Comparative effectiveness of immunotherapy alone or with chemotherapy as first-line treatment for marginal zone lymphoma

Marginal zone lymphoma (MZL) is a heterogeneous indolent B-cell malignancy comprising splenic (SMZL), nodal (NMZL), and extranodal (EMZL) subtypes.[1,2] Owing to its low incidence and variable presentation, prospective randomized data are limited. Most NMZL regimens mirror those for follicular lymphoma, while localized EMZL is frequently treated with local therapies or antibiotics for *Helicobacter pylori*-associated gastric disease. The IELSG-19 trial remains the only histology-specific phase III study of systemic first-line therapy in MZL, demonstrating longer progression-free survival (PFS) with rituximab plus chlorambucil than with either agent alone, but no overall survival (OS) benefit.[3]

Following evidence from trials showing superior PFS with bendamustine-rituximab (BR) compared with cyclophosphamide-based combinations in indolent lymphomas, BR has largely replaced other chemoimmunotherapy regimens in the USA.[4,5] In small series there have been reported 5-year PFS rates of 80-87% across MZL subtypes, yet no study has demonstrated an OS or quality-of-life advantage over rituximab monotherapy, which can yield durable remissions with less toxicity.[6-8] Given bendamustine's prolonged immunosuppression and the indolent nature of relapsed MZL, the comparative survival impact of BR *versus* rituximab alone warrants clarification.

We evaluated PFS and OS using two large real-world datasets: the US National Cancer Data Base (NCDB), which is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society,[9] and a multi-institutional MZL-real world data (MZL-RWD) retrospective cohort, applying causal-inference methods to minimize treatment-selection bias.[10]

The NCDB 2022 file identified adults (≥18 years) diagnosed with MZL from 2013-2018. This period captures the introduction of rituximab-specific coding and ≥5 years of follow-up. NCDB variables include demographics, stage, B symptoms, and initial treatment categorized as immunotherapy (principally, rituximab) or cytotoxic chemotherapy, without drug-level detail (*Online Supplementary Table S1*). We excluded patients untreated at the reporting facility, lacking histological confirmation, not receiving immunotherapy, or with missing diagnosis-to-treatment interval.

The MZL-RWD dataset comprised 878 patients treated at ten centers in the USA between 2010-2020 with detailed clinicopathological, laboratory, treatment, and survival data,[11,12] of whom 541 received first-line rituximab or BR. Missing values were imputed by mean substitution. All data were de-identified and analyses approved by Institutional Review Boards; there was no linkage between datasets.

Analyses were performed separately for NCDB and MZL-RWD using a previously described framework.[4,13] A logistic model produced propensity scores including all variables from the treatment selection mode and interaction between age (with restricted cubic spline in the NCDB data) and MZL subtype. Patients were matched within a 10% caliper of the propensity-score standard deviation (1:1 matching) in NCDB and inverse probability of treatment weighting (IPTW) in MZL-RWD (validated by 1:1 matching). Covariate balance was defined as standardized difference of means (SDM) <0.1.

Outcomes were OS (NCDB) and PFS plus OS (MZL-RWD), analyzed by Cox models with robust standard errors. Results are reported as hazard ratios (HR) with 95% confidence intervals (95% CI). Double-robust models and stratification by treating hospital confirmed stability. Sensitivity analyses addressed potential unmeasured confounding by: (i) trimming patients with extreme propensity scores (≤25%) and (ii) simulating an unmeasured confounder (HR=2.0) with varying prevalence differentials.[14]

In the NCDB dataset (N=8,110), 58% of patients received immunotherapy alone and 42% received immunochemotherapy. The median follow-up was 3.9 years. Five-year OS was 75.8% (95% CI: 74.6-76.9), being highest for EMZL (79.3%), and lower for NMZL (73.0%) and SMZL (74.0%) (Figure 1A, B). Immunochemotherapy recipients were younger, more often male, and more likely to have NMZL, advanced stage, or B symptoms (*Online Supplementary Table S2*). Treatment proportions remained stable (~60% immunotherapy alone) from 2013-2018 (Figure 1C). Facility-level variation was significant ($P<10^{-5}$) but unrelated to academic *versus* community status (Figure 1D). EMZL of gastric, pulmonary, cutaneous, salivary, or ocular origin was most often treated with rituximab monotherapy, whereas patients with central nervous system EMZL most frequently received immunochemotherapy (Figure 1E). Among chemotherapy recipients, 68% were treated with single-agent and 30% with multi-agent regimens, consistent with previously reported predominant BR use.[4]

Propensity matching yielded 2,534 pairs with excellent covariate balance (mean SDM, 0.018) (Figure 2A-C). OS did not differ between groups (HR=1.07; 95% CI: 0.94-1.21; P=0.30) (Figure 2D). Five-year OS was 76.6% (95% CI: 74.4-78.6) for immunotherapy and 76.2% (95% CI: 74.1-78.2) for immunochemotherapy. Results were consistent in hospital-stratified (HR=1.10) and doubly-robust (HR=1.08)

models. Subgroup analyses showed no heterogeneity by age or propensity-score quartile, and low likelihood of significant residual unmeasured confounding, although in SMZL immunochemotherapy use correlated with inferior OS (Figure 2E, F). Histology-specific models confirmed no OS difference for EMZL (HR=1.06; 95% CI: 0.85-1.31) or NMZL (HR=1.08; 95% CI: 0.91-1.28), whereas the SMZL disadvantage (HR=1.42; 95% CI: 1.04-1.96) appeared to be sensitive to moderate simulated confounding. Trimming tails of the propensity-score distribution did not materially alter results (*data not shown*).

From the MZL-RWD cohort, we selected 355 patients who received rituximab and 186 who received BR (total N=541) (Figure 3A). Overall, in the MZL-RWD study, immunochemotherapy consisted of BR in 75% and cyclophosphamide-based regimens in 25%. The median follow-up was 4.6 years. The median PFS was 5.8 years (95% CI: 4.7-7.1); 5-year OS was 86.5% (95% CI: 82.7-89.6). Unadjusted analyses showed longer PFS and OS with BR, but recipients were younger and had higher stage and lactate dehydrogenase concentration (*Online Supplementary Table S3*). Rituximab use predominated in SMZL (74%) and EMZL (69%). Histological transformation occurred in 2.8% of rituximab and 4.3% of BR recipients.

The IPTW model balanced all measured covariates (mean SDM, 0.022) (Figure 3A, B). PFS was significantly superior with BR (HR=0.57; 95% CI: 0.40-0.81; *P*=0.0018), yielding 5-year PFS of 66.3% *versus* 48.7% (Figure 3C). Results remained robust in hospital-stratified and double-robust analyses. No heterogeneity by subtype was observed (Figure 3D), and simulated confounding required ≥30% imbalance to nullify significance (Figure 3E). OS did not differ (HR=0.86;

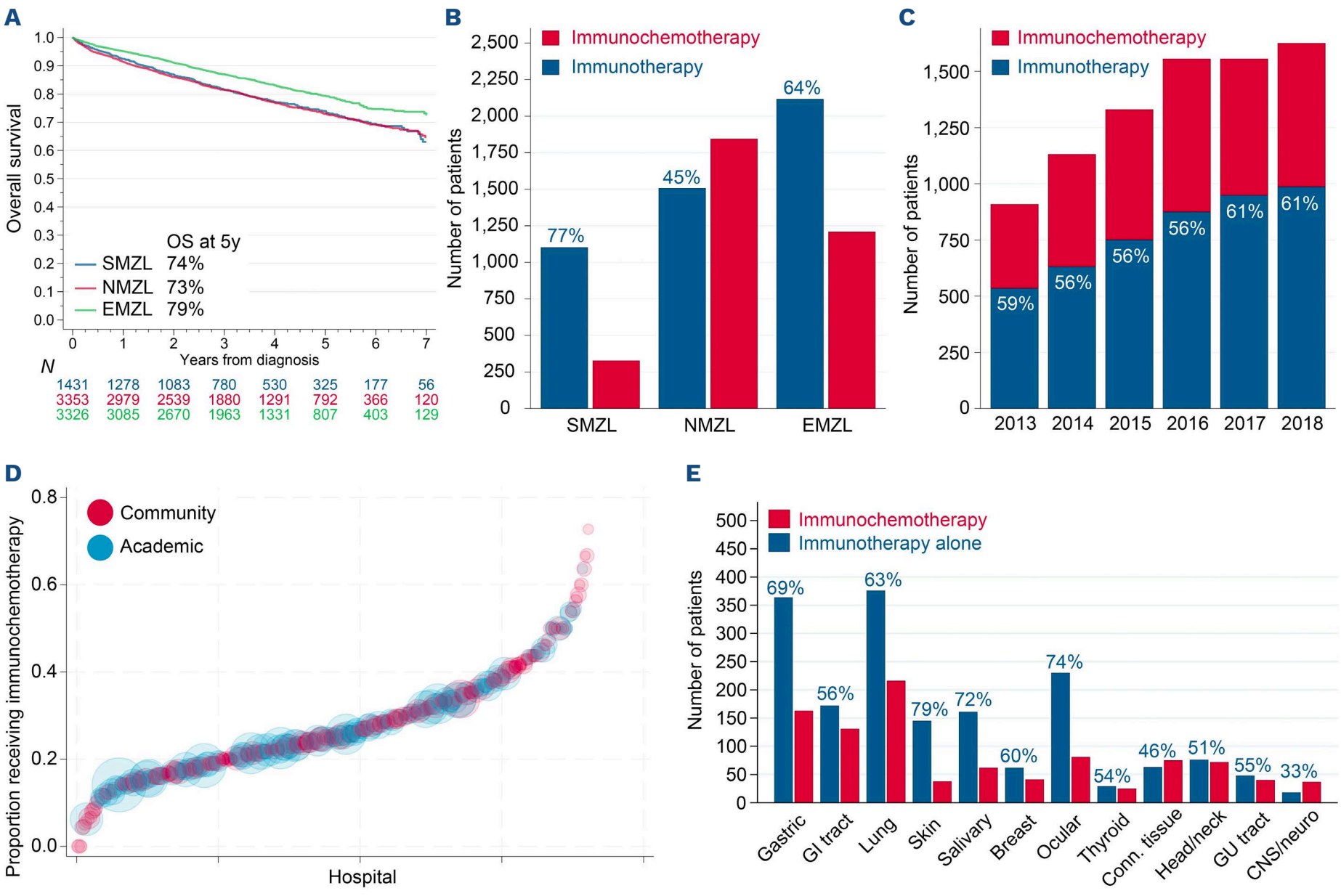
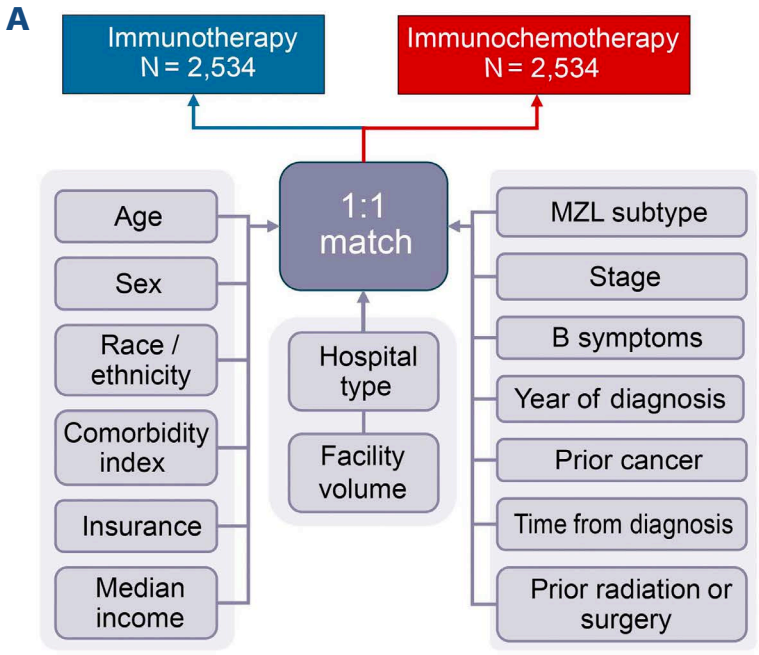
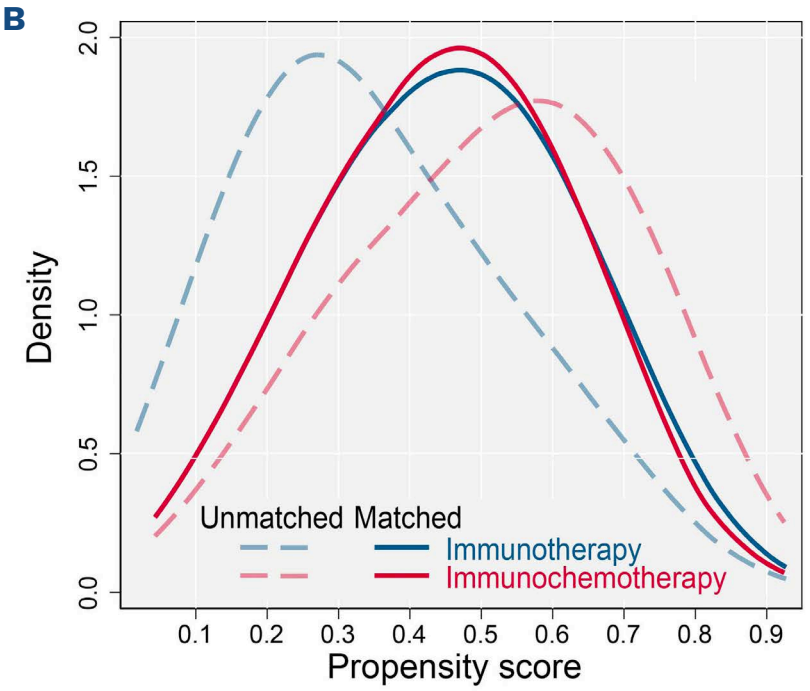
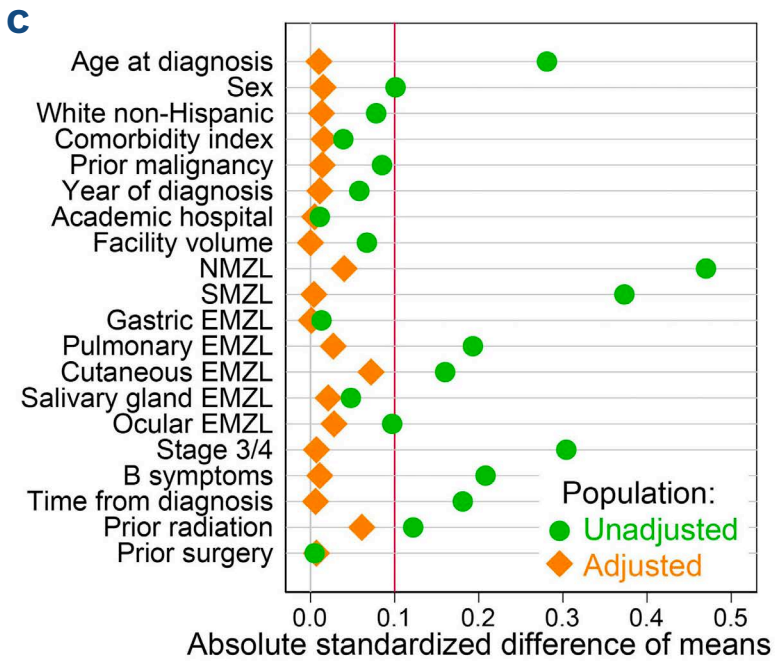
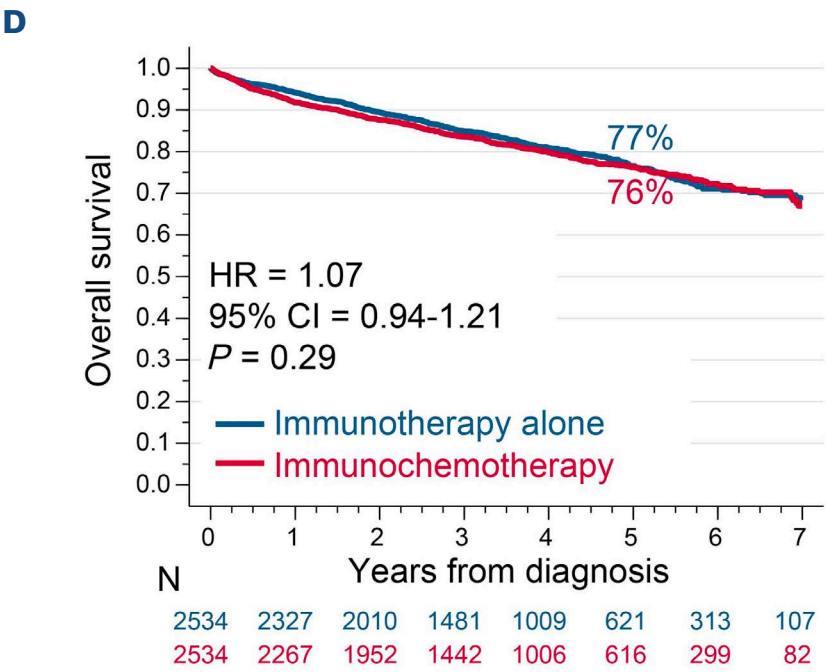


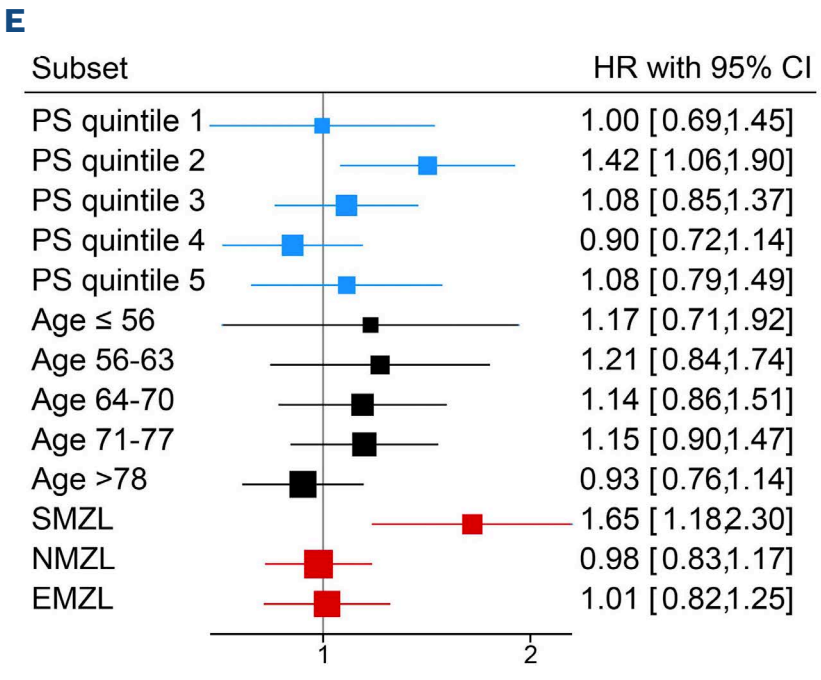
Figure 1. Treatments and outcomes of patients with marginal zone lymphoma in the US National Cancer Data Base, 2013-2018. (A) Overall survival of patients, stratified by marginal zone lymphoma (MZL) histology. (B) Use of immunochemotherapy or immunotherapy alone in MZL histological subtypes (percent of patients with each histology receiving immunotherapy is shown). (C) Use of immunochemotherapy and immunotherapy in each calendar year (percent of patients receiving immunotherapy is shown). (D) Variation in the relative use of immunochemotherapy (*vs.* immunotherapy) in each reporting hospital; the size of the circle corresponds to the number of reported MZL cases from each hospital; facilities are ranked according to the increasing proportion of patients treated with combination immunochemotherapy, and only facilities reporting at least six MZL cases are included. (E) Number of patients with extranodal MZL of specific primary anatomic locations receiving immunochemotherapy or immunotherapy alone. OS: overall survival; y: years; SMZL: splenic MZL; NMZL: nodal MZL; EMZL: extranodal MZL; GI tract: gastrointestinal tract; Conn. tissue: connective tissue; GU tract: genito-urinary tract; CNS/neuro: central nervous system/neurological.











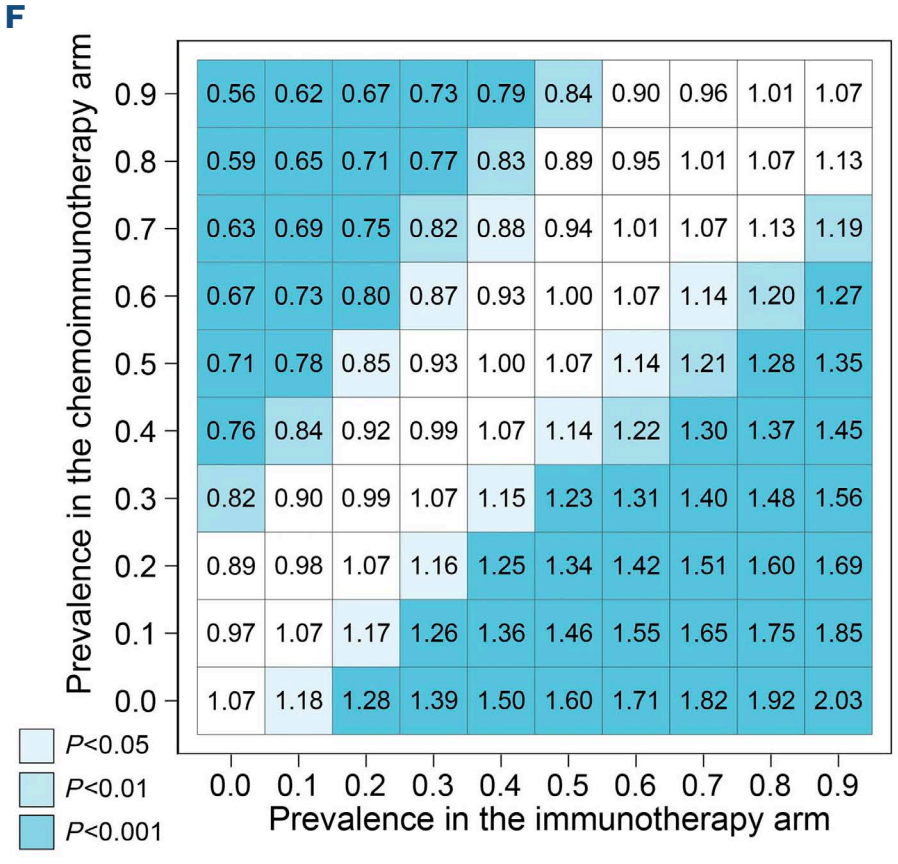


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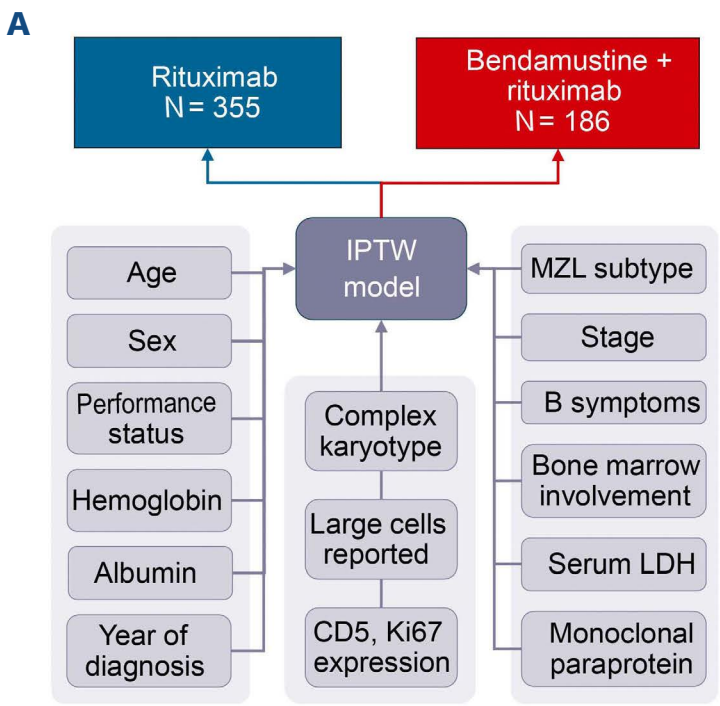
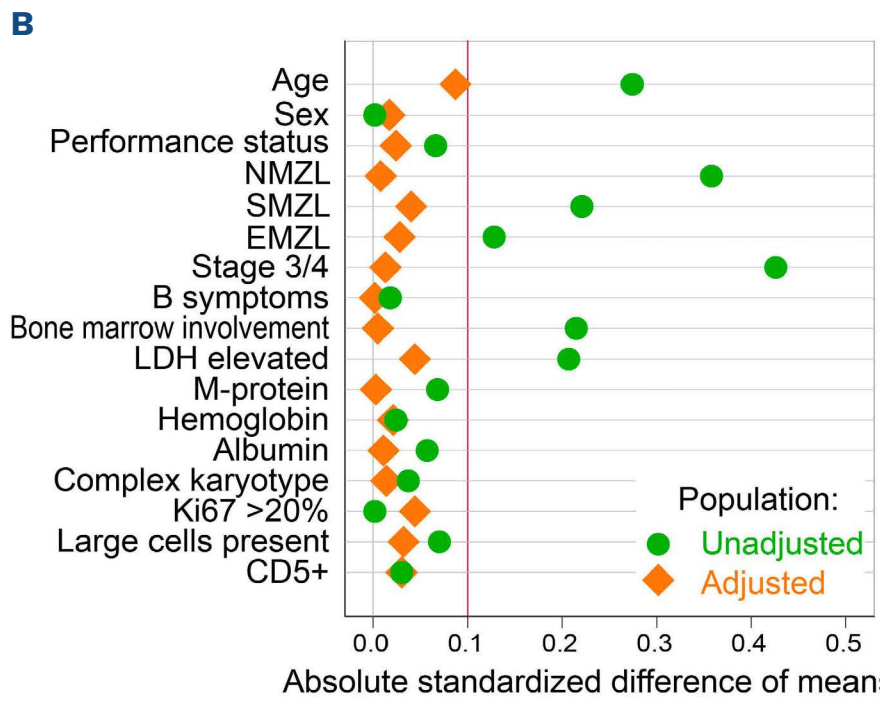
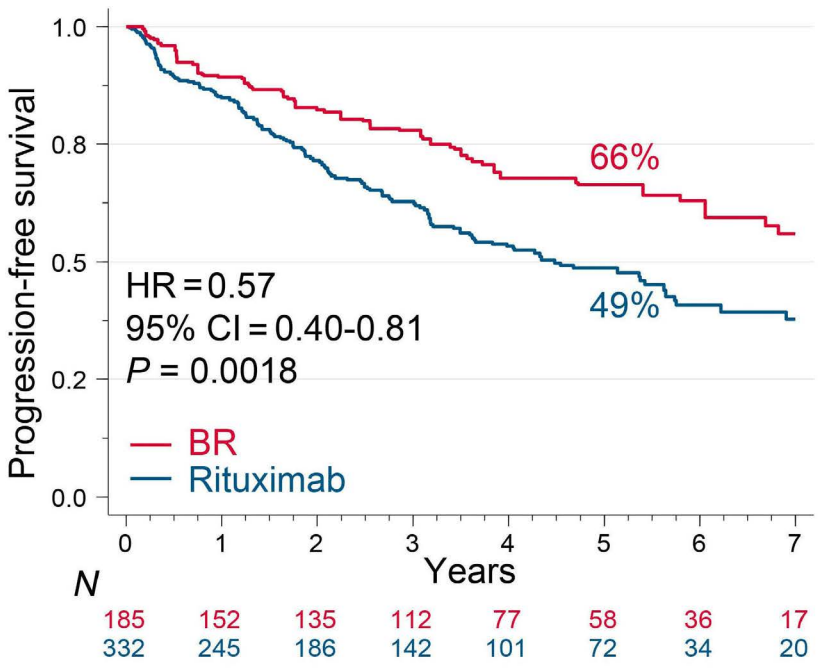
Figure 2. Analysis of the US National Cancer Data Base dataset. (A) Variables used for one-to-one propensity score (PS) matching; the final PS model included all variables listed, with age and time from diagnosis modeled using restricted cubic splines, and with an interaction between age and marginal zone lymphoma (MZL) subtype. (B) Distribution of the PS before and after matching. (C) Absolute standardized differences of means (SDM) for the main confounders included in the PS model; insurance categories and median income were omitted but were adequately balanced (maximum SDM=0.021). (D) Overall survival (OS) in the matched cohort comparing patients treated with immunotherapy alone or with combination immunochemotherapy; OS rates at 5 years are shown. (E) Subset analysis evaluating heterogeneity of OS outcome according to PS quintile, age quintile, or MZL histology. (F) Sensitivity analysis investigating change in the model hazard ratio (HR) and statistical significance (denoted by shading) in models additionally adjusting for a putative unobserved confounder associated with a HR of 2.0, while varying its prevalence in both study arms. NMZL: nodal MZL; SMZL: splenic MZL; EMZL: extranodal MZL; HR: hazard ratio; 95% CI: 95% confidence interval.

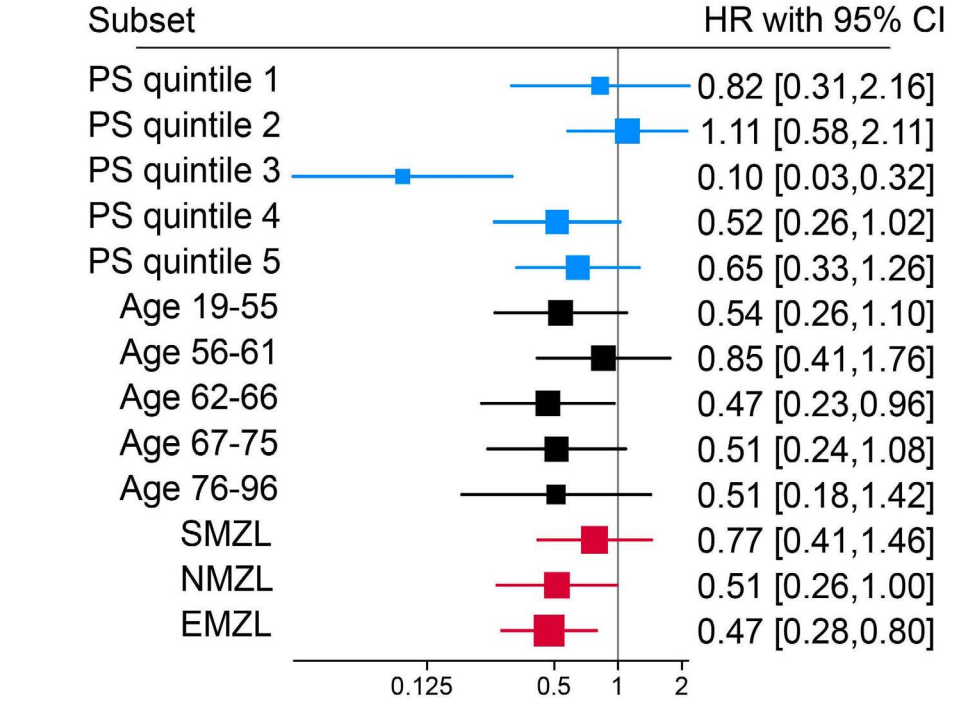
95% CI: 0.46-1.64; *P*=0.65) (Figure 3F); 5-year OS was 86.2% (in BR recipients) *versus* 87.2% (rituximab recipients). Subset analyses by age, subtype, or propensity quintile were concordant (*data not shown*). Patients with SMZL showed a nonsignificant trend toward worse OS (HR=1.50; 95% CI: 0.51-4.44). Confirmatory 1:1 matching (N=314) produced similar findings - better PFS with BR (HR=0.50; 95% CI: 0.34-0.73) but no OS difference (HR=0.82; 95% CI: 0.40-1.68). Results were insensitive to alternative missing data handling strategies (*data not shown*).

Across two complementary real-world datasets, first-line immunochemotherapy and rituximab monotherapy produced comparable OS in MZL, although BR prolonged PFS by roughly 15% at 5 years. These results mirror IELSG-19









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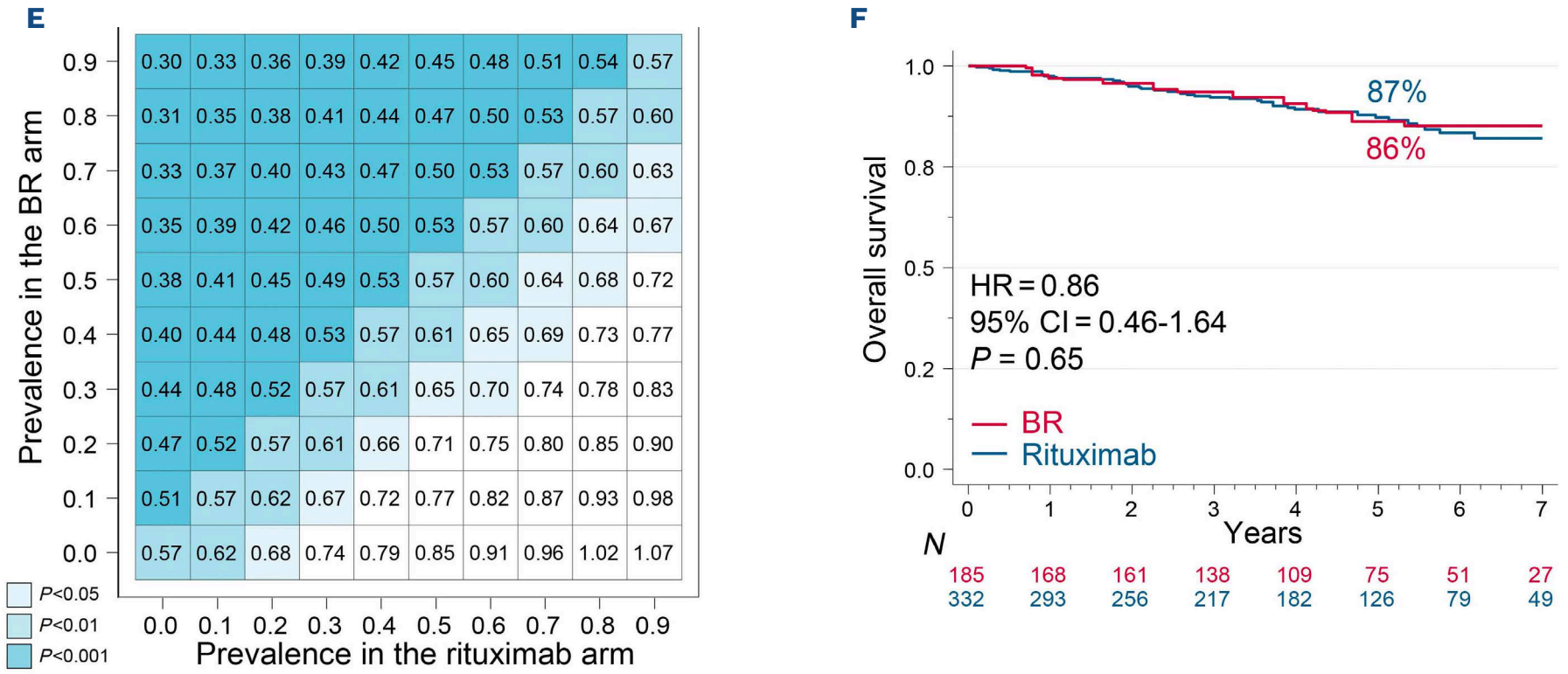

Figure 3. Analysis of the marginal zone lymphoma-real world dataset. (A) Variables used for the inverse-probability-of-treatment weighting propensity score (PS) model; the final PS model included all variables listed, and an interaction between age and marginal zone lymphoma (MZL) subtype. (B) Absolute standardized differences of means for the main confounders included in the PS model. (C) Progression-free survival (PFS) in the adjusted cohort comparing patients treated with rituximab or bendamustine and rituximab (BR); PFS estimates at 5 years are shown. (D) Subset analysis evaluating heterogeneity of the PFS outcome according to PS quintile, age quintile, or MZL histology. (E) Sensitivity analysis investigating change in the model hazard ratio (HR) and statistical significance (denoted by shading) in models additionally adjusting for a putative unobserved confounder associated with a HR of 2.0 while varying its prevalence in both study arms. (F) Overall survival (OS) in the adjusted cohort comparing patients treated with rituximab or BR; OS estimates at 5 years are shown. IPTW: inverse-probability-of-treatment weighting; LDH: lactate dehydrogenase; NMZL: nodal MZL; SMZL: splenic MZL; EMZL: extranodal MZL; HR: hazard ratio; 95% CI: 95% confidence interval.

trial data, which found longer PFS but no OS benefit for rituximab-chlorambucil *versus* rituximab monotherapy.[3]

In patients with MZL, in whom relapses are often indolent and asymptomatic, PFS may not translate into meaningful survival or quality-of-life gains. Demonstrating OS improvement is inherently difficult given prolonged post-relapse survival and availability of effective retreatment options. Our findings reinforce the concept that BR's toxicity profile – prolonged cytopenias, immunosuppression, and potential for secondary myeloid malignancies - should be weighed against PFS extension. Infectious complications in prior studies reached 13%, including 4% herpes zoster, prompting recommendations on prophylaxis.[6] Risks are heightened in older patients and possibly in those with SMZL, as BR showed better outcomes in EMZL (7-year PFS of 93% in the GELTAMO trial) than in SMZL (5-year PFS of 83% in the BRISMA/IELSG36 trial) patients, in whom BR induced significant infectious toxicity.[7,8] Rituximab maintenance or retreatment can prolong PFS, potentially reducing the need for upfront chemotherapy.

The concordance between the NCDB (nationwide coverage, limited clinical detail) and MZL-RWD (clinically rich, multi-center) supports external validity. The apparent OS disadvantage of immunochemotherapy in SMZL should be interpreted with caution, as it was not reproduced in MZL-RWD and may reflect unmeasured confounding. The observed PFS benefit with BR was similar to phase II trial estimates (66% 5-year PFS in this study *vs.* ~80% in trials), suggesting real-world outcomes may modestly underperform trial benchmarks due to older, less selected populations.

Study limitations include lack of toxicity and quality-of-life data, and causes of death, and incomplete variable coverage compared with MZL prognostic scores.[15] It was also not possible to account for patient preferences for treatment, use of antibiotic therapy for EMZL, or underlying specific comorbidities and frailty. Central pathology review is a critical component of a clinical trial approach, but it is not conducted in routine clinical practice, in which some degree of histological misclassification is expected. The NCDB lacked treatment specifics, although proportions mirrored contemporary USA practice with predominant BR use and exceptionally rare use of chlorambucil.[4] We did not analyze maintenance rituximab or variable bendamustine dosing, as such post-treatment factors would introduce immortal-time bias. An international perspective from countries in which the treatment selection process may differ would be of additional value.

In conclusion, in two independent, methodologically robust real-world cohorts, BR achieved longer PFS but no OS advantage over rituximab monotherapy in first-line treatment of MZL. Given similar survival and greater toxicity

with chemotherapy, treatment selection should incorporate patient preferences regarding quality of life, tolerance for treatment risks and burden. Rituximab monotherapy remains a reasonable first-line standard and a platform for future combinations with targeted or biologic agents.

Authors

Adam J. Olszewski,[1] Thomas A. Ollila,[1] Dai Chihara,[2] Geoffrey Shouse,[3] Natalie Grover,[4] Reem Karmali,[5] Pallawi Torka,[6,7] Colin Thomas,[8,9] Praveen Ramakrishnan Geethakumari,[10] Stefan K. Barta,[9] Nancy L. Bartlett[11] and Narendranath Epperla[12]

[1]Department of Medicine, Warren Alpert Medical School of Brown University, Providence, RI; [2]Department of Lymphoma – Myeloma, MD Anderson Cancer Center, Houston, TX; [3]Department of Hematology & Hematopoietic Cell Transplantation, City of Hope National Medical Center, Duarte, CA; [4]Division of Hematology, Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC; [5]Department of Medicine, Northwestern University, Chicago, IL; [6]Roswell Park Comprehensive Cancer Center, Buffalo, NY; [7]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; [8]Division of Hematology, Thomas Jefferson University, Philadelphia, PA; [9]Department of Medicine, University of Pennsylvania, Philadelphia, PA; [10]Harold C. Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX; [11]Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO and [12]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA

Correspondence:
A.J. OLSZEWSKI - adam_olszewski@brown.edu

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Contributions

AJO, TAO, DC and NE designed the study. AJO conducted the statistical analyses and drafted the paper. All authors contributed to the acquisition and interpretation of the data, approved the final version, and agree to be accountable for all aspects of the work.

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Data-sharing statement

The NCDB data are publicly available from the NCDB subject to data-use agreements. The individual patients' data from the MZL-RWD cohort are protected by US privacy laws and institutional data-use agreements; however, aggregate data are available from the corresponding author upon request.

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