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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Comparative analysis of International Prognostic Index for Chronic Lymphocytic Leukemia, progression-risk score, and MD Anderson Cancer Center 2011 score – a single center experience

Biljana Mihaljević[1,2], Vojin Vuković[1], Nataša Milić[2,3], Teodora Karan-Đurašević[4], Nataša Tošić[4], Tatjana Kostić[4], Irena Marjanović[4], Marija Denčić-Fekete[5], Vladislava Đurašinović[1,2], Tijana Dragović-Ivančević[1], Sonja Pavlović[4], Darko Antić[1,2]

[1]University Clinical Center of Serbia, Clinic of Hematology, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[3]University of Belgrade, Faculty of Medicine, Department for Medical Statistics and Informatics, Belgrade, Serbia;
[4]University of Belgrade, Institute of Molecular Genetics and Genetic Engineering, Laboratory for Molecular Biomedicine, Belgrade, Serbia;
[5]University of Belgrade, Faculty of Medicine, Institute of Pathology, Belgrade, Serbia

SUMMARY

Introduction/Objective Prognostication of chronic lymphocytic leukemia (CLL) has been substantially improved in recent times. Among several prognostic models (PMs) focused on the prediction of time to first treatment (TTFT), progression-risk score (PRS), and MD Anderson Cancer Center score 2011 (MDACC 2011) are the most relevant, while CLL-International Prognostic Index (CLL-IPI), although originally developed to predict overall survival (OS), is also being used to estimate TTFT. The aim of this study was to investigate CLL-IPI, PRS, and MDACC 2011 prognostic values regarding TTFT and OS.

Methods The analyzed cohort included 57 unselected Serbian CLL patients from a single institution, with the basic characteristics reflecting more aggressive disease than in the general *de novo* CLL population. The eligible patients were assigned investigated PMs, and TTFT and OS analyses were performed.

Results Patients with higher risk scores according to CLL-IPI, PRS, and MDACC 2011 underwent treatment significantly earlier than patients with lower risk scores ($p = 0.002$, $p = 0.019$, and $p < 0.001$, respectively). In multivariate analysis, MDACC 2011 and CLL-IPI retained their significance regarding TTFT ($p = 0.001$ and $p = 0.018$, respectively), while PRS did not. CLL-IPI was the only significant predictor of OS both at the univariate ($p = 0.005$) and multivariate ($p = 0.013$) levels.

Conclusion CLL-IPI, PRS, and particularly MDACC 2011 are able to predict TTFT even in cohorts with more advanced-disease patients, while for prediction of OS, CLL-IPI is the only applicable among the three PMs. These results imply that PMs should be investigated in more diverse CLL populations, as it is in real-life setting.

Keywords: chronic lymphocytic leukemia; CLL-IPI score; progression risk score; MDACC 2011 score; overall survival; time to first treatment

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the most common leukemia of adults in Western countries, affecting predominantly elderly individuals with the median age of 72 years at diagnosis [1]. Up to 80% of patients are asymptomatic at the time of diagnosis, without indication for treatment [2, 3]. However, most of them will require therapy sooner or later during their disease course, with various outcomes, from refractoriness to long-lasting remissions. Heterogeneity of the clinical course of CLL stems from variability of clinical and biological features of both leukemic clones and hosts, which consequently imposes the need of personalized treatment approach [4].

In an attempt to refine the prognosis for individual patients, different prognostic models (PMs) have been developed. Forty years ago, Rai and Binet staging systems were established for risk stratification of CLL patients by estimating tumor burden using only physical examination and complete blood count [5, 6]. Although they are easily applicable and widely used, these staging systems do not reflect biological diversity of the disease, which limits their accuracy in predicting the disease course and outcome.

During the last two decades, a number of biological and genetic markers with major prognostic significance in CLL have been discovered, such as chromosomal aberrations (del13q, del17p, del11q, trisomy 12) mutational status of *TP53* and immunoglobulin heavy variable (*IGHV*) genes [7, 8]. Some of them have been, in combination with clinical variables, incorporated into different PMs aiming to predict time

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Correspondence to:
Vojin VUKOVIĆ
University Clinical Center of Serbia
Clinic of Hematology
Dr Koste Todorovića 2
11000 Belgrade, Serbia
vojinvukovic@yahoo.com

to first treatment (TTFT), response to particular therapies, and overall survival (OS) [4, 9, 10].

Wierda et al. [11] and Gentile et al. [12] proposed PMs that are able to identify patients with increased risk for treatment commencement among early-stage CLL patients. The former authors introduced MD Anderson Cancer Center 2011 score (MDACC 2011), a nomogram involving unfavorable cytogenetics (del11q and del17p), *IGHV* mutational status, level of lactate dehydrogenase (LDH), size of the largest cervical lymph node (LN) and the number of enlarged LNs. These markers were combined in a complex formula used to calculate the score value for each patient [11]. The latter authors proposed the progression-risk score (PRS), a simple multivariate model which stratifies patients into three risk categories based on stage, absolute lymphocyte count (ALC), serum β_2-microglobulin (β_2m), and *IGHV* mutational status [12, 13].

Recently, the International CLL-IPI Working Group introduced the International Prognostic Index for CLL (CLL-IPI), which resulted from a comprehensive meta-analysis of individual patient data, with the aim to predict the overall survival [14]. Patients were stratified into four risk groups (low, intermediate, high, very high) depending on the status of five variables: age, stage, β_2m, *IGHV* mutational status, and *TP53* status (mutation of *TP53* and/or del17p) [14].

All the mentioned PMs exert good discriminative power between risk-groups regarding either TTFT, OS, or both [14–22]. Even though CLL-IPI emerged as the most relevant one, each of these PMs can be taken into consideration depending on individual center's best practice and possibilities.

It is noteworthy that, for the purpose of TTFT prediction, these PMs have been developed within the cohorts of mostly early-stage patients [11, 12, 14]. Having in mind that, at most centers, genetic analyses necessary for all three scores are not being routinely performed at diagnosis but prior to first therapy, it is of great importance to test PMs in real-life settings [3, 23].

The objective of this study was to compare the prognostic strength of CLL-IPI, PRS, and MDACC 2011 in a cohort of CLL patients treated at a single institution.

METHODS

Study group

A total of 57 CLL patients diagnosed, treated, and followed at the Clinic of Hematology, University Clinical Center of Serbia, (Belgrade, Serbia) 2005–2018 were retrospectively analyzed for parameters within CLL-IPI, PRS, and MDACC 2011. All standard demographic, clinical, and laboratory characteristics were determined at diagnosis, while molecular and genetic markers were determined during the period from diagnosis to first treatment.

The number of patients enrolled in this study was limited by the availability of clinical and molecular data, mainly due to the following reasons: 1) analyses of *IGHV* mutational status, cytogenetic abnormalities and *TP53* mutational status are being performed after setting the indications for treatment, noting that *IGHV* and *TP53* mutational analyses are still not being routinely done at our institution; 2) some of the methods, such as determination of *IGHV* and *TP53* mutational status, were introduced in our institution in 2012 so, for the purpose of this study, we performed these analyses retroactively in patients for whom we had stored pretreatment blood samples.

Common cytogenetic abnormalities associated with CLL (del13q, del17p, del11q, trisomy 12) were detected by fluorescence *in situ* hybridization (FISH). The *TP53* mutational status was determined as recommended in Pospisilova et al. [24]. The *IGHV* mutational status was analyzed as recommended in Ghia et al. [25].

All procedures performed in this study were in accordance with the ethical standards of the Ethics Committee of the University of Belgrade Faculty of Medicine, Belgrade, Serbia (reference number: 29/XII-6) and with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all individual participants included in the study.

Scoring

In order to stratify patients according to CLL-IPI, 1 point was assigned for age > 65 years and stage Binet B–C or Rai I–IV, 2 points for β_2m concentration > 3.5 mg/L and unmutated *IGHV*, and 4 points for the presence of *TP53* mutation and/or del17p. Patients with score ≤ 1 were defined to be low-risk, score 2–3 intermediate-risk, score 4–6 high-risk, and score 7–10 very high-risk [14]. Thirty-eight patients with complete data were assigned CLL-IPI.

PRS was determined in 28/57 patients by scoring four variables: 1 point for Rai stage I–II and 2 points for ALC $\geq 10 \times 10^9$/L, elevated β_2m, and unmutated *IGHV* [12]. Patients with Rai stage III and IV, and those with incomplete data could not be assigned PRS. Low (score 0–2), intermediate (score 3–5), and high-risk (score 6–7) patients were defined by this PM.

MDACC 2011 score was determined in 42/57 patients using the original formula from Wierda et al. [11].

Statistical analysis

Quantitative variables are expressed as medians with 25th–75th percentiles. Categorical data are presented by absolute numbers with percentages. Kolmogorov–Smirnov test was used to assess the data distribution. TTFT was defined as the time from the diagnosis to the first therapy line. Overall survival was defined as time from diagnosis to death from any cause or the last follow-up. The estimates and graphical presentation of TTFT differences were performed via Kaplan–Meier approach. Univariate and multivariate Cox regression analysis was used to identify predictors of TTFT and OS. Variables significant in univariate analysis were entered to multivariate analysis. Hazard ratio (HR) with corresponding 95% confidence interval (CI) is presented for all evaluated predictors. All statistical tests were two

sided. Statistical analysis was performed using the SPSS 21.0 software (IBM Corp., Armonk, NY, USA). In all tests, p value < 0.05 was considered statistically significant.

RESULTS

Description of the cohort

Median age at diagnosis was 56.5 years (range 38–75 years). The cohort consisted of 41 male and 16 female patients (M:F = 2.6:1) and all of them underwent treatment after the median TTFT of 5.5 months (range 0–71 months). All patients received fludarabine-based therapy, 47 of them (82%) in the first treatment line. The remaining 10 patients (18%) were treated in the first line as follows: chlorambucil monotherapy (four patients), cyclophosphamide, vincristine, and prednisone (CVP) (four patients), alemtuzumab (one patient), and splenectomy (one patient). Overall response rate to the first treatment line was 79% (41% achieved complete response and 38% partial response), and 21% were unresponsive (12% stable disease and 9% progressive disease). After the first therapeutic line, 48 patients (84%) experienced disease progression, seven patients (12%) remained in the first remission until the last check-up or disease-unrelated death, and two patients (4%) were lost after completion of the first therapy. During the median follow up of 71.5 months (range 4–142 months), 14 patients (25%) were still alive, while 38 patients (67%) died (five patients were lost to follow-up). Median OS was 77 months (95% CI 69–85 months). Cohort characteristics are given in Table 1.

Assessment of risk

Patients were scored by CLL-IPI, PRS, and MDACC 2011 as described in the Methods section. Considering the fact that there were no patients in the low-risk group according to CLL-IPI and only two low-risk patients according to PRS, for the purpose of TTFT and OS analysis, patients were divided into two risk groups regarding these two PMs: intermediate risk and high / very high risk by CLL-IPI, and low/intermediate and high risk by PRS. In regard to the MDACC 2011, the cohort was dichotomized by the median score value of 53.6 (range 14.2–75). Proportions of patients in each risk group are given in Table 2.

Prediction of TTFT by CLL-IPI, PRS, and MDACC 2011

Higher score values of CLL-IPI and PRS, as well as MDACC 2011 > 53.6, were significant predictors of shorter TTFT in the univariate analysis. Namely, an increase of CLL-IPI and PRS by 1 score point increased the risk of treatment commencement by approximately 1.4 times (HR 1.385; 95% CI 1.121–1.710; p = 0.002 for CLL-IPI and HR 1.414; 95% CI 1.060–1.888; p = 0.019 for PRS). Cox regression analysis identified MDACC 2011 as the strongest predictor of TTFT (HR 1.046; 95% CI 1.020–1.073; p < 0.001) (Table 3).

Table 1. Clinical and biological characteristics of chronic lymphocytic leukemia patients

Characteristics	Patients (%)	Median (Q1, Q3)
Age		56.5 (52.2–65.7)
< 50	9 (16.1)	
50–65	33 (58.9)	
> 65	14 (24.6)	
Sex		
male	41 (71.9)	
female	16 (28.1)	
ALC (x10^9/L)		38.9 (16.1–83.9)
< 10	5 (10.4)	
≥ 10	43 (89.6)	
Hemoglobin (g/L)		128 (114.5–144.5)
≤ 100	7 (14.0)	
> 100	43 (86.0)	
Platelet count (× 10^9/L)		174.5 (112–226.3)
≤ 100	10 (20)	
> 100	40 (80)	
β_2-microglobulin (mg/L)	39 (68.4)	3.98 (2.78–4.86)
LDH (IU/L)	47 (82.5)	383 (315–592)
Lymph node of maximal size (cm)		
< 5	41 (77.4)	
≥ 5	12 (22.6)	
Rai		
0	5 (9.1)	
1–2	38 (69.1)	
3–4	12 (21.8)	
Binet		
A	18 (32.7)	
B/C	37 (67.3)	
CLL score[#]		
3	1 (2)	
4	10 (20.4)	
5	38 (77.6)	
CD38		
Positive (≥ 30%)	19 (36.5)	
Negative (< 30%)	33 (63.5)	
Type of infiltration		
nodular/interstitial	16 (32)	40 (40–58)
diffuse	34 (68)	80 (80–90)
IGHV		
mutated	11 (19.6)	
unmutated	45 (80.4)	
FISH		
del13q/trisomy12/ normal	44 (77.2)	
del11q	10 (17.5)	
del17p	3 (5.3)	
TP53		
wild-type	48 (84.2)	
mutated	9 (15.8)	

Q1 – quartile 1; Q3 – quartile 3; ALC – absolute lymphocyte count; LDH – lactate dehydrogenase; *IGHV* – immunoglobulin heavy variable gene; FISH – fluorescent *in situ* hybridization; CLL – chronic lymphocytic leukemia; [#]Matutes score

Table 2. Scoring of patients according to the CLL-IPI, PRS, and MDACC 2011

Risk assessment	Patients (%)	GfA*
CLL-IPI		
Low	/	
Intermediate	15 (39.5)	15 (39.5)
High	20 (52.6)	23 (60.5)
Very high	3 (7.9)	
PRS		
Low	2 (7.1)	11 (39.3)
Intermediate	9 (32.1)	
High	17 (60.7)	17 (60.7)
MDACC 2011		
≤ median#	21 (50)	
> median	21 (50)	

CLL-IPI – International Prognostic Index for Chronic Lymphocytic Leukemia; PRS – progression-risk score; MDACC 2011 – MD Anderson Cancer Center 2011 score;
*grouping for Kaplan–Meier analysis of time to first treatment and overall survival;
#median score value of MDACC 2011 was 53.6

The ability of these three PMs to predict TTFT was also tested by the Kaplan–Meier method. The patients were firstly dichotomized regarding calculated risk across all three examined PMs (Table 2). It was demonstrated that median TTFTs in groups of higher risk of CLL-IPI, PRS, and MDACC 2011 were three, six, and one month, respectively, as opposed to median TTFTs in groups of lower risk being 21, 38, and 20 months, respectively. The analysis confirmed a strong association between both PRS and MDACC 2011 and treatment-free period (p = 0.007 for PRS and p = 0.001 for MDACC 2011), while CLL-IPI exhibited a trend toward statistical significance (p = 0.074) (Figure1).

At the multivariate level, MDACC 2011 and CLL-IPI emerged as the significant predictors of TTFT (HR 1.051; 95% CI 1.019–1.083; p = 0.001 and HR 1.493; 95% CI 1.071–2.083; p = 0.018, respectively), while PRS did not show statistical significance (Table 3).

Prediction of OS by CLL-IPI, PRS, and MDACC 2011

CLL-IPI appeared to be a significant predictor of OS at the univariate level (HR 1.405; 95% CI 1.110–1.778; p = 0.005), PRS exhibited borderline significance (HR 1.473; 95% CI 0.997–2.177; p = 0.052), while MDACC 2011 was not significant. Multivariate analysis emphasized CLL-IPI as the only significant predictor of OS among three examined PMs (HR 1.657; 95% CI 1.113–2.468; p = 0.013) (Table 3).

DISCUSSION

The anticipation of the disease course has emerged as one of the main goals in the management of CLL and foundation of personalized treatment approach. Baseline clinical, biological and molecular characteristics of individual patients are being used in different patterns in order to predict the disease progression. With this aim, several prognostic models (PMs) have been developed recently, primarily for predicting TTFT and OS [9–12, 14, 26].

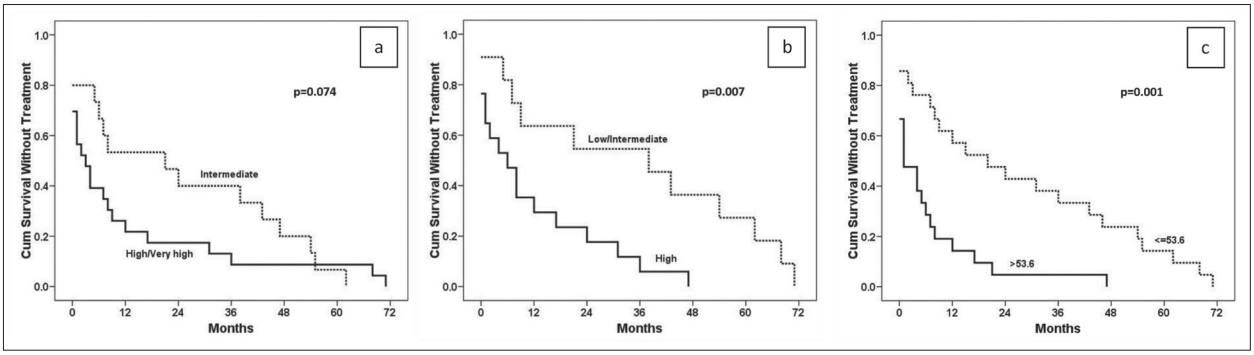

Figure 1. Analysis of time to first treatment for patients stratified according to CLL-IPI (a), PRS (b), and MDACC 2011 (c); for the purpose of Kaplan–Meier analysis, the patients were grouped into two risk categories according to each prognostic model: CLL-IPI – intermediate vs. high / very high (no patients in the low-risk group); PRS – low/intermediate vs. high; MDACC 2011 – the patients were dichotomized by the median score value of 53.6;
(a) CLL-IPI: median TTFT for patients with intermediate risk was 21 months and for high / very high risk three months.
(b) PRS: median TTFT for patients with low/intermediate risk was 38 months and for high risk six months.
(c) MDACC 2011: median TTFT for patients with MDACC 2011 ≤ 53.6 was 20 months and for patients with MDACC 2011 > 53.6 it was one month;
CLL-IPI – International Prognostic Index for Chronic Lymphocytic Leukemia; PRS – progression-risk score; MDACC 2011 – MD Anderson Cancer Center 2011 score

Table 3. Cox regression analysis of the time to first treatment and the overall survival

Score types	Time to first treatment						Overall survival					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	p	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p	HR	95% CI
CLL-IPI	**0.002**	1.385	1.121–1.710	**0.018**	1.493	1.071–2.083	**0.005**	1.405	1.110–1.778	**0.013**	1.657	1.113–2.468
PRS	**0.019**	1.414	1.060–1.888	/	/	/	0.052	1.473	0.997–2.177	/	/	/
MDACC 2011	**< 0.001**	1.046	1.020–1.073	**0.001**	1.051	1.019–1.083	0.167	1.019	0.992–1.047	/	/	/

HR – hazard ratio; CI – confidence interval; CLL-IPI – International Prognostic Index for Chronic Lymphocytic Leukemia; PRS – progression-risk score; MDACC 2011 – MD Anderson Cancer Center 2011 score

In this study, we analyzed a cohort of CLL patients from a single institution for variables that constitute CLL-IPI, PRS, and MDACC 2011 PMs.

Regarding TTFT, our results confirmed high predictive value of all three PMs, underscoring MDACC 2011 as the most significant one. Patients from the analyzed cohort with MDACC 2011 > 53.6 were treated one month after diagnosis, while those with ≤ 53.6 remained asymptomatic for almost two years. It should be noted that the patients included in our cohort exhibited more aggressive clinical course than patients from the cohorts analyzed to date regarding this issue. This aggressiveness is reflected in the fact that our patients were predominantly of intermediate and high risk according to the CLL-IPI and PRS. Also, a median of MDACC 2011 in our cohort was 53.6, which is considerably higher than that in the original MDACC or other validating cohorts [11, 15, 27]. Moreover, the proportion of patients with unmutated *IGHV* was 80%, higher than in the general CLL population (45–65%) [11, 14, 28, 29, 30]. Hence, it is not surprising that all our patients fulfilled criteria for treatment initiation after a median of 5.5 months, and most of them died during the median follow-up of around six years. Along with considerably younger median age at diagnosis in comparison with the general CLL population, the cohort's characteristics are the consequence of the following issues: 1) the majority of the patients were sampled for molecular and cytogenetic analysis and/or for biobanking shortly before the first treatment line, which made only patients with active disease eligible for this study. Knowing that approximately 40% of CLL patients never fulfill the criteria for treatment commencement, we may speculate that these patients carry favorable biological profile, while among those with active disease, unfavorable molecular characteristics are to be expected [31]; 2) as our institution represents the largest tertiary hematology center in Serbia, to which patients from the inner parts of the country are being referred as they develop active disease, this consequently concentrated patients with high tumor burden and more adverse biological features. High proportion of patients younger than in a typical CLL population is consistent with the data showing that younger CLL patients carry more unfavorable biological profile and experience shorter time to treatment [32]. Nevertheless, all three PMs analyzed in this study (CLL-IPI, PRS, and MDACC 2011) predicted shorter TTFT in higher *vs*. lower risk groups (three *vs*. 21 months, six *vs*. 38, and one *vs*. 20, respectively). Multivariate analysis pointed out MDACC 2011 as the strongest predictor of TTFT.

To the best of our knowledge, this is the second study that made comparison between CLL-IPI and MDACC 2011 concerning TTFT prediction, after a comparative study of five PMs by Molica et al [19]. In this research, the authors demonstrated a slight superiority of PRS over four other PMs, among which were MDACC 2011 and CLL-IPI. When focusing on the comparison between MDACC 2011 and CLL-IPI, the result was in favor of MDACC 2011, which is consistent with our findings [19]. In addition, this study clearly showed that PMs defined by both clinical and genetic parameters are more precise in predicting TTFT than those incorporating only variables that indicate tumor burden [17, 21]. When comparing these PMs with regard to TTFT, it should be noted that CLL-IPI was primarily designed to predict OS in contrast to MDACC 2011 and PRS, which were developed to estimate therapy-free period [11, 12, 14]. Although MDACC 2011 and PRS have been developed and validated within the cohorts of mostly early-stage, asymptomatic CLL patients, our results suggest that their use among patients with more advanced disease is equally valuable. Of note, a novel PM named International Prognostic Score for Early CLL (IPS-E) has been developed and externally validated recently [33]. It successfully discriminates patients in early-stage CLL considering TTFT using only three variables: *IGHV* mutational status, ALC > 15×10^9/L, and palpable lymph nodes. Smolej et al. [34] even proposed modified IPS-E called AIPS-E containing *IGHV* mutational status, FISH, and ALC. These newest PMs strongly support the use of combined biological and clinical features in CLL prognostication.

Regarding overall survival, in our cohort CLL-IPI was demonstrated to be a significant predictor of OS at both univariate and multivariate levels, PRS showed borderline significance only in the univariate analysis, while MDACC 2011 was not significant. As mentioned previously, PRS and MDACC 2011 have not been originally designed for prediction of OS and were developed within the cohorts of patients not requiring treatment at the time of study recruitment, while CLL-IPI was built upon participants of prospective treatment trials, which included predominantly symptomatic patients [11, 12, 14]. However, bearing in mind that similar clinical and genetic variables are used for construction of all three PMs, the question arises whether PRS and MDACC 2011 could also be used in estimating OS. Looking into variables of PRS and MDACC 2011, one can notice that three out of four variables of PRS (stage, ALC, and β_2m), and five out of six variables of MDACC 2011 (del11q, del17p, LDH, number of enlarged LNs, and size of the largest cervical LN) may evolve from the time of asymptomatic disease to the moment of the first therapy. Taken that into account, and based on our results, we speculate that MDACC 2011 is probably inapplicable in terms of OS prediction. On the other hand, PRS showed borderline significance with regard to OS, which implies that in a modified manner (i.e., inclusion of patients with advanced stage, higher threshold for ALC) PRS could be investigated also in terms of OS prediction.

The main limitation of our study is the small number of patients in the cohort, which challenges the reliability of the results. Atypical age and prognostic data distribution in comparison with general CLL population represent one center experience which we used to show that even in the circumstances of more aggressive features of the disease, examined PMs may separate the patients in need for immediate or very soon treatment from those who will be stable and free of therapy for some period of time. Nevertheless, studies on larger cohorts of patients with a more aggressive disease profile need to confirm these findings.

CONCLUSION

What is the purpose of anticipating TTFT in patients with CLL? Earlier attempts to treat asymptomatic CLL patients resulted only in extended event-free survival, without impact on OS. However, the development of new targeted therapies and their proven efficacy in high-risk patients, along with the advances in risk stratification, reopened the door for early interventional trials.

PMs consisting of both clinical and genetic variables seem to be efficient enough to predict TTFT. In our cohort, high CLL-IPI, PRS and particularly MDACC 2011 values clearly designated patients who would experience short TTFT, implying that they could be good candidates for interventional treatment. Predicting TTFT will be crucial if research on the early interventional trials in the era of novel targeted drugs demonstrates survival benefit for intermediate and high-risk patients. Until then, improvement of PMs by incorporation of new genetic markers remains an achievable and realistic goal.

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NOTE

Authors Biljana Mihaljević and Vojin Vuković contributed equally to this article.

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Упоредна анализа интернационалног прогностичког индекса за хроничну лимфоцитну леукемију, скора ризика од прогресије и скора Центра за рак *MD Anderson* – искуство једног центра

Биљана Михаљевић[1,2], Војин Вуковић[1], Наташа Милић[2,3], Теодора Каран-Ђурашевић[4], Наташа Тошић[4], Татјана Костић[4], Ирена Марјановић[4], Марија Денчић-Фекете[5], Владислава Ђурашиновић[1,2], Тијана Драговић-Иванчевић[1], Соња Павловић[4], Дарко Антић[1,2]

[1]Универзитетски клинички центар Србије, Клиника за хематологију, Београд, Србија;
[2]Универзитет у Београду, Медицински факултет, Београд, Србија;
[3]Универзитет у Београду, Медицински факултет, Институт за медицинску статистику и информатику, Београд, Србија;
[4]Универзитет у Београду, Институт за молекуларну генетику и генетичко инжењерство, Београд, Србија;
[5]Универзитет у Београду, Медицински факултет, Институт за патологију, Београд, Србија

САЖЕТАК

Увод/Циљ Прогноза хроничне лимфоцитне леукемије (ХЛЛ) значајно је унапређена у последње време. Међу неколико прогностичких модела чији је циљ предвиђање времена до прве терапије (енг. *TTFT*) издвајају се скор ризика од прогресије (енг. *PRS*) и скор Центра за рак *MD Anderson* из 2011. год. (енг. *MDACC* 2011), док се интернационални прогностички индекс за ХЛЛ (енг. *CLL-IPI*), иако примарно установљен за предикцију укупног преживљавања (енг. *OS*), добро показао и у предикцији *TTFT*. Циљ овог рада је да се испита значај поменутих прогностичких модела у погледу предвиђања *TTFT* и *OS*.

Методе Анализирана кохорта је обухватила 57 неселектованих болесника са ХЛЛ Универзитетског клиничког центра Србије са просечно агресивнијим профилом болести у односу на општу популацију *de novo* болесника са ХЛЛ. Болесници су оцењивани према наведеним скоровима уз анализу *TTFT* и *OS*.

Резултати Болесници са вишим вредностима *CLL-IPI*, *PRS* и *MDACC* 2011 примили су прву терапију значајно раније у поређењу са болесницима са нижим вредностима ових скорова ($p = 0,002$, $p = 0,019$ и $p < 0,001$, редом). У мултиваријантној анализи, *MDACC* 2011 и *CLL-IPI* су задржали прогностички значај у предикцији *TTFT* ($p = 0,001$, односно $p = 0,018$), док је *PRS* овај значај изгубио. *CLL-IPI* је био једини значајан предиктор *OS* у униваријантној ($p = 0,005$) и у мултиваријантној анализи ($p = 0,013$).

Закључак *CLL-IPI*, *PRS* и нарочито *MDACC* 2011 су добри предиктори *TTFT* чак и у кохортама болесника са агресивнијом болешћу, док је за предикцију *OS* од ова три прогностичка модела *CLL-IPI* једини применљив. Ови резултати показују да би прогностичке моделе требало испитати на болесницима са ХЛЛ у различитим фазама болести, какви се срећу у реалној клиничкој пракси.

Кључне речи: хронична лимфоцитна леукемија; скор *CLL-IPI*; скор *PRS*; скор *MDACC* 2011; укупно преживљавање; време до прве терапије