# To the editor:

## Validation of the CLL-IPI and comparison with the MDACC prognostic index in newly diagnosed patients

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Recently, an international collaboration collected information from ~3500 chronic lymphocytic leukemia (CLL) patients to develop a comprehensive tool for predicting overall survival (OS) (the international prognostic index for patients with chronic lymphocytic leukemia [CLL-IPI]).[1] This score built on *TP53* deletion and/or mutation, *IGHV* mutational status, β2-microglobulin (β2-M), clinical stage, and age may represent a simple "globally applied" model applicable in daily clinical practice and able to improve risk stratification for all CLL patients. Although it was primarily developed to predict OS, this tool can also predict time-to-first treatment (TTFT) in newly diagnosed patients.[2]

Herein, we evaluated the validity and reproducibility of the CLL-IPI in an independent cohort of newly diagnosed and nonreferred CLL patients collected from 5 Italian centers. We also evaluated whether CLL-IPI could predict TTFT. Finally, we compared this tool with the score proposed by the MD Anderson Cancer Center (MDACC) group[3] in both the Italian cohort and in an additional cohort of newly diagnosed CLL patients from the Mayo Clinic (Rochester, MN). The study was approved by Institutional Review Boards with informed consent in accordance with the Declaration of Helsinki.

CLL databases from 5 Italian centers were established for research purposes (supplemental Appendix, supplemental Figure 1, available on the *Blood* Web site). A total of 858 newly diagnosed and previously untreated CLL patients were included in this analysis. The majority of patients were Binet stage A (79.7%); median age was 65.5 years (supplemental Table 2 lists baseline patient features). After a median follow-up of 5.8 years (range, 3 months to 27.5 years), 167 patients died and 304 were treated (130 patients received chemotherapy and 174 received chemo-immunotherapy).

We evaluated the relationship between CLL-IPI and OS. Due to missing data regarding *TP53* mutations, del17p was used as the sole marker of *TP53* status. All parameters showed an independent prognostic impact (supplemental Table 3).

According to the CLL-IPI, 471 patients were classified as low risk, 214 as intermediate risk, 139 as high risk, and 34 as very high risk. Stratification of patients according to the CLL-IPI showed significant differences in terms of OS (Figure 1A). The median, 5-year, and 10-year OS rates by CLL-IPI category in our cohort are quite similar to those observed in the original study[1] (supplemental Table 4), suggesting that the survival estimates provided by the index are reproducible. The C-statistic was 0.71 (*P* < .0001) for predicting OS,

exceeding the 0.70 threshold and underscoring the prognostic utility at the individual patient level.[4]

A subanalysis of the 407 cases with available data regarding both del17p and *TP53* mutational status confirmed that the CLL-IPI stratified cases according to OS (supplemental Figure 2). The C-statistic was 0.69 (*P* < .0001) for OS prediction.

Finally, the CLL-IPI was also useful for predicting TTFT (supplemental Figure 3; supplemental Table 4), with a C-statistic of 0.74 (*P* < .0001). Thus, our analysis confirms the validity of the CLL-IPI in predicting progression for individual patients.[1]

Next, we applied the MDACC score[3] to our patient cohort. Overall, 307 patients were classified as low risk, 522 as intermediate risk, and 29 as high risk. Stratification of patients using the MDACC score allowed the prediction of prognosis (Figure 1B).

Subsequently, we compared the CLL-IPI with the MDACC score in our cohort. The C-statistic of the MDACC score was 0.68 (*P* < .001), which was lower than that of the CLL-IPI (0.71). The Akaike information criterion (AIC) and the explained variation indicated that the CLL-IPI had a higher prognostic accuracy for mortality compared with that of the MDACC score (Table 1).

Although these scores were initially developed to predict OS, we also compared their ability to predict TTFT in newly diagnosed patients. The C-statistic of the MDACC score was 0.63 (*P* < .001), which was lower than that of the CLL-IPI (0.72, *P* < .001). The AIC and the explained variation indicated that the CLL-IPI had a higher prognostic accuracy for predicting TTFT compared with that of the MDACC score (Table 1).

A second direct comparison of the CLL-IPI and MDACC score was carried out in a validation cohort of 506 CLL patients prospectively diagnosed and followed at the Mayo Clinic. The median age was 62.5 years (range, 36-89 years; supplemental Table 5 lists baseline patient features of the validation set). After a median follow-up of 7.2 years (range, 3 months to 14 years), 114 patients died and 213 were treated.

Both indices could stratify OS in the CLL patients from the Mayo Clinic cohort (supplemental Figure 4A-B). The C-statistic of the CLL-IPI was 0.75 (*P* < .001), which was higher than that of the MDACC score (0.66, *P* < .001). The AIC and the explained variation confirmed that the CLL-IPI had a greater prognostic accuracy for mortality (Table 1).

Finally, we compared the ability of the 2 scores to predict TTFT in the external validation cohort (supplemental Figure 5A-B). The
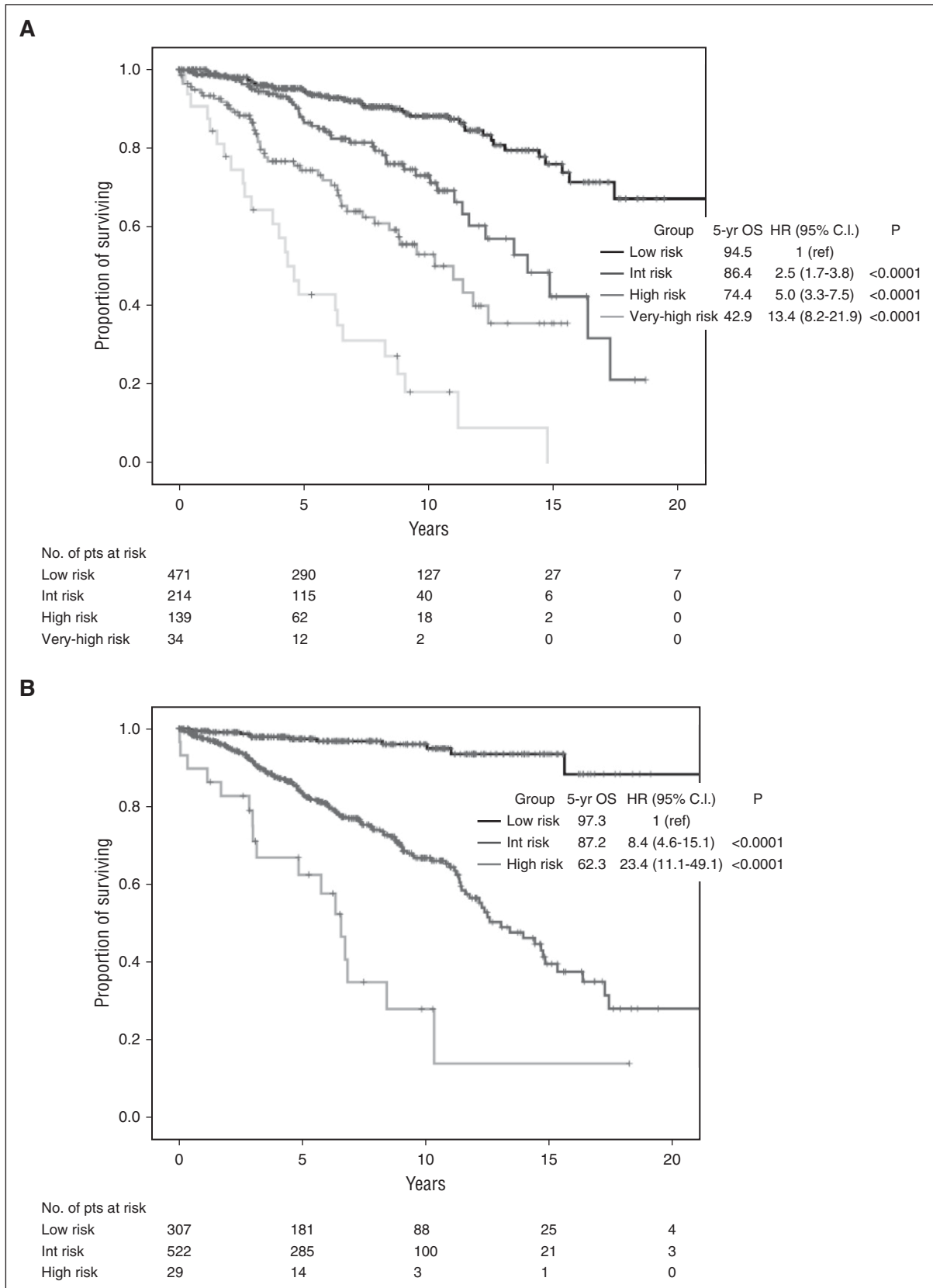
**Figure 1. Overall survival of the entire population of 858 CLL patients.** Patients are stratified according to the CLL-IPI (A) and MDACC score (B).

**Table 1. Comparison of CLL-IPI with MDACC score for prediction of OS and TTFT**

| | Harrel C-index (*P*) | AIC | Chance of being the best model (%) | Explained variation (*P*) |
|---|---|---|---|---|
| **Current Italian series (N = 858)** | | | | |
| Overall survival | | | | |
| CLL-IPI | 0.71 (<.001) | 1870.05 | 99 | 23% (<.001) |
| MDACC score | 0.68 (<.001) | 1878.40 | 1 | 21% (<.001) |
| Time to first treatment | | | | |
| CLL-IPI | 0.72 (<.001) | 2155.80 | 99 | 42% (<.001) |
| MDACC score | 0.63 (<.001) | 2225.64 | 1 | 22% (<.001) |
| **Mayo Clinic series (N = 506)** | | | | |
| Overall survival | | | | |
| CLL-IPI | 0.75 (<.001) | 1189.05 | 99 | 38% (<.001) |
| MDACC score | 0.66 (<.001) | 1251.01 | 1 | 20% (<.001) |
| Time to first treatment | | | | |
| CLL-IPI | 0.74 (<.001) | 3467.39 | 99 | 42% (<.001) |
| MDACC score | 0.66 (<.001) | 3546.29 | 1 | 31% (<.001) |

C-statistic of the MDACC score was 0.66 ($P < .001$), which was again lower than that of the CLL-IPI (0.74, $P < .001$). The AIC and the explained variation confirmed the higher prognostic value of the CLL-IPI compared with that of the MDACC score in predicting TTFT (Table 1).

Our analysis indicates that the CLL-IPI has higher prognostic accuracy for predicting OS than the MDACC score in both cohorts. Although our results also confirm the prognostic utility of the MDACC score, this model had C-statistics below the accepted 0.7 threshold necessary to have significance at the individual patient level in both cohorts.[4] Nonetheless, because the MDACC score can be calculated based on physical examination and β2-M, this index remains a useful prognostic tool in settings in which fluorescence in situ hybridization (FISH) and *IGHV* testing are not readily available.

The CLL-IPI also appeared to be better able to predict progression (a disease-specific end point) than the MDACC score in both cohorts.

Although we confirm that the CLL-IPI remains a significant tool for predicting prognosis in CLL patients, some issues must be considered. First, only a quarter of cases recorded in the Italian cohort were evaluable for this analysis due to missing data for FISH, *IGHV*, and β2-M. Because there was a similar distribution of age, sex, absolute lymphocyte count at baseline, Rai stage, and number of lymph node sites involved, the data from these 858 patients appear representative of all 3815. Second, date of diagnosis for the cases in this study span 30 years, during which considerable advances in the therapeutic approach to CLL have been made. Nonetheless, the addition of immunotherapy to conventional chemotherapy did not seem to impact on the predictive power of the CLL-IPI. The prognostic effectiveness of CLL-IPI needs to be reconsidered in the era of B-cell receptor inhibitors and B-cell lymphoma-2 antagonists to determine whether these drugs will be able to overcome the shorter survival likelihood among cases with higher-risk disease according to CLL-IPI.

Despite these limiting factors, our study has several important strengths, such as the large sample size and the community-based cohort of patients on which the findings are based. Finally, given that Italian CLL patients are usually followed by primary hematology centers (nonreferred patients) and only newly diagnosed patients were used in this analysis, our study allowed a long-term and observational follow-up that is representative of the real-life and natural course of CLL. The same does not always apply for studies dealing with US patients, who are initially followed by their family practitioners or by other hematologists and subsequently referred to academic centers, in view of the influence of both lead-time and time-length bias.[5] Our validation of the CLL-IPI, despite differences in terms of patient selection and characteristics, confirms that this score represents a powerful, easily applicable, and highly reproducible prognostic tool that can predict both TTFT and OS in newly diagnosed CLL patients.

The online version of this article contains a data supplement.

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