Treatment patterns and real-world effectiveness of rituximab maintenance in older patients with mantle cell lymphoma: a population-based analysis

Despite advances in management over recent years,[1-4] mantle cell lymphoma (MCL) remains an incurable disease.[5] The primary objective remains to achieve a long-lasting remission with first-line therapy. In order to achieve this goal, younger patients typically receive induction chemoimmunotherapy followed by consolidative autologous stem cell transplant (ASCT) with or without rituximab maintenance (RM). While many older patients may not be candidates for ASCT due to comorbidities and frailty, RM following induction chemoimmunotherapy is often considered. The clinical benefit of RM for MCL in older, ASCT-ineligible patients was demonstrated in a randomized controlled trial.[6] When compared to interferon, RM prolongs both progression-free (PFS) and overall survival (OS) after R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) as induction therapy (rituximab *vs*. interferon: median PFS: 5.4 *vs*. 1.9 years, median OS: 9.8 *vs*. 7.1 years).[6, 7]

However, since the publication of the efficacy data on RM in 2012, increasing evidence has raised the concern that R-CHOP for induction might be associated with inferior outcomes in MCL compared to bendamustine-rituximab (BR).[8] Consequently, BR is recommended as the preferred first-line regimen for older, ASCT-ineligible patients with MCL in contemporary clinical practice guidelines.[9] With the availability of more effective first-line treatment options (e.g., BR), the clinical benefit of RM has become less certain. In order to address this knowledge gap, we conducted a population-based study using the linked Surveillance, Epidemiology and End Results (SEER)-Medicare 2020 database and hypothesized that i) BR has replaced R-CHOP as the most used first-line regimen for older patients with MCL and ii) despite an evolution of the preferred first-line regimen, RM remains beneficial.

In order to assess the real-world treatment patterns for first-line MCL therapy, we selected adults ≥66 years old who were diagnosed with MCL in 2007-2017, had continuous Medicare A/B/D coverage, and had received ≥ one MCL therapy. We included 1,579 patients (Figure 1A). The median age was 76 years (interquartile range: 71-81 years), 65% were men, 95% were white, and 25% were described as frail with 21% having a comorbidity score ≥3 (Table 1). The median follow-up was 68 months.

We examined details of the first-line regimens among those receiving treatment in the outpatient setting, as chemoimmunotherapy information was only available in the outpatient claims (drug codes included in the *Online Supplementary Table S1*). We evaluated the practice patterns of RM and second-line therapy in a sub-population of patients who received R-CHOP or BR as first-line therapy. We defined RM as rituximab given as a single agent within 200 days after completion of rituximab containing first-line regimen, for ≥ two consecutive doses and lasting for ≥28 days. We used similar criteria to define lines of therapy as those applied in the Flatiron Health dataset.[10] For example, any non-rituximab chemoimmunotherapy agent given within a 30-day window or rituximab within a 90-day window was considered as the same line. Among patients receiving treatment in the outpatient setting (n=1,367; 87%), the most common first-line therapies were bendamustine-based regimens (n=630; 46%), followed by anthracycline-based regimens (n=304; 22%). Novel therapies (including BTK and BCL-2 inhibitors) were rarely administered in the first line (n=72; 5.3%), and only 16 patients (1.2%) received cytarabine-based regimens as first-line therapy. Fifty patients (3.2% among the 1,579 patients) underwent ASCT following the first-line therapies. In order to examine the shift of first-line practice (R-CHOP *vs*. BR), we applied logistic regression models by incorporating year of diagnosis. Use of R-CHOP decreased substantially over time (2007: 43%, 2017: 7.3%, *P* for trend <0.001), with a significant increase in use of BR (2007:1.5%, 2017: 60%, *P*<0.001; Figure 1B). Among patients receiving R-CHOP or BR, 28% (n=244) received RM following the completion of the first-line therapies, with a median number of doses and duration of 9.5 doses and 18 months, respectively. Novel agents have become the most common therapies for the second-line setting (Figure 1C).

In order to examine the real-world effectiveness of RM, we limited the overall study population to those who received R-CHOP or BR as first-line treatment and did not receive consolidative ASCT (transplant codes are included in the *Online Supplementary Table S1*). In order to minimize the potential immortal bias, for the non-RM group, we included patients who had a treatment gap (recipients of second-line therapy) or survival (no second-line therapy given) of ≥200 days after the completion of the first-line therapy, to ensure a sufficient amount of time to have been considered for RM.

We then created a matched study sample using propensity score matching (PSM) (ratio=1:1, greedy nearest neighbor with caliper=0.10) based on age, sex, race, mari-

tal status, Medicaid dual coverage, residence, poverty, frailty,[11] comorbidities (modified Elixhauser index),[12] year of diagnosis, extranodal disease, stage, first-line regimen (R-CHOP *vs*. BR), and duration of first-line therapy. In the PSM cohort, we included 262 patients, with a median age of 75 years, 67% men, >91% White, and 76% receiving first-line BR. The median number of doses and duration of RM in the "intervention arm" was 9.0 doses and 17 months, respectively. All baseline variables were balanced between the RM and non-RM groups (Table 1; *P* values for all variables >0.1). The distributions of probabilities of receiving RM after PSM became very similar between the two comparison groups (*Online Supplementary Figure S1*). The standardized mean differences of all covariates between the two groups were smaller than (or very close to) 10%, which also suggested optimal matching.

In the PSM cohort, we applied the Cox regression model to compare overall survival (OS) and "approximated progression-free survival" ("approximated-PFS") (survival and free of second-line therapy), respectively, based on the re-

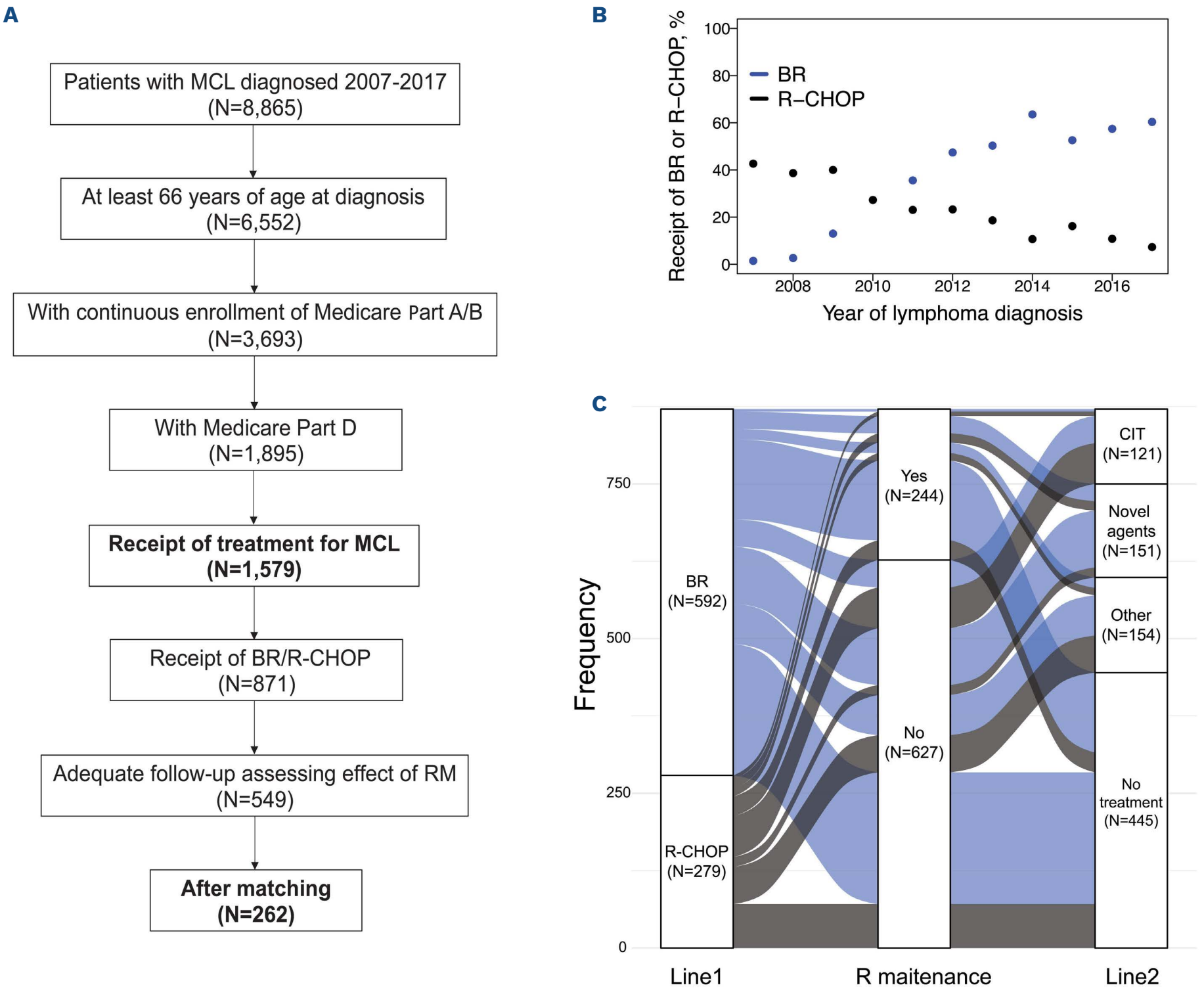

Figure 1. Selection of study population and patterns of real-world practice for management of older patients with mantle cell lymphoma. (A) Flow diagram of patient selection. (B) Trend in use of BR and R-CHOP over time. (C) Real-world practice patterns of rituximab maintenance and second-line therapies following BR and R-CHOP in older, transplant ineligible patients with mantle cell lymphoma (MCL). BR: bendamustine+ rituximab; R-CHOP: rituximab+ cyclophosphamide+ doxorubicin+ vincristine+ prednisone; RM: rituximab maintenance; CIT: chemoimmunotherapy; R: rituximab. CIT includes anthracycline-, bendamustine-, and cytarabine-based chemoimmunotherapy. Novel therapies include ibrutinib, acalabrutinib, venetoclax, lenalidomide, and bortezomib. Other includes chemoimmunotherapy not included in the "CIT" category, rituximab single agent, and inpatient treatment (unknown regimens). Among patients receiving rituximab maintenance, 178 and 66 received BR and R-CHOP, respectively. Among patients who did not receive second-line therapy, 251 remained alive at the end of the study follow-up.

ceipt of RM and reported hazard ratio (HR) with 95% confidence interval (CI). We conducted competing-risk analysis for initiation of second-line therapy, reporting subdistribution HR (sHR) and 95% CI (all-cause mortality as the competing events). We followed patients from the initiation of the first-line therapy until the events of interest (all-cause mortality and initiation of second-line therapy), or the end of follow-up on December 31, 2019, whichever occurred first. Compared to the non-RM group, patients receiving RM had significantly longer OS and "approximated-PFS" and lower likelihood of receiving second-line therapy. In the subgroup analysis in patients receiving first-line BR, there was also significant clinical benefit in all three outcomes with the use of RM (Figure 2). In the sensitivity analyses using i) different definitions of the non-RM group (treatment gap following the completion of the first-line therapy of 150, 180, and 210 days, respectively); ii) earlier definition of RM (RM received ≤120 days following completion of first-line therapy); and iii) follow-up from completion of first-line therapy rather than initiation – our findings were essentially the same (*Online Supplementary Table S2*). Given the missing stage information, we performed simple imputation and the results following imputation were also largely unchanged (*data not shown*). The effectiveness of RM following BR in MCL has been examined in several previous studies.[10,13,14] However, due to the inconsistency of findings and some limitations of these studies, there remains uncertainty in the clinical benefit. Two prior observational studies[10,13] showed similar benefits in the multivariable analysis. In contrast, the MAINTAIN trial showed no significant difference in PFS or OS between the RM and non-RM groups, despite the longer median PFS observed with RM (not reached *vs*. 55 months for non-RM).[14] However, multivariable analysis might not be sufficient to control most potential confounding effects within observational data.[10,13] The non-significant results in the MAINTAIN trial[14] might be attributed to its relatively small sample size (total n=120).

Table 1. Baseline characteristics of the overall cohort for evaluation of first-line therapy and of the propensity score matched cohort for evaluation of real-world effectiveness of rituximab maintenance.

	Overall cohort (N=1,579)	PSM cohort (N=262)	
		RM (N=131)	No RM (N=131)
Age in years, median (IQR)	76 (71-81)	75 (71-79)	75 (71-79)
Sex, male, N (%)	1,025 (65)	86 (66)	89 (68)
Race, White, N (%)	1,495 (95)	>120 (>91)	>120 (>91)
Married, N (%)	719 (46)	60 (46)	64 (49)
Medicaid dual enrollment, N (%)	280 (18)	13 (10)	11 (8)
Residence in metropolitan area, N (%)	1,314 (83)	113 (86)	106 (81)
Poverty rate ≥20% *, N (%)	255 (16)	20 (15)	18 (14)
Frailty, N (%) ** Frail Unfit	 398 (25) 1,053 (67)	 26 (20) 91 (69)	 25 (19) >95 (>73)
Comorbidity score ≥3, N (%)	324 (21)	27 (21)	23 (18)
Year of diagnosis, N (%)[$] BTKi era Pre-BTKi era	 727 (46) 531 (34)	 75 (57) 26 (20)	 78 (60) 24 (18)
Stage, N (%) Stage I/II Stage III/IV Unknown	 166 (11) 724 (46) 689 (43)	 13 (10) 55 (42) 63 (48)	 <11 (<8) 54 (41) >66 (>51)
Extranodal disease, N (%)[$$]	362 (23)	31 (24)	31 (24)
First line therapy, BR, N (%)[§]	592 (43)	98 (75)	100 (76)
Duration of 1st line <130 days, N (%)	886 (56)	33 (25)	34 (26)

RM: rituximab maintenance, PSM: propensity score matching; IQR: interquartile range; BR: bendamustine-rituximab; BTKi era: diagnosis in 2014-2017, pre-BTKi era: diagnosis in 2007-2011. *Prioritizing data from SEER record > census tract linkage > zip code linkage. **In 3 categories: fit, unfit, and frail with no missing data in the study population. [$]In 3 categories: BTKi era, pre-BTKi era, and washout period (2012-2013) with no missing data in the study population. [$$]No missing data in extranodal/nodal disease in the study population. [§]Among patients who received chemoimmunotherapy in the outpatient setting; these were the patients who had treatment regimen information available in the Medicare database. Some of the actual numbers are not reported in the table (e.g., >120 for White) in compliance with the reporting policy of the National Cancer Institute. *P* values for all baseline variables are >0.1

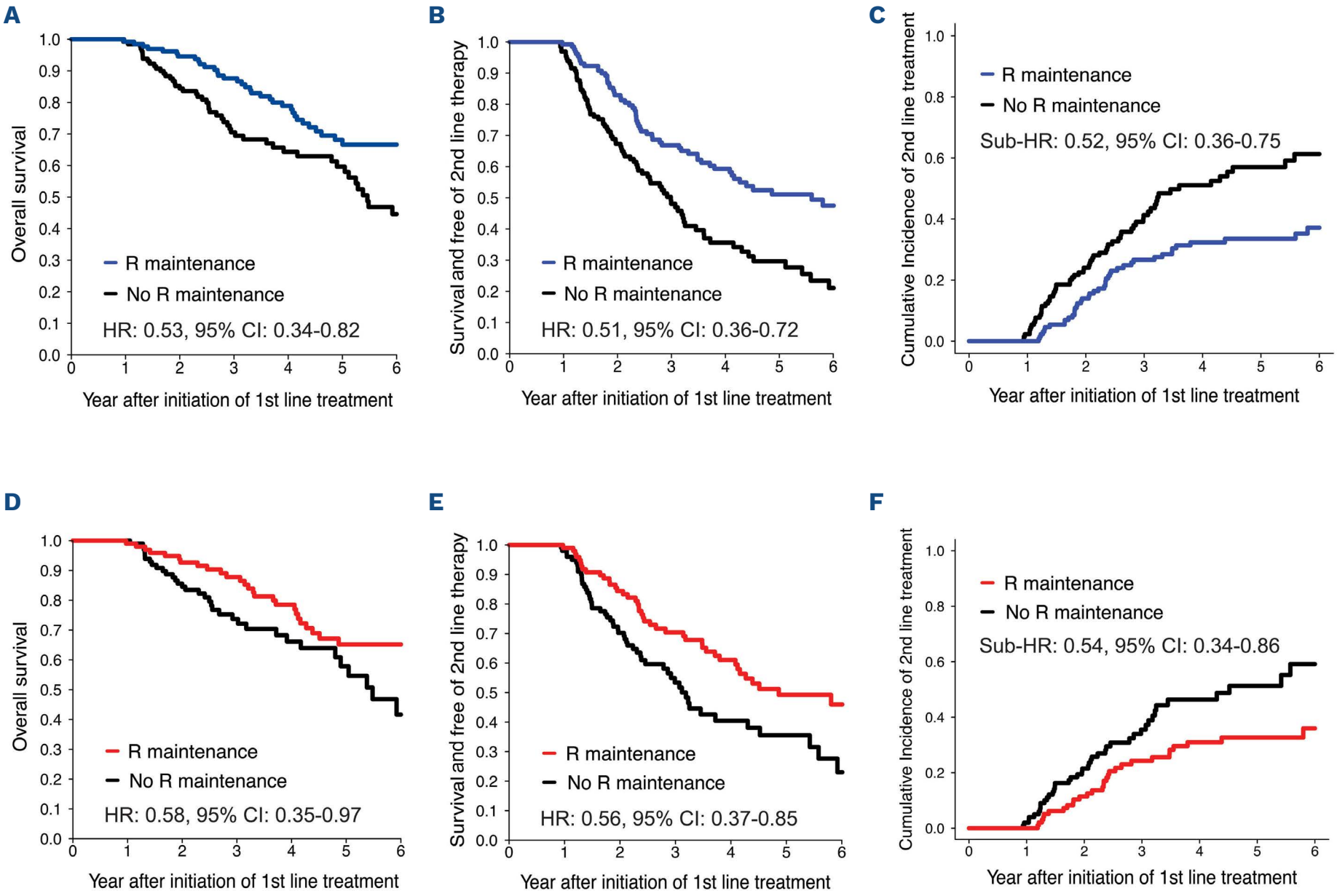

Figure 2. Comparison of patient outcomes between the rituximab maintenance and non-maintenance groups. (A) Overall survival, (B) survival and free of second-line therapy, (C) receipt of second-line therapy in patients receiving either BR or R-CHOP (n at risk=131 for each comparison group), (D) overall survival, (E) survival and free of 2nd line therapy, (F) receipt of second-line therapy in patients receiving BR only (n at risk= 98 for maintenance group and 100 for non-maintenance group). HR: hazard ratio; Sub-HR: subdistribution hazard ratio; CI: confidence interval; BR: bendamustine+ rituximab; R-CHOP: rituximab+ cyclophosphamide+ doxorubicin+ vincristine+ prednisone; R= rituximab.

Our analysis rigorously addressed most potential biases. These include i) the incorporation of most prognostic factors, including comorbidities and frailty; ii) the application of causal inference approach in the comparative effectiveness analysis and use of multiple methods to examine/ensure comparability between the matching groups; iii) the consideration and adjustment for immortal bias in receipt of RM; and iv) the conduction of multiple sensitivity analyses showing robust results. In addition, our study used the population-based US database and focused on the older population, contributing complementarily with the previous observational studies.

Despite the rigorous study design and bias control, our population-based analysis has several limitations. Firstly, we were unable to adjust some potential confounders which were not available in the SEER-Medicare database (e.g., TP53 aberrance status). Although there was a relatively high level of missing data in the lymphoma stage, results following imputation were essentially unchanged. Secondly, in the absence of data on responses to first-line induction from SEER-Medicare, we were unable to examine the potential differential effectiveness of RM based on prior responses. Thirdly, we were unable to compare the duration of remission, as date of relapse was not available in SEER-Medicare. Lastly, our population was not set to evaluate the effectiveness of RM following intensive regimens (e.g., cytarabine-based[15]) in fit, older patients, which should be examined in future studies.

In conclusion, our population-based real-world analysis showed significant benefits of RM in survival and disease control among older patients with MCL who did not receive ASCT, despite the shift from R-CHOP to BR as first-line induction. While prospective randomized trials would help validate the benefit of RM following BR, our study adds to the growing observational data supporting the benefit of RM in this setting.

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https://doi.org/10.3324/haematol.2022.282252

Received: October 20, 2022.
Accepted: January 5, 2023.
Early view: January 19, 2023.

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Disclosures

MD, JBL, TS, and RW do not have any conflict of interest to report. SKK reports consultancy and honoraria from Incyte and Karyopharm Pharmaceuticals. AMZ reports consultancy and research funding from AbbView, Acceleron, Amgen, Aprea, Boehringer Ingelheim, Cardiff Oncology, BMS, Incyte, Novartis; research funding from ADC Therapeutics, Astex, Pfizer; consultancy from Agios, Astellas, BeyondSpring, Daiichi Sankyo, Epizyme, Genentech, Gilead, Kura, Ionis, Loxo Oncology, Janssen, AstraZeneca, Jasper, Jazz; serving on clinical trial committees at AbbVie, BioCryst, BMS, Geron, Gilead, Kura, Loxo Oncology, Novartis; travel support from Cardiff Oncology, Novartis, Pfizer. NAP reports honoraria from Pfizer, Blueprint Medicines, Incyte, Novartis, Celgene, Bristol-Myers Squib, CTI BioPharma, PharmaEssentia, AbbVie, Constellation pharmaceuticals; serving on independent data monitoring committee at Cogent biosciences. RMS reports divested equity in a private or publicly-traded company at Curis and advisory boards for BMS and Gilead Sciences, Inc. XM reports consultancy with Bristol Myers Squibb. SFH reports consultancy from Abbvie, ADC Therapeutics, Arvinas, AstraZeneca, BeiGene, Epizyme, Flatiron Health, Genentech, Janssen, Merck, Novartis, Pharmacyclics, Seagen, Servier, TG therapeutics, and Thyme Inc.; research funding from Celgene, DTRM Biopharm, TG Therapeutics; honoraria from Pharmacyclics, AstraZeneca, Bayer.

Contributions

Conceptualization, formal analysis, data interpretation, writing-original draft, writing-review and editing by MD. Conceptualization, formal analysis, data interpretation, writing-review and editing by SFH. Conceptualization, data accrual, formal analysis, data interpretation, writing-review and editing by JBL. Conceptualization, data interpretation, writing-review and editing by SKK, TS, AMZ, NAP, RMS, RW, and XM.

Acknowledgments

This study used the linked SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors. The authors acknowledge the efforts of the National Cancer Institute, the Office of Research, Development and Information, CMS, Information Management Services (IMS), Inc. and the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries in the creation of the SEER-Medicare database.

Data-sharing statement

This study used Surveillance, Epidemiology, and End Results-Medicare database, which can be available upon application for the database through the National Cancer Institute.

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