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Increase in survival for patients with mantle cell lymphoma in the era of novel agents in 1995–2013: Findings from Texas and national SEER areas

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ABSTRACT

Background: Over the past 20 years, many novel agents and treatment regimens have been developed to treat mantle cell lymphoma (MCL). This study aimed to determine the impact of these new regimens on the survival of MCL patients from 1995 to 2013.

Methods: All newly diagnosed adult MCL patients in the Surveillance, Epidemiology, and End Results (SEER) and Texas Cancer Registry (TCR) databases were included. Patients were grouped into 4 calendar periods based on the time when new novel agents became available: chemotherapy-only (1995–1998, P1), rituximab + chemotherapy (1999–2004, P2), bortezomib and HyperCVAD (2005–2008, P3), bendamustine and Nordic regimen (2009–2013, P4). Associations between these time periods and survival outcomes were analyzed using the Kaplan-Meier method and Cox proportional hazard regressions.

Results: A total of 7,555 SEER patients and 2,055 TCR patients were identified. All-cause mortality rates decreased significantly from 1995 to 2013 (SEER, $P < 0.001$; TCR, $P = 0.03$). Multivariable analysis of SEER data showed that the risk of MCL-specific death decreased significantly over the study period with hazard ratios of 0.82 (P2 vs. P1), 0.66 (P3 vs. P1), and 0.58 (P4 vs. P1) ($P < 0.0001$). Similar results were observed for TCR data ($P < 0.0001$). In an analysis stratified by tumor stage, only patients with advanced- stage tumors showed a significantly decreased risk of death in both SEER ($P < 0.0001$) and TCR ($P = 0.002$) datasets.

Conclusion: Survival outcome for MCL patients improved from 1995 to 2013, especially for patients with advanced-stage tumors, potentially reflecting the impact of the introduction of novel agents and new therapeutic regimens.

1. Introduction

Mantle cell lymphoma (MCL) is a rare and aggressive subtype of B-cell non-Hodgkin lymphoma (NHL) associated with a poor prognosis. MCL was established as a distinct type of lymphoma in 1992 [1], and it affects about 4% to 6% of all NHL patients [2]. The incidence of MCL substantially increased from 1992 to 2013 in the United States, with the largest increases observed among male, white, and elderly populations [3–5]. Over the past 2 decades, MCL treatment has changed dramatically. Before 1999, chemotherapy using cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) was the standard induction protocol for MCL. After 1999, a series of new regimens and novel agents to treat MCL were approved by the Food and Drug Administration (FDA). The regimens and agents approved between 1999 and 2013 included rituximab + CHOP (R-CHOP); hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD); bortezomib; the Nordic regimen (dose-intensified induction immunochemotherapy with R-CHOP [maxi-CHOP]); bendamustine; and temsirolimus [6–14]. Since 2013, lenalidomide, ibrutinib, and acalabrutinib have also been approved to treat MCL patients [15–17].

Most data on the effect of these newly developed regimens on MCL patients' survival come from a limited number of randomized controlled trials (RCTs) [8,13,18–21]. However, because of the stringent eligibility criteria for clinical trials, patients enrolled in trials tend to be

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healthier and younger than patients in the community, limiting the generalizability of RCTs' conclusions. Hence, community-based studies involving large numbers of patients outside RCTs are needed. A recent population-based cohort study by Chandran et al. [22] showed that survival improved significantly over the period from 1992 to 2007, both in the overall population of MCL patients and in patients with advanced-stage tumors, suggesting that the development of novel agents and aggressive treatment regimens may have a significant impact on the survival of MCL patients.

Analysis of survival trends among MCL patients diagnosed at different times could provide insight into whether the introduction of new treatments has affected survival over time. In this population-based study, we aimed to determine survival outcomes for adult patients with MCL diagnosed between 1995 and 2013. We used data from both the Texas Cancer Registry (TCR) and the national Surveillance, Epidemiology and End Results (SEER) databases. We included the TCR because Texas is not included in the national SEER data. We grouped the patients into 4 cohorts on the basis of the year of diagnosis and hypothesized that the improvement in survival outcomes for MCL patients over the study period can be explained by the development and use of new regimens for the treatment of MCL.

2. Methods

2.1. Data sources

Two databases were used for the study. SEER encompasses 18 cancer registries across the United States, accounting for over 26% of the US population [23]. TCR is one of the largest state cancer registries in the United States; it collects information on cancer burden, diagnosis, treatment, and survivorship in Texas, which accounts for around 8% of the US population [24]. For this study, data were collected for the years 1995 through 2013. These datasets included demographic and clinical variables and cause of death.

2.2. Human subjects

The Committee for the Protection of Human Subjects at The University of Texas Health Science Center at Houston approved this study with a waiver of the informed consent requirement because the data were obtained from existing databases with no patient contact.

2.3. Study design and study population

In this retrospective cohort study, we identified all adult patients who received a new diagnosis of MCL between January 1, 1995 and December 31, 2013 in the SEER and TCR data sets. Patients were included if they: (i) had a primary diagnosis of MCL (ICD-O-3; site code: 9673) and (ii) were 20 years of age or older at the time of diagnosis. Patients whose MCL was identified on autopsy or by death certificate only were excluded.

2.4. Study variables

2.4.1. Main exposure variable

The main exposure variable was the year of diagnosis, which was divided into 4 periods defined by the main FDA-approved drugs available during the study period. Since specific treatment regimen information for each patient was not available in the databases, we used the date of diagnosis as a proxy. The years of diagnosis were categorized into the following 4 groups: based on the time when new novel agents became available: chemotherapy-only (1995–1998, P1), rituximab + chemotherapy (1999–2004, P2), bortezomib and HyperCVAD (2005–2008, P3), bendamustine and Nordic regimen (2009–2013, P4).

2.4.2. Main outcome variables

The primary outcome variables were the median overall survival (OS) duration, the all-cause mortality rate, and the MCL-specific mortality rate. OS and mortality rates were calculated from the time of MCL diagnosis to the time of death or date of last follow-up (December 31, 2013).

2.4.3. Other variables

Covariates included in the survival analyses included age at diagnosis, sex, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, and other), tumor stage (localized, regional, advanced, and unknown), marital status (married, single, and unknown), and median household income at the county level (by quartile).

2.5. Statistical analysis

Median OS time for all-cause mortality was estimated for patients diagnosed in each calendar period using Kaplan-Meier survival curves. We also used Kaplan-Meier curves to estimate 3-year and 5-year all-cause mortality rates for each of the 4 time periods. For MCL-specific mortality, we estimated the cumulative incidence probability [25] of MCL-related death while accounting for competing risks, where a competing risk was defined as a cause of death other than MCL. We also determined 3-year and 5-year MCL-specific mortality rates. Rates of all-cause mortality and MCL-specific mortality for the periods 1995–1998 (P1) to 2009–2013 (P4) were compared using a log-rank trend test and Gray's test, respectively [26,27]. The 5-year cumulative probability of mortality curves were plotted to illustrate the probability of death by period of diagnosis. The 5-year cumulative probability of mortality curves stratified by tumor stage and age group were also plotted for the cohorts.

Fine and Gray competing-risk proportional hazard regressions were performed to determine the association between major milestone drugs (represented by the 4 diagnostic periods) and MCL-specific mortality, accounting for competing risks as non-MCL death [28]. Age, sex, race/ethnicity, tumor stage, marital status, and median household income were adjusted for as covariates in the regression models. The proportional hazard assumption was confirmed for each calendar period of diagnosis before applying proportional hazard regression, and the hazard function for each stratum was proportional over time. Because tumor stage and age at diagnosis are important prognostic factors, we also performed proportional hazard regression analyses for each tumor stage and age group. All statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Baseline characteristics

Table 1a, 1b presents the baseline characteristics by diagnosis time for SEER and TCR patients, respectively. A total of 7,555 MCL patients from SEER and 2,055 MCL patients from TCR were included. Among the SEER patients (Table 1a), 28.6% were between 60 and 69 years old, 26.9% were between 70 and 79 years old, 69.6% were male, 81.0% were non-Hispanic white, 62.1% were married, and 76.2% were diagnosed with advanced-stage tumors. All baseline characteristics among the SEER patients were significantly different among the 4 time periods ($P < 0.05$). Among the TCR patients (Table 1b), 30.5% were 60 to 69 years old, 70.8% were male, 77.8% were non-Hispanic white, 38.7% were married, and 61.6% had advanced-stage tumors. In the TCR population, only race/ethnicity, marital status, and tumor stage were significantly different among the 4 time periods ($P < 0.05$).

3.2. Median OS, all-cause mortality, and MCL-specific mortality

Fig. 1 and Table 2 present the crude mortality rates for the 4

Table 1a
Baseline characteristics of MCL patients from SEER areas by calendar period of diagnosis.

Characteristics	SEER					
	1995-1998 (n = 592)	1999-2004 (n = 2226)	2005-2008 (n = 1939)	2009-2013 (n = 2798)	Total (n = 7555)	P-value*
Age at diagnosis						< .0001
< 50	80 (13.5)	198 (8.9)	161 (8.3)	203 (7.3)	642 (8.5)	
50-59	104 (17.6)	464 (20.8)	415 (21.4)	538 (19.2)	1521 (20.1)	
60-69	164 (27.7)	588 (26.4)	539 (27.8)	866 (31)	2157 (28.6)	
70-79	173 (29.2)	618 (27.8)	508 (26.2)	732 (26.2)	2031 (26.9)	
80 +	71 (12.0)	358 (16.1)	316 (16.3)	459 (16.4)	1204 (15.9)	
Gender						0.02
Female	204 (34.5)	705 (31.7)	557 (28.7)	833 (29.8)	2299 (30.4)	
Male	388 (65.5)	1521 (68.3)	1382 (71.3)	1965 (70.2)	5256 (69.6)	
Race/Ethnicity						< .0001
non-Hispanic White	500 (84.5)	1851 (83.2)	1570 (81)	2199 (78.6)	6120 (81)	
non-Hispanic Black	32 (5.4)	91 (4.1)	86 (4.4)	115 (4.1)	324 (4.3)	
Hispanic	31 (5.2)	171 (7.7)	186 (9.6)	310 (11.1)	698 (9.2)	
Other	29 (4.9)	113 (5.1)	97 (5)	174 (6.2)	413 (5.5)	
Marital status						0.01
Married	389 (65.7)	1385 (62.2)	1196 (61.7)	1721 (61.5)	4691 (62.1)	
Single	174 (29.4)	741 (33.3)	626 (32.3)	886 (31.7)	2427 (32.1)	
Unknown	29 (4.9)	100 (4.5)	117 (6)	191 (6.8)	437 (5.8)	
Tumor Stage						< .0001
Localized	88 (14.9)	258 (11.6)	180 (9.3)	233 (8.3)	759 (10.1)	
Regional	52 (8.8)	191 (8.6)	152 (7.8)	198 (7.1)	593 (7.9)	
Advanced	416 (70.3)	1626 (73.1)	1509 (77.8)	2206 (78.8)	5757 (76.2)	
[OTHER]	36 (6.1)	151 (6.8)	98 (5.1)	161 (5.8)	446 (5.9)	
Median household income						< .0001
1st quartile	62 (10.5)	547 (24.6)	510 (26.3)	769 (27.5)	1888 (25)	
2nd quartile	163 (27.5)	531 (23.9)	471 (24.3)	638 (22.8)	1803 (23.9)	
3rd quartile	210 (35.5)	553 (24.8)	501 (25.8)	690 (24.7)	1954 (25.9)	
4th quartile	157 (26.5)	595 (26.7)	457 (23.6)	701 (25.1)	1910 (25.3)	

* Chi-square test was performed to compare the baseline characteristics over time.

Table 1b
Baseline characteristics of MCL patients from TCR area by calendar period of diagnosis.

Characteristics	TCR					
	1995-1998 (n = 282)	1999-2004 (n = 617)	2005-2008 (n = 474)	2009-2013 (n = 682)	Total (n = 2055)	P-value*
Age at diagnosis						0.21
< 50	36 (12.8)	63 (10.2)	38 (8)	54 (7.9)	191 (9.3)	
50-59	62 (22)	108 (17.5)	85 (17.9)	139 (20.4)	394 (19.2)	
60-69	81 (28.7)	180 (29.2)	145 (30.6)	221 (32.4)	627 (30.5)	
70-79	68 (24.1)	178 (28.9)	131 (27.6)	185 (27.1)	562 (27.4)	
80 +	35 (12.4)	88 (14.3)	75 (15.8)	83 (12.2)	281 (13.7)	
Gender						0.23
Female	80 (28.4)	190 (30.8)	122 (25.7)	209 (30.7)	601 (29.3)	
Male	202 (71.6)	427 (69.2)	352 (74.3)	473 (69.4)	1454 (70.8)	
Race/Ethnicity						0.03
non-Hispanic White	220 (78)	501 (81.2)	366 (77.2)	512 (75.1)	1599 (77.8)	
non-Hispanic Black	21 (7.5)	22 (3.6)	21 (4.4)	26 (3.8)	90 (4.4)	
Hispanic	38 (13.5)	86 (13.9)	78 (16.5)	126 (18.5)	328 (16)	
Other	3 (1.1)	8 (1.3)	9 (1.9)	18 (2.6)	38 (1.9)	
Marital status						< .0001
Married	15 (5.3)	283 (45.9)	204 (43)	293 (43)	795 (38.7)	
Single	7 (2.5)	121 (19.6)	101 (21.3)	134 (19.7)	363 (17.7)	
Unknown	260 (92.2)	213 (34.5)	169 (35.7)	255 (37.4)	897 (43.7)	
Tumor Stage						< .0001
Localized	51 (18.1)	78 (12.6)	56 (11.8)	71 (10.4)	256 (12.5)	
Regional	28 (9.9)	42 (6.8)	40 (8.4)	38 (5.6)	148 (7.2)	
Advanced	127 (45)	395 (64)	314 (66.2)	430 (63.1)	1266 (61.6)	
[OTHER]	76 (27)	102 (16.5)	64 (13.5)	143 (21)	385 (18.7)	
Median household income						0.44
1st quartile	64 (22.7)	157 (25.5)	116 (24.5)	175 (25.7)	512 (24.9)	
2nd quartile	57 (20.2)	156 (25.3)	116 (24.5)	182 (26.7)	511 (24.9)	
3rd quartile	73 (25.9)	134 (21.7)	99 (20.9)	139 (20.4)	445 (21.7)	
4th quartile	88 (31.2)	170 (27.6)	143 (30.2)	186 (27.3)	587 (28.6)	

* Chi-square test was performed to compare the baseline characteristics over time.

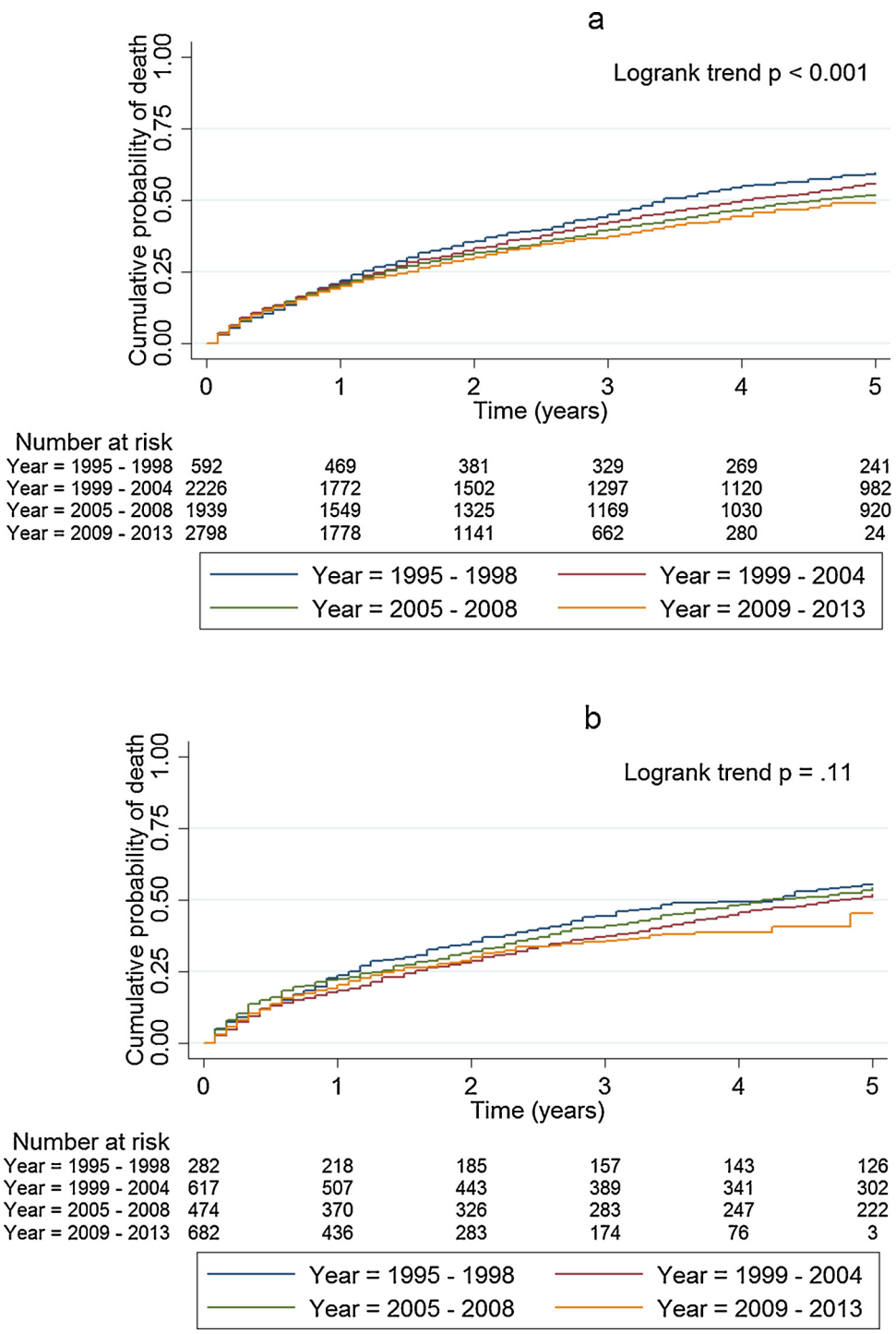

Fig. 1. 5-year cumulative probability of death for MCL patients by calendar period of diagnosis in SEER and TCR. **(1a) SEER data; (1b) TCR data.**

calendar periods of diagnosis. In the SEER data (Fig. 1a), the 5-year cumulative probability of death decreased significantly with the calendar period of diagnosis ($P < 0.001$). In the TCR data (Fig. 1b), the 5-year cumulative probability of death did not decrease significantly with the calendar period of diagnosis ($P = 0.11$). Table 2 presents the median survival time for all-cause mortality, 3-year and 5-year all-cause mortality, and MCL-specific mortality rates for both SEER and TCR. In the SEER analysis, median survival time was 41 months for the P1 cohort, 48 months for the P2 cohort, 55 months for the P3 cohort, and 52 months for all patients during the entire study period (1995 to 2013). The estimated median survival time was not reached for the P4 cohort. The estimated 3-year all-cause mortality rate decreased from 44% to 38% from P1 to P4 ($P = 0.0006$), and the 5-year all-cause mortality rate decreased from 59% to 51% over the same time ($P < 0.0001$). The 3-year MCL-specific mortality rate decreased from 37% to 30% from P1 to P4 ($P = 0.01$), and the 5-year MCL-specific mortality rate decreased from 49% to 38% over this time ($P < 0.0001$).

For the TCR group, the median OS was 52 months for P1, 57 months for P2, 51 months for P3, not reached for P4, and 57 months for all patients diagnosed from 1995 to 2013. The estimated 3-year all-cause mortality rate decreased from 44% in P1 to 37% in P4 ($P = 0.21$), and the 5-year all-cause mortality rate decreased from 55% in P1 to 45% in P4 ($P = 0.11$). The 3-year MCL-specific mortality rate was 36% in P1 and 29% in P4 ($P = 0.47$) and the 5-year MCL-specific mortality rate

Table 2
Median OS, 3-year and 5-year mortality rate by calendar period of diagnosis in SEER and TCR.

Survival statistics	Calendar Period of Diagnosis					
	1995 - 1998 (P1)	1999 - 2004 (P2)	2005 - 2008 (P3)	2009 - 2013 (P4)	Total (P1, P2, P3 and P4)	P-value
SEER						
Total cases, N	592	2226	1939	2798	7555	
Death cases, N (%)	506 (85.47)	1729 (77.67)	1148 (59.21)	877 (31.34)	4260 (56.39)	< 0.0001[c]
Median OS (months, 95% CI)	41 (37-47)	48 (46-54)	55 (50-61)	–	52 (49-55)	
3-year all-cause mortality [a], (95% CI)	0.44 (0.40-0.48)	0.42 (0.40-0.44)	0.39 (0.37-0.41)	0.38 (0.36-0.40)	0.40 (0.39-0.41)	0.0006 [a]
5-year all-cause mortality [a], (95% CI)	0.59 (0.55-0.63)	0.56 (0.54-0.58)	0.52 (0.50-0.54)	0.51 (0.47-0.54)	0.54 (0.52-0.55)	< 0.0001 [a]
3-year MCL-specific mortality [b], (95% CI)	0.37 (0.02-0.33)	0.35 (0.01-0.33)	0.32 (0.01-0.3)	0.30 (0.01-0.28)	0.33 (0.01-0.32)	0.01 [b]
5-year MCL-specific mortality [b], (95% CI)	0.49 (0.02-0.45)	0.46 (0.01-0.44)	0.42 (0.01-0.39)	0.38 (0.01-0.35)	0.43 (0.01-0.42)	< 0.0001 [b]
TCR						
Total cases, N	282	617	474	682	2055	
Death cases, N (%)	236 (83.69)	463 (75.04)	294 (62.03)	204 (29.91)	1197 (58.25)	0.03[c]
Median OS (months, 95% CI)	51.5 (35-62)	57 (49-64)	50.5 (44-61)	–	57 (52-61)	
3-year all-cause mortality [a], (95% CI)	0.44 (0.39-0.50)	0.37 (0.33-0.41)	0.40 (0.36-0.45)	0.37 (0.32-0.41)	0.39 (0.37-0.41)	0.21 [a]
5-year all-cause mortality [a], (95% CI)	0.55 (0.50-0.61)	0.51 (0.47-0.55)	0.53 (0.49-0.58)	0.45 (0.39-0.52)	0.52 (0.49-0.54)	0.11[a]
3-year MCL-specific mortality [b], (95% CI)	0.36 (0.03-0.3)	0.32 (0.02-0.29)	0.31 (0.02-0.27)	0.29 (0.02-0.25)	0.32 (0.01-0.3)	0.47[b]
5-year MCL-specific mortality [b], (95% CI)	0.45 (0.03-0.39)	0.44 (0.02-0.4)	0.4 (0.02-0.36)	0.36 (0.05-0.26)	0.42 (0.01-0.39)	0.21[b]

- median follow-up was not reached.

[a] 3-year and 5-year all-cause mortality was estimated for each calendar period of diagnosis from Kaplan-Meier survival curve estimates, the trend of mortality was tested by log-rank trend test.

[b] 3-year and 5-year MCL-specific mortality rates were estimated using cumulative incidence function to account for competing risk, the trend of MCL-specific mortality was test by Gray's test.

[c] trend of overall survival to the maximum of follow-up over calendar period of diagnosis was tested using log-rank trend test.

Table 3
Risk of death among MCL patients in relation to calendar period of diagnosis in SEER (N = 7555) and TCR (N = 2055)[*].

Predictors	SEER				Texas			
	Cases N	Death N	Model HR (95% CI)	P-value < .0001	Cases N	Death N	Model HR (95% CI)	P-value
Calendar period of diagnosis								< .0001
1995-1998	592	506	1.00 (Reference)		282	236	1.00 (Reference)	
1999-2004	2226	1729	0.82 (0.73-0.92)		617	463	0.85 (0.70-1.02)	
2005-2008	1939	1148	0.66 (0.59-0.75)		474	294	0.66 (0.53-0.81)	
2009-2013	2798	877	0.58 (0.51-0.66)	< .0001	682	204	0.63 (0.51-0.79)	
Age at diagnosis group								< .0001
< 50	642	227	1.00 (Reference)		191	69	1.00 (Reference)	
50-59	1521	637	1.30 (1.11-1.53)		394	166	1.52 (1.11-2.10)	
60-69	2157	1084	1.64 (1.41-1.91)		627	344	2.26 (1.68-3.05)	
70-79	2031	1357	2.35 (2.02-2.73)		562	389	3.03 (2.25-4.07)	
80+	1204	955	3.54 (3.02-4.16)	< .0001	281	229	3.40 (2.46-4.71)	
Gender								0.02
Female	2299	1289	1.00 (Reference)		601	339	1.00 (Reference)	
Male	5256	2971	1.19 (1.10-1.29)	< .001	1454	858	1.17 (1.01-1.35)	
Race/Ethnicity								0.39
non-Hispanic Black	324	173	1.00 (Reference)		90	52	1.00 (Reference)	
Hispanic	698	382	1.36 (1.10-1.70)		328	180	1.25 (0.88-1.77)	
non-Hispanic White	6120	3502	1.12 (0.93-1.35)		1599	950	1.08 (0.79-1.48)	
Other	413	203	1.13 (0.89-1.44)	< .0001	38	15	0.90 (0.47-1.74)	
Marital status								0.53
Married	4691	2502	1.00 (Reference)		795	425	1.00 (Reference)	
Single	825	460	1.22 (1.13-1.32)		121	66	1.56 (1.17-2.09)	
Unknown	437	201	0.72 (0.61-0.86)	< .0001	897	562	1.07 (0.92-1.25)	
Tumor stage								< .0001
Localized	759	374	1.00 (Reference)		256	137	1.00 (Reference)	
Regional	593	340	1.54 (1.29-1.84)		148	81	1.37 (0.99-1.88)	
Advanced	5757	3264	2.06 (1.81-2.35)		1266	769	1.80 (1.45-2.24)	
Other	446	282	1.88 (1.56-2.26)	< .001	385	210	1.43 (1.11-1.84)	
Median household income								0.50
1st quartile	1888	1088	1.00 (Reference)		512	318	1.00 (Reference)	
2nd quartile	1803	1061	0.88 (0.79-0.97)		511	290	1.00 (0.84-1.20)	
3rd quartile	1954	1071	0.83 (0.75-0.91)		445	271	0.87 (0.72-1.06)	
4th quartile	1910	1040	0.83 (0.75-0.91)	< .0001	587	318	0.97 (0.81-1.16)	

* Fine and Gray competing risk proportional hazard model was performed to estimate the association between calendar period of diagnosis and the hazard of death, adjusted for age, gender, race/ethnicity, marital status, tumor stage, and median household income.

was 45% in P1 and 36% in P4 ($P = 0.21$).

3.3. Multivariable survival analysis

The results of the multivariable Fine and Gray proportional hazard regression analyses are presented in Table 3. In the SEER group, with P1 as the reference group and controlling for age, sex, race/ethnicity, marital status, and median household income, the adjusted subdistribution hazard ratios (HRs) for MCL-specific mortality were 0.82 (95% confidence interval [CI]: 0.73-0.92) for P2, 0.66 (0.59-0.75) for P3, and 0.58 (0.51-0.66) for P4. The hazard of MCL-specific death also increased with patient age, with HRs of 1.30, 1.64, 2.35, and 3.54 for patients aged 50 to 59, 60 to 69, 70 to 79, and 80 or older, respectively, compared to patients younger than 50. The hazard of death for men was 1.19 times that of women. The hazard of death for Hispanic patients was 1.36 times that of non-Hispanic black patients. The hazard of death for single patients was 1.22 times that of married patients. The hazards of death for patients with regional and advanced-stage tumors were 1.54 and 2.06 times, respectively, that of patients with localized tumors. The hazards of death for patients in the second, third, and fourth quartiles of median household income were 0.88, 0.83, and 0.83 times, respectively, that of patients with first-quartile median household incomes. In the TCR cohort, the hazard of death for P2, P3, and P4 was 0.85, 0.66, and 0.63 times that of P1, respectively. The hazards of death for age and sex were similar to those in the SEER data and significantly different from the reference groups. However, for race/ethnicity, marital status, tumor stage, and median household income, the hazards of death were not significantly different from the reference groups.

3.4. Sensitivity analyses

3.4.1. Sensitivity analyses by tumor stage

Fig. 2 presents the 5-year cumulative probability of death for MCL patients with advanced stage tumor in SEER (Fig. 2a) and TCR (Fig. 2b). In SEER, only patients with advanced stage tumor had significant decrease in the 5-year cumulative probability of death over the study period ($p < 0.001$), while patients with localized and regional stage tumors did not show significant improvement (Supplemental Figures S1a and S1b; all $p > 0.05$). In TCR, there was no significant decrease observed in the cumulative probability of death over the calendar period of diagnosis in patients with any of tumor stages (Fig. 2b, Supplemental Figs. S2a, and S2b; all $p > 0.05$).

Sensitivity analyses were conducted by performing multivariable Fine and Gray proportional hazards regression among patients with different tumor stages (Table 4). In SEER areas, the hazards of MCL-specific death for P2, P3, and P4 in patients with localized tumor were 0.82, 0.60, and 0.63 times that of P1, respectively, with only the latter two periods having hazards of death significantly different from 1. The hazards of death for patients with regional stage tumor for P2, P3, and P4 were 0.96, 0.71 and 0.77 times that of P1 (none of them significantly different from 1). The hazards of death for patients diagnosed with advanced stage tumor in P2, P3, and P4 were 0.80, 0.64 and 0.55 that of P1 (all significantly different from 1), respectively. In TCR, the hazards of death for P4 were 0.46, 0.40, and 0.70 times that of P1 for patients diagnosed with localized, regional, and advanced stage tumors (significantly different from that of P1), respectively. For patients with advanced stage tumor, the hazard of death for P3 was 0.63, significantly different from 1. None of the other HRs were statistically different from that of P1.

3.4.2. Sensitivity analyses by combining the SEER and TCR databases

Multivariable Fine and Gray proportional hazard regression was also performed on the combined SEER and TCR population (Supplemental Table 1). The results for the combined population were similar compared to those for SEER or TCR alone. In the combined cohort, compared to patients in P1, the adjusted subdistribution hazard ratio (HR) of MCL-specific mortality were 0.81 (95% CI: 0.74-0.89), 0.65 (95% CI: 0.59-0.72), and 0.58 (95% CI: 0.52-0.65) for patients in P2, P3, and P4, respectively, controlling for age, gender, race/ethnicity, marital status, and median household income. Factors significantly associated with a higher risk of MCL-specific death included older age, male, Hispanic, single, advanced tumor stage, and lower income level.

3.4.3. Sensitivity analyses by age group

Sensitivity analyses by age group were also conducted on the combined cohort since age was an important prognostic factor for MCL. Supplemental Table 2 showed the multivariable Fine and Gray proportional regression stratified by age group. The hazards of MCL-specific death significantly decreased over the study period among all age groups. Only in age groups 50–59 and 60–69, the hazards of death decreased significantly for all three time periods compared with period 1. Supplemental figure S3 presented the logrank trend test results of 5-year cumulative death probability for each age group (figure S3a-S3e). The figures showed that for all age groups, there was a significant decrease in the 5-year cumulative death probability over the study period.

4. Discussion

This study investigated the OS and mortality rates for MCL patients diagnosed from 1995 to 2013. The median OS for MCL patients in SEER and TCR areas were 52 and 57 months, respectively. In the unadjusted analyses, the cumulative probability of death for MCL decreased significantly from P1 to P4 in both SEER and TCR. When adjusting for demographic characteristics and tumor stage in the multivariable regression, the risk of MCL death decreased significantly over the study periods in both SEER and TCR.

The findings of our study further confirmed the impact of novel agents on improved survival over time that was shown in other studies. A previous study by Chandran et al. [22] examined the survival trends in MCL in the U.S. from 1992 to 2007 using SEER database, and found no change in OS, but after adjusting for age, gender, and stage of disease, there was significant improvement in survival in both the entire group of patients and in patients with advanced tumor stage. Our study updated the data to more recent time period and the findings suggested that in both SEER and TCR, the introduction of novel agents over time had a significant impact on the survival of MCL patients. In the Nordic Lymphoma Group observational study conducted by Abrahamsson et al., the patients treated with rituximab had significantly improved OS compared to those who did not receive rituximab [29]. In another study conducted by Smith et al., the median survival for MCL patients increased by 1.5 years from 2004 to 2011 to 2012–2015 [30].

After conducting subgroup analyses by tumor stage, the survival outcome for MCL patients with advanced stage tumor improved in both SEER and TCR, but not in patients with other tumor stages. In the unadjusted analysis, significant decrease in the cumulative probability of death for MCL was observed in patients with advanced stage tumor in SEER, but not in TCR. In the adjusted analysis, patients with advanced stage tumor had a decreased risk of death over the study period in both SEER and Texas areas. These results suggested that the demographic variables are potential confounders for the survival of MCL patients, and MCL patients with advanced stage tumor benefitted most from the introduction of newly developed regimens. Tumor stage may also explain the different survival trend observed in different tumor stage, since patients with localized and regional tumor stage are more likely to receive radiation alone and the development of novel agents may have less impact on this group of patients compared to those with advanced tumor stage.

The findings from our subgroup analyses by tumor stage were consistent with those of previous studies in that significant improvement in survival was observed in MCL patients with advanced stage tumor [22,31]. Hermman et al. [31] studied the OS in MCL patients with advanced stage tumor by comparing the survival outcome of the

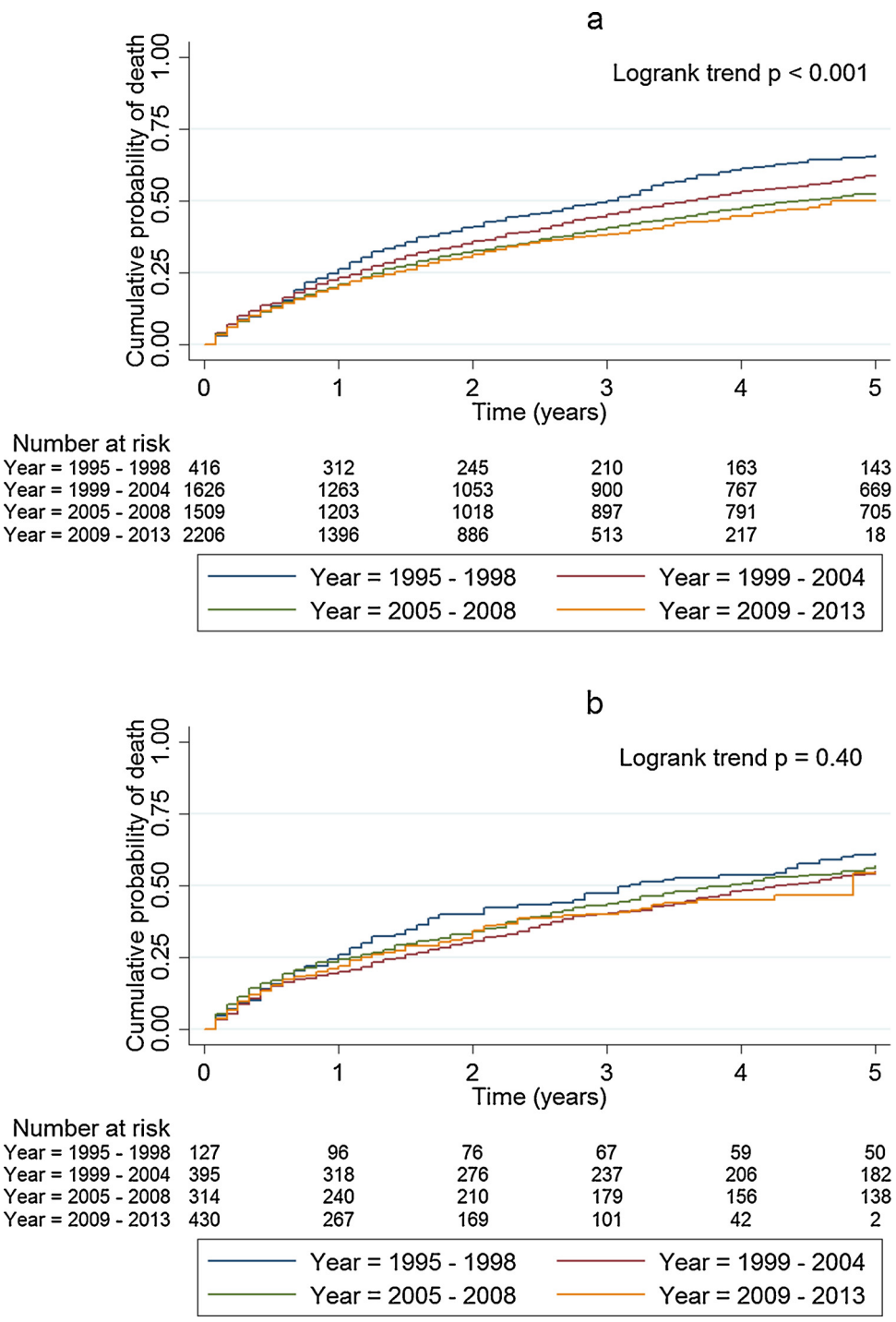

Fig. 2. 5-year cumulative probability of death for MCL patients with advanced stage tumor in SEER and TCR. **(2a) SEER data; (2b) TCR data.**

German Low Grade Lymphoma Study Group (GLSG; 1996 TO 2004) and the Kiel Lymphoma Study Group (KLSG; 1975 TO 1986), and found that the median OS of advanced stage MCL almost doubled during the past 30 years. Chandran et al. [22] also found that patients with advanced stage tumor had an improved survival from 1992 to 2007.

The study is prone to several limitations. The first limitation is that we focused on the overall survival trend analyses for different diagnostic periods, but treatment regimen-specific survival was not evaluated. We were only able to estimate the trend in survival for the entire MCL population, but not able to precisely distinguish the survival outcome of each treatment regimen. The second limitation is that we used time period as a surrogate on the impact of new regimens, but we had no information on how quickly the newly approved agents were adapted to real-world medical practice. Further analysis evaluating the treatment modality-specific survival is warranted to confirm to what extent each modality improved the survival outcome. In addition, lenalidomide, ibrutinib, and acalabrutinib were approved to treat MCL by FDA after 2013, therefore further analyses are needed to evaluate those drugs when the data is available. Furthermore, about 6% of patients from SEER and 18.7% of patients from TCR had unknown tumor stage, leading to potential misclassifications and statistical uncertainties.

The study has several strengths as well. First, SEER and TCR data are highly valuable sources of patient information, tumor variables and survivorship. Both SEER and TCR met the national Centers for Disease

Table 4
Risk of death among MCL patients in relation to calendar period of diagnosis in SEER (N = 7555) and TCR (N = 2055), stratified by tumor stage.

Registry	Diagnosis year	HR* (95% CI)					
		Localized stage	P-value	Regional stage	P-value	Advanced stage	P-value
SEER	1 1995-1998	1.00 (Reference)	0.06	1.00 (Reference)	0.23	1.00 (Reference)	< .0001
	2 1999-2004	0.82 (0.57-1.18)		0.96 (0.62-1.50)		0.80 (0.70-0.90)	
	3 2005-2008	0.60 (0.40-0.91)		0.71 (0.44-1.16)		0.64 (0.56-0.73)	
	4 2009-2013	0.63 (0.40-1.00)		0.77 (0.47-1.27)		0.55 (0.48-0.63)	
TCR	1 1995-1998	1.00 (Reference)	0.28	1.00 (Reference)	0.24	1.00 (Reference)	0.002
	2 1999-2004	0.95 (0.55-1.62)		1.28 (0.55-3.00)		0.87 (0.67-1.12)	
	3 2005-2008	0.90 (0.49-1.66)		1.06 (0.42-2.64)		0.63 (0.48-0.84)	
	4 2009-2013	0.46 (0.20-1.04)		0.40 (0.12-1.26)		0.70 (0.52-0.95)	

* hazard ratios were estimated using Fine and Gray competing risk proportional hazard model, adjusted for age, gender, race/ethnicity, median household income.

Control (CDC) "high quality" data standards and received Gold certification (highest level) from North American Association of Central Cancer Registries (NAACCR). The completeness of case ascertainment in SEER program is as high as 98% [32] and is over 95% for TCR. The two datasets have a broad coverage of the U.S. population. Second, both datasets have a long follow-up time period, with SEER data available from 1975 to 2013 and TCR from 1995 to 2013, which allowed us to generate time trend analysis and long term survival analysis. Third, the study revealed the survival outcome for MCL patients in Texas for the first time, and the results suggest that TCR mirrors SEER. Lastly, this study updated the survival outcome for MCL patients to the most recent available years.

5. Conclusion

During the study period from 1995 to 2013, MCL patients in both SEER and TCR areas had a significant improvement in survival outcome. When stratified by tumor stage, the improvement of survival was observed in patients with advanced stage tumor only. The increase of survival was also observed in all age groups. We conclude that the survival outcome for MCL patients improved from 1995 to 2013, which may reflect the potential impact of newly developed treatment regimens.

Author contributions

Shuangshuang Fu: Conceptualization, data curation, formal analysis, writing original draft, review, and editing.

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Xianglin L. Du: Conceptualization, methodology, supervision, review, and editing.

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Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2018.12.002.

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