# A systematic literature review of prognostic factors and surrogate endpoint analyses in chronic lymphocytic leukemia and small lymphocytic lymphoma

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## Background

- Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) comprise a group of malignancies that share a common pathology, with differing manifestations[1]
- Current treatment options for CLL/SLL are only partially effective in relapsed or refractory (R/R) disease,[2] and there is a need to identify patients who might benefit from individual therapies
- An understanding of prognostic factors and the association between intermediate endpoints (surrogates) and survival is important for comparison of efficacy among current treatments
- Given the challenges of lengthy and confounded survival endpoints and the high unmet need for more effective treatments in particular groups of patients with CLL/SLL, trials used to evaluate novel treatments, such as chimeric antigen receptor (CAR) T cell therapies, are often based on more immediate endpoints, such as response to treatment, minimal residual disease (MRD), and disease progression[2–7]

## Objective

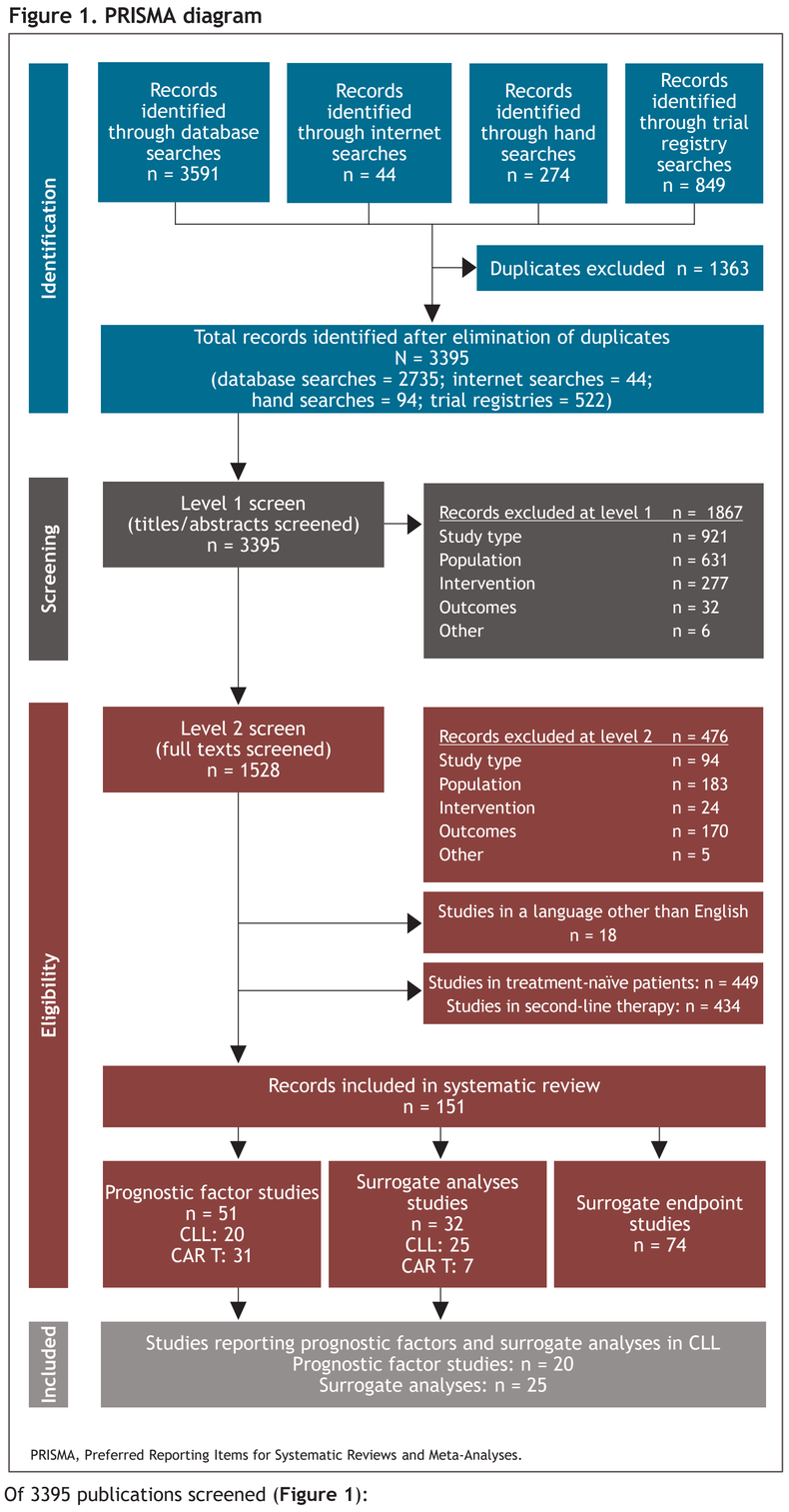
- To identify overall survival (OS) prognostic factors in patients with heavily pretreated CLL/SLL and to identify surrogate endpoint analyses considering OS or progression-free survival (PFS) as final endpoints in any line of therapy of CLL/SLL treatment

## Methods

- A systematic literature review (SLR) was conducted on July 30, 2021, according to a prespecified protocol. Electronic databases (Embase, MEDLINE and MEDLINE In-Process, and Cochrane Library®) were searched with no date or language limits
- Additional searches were conducted of key conferences (since 2019) and trial registries. Reference lists of relevant identified SLRs were also considered
- Search terms included terms relating to the population (eg, "chronic lymphocytic leukemia" OR "small lymphocytic lymphoma"), interventions (eg, "chimeric antigen receptor immunotherapy"), and exclusionary terms such as those for animals
- Publications were included if they reported any prognostic factor of OS in third-line or later (3L+) or surrogate endpoint analysis for PFS or OS for any line of therapy for CLL/SLL
- This presentation focuses on studies that report prognostic factors in heavily pretreated (ie, patients with 3 or more treatment lines or studies with >60% of patients with 2 or more prior lines) CLL/SLL and surrogate analysis for CLL/SLL
- Real-world evidence, observations, and registry data were assessed for prognostic factors; real world evidence, observations, registry data, and clinical trials were assessed for surrogate endpoint analysis studies
- Single screening followed by a second independent review of 10% of the screened sample with reconciliation of discrepancies was performed at all screening levels. All extracted data were quality checked by a second researcher
- Included studies were assessed according to the Joanna Briggs Institute critical appraisal tools[8]

## Results

**Figure 1. PRISMA diagram**




PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

- Of 3395 publications screened (**Figure 1**):
  - Twenty[4,9–27] unique studies that reported on prognostic factors for a heavily pretreated population with CLL/SLL were identified
  - Twenty-five[4,6,7,11,12,14,16,19,23,26,28–42] unique studies that reported surrogate analyses for CLL or SLL were identified

### Studies identifying prognostic factors

- The most common type of study identifying prognostic factors was chart reviews/retrospective cohort studies (n = 7).[11,15–17,19,21,22] Five of the 20 identified studies were multinational,[12,14,23,26,27] 8 were conducted in the United States,[4,9,10,13,15,18,22,24] 2 were conducted in France,[16,17] 2 were conducted in Italy,[20,21] and 1 study each was conducted in Austria,[11] Canada,[19] and Germany[25]
- Study sample sizes ranged from 24[4] to 261[27] patients, with 9 studies including more than 100 patients[9,11,13,14,20,21,23,26,27]; follow-up duration or average follow-up ranged from 6.6[4] to 120[18] months in the 19 studies reporting this information[4,9–12,14–27]
- The studies investigated different treatments, including but not limited to stem cell transplantation (5 studies),[9,16,19,22,25] ibrutinib (3 studies),[14,21,24] ofatumumab (3 studies),[23,26,27] alemtuzumab (2 studies),[11,12] and CAR T therapy (1 study)[4]
- Prognostic factors identified included increased age, fludarabine use or alkylator-refractory disease, ≥ 3 prior therapies, bulky disease, and 17p deletion. These factors were found to be independently associated with shorter OS in the heavily pretreated CLL/SLL population (**Table 1**)
- No statistically significant relationships were found between OS and sex,[9,18] OS and Rai cancer stage,[12,18] or OS and immunoglobulin heavy chain gene status[4,15,24]
- Five studies considered treatment to be a prognostic factor, including idelalisib treatment (1 study)[27] and initiation of ofatumumab (1 study).[26] Two studies reported an association between alemtuzumab treatment and OS,[12,19] and 1 study reported a shorter OS in patients who had gone through more cycles of treatment[18]
- None of the identified studies considered the relationship between OS and Binet stage or Eastern Cooperative Oncology Group status in patients heavily pretreated for CLL

**Table 1. Summary of identified studies considering prognostic factors for OS in heavily pretreated patients with CLL/SLL**

| Prognostic factor | Studies reporting significant effect/studies identified with information on prognostic factor | Summary of significant relationships |
|---|---|---|
| **Age**[9–19] | 5/11 | Increased age was related to shorter OS |
| **Prior lines**[9–11,14,16–18,20–22] | 8/10 | More prior treatments were related to shorter OS |
| **Prior purine analog (fludarabine)**[9–11,17–19,23] | 5/7 | Fludarabine refractoriness was related to shorter OS |
| **17p deletion**[15,18,19,24] | 3/4 | 17p deletion was related to shorter OS |
| **Combined molecular aberrations**[10,14,24] | 2/3 | Absence of chromosome 17 aberrations was associated with longer OS[a] |
| **Beta-2 microglobulin**[11,18] | 1/2 | Higher levels of beta-2 microglobulin were associated with shorter OS |
| **Bulky disease**[9,11,12,18,25] | 4/5 | Bulky disease was associated with poor OS[b] |
| **Absolute lymphocyte count**[9,10,22] | 1/3 | Absolute lymphocyte count ≥ $100 \times 10^9$/L was associated with longer OS[c] |
| **Bone marrow involvement**[9,15,22] | 3/3 | Higher degree of bone marrow involvement was associated with shorter OS |

[a]Both studies that considered the absence of complex karyotype or abnormalities of chromosome 17 found this to be significantly associated with longer OS. The further study explored whether having 17p or 11q deletions was related to OS and found no significant difference
[b]Among studies that reviewed lymph node size as a prognostic factor, 1 study found no relationship using stricter criteria to define bulky disease;
[c]Only 1 study found a relationship when using categoric groups for absolute lymphocyte count.

### Studies identifying surrogate analysis

- Only 4 studies were identified that reported surrogate analyses in populations of patients with 3L+ treatment in CLL/SLL[4,6,12,14]
  - 9 surrogate analysis studies were conducted with treatment-naïve patients[29,30,32,34,37–39,41,42]
  - 10 were conducted with patients who have R/R disease
  - 1 study included mixed treatment lines including treatment naïve[36]
  - 1 study did not report treatment lines[28]
- A mix of study types was identified, including observational and individual or pooled clinical trial studies
- Six studies were multinational,[12,14,23,26,31,39] but most were performed in a single country
- Five publications used individual participant data (IPD) or aggregate data from more than 1 study[28–31,41]
- The sample sizes ranged from 24[4] to 2457[29] in the included studies. The follow-up duration or average follow-up ranged from 6.6[4] months to 10.1 years[36], where reported
- The most frequently reported relationship was between MRD and OS (12 studies) [6,7,16,29,32,35–41]; MRD negativity was associated with longer OS in 11 of the 12 studies ($P < 0.05$) in patients in any line of therapy
  - Ten studies evaluated the relationship between MRD and PFS.[7,16,29,30,32,35–37,39,41] MRD negativity was associated with longer PFS in 9 of 10 studies ($P < 0.05$)
  - One study used IPD data from multiple trials,[41] and the remaining studies used IPD from individual trials
- Multiple publications reported an association between response and OS[4,6,7,11,12,14,19,23,26,33,37] (10 of 11 studies; $P < 0.05$) and PFS[4,6,7,12,31,37] (all 6 studies, $P < 0.05$)
- Other surrogate endpoints reported were PFS as a surrogate for OS[28] (1 study; $P < 0.05$) and disease progression[19,34,42] (2 of 3 studies; $P < 0.05$)
- Only 1 publication used meta-regression to perform surrogate endpoint analysis on treatment effects, with increased MRD response between treatments associated with improved PFS ($R^2 = 0.44$).[30] This analysis did not use bivariate random-effects meta-analysis, which may be considered more robust[43]

**Table 2. Summary of identified studies considering surrogates for PFS and OS in patients with CLL/SLL**

| | Studies reporting significant associations | Summary of key findings |
|---|---|---|
| **Surrogates considered for PFS** | | |
| **Response**[4,6,7,12,31,37] | 6/6 | • Achievement of CR was associated with longer PFS<br>• Patients who were heavily pretreated and had a response (CRi/CR[6,7]; CR/PR[4]) experienced longer PFS |
| **MRD**[7,16,29,30,32,35–37,39,41] | 9/10 | • Patients with undetectable MRD had a longer PFS than those with detectable MRD<br>• An increase in MRD response relative risk between trial arms was associated with improved PFS outcomes<br>• Patients with MRD-negative CR showed a significantly longer PFS than those who achieved MRD-positive CR or PR<br>• A significant correlation was observed between MRD-negative status and longer PFS, regardless of treatment line, treatment, analysis method, and MRD definition |
| **Surrogates considered for OS** | | |
| **Response**[a,4,6,7,11,12,14,19,23,26,33,37] | 10/11 | • A lack of response was associated with shorter OS<br>• Patients with PR had improved OS compared with stable disease, progressive disease, or not estimable<br>• Achievement of CR was associated with longer OS<br>• OS was similar regardless of whether patients achieved a PR with lymphocytosis or CR/PR within the first year of ibrutinib treatment |
| **MRD**[6,7,16,29,32,35–41] | 11/12 | • Patients with undetectable MRD had a longer OS than those with detectable MRD<br>• Patients with MRD-negative CR and MRD-positive CR had significantly longer OS than those with MRD-positive PR<br>• MRD-negative status was statistically significantly associated with longer OS, regardless of treatment line, MRD definition, and sensitivity |
| **PFS**[28] | 1/1 | • A very strong association was observed between PFS or time to progression and OS, with higher correlation in patients with median follow-up ≤ 30 months, age > 65 years, 3L+ therapy, treatment with immunochemotherapy, and intermediate to high-risk profile, and had Rai class 4 CLL |
| **Disease progression**[19,34,42] | 2/3 | • A significant association was observed between disease progression at ≥ 12 and ≥ 24 months and worse OS |

[a]Response was considered using a range of endpoints, including but not limited to CR, PR, overall response rate, progressed disease, and stable disease, as well as complete remission with incomplete hematologic recovery.
CR, complete response; CRi, complete response with incomplete hematologic response; PR, partial response.

## Conclusions

- The most common prognostic factors considered for OS were age, prior lines of treatment, and prior purine analog (fludarabine) use, with increased age, more prior treatments, and fludarabine refractoriness found to be associated with shorter OS
- The most common surrogate endpoints considered for PFS or OS were response and MRD, which were both found to be associated with PFS and OS
- Despite a large body of literature, few publications reported analyses of surrogate endpoints, particularly in heavily pretreated patients, or used the latest bivariate meta-analysis methods

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