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Assessment of the 4-factor score: Retrospective analysis of 586 CLL patients receiving ibrutinib. A campus CLL study

To the Editor:

Recently, the National Institutes of Health (NIH) chronic lymphocytic leukemia (CLL) group collected information from 804 CLL patients treated with ibrutinib as first-line or salvage therapy in six clinical trials, and developed a comprehensive tool for predicting the outcome,[1] termed the 4-factor score, based on *TP53* aberration, β2-microglobulin (β2-M), lactate dehydrogenase (LDH) and disease status [treatment naïve (TN) vs relapsed/refractory (R/R)]. This score, derived from the application of both traditional and machine-learning methods, may serve as a useful model applicable in daily clinical practice and may help identify patients at higher risk of treatment failure and death during ibrutinib therapy (Table S1). Interestingly, the 4-factor model outperformed the CLL International Prognostic Index (CLL-IPI, scored as in Table S2)[2] in the ibrutinib setting, leading to an improved prediction of progression.[1]

In the study reported here, utilizing an institutional Italian multicenter working group on CLL ("Campus CLL dataset"), we evaluated the validity and reproducibility of this 4-factor score, both in terms of progression-free survival (PFS) and overall survival (OS), in an independent cohort of TN and R/R CLL patients treated with ibrutinib as monotherapy outside of clinical trials. All patients received ibrutinib at a dose of 420 mg once per day.

The CLL databases from 21 Italian, one Swiss, and one Israeli centers were combined to compile a large meta-database for research purposes (see supplementary appendix). This meta-database included 660 consecutive cases of CLL treated with ibrutinib between June 2013 and May 2019. A total of 586 out of 660 patients were evaluable for the 4-factor score.[1] Missing data for the *TP53* aberration were the reason for the exclusion of the 74 remaining cases. A total of 586 patients with CLL (147 TN and 439 R/R) were included in this analysis. Two hundred and fifty-four patients were Binet stage C (43.3%); median age was 70.6 years (see Table S3 for baseline patient features). The *TP53* aberration was detected in 270 patients (46.1%); 407 cases (69.5%) showed an unmutated *IGHV* status. After a median follow-up of 2 years (range, 1 month - 6 years), 93 patients had died, and 195 showed CLL progression.

First, we assessed the relationship between the 4-factor score and OS. In particular, the four factors (*TP53* aberration, R/R-CLL, high LDH, and high β2-M; Table S4), all significantly validated by univariate analysis in our setting, were introduced into a Cox multivariate model,

confirming their independent prognostic value. According to the scoring reported by Ahn et al.,[1] 239 patients (94 TN and 145 R/R) were classified as low risk (with zero to one factor present at the start of ibrutinib therapy), 220 (43 TN and 177 R/R) as intermediate risk (with two factors), and 127 (10 TN and 117 R/R) as high risk (with three to four factors). According to the 4-factor score, patients' stratification showed significant differences in terms of OS (Figure 1(A)). The 3-year OS rates by 4-factor score category in our cohort are quite similar to those observed in the original study (Table S5),[1] suggesting that the survival estimates provided by the index are indeed reproducible.

We also examined the correlation between 4-factor and PFS, and once again, the four single factors had an independent predictive impact on PFS (Table S6). Similarly, the score could also categorize patients for predicting PFS (Figure 1(B) and Table S5). The 3-year PFS rates by 4-factor score category in our cohort are lower than those observed in the original study (Table S5),[1] probably due to a higher rate of R/R cases (74.9% vs 58.7%) included in our study.

Considering the variation in reference ranges, we also tested LDH > upper limit of normal (ULN) as an alternative to the less consistent cut-off of 250 U/L. Table S7 shows that LDH > ULN achieved equivalent performance scores compared to the original 4-factor model in predicting PFS and OS.

Our group recently proposed a survival risk score for R/R CLL patients treated with ibrutinib (SRS_I) based on three laboratory parameters, that is β2-M, LDH, and anemia (Table S8).[3] Of note, the SRS_I shares with the 4-factor score two of its three prognostic indicators (ie, β2-M and LDH). Since all R/R patients enclosed in this analysis have been used in the training cohort for the SRS_I, we did feel appropriate to compare the SRS_I score with the 4-factor score. Nevertheless, stratification of patients according to the SRS_I showed significant differences in terms of OS (C-statistic 0.67, $P < .001$; Figure S1A), suggesting the usefulness of this scoring model in an even more heterogeneous cohort that includes TN and R/R patients. Similarly, SRS_I successfully clustered cases with a specific risk of progression (C-statistic of 0.60, $P < .001$; Figure S1B).

Next, we compare the CLL-IPI performance (Table S2)[2] and the 4-factor model since the data necessary for risk categorization according to both prognostic scores were available in all the 586 patients in our cohort. According to the CLL-IPI, most patients were in the high- (41.5%) or very high-risk groups (41.5%), 13.5% in the intermediate-risk group, while only 3.6% were in the low-risk group (Table S9). This notwithstanding, more than half (134/243, 55.1%) of the patients in the very high-risk group of the CLL-IPI fell into the low-risk or intermediate-risk category of the 4-factor model. A concordance test carried out by excluding the few cases categorized in the CLL-IPI low-risk group in keeping with Ahn et al.,[1] confirmed the lack of substantial agreement between the two prognostic tools (weighted k = 0.13), again highlighting the limits of the CLL-IPI for patients treated with ibrutinib, as previously reported.[1] The superiority of the novel 4-factor model[1] over the CLL-IPI[2] was not that unexpected since it is well-known that CLL-IPI was custom-built for chemo-immunotherapy and not for targeted therapy. Moreover, all the three factors (disease stage, age, and *IGHV* mutational status) used in the CLL-IPI but not in the 4-factor model did not show an independent prognostic significance in our and other ibrutinib cohorts.[1,3,4] Accordingly, we failed to demonstrate significant differences in both OS (Figure S2A) and PFS (Figure S2B) when patients were stratified according to the CLL-IPI, confirming its inability to predict the clinical outcome of TN and R/R patients treated with ibrutinib.

Our study's limitation is that our median follow-up is only 2 years, whereas the Ahn cohort is roughly 4 years.[1] These data are essential, especially in the light of the efficacy of ibrutinib. Simultaneously, a possible strength of the present is the well-characterized large cohort of CLL patients.

In conclusion, data presented here indicate that the 4-factor model provides adequate risk stratification concerning OS and PFS in a large multicenter retrospective cohort of patients, thereby

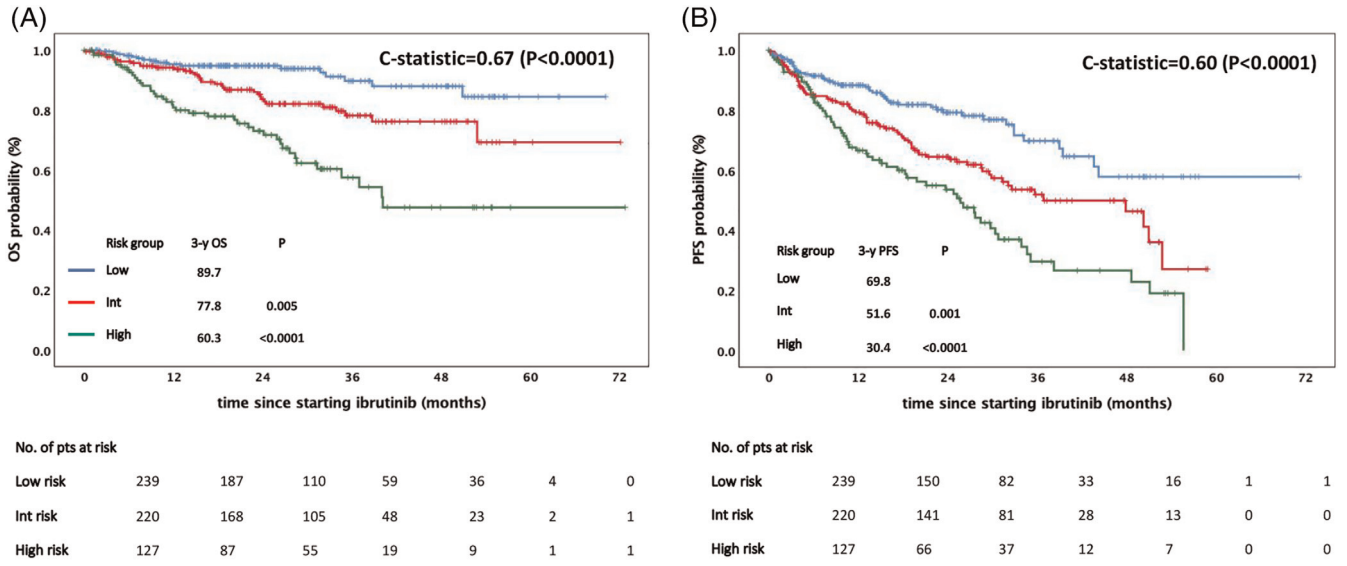

FIGURE 1 (A) Overall survival and (B) progression-free survival of the entire cohort of 586 CLL patients, according to the 4-factor score

confirming that it can serve as a robust, easily applicable, and highly reproducible tool for the clinical management and counseling of CLL patients treated with ibrutinib in daily practice, despite the differences in terms of patient selection and characteristics.

Nevertheless, the prognostic significance of prior treatment, one of the 4-factors prognostic tool, needs to be re-evaluated in light of the increase of chemo-free treatment strategies.

Integration with other ibrutinib-specific risk scorings[4] and/or implementation with other biomarkers with demonstrated impact in the ibrutinib setting, for example, CD49d,[5,6] may well contribute to improving the performance of the model in the future.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Fortunato Morabito, Massimo Gentile, Manlio Ferrarini, Giovanni Del Poeta, Francesca Romana Mauro, Davide Rossi, Francesco Di Raimondo, Antonio Cuneo, Gianluca Gaidano, Livio Trentin, Aaron Polliack, Annalisa Chiarenza, Robin Foà, Valter Gattei designed the study, analyzed and interpreted data, and wrote the manuscript; Massimo Gentile, Giovanni Tripepi, Giovanni Del Poeta, Fortunato Morabito performed statistical analysis; Giovanna Cutrona, Gilberto Fronza, Francesca Romana Mauro, Antonella Zucchetto, Ilaria Del Giudice, Riccardo Bomben, Antonino Neri, Manlio Ferrarini performed central laboratory tests; Gianluigi Reda, Paolo Sportoletti, Luca Laurenti, Marta Coscia, Yair Herishanu, Marzia Varettoni, Roberta Murru, Annalisa Chiarenza, Adalgisa Condoluci, Riccardo Moia, Andrea Visentin, Daniela Pietrasanta, Giacomo Loseto, Ugo Consoli, Ilaria Scortechini, Ernesto Vigna, Enrica Antonia Martino, Cirino Botta, Daniele Caracciolo, Francesco Mendicino, Ramona Cassin, Angela Rago, Ilaria Angeletti, Annalisa Biagi, J.O. and Sara Galimberti provided the patients and collected clinical data; and all authors gave final approval for the manuscript.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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The prognosis and durable clearance of RAS mutations in patients with acute myeloid leukemia receiving induction chemotherapy

To the Editor:

The RAS oncogenes, *NRAS* and *KRAS* are frequently mutated in AML, occurring in 11% and 5% of patients, respectively.[1] These gain-of-function mutations produce altered RAS-GTPase proteins locked in an active GTP-bound state resulting in constitutive activation of the mitogen activated protein kinase (MAPK), and phosphoinositide-3 kinase (PI3K) pathways that impact cell proliferation and survival. Although among patients receiving induction chemotherapy, the presence of *RAS* mutations do not significantly impact prognosis,[1] mounting evidence suggests that *RAS-pathway* mutated leukemic clones are more likely to be cleared. Targeted next generation sequencing performed at diagnosis and at time of complete remission (CR) after induction chemotherapy revealed that *RAS*-pathway mutations including *NRAS*, *KRAS*, *NF1*, *PTPN11* had higher clearance rates relative to other mutations