RESEARCH LETTER

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TO THE EDITOR:

CLL-IPI applied in Binet A CLL: a nationwide cohort study

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The Chronic Lymphocytic Leukemia International Prognostic Index (CLL-IPI) is thoroughly validated and commonly applied in clinical practice and research in chronic lymphocytic leukemia (CLL).[1-3] In a recent single-center study, Parikh et al[4] demonstrated that CLL-IPI can also predict time to first treatment (TTFT) and overall survival (OS) in newly diagnosed patients with Rai stage 0 CLL or monoclonal B-cell lymphocytosis. In the present study, we validated these in patients with early-stage CLL in a population-based cohort.

We analyzed TTFT and OS in patients diagnosed with Binet stage A CLL from the Danish National Chronic Lymphocytic Leukemia Register (DCLLR), a nationwide mandatory register containing information on all patients diagnosed with CLL since 2008.[5] As of January 2020, the DCLLR comprised 5472 patients with complete follow-up. All patients diagnosed with Binet stage A disease and complete or imputed CLL-IPI data were included in the study. Information on treatment regimen was available for a geographically defined subgroup (supplemental Figure 1). TTFT was defined as time from diagnosis until treatment or end of follow-up in September 2020, whichever occurred first, treating death as a competing risk, and analyzed using cumulative incidence curves with corresponding 4-year estimates. OS was defined as time from diagnosis until death or end of follow-up in September 2020, whichever occurred first, and analyzed using Kaplan-Meier plots with corresponding 4-year estimates. Harrell C-index was calculated to evaluate discriminatory power, and confidence intervals (CIs) were obtained using bootstrapping. Gray K-sample and log-rank tests were used to compare TTFT and OS, respectively. Univariable and multivariable Fine-Gray and Cox proportional hazards regressions were used to compare TTFT and OS, respectively, across CLL-IPI groups, individual CLL-IPI factors, fluorescence in situ hybridization according to Döhner classification, and Eastern Cooperative Oncology Group (ECOG) performance status (PS).[6,7] Statistical analyses were performed using R version 3.6.0. The study was approved by the Danish Data Protection Agency (jr.no RH-2015-96 03856) and conducted in accordance with the Declaration of Helsinki.

We included 2722 patients diagnosed with Binet stage A CLL with a median follow-up of 4.9 years (interquartile range, 2.6-7.4 years); 545 patients received treatment, and a total of 628 died. Table 1 shows baseline characteristics for the cohort; the median age was 70 years, and the proportions of patients with CLL-IPI low, intermediate, high, and very high risk were 63%, 28%, 7%, and 2%, respectively.

CLL-IPI was associated with TTFT in the overall cohort ($P < .0001$; C-statistic, 0.68; 95% CI, 0.66-0.70), with 4-year risks of treatment of 18% for the overall cohort and 9% (95% CI, 7% to 10%), 33% (95% CI, 29% to 36%), 37% (95% CI, 29% to 45%), and 40% (95% CI, 27% to 54%) for patients with CLL-IPI low, intermediate, high, and very high risk, respectively (Figure 1A). All individual CLL-IPI groups had a higher risk of treatment compared with the low-risk group (hazard ratio [HR] range, 3.9-4.6; supplemental Table 1), although results were similar across the higher-risk groups (supplemental Table 2). In a multivariable model, age ≥65 years (HR, 0.8; 95% CI, 0.7-1.0), unmutated IGHV status (HR, 3.8; 95% CI, 3.2-4.5), and elevated β2-microglobulin (HR, 1.8; 95% CI, 1.4-2.3) were associated with a higher risk of treatment ($P < .0001$), whereas del(17p) was not (HR, 1.4; 95% CI, 0.9-2.0; $P = .12$).

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Requests for data sharing may be submitted to Emelie C. Rotbain: erot0006@regionh.dk.

The full-text version of this article contains a data supplement.

Table 1. Baseline data for patients diagnosed with Binet stage A CLL with data available on CLL-IPI from DCLLR (n = 2722)

	Patients with Binet stage A CLL (n = 2722)
Age at diagnosis,y	
Median (Q1-Q3)	70 (63-76)
<65	933 (34)
≥65	1789 (66)
Sex	
Female	1073 (39)
Male	1649 (61)
IGHV status	
Mutated	1952 (72)
Unmutated	757 (28)
Missing	13
FISH	
del(13q)	1263 (46)
Normal	856 (31)
Trisomy 12	307 (11)
del(11q)	146 (5)
del(17p)	150 (6)
β2-microglobulin >4.0 mg/L	
No	2435 (90)
Yes	277 (10)
Missing	10
CLL-IPI	
Low	1713 (63)
Intermediate	767 (28)
High	180 (7)
Very high	62 (2)

Data are presented as n (%) unless otherwise indicated.
del, deletion; FISH, fluorescence in situ hybridization; IGHV, immunoglobulin heavy-chain variable gene region.

CLL-IPI was associated with OS in the overall cohort ($P < .0001$; C-statistic, 0.60; 95% CI, 0.58-0.62), with 4-year OS rates of 89% (95% CI, 88% to 91%), 80% (95% CI, 77% to 83%), 72% (95% CI, 64% to 79%), and 58% (95% CI, 44% to 72%) for patients with CLL-IPI low, intermediate, high, and very high risk, respectively (Figure 1B). OS differed across all individual CLL-IPI groups (HR range, 1.3-4.4; supplemental Tables 1 and 2). In a multivariable model, age ≥65 years (HR, 4.7; 95% CI, 2.3-3.4), unmutated IGHV (HR, 1.5; 95% CI, 1.3-1.8), and elevated β2-microglobulin (HR, 2.8; 95% CI, 1.4-2.3) were associated with shorter survival ($P < .0001$). Of note, del(17p) was not associated with shorter OS (HR, 1.1; 95% CI, 0.8-1.5). However, when adjusting for an interaction with age, del(17p) was associated with shorter OS in patients age <65 years (HR, 2.8; 95% CI, 1.1-6.8; $P = .03$).

OS estimates for 1580 patients diagnosed from 2014 to 2020 were similar to those of the overall cohort (4-year OS, 90%, 77%, 69%, and 62% for low, intermediate, high, and very high risk patients, respectively), and CLL-IPI retained its prognostic ability ($P < .0001$; C-statistic, 0.62; 95% CI, 0.59-0.66; data not shown). Among patients treated after 2014, 12% received novel therapies as first-line treatment and 45% as second-line treatment (supplemental Table 3). In subgroup analyses of patients age >70 or >80 years, CLL-IPI retained its association with TTFT and OS ($P < .0001$) and with OS from 2014 to 2020 ($P < .0001$ and $P = .003$, respectively).

ECOG PS was associated with TTFT and OS independently of CLL-IPI, but C-statistics when PS was added were similar to those of CLL-IPI alone (supplemental Tables 4 and 5). C-statistic for IGHV status was similar to that of CLL-IPI for TTFT but lower than that for OS. The fluorescence in situ hybridization Döhner classification was associated with both TTFT and OS but had lower C-statistics compared with CLL-IPI (supplemental Tables 5 and 6). Notably, del(11q) was strongly associated with shorter TTFT, illustrating is usefulness as a prognostic marker alongside del(17p) in early-stage CLL.[8]

In this nationwide cohort study, we demonstrate that CLL-IPI can be used to predict OS in patients diagnosed with Binet stage A disease. Moreover, our findings suggest that CLL-IPI remains

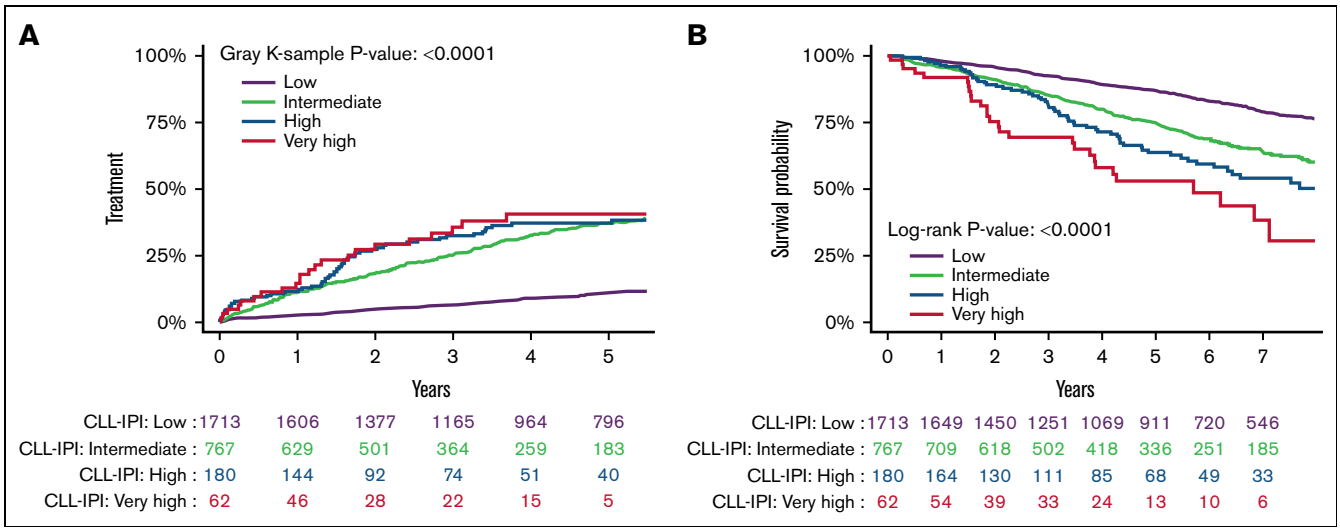

Figure 1. Outcomes in patients with Binet stage A CLL. TTFT (A) and OS (B) by CLL-IPI risk score.

robust in the novel therapy era. In terms of TTFT, our findings show that CLL-IPI is mainly useful in predicting which patients will not require treatment but less efficient in stratifying higher-risk patients. While not increasing the C-statistics, ECOG PS may be considered as an addition to CLL-IPI, because it has independent value and comes at no extra cost.

C-statistics for the prediction of OS and TTFT using CLL-IPI in this cohort did not reach 0.7. However, they were similar to previous findings for TTFT and treatment-free survival (TFS) in newly diagnosed Binet stage A (0.69-0.70) and Rai stage 0 (0.61-0.75) and OS in Rai stage 0 (0.65), with most estimates overlapping our CIs.[4,9-11]

Several approaches have been developed for assessing the prognosis of newly diagnosed patients with CLL, although the performance of the predictions has not improved over time.[1,12-18] A recently developed laboratory-based prognostic calculator demonstrated superior or equal discriminatory power compared with CLL-IPI for TFS across validation cohorts (0.63-0.72 vs 0.61-0.70), with most estimates within the CI of TTFT in our study.[11] The International Prognostic Score-A, a novel score including genetic and clinical variables for predicting TTFT in early-stage CLL, has exhibited C-statistics (0.66-0.75) similar to those of CLL-IPI in direct comparison and with estimates within our CIs.[9,18] Studies applying the observational CLL1 score for TTFT or TFS, which uses genetic and clinical variables, have also found C-statistics (0.69-0.75) comparable to ours and with identical estimates or overlapping CIs when comparing directly with CLL-IPI.[9,17,19] Likewise, the Barcelona-Brno Prognostic Index, using genetic variables only, has demonstrated a C-statistic (0.67) comparable to that of CLL-IPI in both the same study and in ours.[9,14] The MD Anderson Cancer Center scores from 2007[15] (0.65) and 2011[20] (0.71) and the German Chronic Lymphocytic Leukemia Study Group score[13] (0.69) have exhibited C-statistics for TTFT or TFS similar to those of CLL-IPI in the same study and in our results, with overlapping CIs.[17,19] The C-statistic for TTFT in our study was higher compared with those of the tailored approach[16] in IGHV-mutated (0.61) and -unmutated (0.58) CLL, respectively, and compared with that of CLL-IPI in the same study.[9]

This study provides evidence that CLL-IPI can be used in older patients with Binet stage A CLL, including those in the highest age groups. The high median age in our study also enabled us to detect an interaction between age and del(17p), suggesting that age-adjusted prognostic tools might improve prediction in CLL. In cardiology, the interaction between age and other risk factors for fatal cardiovascular disease has long been included in risk stratifications and recommendations for antilipid treatment, whereas in CLL, age is generally used only as an additive factor in prognostic models.[21,22]

A weakness in our study is that targeted treatments are only reimbursed in Denmark for treatment-naïve patients with *TP53* aberrations; however, novel therapies are reimbursed irrespective of *TP53* in the relapsed/refractory setting. Additionally, through clinical trials, patients with wild-type *TP53* have also received novel therapies, resulting in a substantial proportion of the cohort receiving novel therapies. Another limitation is that β2-microglobulin is reported as >4 or <4 mg/L in the DCLLR, possibly leading to misclassification of CLL-IPI category in a limited number of patients.

In this study, *TP53* aberrations were seen only in patients in higher-risk CLL-IPI groups; they were present in half of patients at high risk and mandatory in those at very high risk. Because *TP53* is mainly associated with chemorefractoriness and response duration for targeted therapies, the similar TTFTs for all CLL-IPI groups except the low-risk group were anticipated. Contrary to previous findings, the risk of requiring therapy was lower in our study compared with estimates for those with Rai stage 0 disease in the study by Parikh et al.[4,23] However, our cohort underwent follow-up from the time of diagnosis, whereas the study by Parikh et al included patients seen within 3 years of diagnosis. Even so, it should be emphasized that patients with Rai stage 0 and Binet stage A disease may not necessarily represent the same patient population.[23]

In conclusion, using data from a large population-based cohort, we demonstrate that CLL-IPI is a useful tool in predicting OS in patients with Binet stage A CLL, as well as in older patients. Additionally, tCLL-IPI may be used to predict which patients with Binet stage A disease will not require therapy.

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