.4* (−3.4 to −1.4)	1983–1998 1998–2001 2001–2016	0.4 (−1.6 to 2.3) −26.4 (−55.3 to 21.2) 2.6* (0.5 to 4.7)	1983–2016	−1.5* (−2.8 to −0.2)
Female	1983–2016	−1.7* (−2.8 to −0.6)	1983–2016	−1.2 (−2.4 to 0.1)	1983–2010 2010–2016	−1.8* (−3.3 to −0.4) 11.5 (−0.4 to 24.8)
Age, years						
⩽14	1983–2016	−3.8* (−5.6 to −2)	–	–	–	–
15–39	1983–2016	−1.5 (−3.1 to 0.2)	1984–2016	−1.3 (−3.7 to 1.2)	–	–
40–64	1983–2016	−1.5* (−2.6 to −0.3)	1983–2016	−1 (−2.2 to 0.3)	1984–2016	1.7* (0.1 to 3.3)
65–79	1983–2016	−1.2 (−2.7 to 0.4)	1983–1998 1998–2001 2001–2016	2.6 (−0.7 to 5.9) −25.6 (−64 to 53.9) 3.4* (0.1 to 6.7)	1983–2007 2007–2016	−3.1* (−5.5 to −0.6) 7 (−1.8 to 16.7)
80+	1983–2016	−2.6* (−4.6 to −0.5)	1983–1998 1998–2001 2001–2016	−0.1 (−3.3 to 3.2) −28.4 (−74 to 97) 3.2 (−0.4 to 7.1)	1983–1998 1998–2001 2001–2016	3.2 (−0.6 to 7.2) −36.3 (−83.8 to 151.3) 2.9 (−1.5 to 7.5)
Race						
White	1983–2016	−2.3* (−3 to −1.5)	1983–1998 1998–2001 2001–2016	2 (−0.2 to 4.2) −25.1 (−55.9 to 27.2) 2.9* (0.6 to 5.1)	1983–1997 1997–2000 2000–2016	2 (−1.2 to 5.3) −25.9 (−68.2 to 72.5) 2.8* (0.1 to 5.5)
Black	1983–2016	−1.3 (−2.9 to 0.4)	1983–2016	−1.3 (−3.4 to 0.9)	1983–2016	1 (−0.6 to 2.5)
Other	1984–2016	−2.5* (−4.8 to −0.1)	1983–2016	−1.3 (−4.2 to 1.6)	1984–2016	−2.2 (−4.7 to 0.4)
Characteristic	**HL**	**NHL**				
	Calendar period	**APC (95% CI)**	**Calendar period**	**APC (95% CI)**		
Overall	1983–1988 1988–2015	20.1 (−0.9 to 45.4) −1.3* (−2.4 to −0.1)	1983–1990 1990–1994 1994–1999 1999–2015	21.5* (15.7 to 27.7) 6.5 (−4.6 to 18.8) −14.3* (−20.4 to −7.7) −0.8 (−1.9 to 0.2)		
Sex						
Male	1983–2015	−0.7 (−1.8 to 0.5)	1983–1990 1990–1994 1994–1999 1999–2015	24.8* (17.9 to 32) 3.9 (−7.1 to 16.2) −15.3* (−21.7 to −8.3) −1.6* (−2.7 to −0.4)		
Female	1983–2015	0.5 (−1.4 to 2.4)	1983–1994 1994–2001 2001–2015	9.1* (4.8 to 13.5) −6.1 (−13.5 to 2) 1.6 (−0.6 to 3.8)		

(Continued)

Table 3. (Continued)

Characteristic	HL		NHL	
	Calendar period	APC (95% CI)	Calendar period	APC (95% CI)
Age, years				
⩽14	1986–2015	−3.2 (−7.2 to 1)	1989–1994 1994–2013	−14.5* (−16.8 to −12.3) 0.3 (−0.3 to 0.9)
15–39	1983–2015	−0.3 (−1.7 to 1.2)	1983–1988 1988–1994 1994–1998 1998–2015	97.2* (41.3 to 175.2) 13.0* (2.3 to 24.8) −23.6* (−40.4 to −2.2) −7.5* (−10.4 to −4.5)
40–64	1983–2015	0.3 (−1.3 to 1.9)	1983–1990 1990–1994 1994–1998 1998–2015	35.3* (23.8 to 47.8) 3.8 (−12.5 to 23.2) −15.7 (−29 to 0.2) −1.5* (−2.9 to 0)
65–79	1983–2015	−2.7* (−5 to −0.4)	1983–1997 1997–2001 2001–2015	5.6* (2.8 to 8.4) −15.4 (−32.4 to 5.9) 3.0* (0.7 to 5.5)
80+	1986–2015	−4.3* (−6.7 to −1.8)	1983–1994 1994–2004 2004–2015	2.6 (−2.2 to 7.7) −6.2* (−11.9 to −0.1) 3.8 (−0.5 to 8.3)
Race				
White	1983–1988 1988–2015	20.2 (−1.2 to 46.3) −2.3* (−3.6 to −1)	1983–1990 1990–1994 1994–1999 1999–2015	22.0* (16.6 to 27.6) 5.3 (−4.9 to 16.6) −15.1* (−20.7 to −9.1) −0.9 (−1.9 to 0.1)
Black	1983–2015	2 (−0.2 to 4.2)	1983–1992 1992–2015	24.5* (10.5 to 40.2) −2.9* (−4.4 to −1.3)
Other	1986–2015	0 (−2.8 to 3)	1983–2015	−0.9 (−2.4 to 0.7)
Ann Arbor stage				
Early (I/II)	1984–2015	−0.3 (−2.4 to 1.8)	1983–1989 1989–1994 1994–1999 1999–2015	57.5* (35.4 to 83.4) 13.7* (2.8 to 25.8) −17.2* (−25.6 to −7.9) −1.4 (−2.9 to 0.1)
Advanced (III/IV)	1984–2015	−0.2 (−1.5 to 1.1)	1983–1988 1988–1994 1994–1998 1998–2015	55.4* (23.6 to 95.3) 9.6 (−0.4 to 20.6) −16.7 (−32.6 to 3) −0.6 (−2.3 to 1)

AL, acute leukemia; APC, annual percentage change; CI, confidence interval; CL, chronic leukemia; HL, Hodgkin lymphoma; MM, multiple myeloma; NHL, non-Hodgkin lymphoma.
*$p < 0.05$.

trends in mortality (Supplementary Figure S7A and B), we observed three different patterns: (1) after an initial period of substantial and sustained growth, there has been a promising decline in recent years (including in the groups aged 15–39 years and 40–64 years and all stage subgroups); (2) after an initial steep decline, the mortality rate showed a relatively stable trend (including in the group aged <14 years); and (3) after an initial steep increase and subsequent decrease, the mortality rate has started to increase in recent years (including in the groups aged 65–79 years and 80+ years). With regard to race-specific mortality, the mortality rate decreased in all race subgroups in recent years (Supplementary Figure S7C and Table 3).

Discussion

Population-based monitoring of ISM trends not only provides an assessment of the effectiveness of public health measures but also deepens the current understanding of the risk factors and patterns of infection, supporting the development of future interventions and initiatives. To the best of our knowledge, this is the first large population-based study to provide updated ISM patterns and temporal trends among patients with hematologic malignancies based on comprehensive 40-year data, with detailed evaluations stratified according to race, age, sex, and stage. We demonstrate that in recent years, there has been a promising downward trend in ISM in patients with AL, HL, and NHL; however, the ISM rate has increased dramatically in patients with CL and MM. Moreover, male sex, older age at diagnosis, black race, and unmarried status were negative prognostic factors for ISM across all hematologic malignancy subtypes.

We observed a promising downward trend in ISM in recent years in patients with AL, HL, and NHL. There are a number of reasons for this observation. (1) Better supportive treatment is currently available. First, there has been improvement in the prevention, identification, and management of infection by nurses. This, in turn, is due to the use of appropriate hand hygiene, the provision of periodic oral care, the identification of complications at intravenous sites, and the determination of the need for indwelling urinary catheters, which may lead to improved outcomes. Second, there has been improvement in patients' health awareness. For example, there has been increased emphasis on hand washing and drying after touching patients to avoid the transmission of health care–associated pathogens,[10] and radical smoking cessation campaigns have been initiated. (2) Pneumococcal and influenza vaccines have been recommended as prophylactic measures for hematologic malignancy patients, especially the elderly population older than 65 years.[11] This also explains the results of this study; there was a gradual increase in ISM with advancing age until the age group from 40 to 64 years, after which the mortality rate decreased. (3) Colony-stimulating factors are administered 24 h after chemotherapy, which could cause a significant increase in white blood cells, reducing the severity and duration of febrile neutropenia.[12] (4) The methods for diagnosing infections have substantially improved. For example, matrix-assisted laser desorption/ionization time of flight mass spectrometry can be used to quickly identify bacterial and fungal pathogens, which can shorten the time from diagnosis to treatment and reduce 30-day mortality.[13] (5) There have been substantial improvements in the prevention of the spread of resistant bacteria. Not only do the latest guidelines from the European Society of Clinical Microbiology and Infectious Diseases provide evidence supporting infection control measures for drug-resistant bacteria,[14] but many countries and regions have also developed their own policies to limit the spread of drug-resistant bacteria in hospitals. Transmission-based prevention measures are tailored for specific infections and different levels of transmission, with particular emphasis on practicing good hand hygiene, ensuring food hygiene, regular room cleaning, active monitoring and screening, tracking infections, implementing exposure prevention measures, identifying responsibly pathogens, and isolating infected patients.[15] (6) Antibiotic management and the standardized use of international antibiotic guidelines have become more widespread.[16] The understanding of antibiotic pharmacokinetics and pharmacodynamics could help optimize the selection of the type, dose, and route of the antibiotic according to the characteristics of the host, infection site, and infection severity. In addition, drug levels are monitored to ensure treatment effectiveness and reduce side effects.

We noticed an increasing trend in ISM starting in approximately 2000 in patients with MM and CL, which is consistent with previous reports.[17] The main reason for this trend may be that the novel treatments developed in recent years have transformed MM and CL into chronic diseases, and thus, these patients undergo prolonged therapy and are frequently in hospitals; this, in turn, is associated with a high risk of infections, particularly with multidrug-resistant organisms, including multidrug-resistant *Pseudomonas aeruginosa*, carbapenem-resistant Enterobacteriaceae, and methicillin-resistant *Staphylococcus aureus*, all of which are related to high rates of therapeutic failure and mortality.[18] In addition, the proportion of older patients with MM and CL is increasing, which may be associated with recent increases in ISM. Older patients are more susceptible to infections, and a relatively higher risk of infection could potentially translate to an increased risk of death from infection. Furthermore, older patients are relatively more likely to have comorbidities, which could promote multiple organ dysfunction and lead to poor outcomes. A low immune

response to seasonal influenza and pneumococcal vaccines in MM and CL patients[19,20] could be another cause of the increased ISM rate. In fact, the diagnoses of MM and CL are associated with a relatively high level of risk for ISM. Immunodeficiency in patients with MM and CL stems from multiple sources, such as B-cell dysfunction with hypogammaglobulinemia and dendritic cell, T-cell and natural killer (NK) cell abnormalities.[21,22]

We observed a sex-based discrepancy in ISM rates, with higher rates in males than in females across all hematologic malignancy subtypes, especially in NHL. The reasons might be as follows. (1) There is a better humoral and cellular immune response in females than in males.[23] (2) There are differences in health awareness, occupational exposure factors, and lifestyles between the sexes.[24] For example, higher rates of smoking in males are associated with a predisposition to respiratory infections. (3) There may be differences in drug metabolism and response between men and women.[25] (4) The differences in hormones between the sexes result in differences in the hormonal regulation of the immune response between men and women.[26]

Being married was found to be a protective factor against ISM, which is in line with previous studies.[27] The specific mechanism underlying this effect is unclear. We hypothesize that the main reason for this phenomenon is that married people may have improved opportunities for obtaining health care through their spouse's insurance.[28] Furthermore, married people who receive support and encouragement from their spouses tend to have a more positive attitude toward their disease, with increased compliance and adherence to treatment and follow-up, thus improving their prognosis.[29] Married patients also have healthier lifestyles and receive better supportive care from their spouses, which may help reduce ISM.[30]

There are some limitations of this study, as it was based on the information available in the SEER database. First, there was no record of prophylactic antibiotic regimens, which play a key role in antibiotic resistance and ISM. Second, treatment details are limited in the SEER database. Thus, we could not further explore the risk of ISM based on treatment. Third, Table 3 shows a dramatic decrease in ISM between 1997 and 2000 for patients with MM and CL. The data for this period may be flawed, or the analysis may be biased in some way. Finally, comorbidities and clinical stages could not be obtained from the SEER database. Older cancer patients, especially MM and CL patients, are very likely to have comorbidities, which are closely related to worse infection outcomes.

Conclusion

In summary, this study provides updated ISM patterns and temporal trends among patients with hematologic malignancies in the United States via a comprehensive analysis of data over a 40-year period. The mortality trends significantly differed according to race, age, sex, and stage; these data could be useful in further studies on specific etiologies. Moreover, according to the multivariate analysis, male sex, older age at diagnosis, black race, and unmarried status were negative prognostic factors for ISM across all hematologic malignancy subtypes. These data may play an important role in the generation of public health strategies and may help guide clinicians when managing infections in patients with hematological malignancies.

Declarations

Ethics approval and consent to participate

This study was fully compliant with the publication guidelines provided by SEER. The data were obtained from SEER, so the approval of the ethics committee was not needed.

Consent for publication

Not applicable.

Author contributions

Xuejiao Yin: Data curation; Investigation; Methodology; Software; Supervision; Writing – original draft.

Xuelian Hu: Funding acquisition; Investigation; Methodology; Writing – review & editing.

Hongyan Tong: Formal analysis; Methodology; Writing – review & editing.

Liangshun You: Conceptualization; Project administration; Software; Supervision.

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Availability of data and materials
The data were obtained from the SEER database (https://seer.cancer.gov/seerstat/), which is freely accessible to the public.

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