RESEARCH ARTICLE

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

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The chronic lymphocytic leukemia International Prognostic Index (CLL-IPI) combines 5 parameters (age, clinical stage, *TP53* status [normal vs. del(17p) and/or TP53 mutation], *IGHV* mutational status, serum β2-microglobulin) to predict survival and time-to-first-treatment (TTFT) in CLL patients. We performed an observational study in 337 prospectively collected, Binet stage A patients to validate the ability of the CLL-IPI to predict TTFT in an independent cohort of early stage CLL patients. The CLL-IPI score stratified Binet stage A patients into three subgroups with different outcome. Since the CLL-IPI was originally developed to predict survival, we next investigated the optimal cut-off score to predict TTFT in Binet stage A patients. Recursive partitioning analysis identified three subsets with scores of 0 ($n = 139$), 1 ($n = 90$), and ≥ 2 ($n = 108$). The probability of remaining free from therapy 5 years after diagnosis was 85%, 67% and 46% in these three categories ($P < 0.0001$.; C-statistic:c = 0.72; 95% CI:0.58-0.81). This optimized CLL-IPI scoring for TTFT was subsequently validated in an independent cohort of Binet A patients from the Mayo Clinic ($n = 525$). The ability of either original or optimized CLL-IPI to predict TTFT was equivalent to other prognostic models specifically designed for this endpoint (2011 MDACC score and O-CLL1 score). Although originally developed to predict suvival, the CLL-IPI is useful for predicting TTFT in early stage CLL patients.
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Introduction

The Rai and Binet clinical staging systems, which rely on physical examination and blood counts, have represented the basis for prognostication in chronic lymphocytic leukemia (CLL) for more than 40 years [1,2]. In recent years, insights into the genetic and molecular pathogenesis of CLL have led to the identification of new markers (e.g., *IGHV* mutational status, cytogenetics, mutations of *TP53*, NOTCH1, SF3B1, BIRC3) that add complementary prognostic information to clinical staging [3–7]. To date, however, not all of these markers are widely available in routine clinical practice.

With the identification of multiple prognostic parameters over the last 15 years, it has also become challenging to know how best to combine different tests to predict outcome for individual patients. Over the last decade, several groups have attempted to develop prognostic scores which incorporate multiple prognostic markers into a single model. These models, however, were frequently generated using data from patients cared for in academic referral centers. To date, their use has not been widely adopted in routine clinical practice due to their complexity and the fact that, in some cases, they are based on laboratory tests that are not widely available [8–10].

Additional Supporting Information may be found in the online version of this article.

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Recently, an international group of investigators analyzed data from patients participating in eight randomized clinical trials from Europe and the US to develop a prognostic index which includes widely available clinical, biologic, and genetic prognostic parameters [11]. Results of this international project generated a relatively easily to use prognostic score: the CLL International Prognostic Index (CLL-IPI). This prognostic model uses 5 parameters (age, clinical stage, *TP53* status [normal vs. del(17p) and/or TP53 mutation], *IGHV* mutational status,serum β2-microglobulin) to stratify patients into four distinct groups with significantly different overall survival. The prognostic utility of the CLL-IPI was subsequently validated in two independent cohorts of newly diagnosed patients from Mayo Clinic and the Swedish CLL registry [11].

Although the CLL-IPI was originally developed to predict overall survival, the index was also shown to predict time to first treamtent (TTFT) in newly diagnosed CLL patients. Nonethless, only 20% of patients included in the original dataset had early disease and, to date, no attempt has been made to optimize the CLL-IPI risk score to stratify TTFT among early stage patients. Of note, TTFT is an important and more disease specific endpoint than overall survival for newly diagnosed early stage patients [9,12,13].

With this in mind we used a cohort of newly diagnosed, early stage CLL patients, seen in daily practice, registered in a national database, and prospectively followed to validate the utility of the CLL-IPI to predict TTFT and to optimize CLL-IPI scores for this outcome.

Methods

Patients. Newly diagnosed CLL patients from several Italian Institutions who were seen within 12 months of diagnosis were prospectively enrolled into the O-CLL1-GISL protocol (clinicaltrial.gov identifier: 115 NCT00917540). The median time elapsed between the date of diagnosis and the date of database registration was 3 months (range, <1–12 months). Recruitment began in January 2007 and the criteria for CLL diagnosis employed were the 1996 National Cancer Institute (NCI)-sponsored Working Group guidelines (NCI-WG) [14]. Patients enrolled did not require therapy according to NCI-WG guidelines (i.e., asymptomatic Binet stage A). Peripheral blood flow cytometry for immunophenotype, CD38 and ZAP-70 expression, and IGHV mutational status were all analyzed in a central laboratory in Genova (Molecular Diagnostics IRCCS S. Martino-IST, Genova), while all FISH and genetic (i.e., *TP53*) analyses were performed in Milan (University of Milano and Hematology CTMO, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano). The study was approved by the ethics committees from each participating center.

Indications for therapy. Patients underwent sequential monitoring every 3-6 months based on physician judgement (median 4 months). NCI-WG guidelines were used to initiate therapy [14]. Active disease requiring therapy, was defined when at least one of the criteria set out in the NCI-WG guidelines was satisfied [14,15].

Cll-ipi. The CLL-IPI is based on five prognostic variables: age (i.e., > 65 years), serum ß2-microglobulin (i.e., >3.5 mg/L), clinical stage (i.e., Rai stage > I), IGHV mutational status (i.e., unmutated IGHV), *TP53* status (i.e., del(17p) and/or TP53 mutation deleted and/or mutated). A point score is assigned to each variable in accord with the original publication [11]. The total CLL-IPI risk score is calculated by summing the single ratings of 5 individual factors (range, 0–10) (Supporting Information Table 1). In the original CLL-IPI scoring system, patients are segregated into four risk groups: low (Scores 0-1), intermediate (Scores 2-3), high (Scores 4-6), and very high risk (Scores 7-10) [11].

Validation cohort. External validation of the revised scoring system to predict TTFT was performed in an independent cohort of newly diagnosed CLL patients (B-cell count $\geq 5 \times 10^9$/L) from the Mayo Clinic. This cohort of prospectively followed CLL patients recruited between 2001 and 2014 was previously used for validation of the original CLL-IPI score [11]. The present analysis, however, was restricted to the 525 patients (out of 838) with Rai stage 0-II disease. Due to missing data on *TP53* mutations, del(17p) was used as the sole marker of *TP53* status.

Comparison to other prognostic indices designed to predict TTFT. To explore the ability of the CLL-IPI to predict TTFT relative to other prognostic indices specifically developed to predict this endpoint, we also evaluated the 2011 MDACC score and the O-CLL1 score in this cohort [9,13]. The 2011 MDACC score was calculated according to the following formula: I(No. of lymph node sites involved = 3) × 7.370 + I(FISH = del11q) × 9.312 + I(FISH = del17p) × 11.285 + (diameter of largest cervical lymph node in cm) × 4.172 + (LDH/100) × I([IGHV gene = mutated] × 5.000 + (LDH ÷ 100) × I(IGHV gene = unmutated)×1.065] + 35.467. The indicator function (I) is equal to 1 if the statement in the parentheses is true and is equal to 0 otherwise [9]. The OCLL-1 was defined as the sum of the risk scores of the four individual parameters (i.e., Rai stages, ß2-microglobulin, absolute lymphocyte count, mutational status of IGHV). According to the these criteria, 3 different risk categories for TFS were determined: low (Score 0–2), intermediate (Score 3–5), and high (Score 6–7) [13].

Statistical analysis. The primary endpoint, TTFT, was defined as the interval between the date of registration and the date of initiation of first CLL treatment. Estimates of TTFT were calculated using the Kaplan–Meier method. Likelihood ratio tests were used to test effects of individual factors, either in univariate analysis or jointly. Hazard ratios (HR) and confidence intervals (CI) for HRs were calculated according to the Cox models. Since the grouping of point scores to define the original CLL-IPI risk categories was devised to predict overall survival, we also used recursive partitioning (RPART) to search for optimal cut-off points for the CLL-IPI score to predict TTFT in Binet stage A patients. Harrell's c index was calculated to assess the discriminatory power of the models ($c = 1$ indicates perfect discrimination; $c = 0.5$ indicates complete absence of prognostic accuracy). Akaike information criteria (AIC, lower is better) were used to assess the relative goodness of fit.

Results

Patient characteristics

In total, 337 patients with CLL Binet stage A were included in the initial analysis. The median age at diagnosis was 61 years (range, 33 − 70 years) and 57.2% were men. In this patient cohort, 77.8% were Rai stage 0 and 22.2% had Rai stage I-II. With respect to prevalence of other prognostic parameters incorporated into CLL-IPI, 28.1% patients had unmutated IGHV status, 2.6% had del(17p) and/or *TP53* mutation and 2% had a ß2-microglogulin level higher than 3.5 mg/L (Table I).

Patient follow-up

Patients were followed for a total of 2038 person-years (median, 42 months; range, 1 − 82 months), during which 91 patients (26.9%) required therapy. The probability of remaining free from therapy was 65% at 5 years and no plateau was reached (Supporting Information Fig. 1A). When the analysis was restricted to patients who received therapy, the median time to treatment was 24 months (range, 2 − 5 months).

Utility of CLL-IPI for predicting TTFT

Next, we calculated the CLL-IPI score in each patient. Consistent with the clinical characteristics of the patients included in this study (i.e., all with Binet stage A disease) only 2 patients had a risk score of 7 or higher (e.g., were in the very high risk category). Accordingly, these 2 patients were grouped with patients with scores between 4 and 6 such that patients were classified into one of three risk categories: low (Score 0-1, $n = 229$ or 67.9%), intermediate (Score 2-3, $n = 92$ or 27.2%), high (Score ≥ 4, $n = 16$ or 4.7%).

Clinico-biologic characteristics of patients according to the CLL-IPI are presented in Table I. As expected, patients classified as high-risk by the CLL-IPI were older ($P = 0.005$), more likely to be Rai Stage I-II ($P < 0.0001$), had higher levels of $ß_2$-microglobulin ($P < 0.0001$), unmutated *IGHV* status ($P < 0.0001$), and del 17p/*TP53* deleted or mutated ($P < 0.0001$). Under the original CLL-IPI scoring system, the probability of remaining free from therapy at 5 years was 76% (95% CI: 71-86%%) in the low risk group, 45% (95% CI: 33-58%) in the intermediate risk group and 41% (95% CI: 8-75%) in the high risk group ($P < 0.0001$). Estimated median TTFT was not reached for the low risk group, while it was 55 (95% CI, 37 − 73) and 28 (95% CI, 4 − 53) months, respectively, for patients in the intermediate- and high-risk categories (Fig. 1A). *C* statistic analysis demonstrated that CLL-IPI accurately predicted the TTFT (*C*-statistic: $c = 0.70$; 95% CI:0.58-0.81).

A revised scoring system improves the ability of the CLL-IPI to stratify TTFT in early stage CLL patients

Since the CLL-IPI risk categories were originally developed to predict overall survival, we next explored whether different cut-off scores would better predict TTFT in early stage patients.

TABLE I. Clinical, Biological, and Genetic Characteristics of Patients Stratified According to the CLL-IPI Score

Variable	All patients (n = 337)	CLL-IPI score 0-1 Low-risk (n = 225)	CLL-IPI score 2-3 Intermediate-risk (n = 96)	CLL-IPI score ≥ 4 High-risk (n = 16)	P-value
Age > 65 yrs	86 (25.5%)	49 (21.7%)	28 (29.1%)	9 (56%)	0.005
Gender (M/F)	193/144	122/103	60/36	7/9	0.16
Rai stage (≥ I)	75 (22.2%)	36 (16%)	29 (30.2%)	10 (62.5%)	<0.0001
ALC (10^9/L)	11.2 (1.2 – 131.0)	10.9 (1.2 – 131.0)	11.4 (3.0 – 64.5)	15.4 (8.7 – 101.4)	0.17
LDH (>UNL)	17 (5%)	7 (3.1%)	8 (8.3%)	2 (12.5%)	0.02
B2-M > 3.5 mg/L	7 (2%)	2 (0.9%)	1 (1%)	4 (25%)	<0.0001
FISH negative	111 (32.9%)	71 (31.5%)	40 (41.6%)	4 (25%)	
13q del	153 (45.4%)	123 (54.6%)	22 (23%)	8 (55%)	
trisomy 12	34 (10%)	13 (5.7%)	21 (21.8%)	0	
11q del	14 (4.5%)	1 (0.4%)	13 (13.5%)	0	
TP53 status [normal vs.del(17p) and/or TP53 mutation]	9 (2.6%)	0	0	9 (56%)	<0.0001
IGHV unmutated	95 (28.1%)	0	79 (82%)	16 (100%)	<0.0001
CD38-expression (<30%/≥30%)	274/63	206/19	55/41	7/9	<0.0001
ZAP-70 expression <20%/≥20%)	60/261	51/166	9/86	0/9	0.005

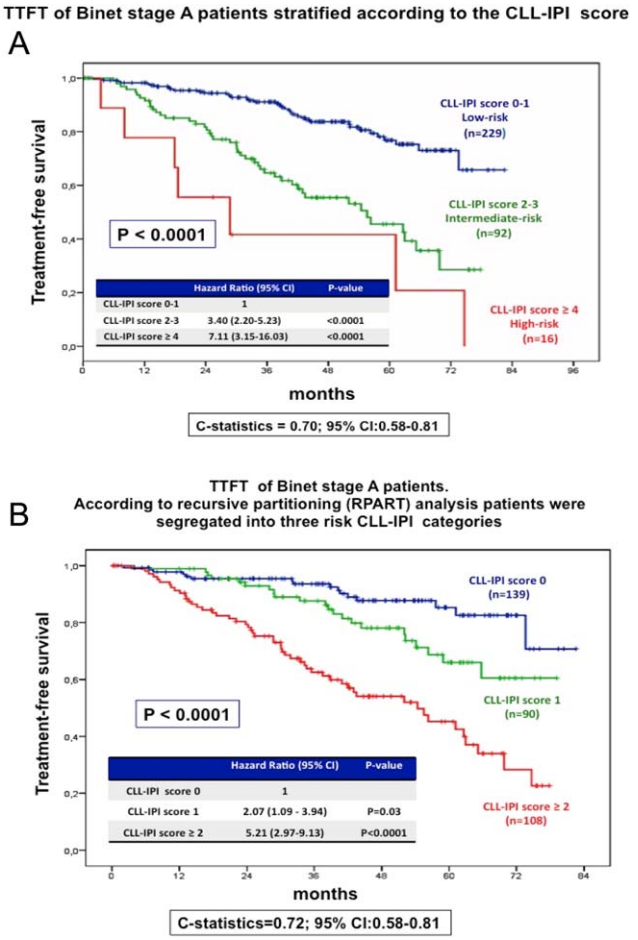

Figure 1. A: Kaplan-Meier estimate of time to first treatment (TTFT) of Binet stage A patients stratified according to CLL-IPI score: Low-risk (CLL-IPI score 0-1); Intermediate-risk (CLL-IPI score 2-3); High-risk (CLL-IPI score ≥ 4). B: TTFT of Binet A CLL patients based on Revised Scoring System Derived from Recursive Partitioning (RPART). The CLL-IPI risk categories were the following: Low-risk (CLL-IPI score 0); Intermediate-risk (CLL-IPI score 1); High-risk (CLL-IPI score ≥ 2). [Color figure can be viewed at wileyonlinelibrary.com]

Results of the RPART analysis to determine optimal cut-off scores for predicting TTFT identified three patient subsets whose scores were: 0 (low risk, n = 139 or 41.2%), 1(intermediate risk, n = 90 or 26.7%), and ≥ 2 (high risk, n = 108 or 32.0%) (Supporting Information Fig. 1B). The probability of remaining free from therapy at 5 years was 85% (95% CI: 77-93%) in the low risk group, 66% (95% CI: 53-78%) in the intermediate risk group and 46% (95% CI: 33-57%) in the high risk group ($P < 0.0001$) (Fig. 1B). Estimated median TTFT was not reached for the low risk and intermediate risk group while it was 54 months (95% CI, 35-70 months), for patients of high-risk category. The modified CLL-IPI provided a slightly higher C-statistic value in comparison to the original CLL-IPI (*C*-statistic:c = 0.72; 95% CI:0.58-0.81).

Subgroup analyses confirmed the discriminant power of revised CLL-IPI across Rai clinical stages. Although the three risk groups were only partially reproduced within Rai stage 0 that accounted for the majority of our patient cohort (262 out of 337 or 77.7%). As shown in Fig. 2A, the TTFT of patients with score 0 and 1 were almost superimposed such that only 2 risk categories were apparent in the Rai 0 subset. In contrast, the original CLL IPI scoring system identified 3 prognostic groups within the Rai 0 subset, although only 3 patients fell in the high-risk category (Fig. 2B). The C statistic for TTFT was 0.69 (95% CI:0.55-0.82) and 0.68 (95% CI:0.53-0-83) for the original and revised CLL-IPI scoring system, respectively, for the Rai stage 0 patients.

Validation of revised scoring system for TTFT

Next, we evaluated the ability of both the original and revised CLL-IPI scoring systems to predict TTFT in an independent cohort of newly diagnosed, Rai stage 0-II CLL patients from the Mayo Clinic. Clinical characteristics of this cohort are shown in Supporting Information Table 2. Since the number of patients belonging to the very high risk group was small (e.g., 15 patients or 2.8%) and the last reasonable estimate for these patients, all dead within 30 months, was at 2 years they were grouped with patients with scores between 4-6 to form the high risk group. Using the original CLL-IPI scoring system, 239 (45.5%) patients were classified as low risk (score 0-1), 189 (36%) as intermediate risk (score 2-3), 97 (18.4%) as high risk (score ≥ 4). The probability of remaining free from therapy at 5 years was 75% (95% CI: 69-83%) in the low risk group, 39% (95% CI: 31-49%) in the intermediate risk group and 23% (95% CI: 13-38%) in the high risk group ($P < 0.0001$). Under the revised scoring system for TTFT patients were classified as follows: low risk (score 0), 124 (23.6%), intermediate risk (score 1), 115(21.9%) and high risk (score ≥ 2) 286 (54.4%). The probability of remaining free from therapy at 5 years was 82% (95% CI: 74-91%) in the low risk group, 68% (95% CI: 58-80%) in the intermediate risk group and 34% (95% CI: 27-42%) in the high risk group ($P < 0.0001$). TTFT by risk category using the

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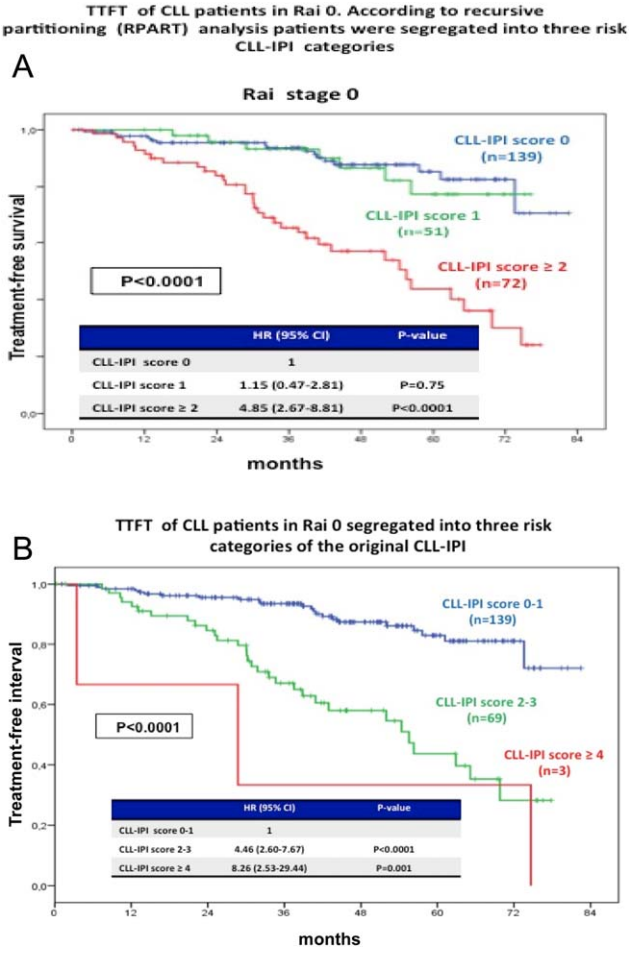

Figure 2. A: TTFT of Rai stage 0 patients based on revised scoring system derived from Recursive Partitioning (RPART). The CLL-IPI risk categories were the following: Low-risk (CLL-IPI Score 0); Intermediate-risk (CLL-IPI Score 1); High-risk (CLL-IPI Score $\geq$ 2). B: TTFT of Rai Stage 0 patients based on the original CLL-IPI: Low-risk (CLL-IPI Score 0-1); Intermediate-risk (CLL-IPI Score 2-3); High-risk (CLL-IPI Score $\geq$ 4). [Color figure can be viewed at wileyonlinelibrary.com]

original and revised scoring systems are shown in Fig. 3A,B. The *C* statistic for TTFT was 0.70 (95% CI:0.67-0.74) and 0.69 (95% CI:0.64-0.73) for the original and revised CLL-IPI scoring system, respectively. Similar to the results in the Italian cohort, when analysis was restricted to Rai stage 0 patients in the validation cohort the TTFT outcomes for patients with scores of 0 and 1 were alike such that the revised scoring system only identified 2 prognostic groups in the Rai 0 subset (Supporting Information Fig. 2A). In contrast, the original CLL IPI scoring system identified 3 prognostic groups within the Rai 0 subset (Supporting Information Fig. 2B). In the Rai 0 subset, the *C* statistic for TTFT was 0.73 (95% CI:0.68-0.79) and 0.71 (95% CI:0.64-0-77) for the original and revised CLL-IPI scoring system, respectively.

Comparison to other indices designed to predict TTFT

We compared the ability of the CLL-IPI and its revised version to predict TTFT in relation to the 2011 MDACC score the O-CLL1 score which were specifically designed to predict TTFT. The comparisons in terms of discriminatory power of models and relative goodness of fit (lower is better) are shown in Supporting Information Table 3. The Harrell's c value was highest for the O-CLL1 score (c-index, 0.75) and similar for the CLL-IPI (c-index, 0.70), the revised CLL-IPI (c-index, 0.72) and the 2011 MDACC score (c-index, 0.71). Finally, values of AIC test were best for the O-CLL1 score (AIC, 813) and similar for the CLL-IPI (AIC, 849), the revised CLL-IPI (AIC, 844) and the 2011 MDACC score (AIC, 842) (Supporting Information Table 3).

Discussion

Prognostication is an essential component in the management of CLL patients. Beside clinical stages, a plethora of new prognostic markers have been identified and different prognostic models proposed [8–10,16]. How best to combine these factors into an integrated risk stratification model for CLL patients has been challenging. Although several recent efforts to develop prognostic indices have been made, the exclusion of major genetic markers or the lack of consideration of clinical characteristics in some models [8,16] and the inclusion of markers not routinely available in others [10] represents the main obstacle for the implementation of these systems in routine clinical practice.

The recently developed CLL-IPI, based on five widely available parameters (i.e., *TP53* status [normal vs. del(17p) and/or *TP53* mutation], IGHV mutational status, B2M level, clinical stage, and age), represents an important step forward. The model combines genetic, biologic and traditional clinical prognostic parameters and separates four distinct groups of patients with significantly different prognosis. Moreover, the modular structure of CLL-IPI might allow the integration of genetic variables and/or other markers of proven prognostic value in the future [17]. It should be noted, however, that common recurring genetic defects identified on sequencing were evaluated during the development of the CLL-IPI and did not demonstrate independent prognostic value after adjusting for the other factors in the index [11]. Larger studies analyzing this aspect are needed.

Our study was aimed at validating the CLL-IPI in an independent, community-based cohort of CLL patients with early, Binet A clinical stage who were registered at diagnosis and followed prospectively.

As noted the CLL-IPI was originally developed to predict overall survival. Although it was shown to predict TTFT in a subset of watch-and-wait patients from the CLL1 trial as well as cohorts of newly diagnosed patients from Mayo Clinic and Sweden, the optimal, grouping of CLL-IPI scores to predict TTFT has not been established. Survival and TTFT are complementary endpoints; however, TTFT may be more appropriate endpoint for early stage CLL patients since it is a disease specific endpoint that is not influenced by competing risks for death, histologic transformation, or deaths due to other causes [18]. It should also be noted that, unlike overall survival, this end point has not been influenced by advances in treatment and the introduction of new therapies since observation remains the standard management approach for asymptomatic early stage patients [19–22].

Given this background, we evaluated whether a refined scoring system would improve the utility of the CLL-IPI for predicting TTFT in early stage disease. Although recursive partitioning, analysis suggested that somewhat different point groupings may slightly improve the ability of the CLL-IPI to stratify TTFT in Binet A patients in the Italian cohort, this revised scoring was not clearly better than the original scoring in the validation cohort from Mayo Clinic. Notably, for the subset of Binet A patients who are Rai stage 0, the original CLL-IPI scoring system distinguished 3 risk categories while the revised scoring system only identified two suggesting the original scoring system may have advantages within this patient group.

Regardless of the scoring approach used, the ability of the revised the CLL-IPI scoring system to predict TTFT was actually similar to two other prognostic tools specifically designed to predict TTFT (2011 MDACC score and O-CLL score) [9,13]. Given that it has already proved to be one of the most accurate predictors of survival

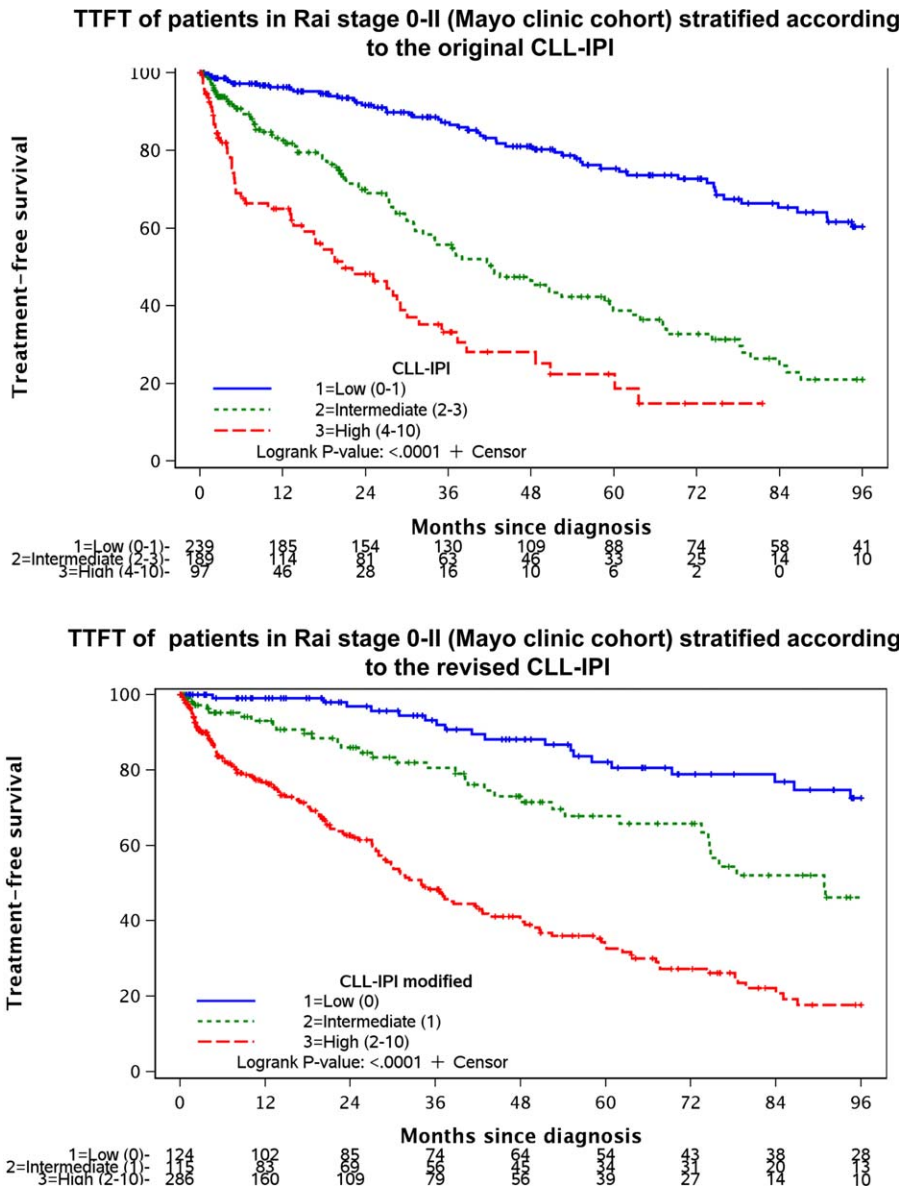

Figure 3. A: TTFT of Rai Stage 0-II patients (Mayo clinic cohort) based on the original CLL-IPI: Low-risk (CLL-IPI Score 0-1); Intermediate-risk (CLL-IPI Score 2-3); High-risk (CLL-IPI Score $\geq$ 4). B: TTFT of Rai Stage 0-II patients (Mayo clinic cohort) based on the revised CLL-IPI: The CLL-IPI risk categories were the following: Low-risk (CLL-IPI Score 0); Intermediate-risk (CLL-IPI Score 1); High-risk (CLL-IPI Score $\geq$ 2). [Color figure can be viewed at wileyonlinelibrary.com]

developed for CLL, this finding suggests that the CLL-IPI is a simple and readily available prognostic tool that can be routinely used to predict both survival and TTFT. This fact may allow a consistent prognostic platform for CLL patients around the world and encourage researchers to explore new ways to improve upon this platform rather than devising new systems with different markers and distinctive endpoints.

The current analysis has some weakness. The median age of patients in our series was lower than the median age of CLL patients in the general population (61 years versus 72 years) and only 25.5% of patients were older than 65 years, the age cut-off used for the CLL-IPI. Additional studies should be pursued to validate the CLL-IPI in larger samples of older patients. This limitation, however, may be less relevant for the TTFT endpoint (the focus of our study) than the overall survival endpoint which is more dependent on age [23]. Previous multivariate analysis also suggested that all five factors included in CLL-IPI have prognostic relevance in older as well as younger CLL patients [11]. Our attempt to develop an optimized scoring system for the TTFT endpoint explored a different way to group the risk score of the original CLL-IPI rather than evaluate whether the components used to calculate the risk score should be weighted differently for this endpoint. This latter analysis could only be performed in samples of several thousand patients and was beyond the scope of our analysis.

Our study has important strengths. All patients had early stage disease and are therefore representative of the majority of patients who are diagnosed with CLL in routine clinical practice. We were able to evaluate the utility of the revised scoring system in an independent cohort of early stage patients. The 5-year TTFTs for the low, intermediate, and high-risk patients under the revised scoring system in the validation cohort were nearly identical to those of patients in the initial Italian cohort. The slight decrease of c-statistic (e.g., from 0.72 to 0.69) observed in the external validation set reflects rather differences in the clinico-biologic features at diagnosis between patient populations such as an increased number of patients with unmutated *IGHV* (46% versus 28%) and Rai Stage I−II (44% versus 22%) that characterizes the validation cohort.

Although the wide use of prognostic models that incorporates IGHV and FISH may have limited application in some countries, these tests are standard assays in the U.S as well as many European countries. In this regard, a recently published systematic review and meta-analysis recommend *IGHV* mutational status and FISH be performed in all newly diagnosed CLL patients "in those countries with the resources to do so" [24]. Both these tests are considered standard of care in the National Cancer Comprehensive Network (NCCN) guidelines, which are widely used as national guidelines for routine clinical practice in the U.S. [25]. This at least implies the CLL-IPI and the tests used to derive it could be performed in all patients with newly diagnosed CLL in many Western countries. By identifying which parameters are most critical for assessing prognosis, the CLL-IPI also may help other countries determine how best to allocate resources by defining which parameters they can stop performing/pursuing (e.g., CD38, Zap-70) and which they should make certain are available (e.g., FISH, IGHV).

In conclusion, the CLL-IPI score, based on the use of five widely employed parameters represents a step forward in CLL prognostication, easily applicable in daily clinical practice. Although developed to predict overall survival, the CLL-IPI also predicts TTFT with an accuracy not inferior to other recently developed tools specifically designed to predict this endpoint. The ultimate clinical impact of the CLL-IPI in the management of early stage CLL patients should be determined in large, well-designed, prospective clinical trials including randomized trials evaluating the benefit of early intervention for high-risk early stage patients.

Author Contributions

S.M.,F.M. designed the study. S.M. and T.D.S. interpreted data and wrote the paper. D.G. and K.G.C. were responsible for statistical analysis. M.G., R.M., L.L., N.D.R., F.D.R., C.M, F.A., A.F. recruited patients for this observational study and participated in the management of patient care. T.D.S. and N.E.K. provided patients for validation analysis.

G.C., A.G.R., A.N. performed genetic studies. A.N.,F.M,M.G, M.F.,S.M. were the principal investigators of the observational trial. All authors approved the manuscript.

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