TO THE EDITOR:

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

Emelie C. Rotbain,1,2 Caspar da Cunha-Bang,1 Christian Brieghel,1,3 and Carsten U. Niemann1

1Department of Hematology, Rigshospitalet–Copenhagen University Hospital, Copenhagen, Denmark; 2Danish Cancer Society Research Center, Copenhagen, Denmark; and 3Department of Hematology, Roskilde Hospital–University Hospital Zealand, Roskilde, Denmark

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 al4 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).

Submitted 27 September 2021; accepted 20 January 2022; prepublished online on Blood Advances First Edition 28 January 2022. https://doi.org/10.1182/bloodadvances.2021006259.

Requests for data sharing may be submitted to Emelie C. Rotbain: erot0006@regionh.dk.
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 $\geq 65$ years (HR, 4.7; 95% CI, 2.3-8.4), unmutated IGHV (HR, 1.5; 95% CI, 1.3-1.8), and elevated $\beta_2$-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 its usefulness as a prognostic marker alongside del(17p) in early-stage CLL.

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

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

| Treatments | Low (n = 1713) | Intermediate (n = 1606) | High (n = 767) | Very high (n = 183) |
|------------|---------------|------------------------|---------------|---------------------|
| CLL-IPI: Low | 1713 | 1606 | 767 | 183 |
| CLL-IPI: Intermediate | 1377 | 1165 | 364 | 259 |
| CLL-IPI: High | 624 | 462 | 282 | 222 |
| CLL-IPI: Very high | 15 | 10 | 5 | 1 |

Data are presented as n (%) unless otherwise indicated.

del, deletion; FISH, fluorescence in situ hybridization; IGHV, immunoglobulin heavy-chain variable gene region.

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**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.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 TFFT 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 TFFT 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.9,17,18 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 (0.65) and 2011 (0.71) and the German Chronic Lymphocytic Leukemia Study Group score (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 approach16 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.

Acknowledgments: The authors thank Noomi Vainer for her work in collecting information from medical records.

This work was supported in part by Novo Nordisk Foundation grant NNF16OC019302 (C.U.N.).

Contribution: E.C.R. and C.U.N. designed the study. E.C.R. performed the statistical analysis and wrote the first draft of the manuscript. All authors contributed to data interpretation, manuscript revision, and approved the final manuscript.

Conflict-of-interest disclosure: E.C.R. has received consultancy fees or travel grants from AbbVie, Janssen, and AstraZeneca. C.d.C.-B. has received consultancy fees and/or travel grants from AbbVie and Gilead. C.U.N. has received support, consultancy fees, or travel grants from AbbVie, Gilead, Janssen, Roche, CSL Behring, Acerta, Genmab, Sunesis, Octapharma, Takeda, and AstraZeneca outside this work. C.B. declares no competing financial interests.

ORCID profiles: E.C.R., 0000-0002-4199-772X; C.B., 0000-0002-1816-8106; C.U.N., 0000-0001-9880-5242.

Correspondence: Emelie C. Rotbain, Department of Hematology, Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, DK-2100 Copenhagen, Denmark; email: erot0006@regionh.dk.

References

1. International CLL-IPI working group. An international prognostic index for patients with chronic lymphocytic leukaemia (CLL-IPI): a meta-analysis of individual patient data. Lancet Oncol. 2016;17(6):779-790.
2. da Cunha-Bang C, Christiansen I, Niemann CU. The CLL-IPI applied in a population-based cohort. Blood. 2016;128(17):2181-2183.
3. Gentile M, Shanafelt TD, Rossi D, et al. Validation of the CLL-IPI and comparison with the MDACC prognostic index in newly diagnosed patients. Blood. 2016;128(18):2093-2095.
4. Parikh SA, Rabe KG, Kay NE, et al. The CLL International Prognostic Index predicts outcomes in monoclonal B-cell lymphocytosis and Rai 0 CLL. Blood. 2021;138(2):149-159.
5. da Cunha-Bang C, Geisler CH, Enggaard L, et al. The Danish National Chronic Lymphocytic Leukemia Registry. Clin Epidemiol. 2016;8:561-565.

6. Döhner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med. 2000;343(26):1910-1916.

7. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-655.

8. Hoechstetter MA, Busch R, Eichhorst B, et al. Prognostic model for newly diagnosed CLL patients in Binet stage A: results of the multicenter, prospective CLL1 trial of the German CLL study group. Leukemia. 2020;34(4):1038-1051.

9. González-Gascón-Y-Marín I, Muñoz-Novas C, Figueroa I, et al; Grupo Español de Leucemia Linfática Crónica and Grupo Cooperativo Español de Citogenética Hematológica. Prognosis assessment of early-stage chronic lymphocytic leukemia: are we ready to predict clinical evolution without a crystal ball? Clin Lymphoma Myeloma Leuk. 2020;20(8):548-555.e4.

10. Molica S, Shanafelt TD, Giannarelli D, et al. The chronic lymphocytic leukemia international prognostic index predicts time to first treatment in early CLL: Independent validation in a prospective cohort of early stage patients. Am J Hematol. 2016;91(11):1090-1095.

11. Cohen JA, Rossi FM, Zucchetto A, et al. A laboratory-based scoring system predicts early treatment in Rai 0 chronic lymphocytic leukemia. Haematologica. 2020;105(6):1613-1620.

12. Agius R, Parviz M, Niemann CU. Artificial intelligence models in chronic lymphocytic leukemia - recommendations toward state-of-the-art. Leuk Lymphoma. 2021;6:1-14.

13. Pflug N, Bahlo J, Shanafelt TD, et al. Development of a comprehensive prognostic index for patients with chronic lymphocytic leukemia. Blood. 2014;124(1):49-62.

14. Delgado J, Doubek M, Baumann T, et al. Chronic lymphocytic leukemia: a prognostic model comprising only two biomarkers (IGHV mutational status and FISH cytogenetics) separates patients with different outcome and simplifies the CLL-IPI. Am J Hematol. 2017;92(4):375-380.

15. Wierda WG, O’Brien S, Wang X, et al. Prognostic nomogram and index for overall survival in previously untreated patients with chronic lymphocytic leukemia. Blood. 2007;109(11):4679-4685.

16. Bălaşa P, Moysiadis T, Hadzidimitriou A, et al; European Research Initiative on CLL (ERIC). Tailored approaches grounded on immunogenetic features for refined prognostication in chronic lymphocytic leukemia. Haematologica. 2019;104(2):360-369.

17. Molica S, Giannarelli D, Levato L, Mirabelli R, Gentile M, Morabito F. Assessing time to first treatment in early chronic lymphocytic leukemia (CLL): a comparative performance analysis of five prognostic models with inclusion of CLL-international prognostic index (CLL-IPI). Leuk Lymphoma. 2017;58(7):1736-1739.

18. Condoluci A, Terzi di Bergamo L, Langerbeins P, et al. International prognostic score for asymptomatic early-stage chronic lymphocytic leukemia. Blood. 2020;135(21):1859-1869.

19. Gentile M, Shanafelt TD, Cutrera G, et al. A progression-risk score to predict treatment-free survival for early stage chronic lymphocytic leukemia patients. Leukemia. 2016;30(8):1440-1443.

20. Wierda WG, O’Brien S, Wang X, et al. Multivariable model for time to first treatment in patients with chronic lymphocytic leukemia. J Clin Oncol. 2011;29(31):4088-4095.

21. Conroy RM, Pyörälä K, Fitzgerald AP, et al; SCORE project group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J. 2003;24(11):987-1003.

22. Agius R, Brieghel C, Andersen MA, et al. Machine learning can identify newly diagnosed patients with CLL at high risk of infection. Nat Commun. 2020;11(1):363.

23. Apelgren P, Hesselblom S, Werlenius O, Nilsson-Ehle H, Andersson PO; Western Sweden Lymphoma Group. Evaluation of clinical staging in chronic lymphocytic leukemia-population-based study. Leuk Lymphoma. 2006;47(12):2505-2516.