Unmet Needs and Evidence Gaps in Relapsed/Refractory Marginal Zone Lymphoma: Findings From a Systematic Literature Review

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INTRODUCTION

- Marginal zone lymphoma (MZL) is a rare disease accounting for 8% to 12% of all non-Hodgkin lymphomas[1,2]
- Many patients experience relapse, and with limited treatment options, their risk increases over time[3]
- This review aimed to identify evidence on the epidemiology and clinical, humanistic, and economic outcomes of relapsed/refractory (R/R) MZL

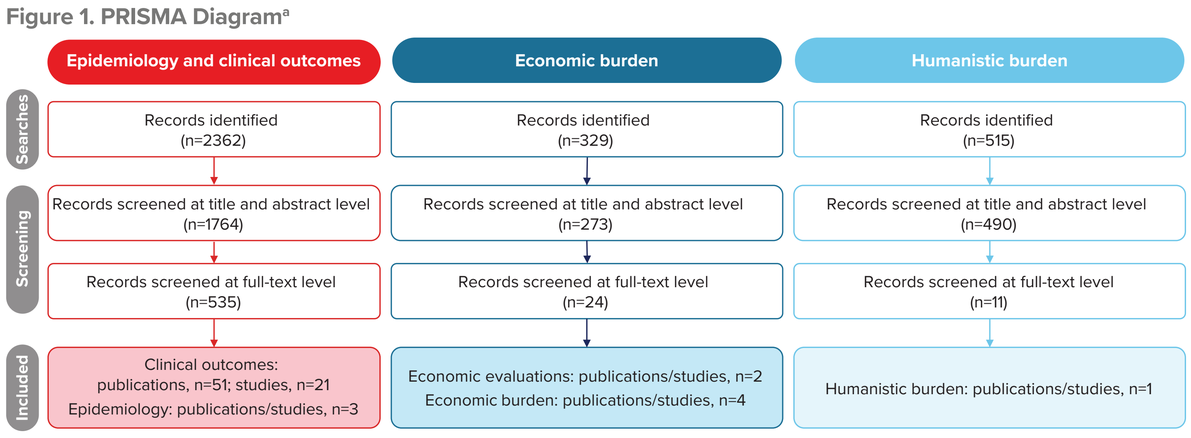
METHODS

- A systematic literature review was conducted that searched MEDLINE, EMBASE, Cochrane Library, EconLit, and PsycInfo via Ovid in November 2022 with no time limit. Selected congress proceedings from the past 2 meetings were also searched
- Two reviewers independently screened the articles. Extraction was performed by a single reviewer, and validation was conducted by a second reviewer
- Studies in English reporting on epidemiology and clinical efficacy of interventions for patients with R/R MZL treated previously with anti-CD20 therapy were eligible for inclusion. Given the rarity of R/R disease, we included any evidence on the humanistic and economic burden of MZL, regardless of previous treatments

RESULTS

- A total of 31 studies reported across 61 publications were identified, including 21 clinical,[4-24] 3 epidemiologic,[25-27] 1 humanistic burden,[28] and 6 economic studies[29-34] (**Figure 1**)

Figure 1. PRISMA Diagram[a]



[a] The selection criteria of this systematic literature review allowed the inclusion of mixed population studies, as long as patients with R/R MZL previously treated with anti-CD20 therapy were reported as a separate subgroup, or made up ≥80% of the studied sample.

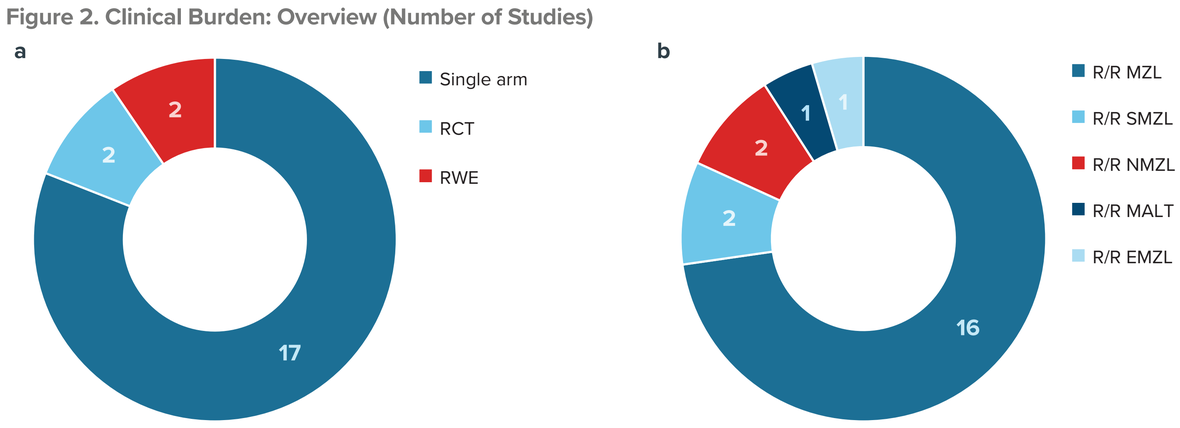
Epidemiology

- None of the 3 included epidemiology studies[25-27] reported true incidence or prevalence estimates of R/R MZL. Using the information on the proportion of patients who developed R/R disease after anti-CD20 therapy, the first-line relapse rate was 1.4%[26] in Europe and 30.8% in South Korea.[25] In Europe, 15% and 46% of patients treated with first- and second-line rituximab-based therapy, respectively, developed treatment-refractory disease[26]
- The survival rate in US patients who had relapsed was 75% at 2 years[27]; European patients with refractory disease had a 4-year overall survival (OS) probability of 57%[26]

Clinical Burden

- Of the 21 studies evaluating clinical outcomes with systemic treatments in patients with R/R MZL previously treated with anti-CD20 therapy, 17 were single-arm clinical trials,[4-20] 2 were randomized controlled trials (RCTs),[21,22] and the other 2 were retrospective cohort studies[23,24] (**Figure 2a**). Among RCT and single-arm trials, 15 were phase 2[4-12,15-20] and 4 were phase 3[13,14,21,22]
- The most commonly investigated group was the overall R/R MZL population (n=16),[4-6,8,10-12,14,15,17-22,24] followed by R/R splenic MZL (SMZL)[16,23] and R/R nodal MZL (NMZL),[7,13] evaluated in 2 studies each. R/R mucosa-associated lymphoid tissue (MALT)[9] and R/R extranodal MZL[13] populations were assessed in 1 study each (**Figure 2b**)

Figure 2. Clinical Burden: Overview (Number of Studies)



EMZL, extranodal MZL; MALT, mucosa-associated lymphoid tissue; MZL, marginal zone lymphoma; NMZL, nodal MZL; RCT, randomized controlled trial; R/R, relapsed/refractory; RWE,real-world evidence; SMZL, splenic MZL.

- Over half of the studies (n=11)[5,6,11-14,18-22] were designed to test the treatment of interest in a wider group, and the R/R MZL population was analyzed as a subgroup
- None of the RCTs identified was designed for the R/R MZL population specifically
- Across 19 systemic treatments being studied, rituximab-based regimens were the most commonly evaluated (n=3),[14,21,22] followed by zanubrutinib (n=2)[6] and ibrutinib (n=2).[17,24] The remaining systemic treatments (n=12)[4,5,7,9-13,16,18-20] were investigated in 1 study each
- The majority of agents were investigational; only 1 regimen (zanubrutinib)[6] was currently approved in Europe for R/R MZL
- Typically, systemic treatments were evaluated in second- and later-line settings (n=19),[4,6-18,20-24] and only 2 single-arm studies enrolled patients after ≥2 previous treatment lines[5,19]
- In all 9 clinical trials reporting on R/R MZL OS, the median OS was not reached.[4,6,11,15-19,22] In 19 trials providing progression-free survival (PFS) results,[4-7,9-22] the median PFS varied from 5.5 months (median follow-up, 3.6 months)[5] to 41.2 months (follow-up not reported).[14] Most of the clinical trials reported a median PFS of 20.2[21] to 27.4[4] months
- Evidence from RWE studies[23,24] was limited, and survival rates were generally lower than in clinical trials, indicating a lack of effective treatment options for patients with R/R MZL

Humanistic Burden

- Humanistic burden associated with MZL was underreported; only 1 study in newly diagnosed patients with MALT from Germany was identified.[28] The Gastrointestinal Quality of Life Index scores increased over time for patients with MALT; however, more substantial improvement was observed in patients who underwent radiotherapy compared with surgery[28]

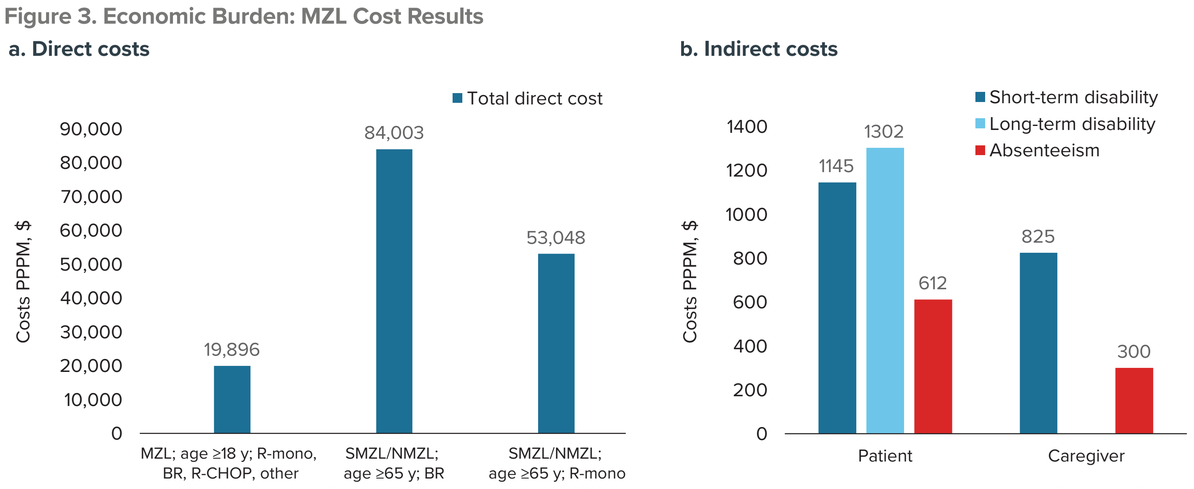
CONCLUSIONS

- Review of the clinical evidence highlights a lack of RCTs conducted in R/R MZL and a sparsity of treatment options available in the real-world setting
- More research, in the form of RCTs and RWE studies, is needed in the MZL population and its subgroups
- A significant evidence gap exists for the epidemiologic, humanistic, and economic burden in the R/R MZL population, and there is very little evidence from European countries

Economic Burden

- Among economic burden studies, 2 were economic evaluations[30,32] and 4 reported on costs or healthcare resource utilization (HCRU).[29,31,33,34] All studies but one[29] were conducted in the US[30-34]
- Economic burden evidence, although limited, suggested a substantial burden of MZL. None of the included studies provided data for the patients with R/R disease
- The total direct cost was reported in 2 studies in patients with newly diagnosed MZL (**Figure 3a**) and ranged from $19,896 per patient per month (PPPM)[34] in adults treated with first-line R-mono, bendamustine + rituximab (BR), rituximab + cyclophosphamide + doxorubicin + vincristine, ibrutinib, or other regimens to $84,003 PPPM in older patients with SMZL/NMZL treated with first-line BR.[31] The total direct cost was significantly higher in patients who received BR than in patients who received R-mono ($84,003 vs $53,048; *P*<.001)[31]
- Indirect cost data for the MZL population (**Figure 3b**) were available from 1 study and were numerically higher for patients with long-term disabilities compared with those with short-term disabilities or absentee claims ($1302 vs $1145 vs $612) and for patients compared with caregivers (short-term disability related: $1145 vs $825; absenteeism related: $612 vs $300 PPPM), suggesting substantial disease burden not only for patients with MZL but also for caregivers[33]

Figure 3. Economic Burden: MZL Cost Results



BR, bendamustine + rituximab; MZL, marginal zone lymphoma; NMZL, nodal MZL; PPPM, per person per month; R-CHOP, rituximab + cyclophosphamide + doxorubicin + vincristine; R-mono, rituximab monotherapy; SMZL, splenic MZL. Data from Yang (2022),[34] Olszewski (2019),[31] and Yang (2021).[33]

- HCRU was reported in 3 studies (**Table 1**).[29,31,34] Results indicated a high risk of hospitalization in the US in older patients with SMZL/NMZL treated with first-line rituximab-based regimens (R-mono, 26%; BR, 37%). A similar pattern was observed for the risk of transfusion (R-mono, 22%; BR, 9%).[31] Adult patients with newly diagnosed MZL required a median of 4.6 outpatient visits and 0.5 hospitalizations PPPM; the median length of stay was 2.6 days.[34] Among patients treated for MALT with conventional therapy, 16.7% required intensive care unit hospitalization due to pneumonia[29]

Table 1. HCRU in MZL Population

Author, year	Country	Population (sample size)	Results
Hospitalizations			
Yang, 2022[34]	US	Adult patients with newly diagnosed MZL treated with R-mono, BR, RCHOP, or other (N=2491)	Number of hospitalizations PPPM: 0.5
Olszewski, 2019[31]	US	Patients with SMZL/NMZL aged ≥65 years (N=958)	Proportion of patients who were hospitalized: • Treated with BR (n=235): 87 (37%) • Treated with R (n=723): 188 (26%)
Length of stay			
Yang, 2022[34]	US	Adult patients with newly diagnosed MZL treated with R-mono, BR, RCHOP, or other (N=2491)	Mean number of days PPPM: 2.6
ICU hospitalizations			
Hoffmann, 2011[29]	Austria	Patients who received conventional therapy for MALT lymphoma (N=6)	Proportion of patients hospitalized in ICU due to pneumonia: 1 (16.7%)
Outpatient visits			
Yang, 2022[34]	US	Adult patients with newly diagnosed MZL treated with R-mono, BR, R-CHOP, or other (N=2491)	Number of outpatient visits PPPM: 4.6
Transfusion procedure			
Olszewski, 2019[31]	US	Patients with SMZL/NMZL aged ≥65 years (N=958)	Proportion of patients who were hospitalized: • Treated with BR (n=235): 52 (22%) • Treated with R (n=723): 65 (9%)

BR, bendamustine + rituximab; HCRU, healthcare resource utilization; ICU, intensive care unit; MALT, mucosa-associated lymphoid tissue; MZL, marginal zone lymphoma; NMZL, nodal MZL; PPPM, per person per month; R, rituximab; R-CHOP, rituximab + cyclophosphamide + doxorubicin + vincristine; R-mono, rituximab monotherapy; SMZL, splenic MZL.

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DISCLOSURES

SD, **KB**, **PW:** Employment: Evidera, a part of PPD, which received funding from BeiGene to conduct this study. **LM**, **KY**, **DW:** Employment: BeiGene.

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