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A PREDICTIVE INSTRUMENT FOR ASYMPTOMATIC EARLY-STAGE CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS-SINGLE CENTE EXPERIANCE

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Abstract

Early-stage patients with Chronic lymphocytic leukemia (CLL) are diagnosed without need for treatment, managed with following. The distinct course of the disease is diverse, and planing treatment is barely projected at diagnosis.

The aim of the study was first-time evaluation of international prognostic score to predict time to first treatment (TFT) in patients with early stage CLL (International Prognostic Score for Early-stage CLL IPS-E).

Retrospective study of asymptomatic patients with CLL at early stage of disease in a period of time from January 2011 to January 2021.

The median follow-up was 60 months (1-120 months). Individual patient data from 120 treatment-naïve CLL patients with Binet A stage were analyzed to composed International Prognostic Score for Early-stage CLL and correlated with Time to treatment failure (TTF).

Using IPS-E patients were distributed in three groups: low risk with 7, 5%, intermediate risk with 44 % and high risk patients 49%.

Average TFS was 29, 3 months for low risk group, 28, 6 months for intermediate-risk group and 27,1 months for high-risk group. Using prognostic nomogram we calculated 5 years probability of survival for low, intermediate and high risk group: 73%, 72% and 70% respectively with projected median survival of 9, 1 year for low risk group and 9, 0 year, 8, 9 years for intermediate and high risk groups.

The IPS-E is a simple prognostic model that predicts the probability of treatment necessity in patients with early-stage CLL.

***Keywords**:* CLL, asymptomatic, early stage, IPS-E.

Introduction

Chronic lymphocytic leukemia (CLL) is characterized by the moderate accumulation of monoclonal B lymphocytes in peripheral blood, bone marrow, and lymphoid organs. In most cases, CLL is diagnosed during routine laboratory settings, and most of patients present in an early phase of the disease, without clinical findings and no anemia, no thrombocytopenia [1]. Corresponding to actual guidelines, asymptomatic early-stage CLL patients should not be treated until disease progression [2]. Early treatment strategies were research starting point of several clinical trials [3,4] but they did not present better survival rates after application of immuno-chemotherapy.

One of the characteristics of patients with early-stage CLL is unpredictable progression [5]. The heterogeneous clinical course requires watchful monitoring of patients or immediate initiation of treatment.The number of patients which are on monitoring is very impressive. That population is managing with two W strategy: watch and wait, but there is place for one more W like worry.

Therefore, there is a need to use a prognostic model that will predict the progression of the disease in patients with asymptomatic early-stage CLL. The new therapy that is available has imposed the need to identify patients who will have rapid disease progression and will need therapy [6]. Condoluci at all. composed and validated a simple but strong, predictor of disease progression and the need for treatment in patients with asymptomatic early-stage CLL [7].

They developed an international prognostic score to predict time to first treatment (TFT) in patients with CLL with early, asymptomatic disease (International Prognostic Score for Early-stage

CLL [IPS-E]). Patient data from 11 international cohorts of patients with early-stage CLL (4933 patients) were analyzed to build and validate the prognostic score.

Three covariates were consistently and independently correlated with TFT: unmutated immunoglobulin heavy variable gene (IGHV), absolute lymphocyte count higher than $15 > 10^9$/L, and presence of palpable lymph nodes. The IPS-E was the sum of the covariates (1 point each), and separated low-risk (score 0), intermediate-risk (score 1), and high-risk (score 2-3) patients showing a diferent TFT.

The score accuracy was validated in 9 cohorts staged by the Binet system and 1 cohort staged by the Rai system [7]. The aim of the study was first-time evaluation of international prognostic score to predict time to first treatment (TFT) in Macedonian patients with asymptomatic early stage CLL.

Material and methods

Patients and specimens

This is a retrospective study that includes 120 patients with asymptomatic early stage Binet-A CLL diagnosed and treated at the University Clinic of Hematology for a period of time from January 2011 to January 2021. The median follow-up was 60 months (1-120 months). The diagnosis of patients with CLL was established according to the recommendations of the International Working Group on CLL (IWCLL), [2].

All the patients were evaluated for traditional clinical and laboratory prognostic factors and newer prognostic factors including IGHV mutation status and CLL prognostic and predictive *genetic* abnormalities.

Traditional prognostic factors and clinical and laboratory variables included sex, age, Binet stage, physical examination with evaluation of number of involved lymph node sites (cervical, axillary, and inguinal), measurement of liver and spleen size, white blood cell count (WBC), absolute lymphocyte count (ALC), hemoglobin level, platelet count, Beta-2 microglobulin (B-2M). IGHV mutation status and prognostic molecular markers like: deletion 17p/TP53 mutation, deletion 11q, trisomy 12, deletion 13q, SF3B1, NOTCH1, MYD88 were characterized by the direct sequencing method.

Patients were categorized as unmutated (IGHV $\geq$ 98% germline homology) or mutated (< 98% homology). IGHV mutation status and detection of *genetic* abnormalities were performed by the Center for Biomolecular Pharmaceutical Analyses at the Faculty of Pharmacy, Skopje, Republic of Northern Macedonia.

In line to predict time to first treatment (TFT) in Macedonian patients with asymptomatic early stage CLL we used IPI-E.

We incorporated the data of absolute lymphocyte count higher than $15 > 10^9$/L, presence of palpable lymph nodes and unmutated immunoglobulin heavy variable genea and the sum of the three covariates (1 point each), we separated low-risk (score 0), intermediate-risk (score 1), and high-risk (score 2-3) patients.

For prognostic differentiation we used Wierda`s prognostic nomogram (8) for 5-year probability of survival and to determine the estimated median survival.

Statistical analysis

Statistical analysis was performed using the SPSS software package version 21.0. Overall survival (OS) was calculated from the time of diagnosis to death or last follow-up and time to first therapy (TFT) from the date of diagnosis to first treatment or last follow-up. Both variables were estimated by the Kaplan-Meier method and assessed by the log-rank test.

These data were expressed as the hazard ratio (HR) with a 95% confidence interval (95% CI). The value of $p<0.05$ was considered significant for all analyses.

Results

We analyzed data of 120 early stage CLL patients, diagnosed and treated at University Clinic for Hematology within 12 months of diagnosis and who had complete data available for all parameters used to calculate the international prognostic score. According to gender distribution there was male predomination, 55% patients were male and 45% were female.

Average age was 64 years (41-85) years old.

To perform the prognostic value of IPS-E in Macedonian CLL patients with Binet A stage we incorporated the data of three covariant: unmutational status of immunoglobulin heavy chain, absolute lymphocyte count higher than 15 x 10^9/L, and presence of palpable lymph nodes.

The IPS-E was the sum of the covariates (1 point each), and separated low-risk (score 0), intermediate-risk (score 1), and high-risk (score 2-3).

On table 1 we presented distribution of patients in IPS-E risk groups.

IPS-E risk groups	Number 120	Percent % 100%
Low risk score 0	9	7,5%
Intermediate risk, score 1	53	44%
High risk score 2.3	59	49%

Table 1. Patients distribution according to IPS-E risk group

The study end point was time to first treatment (TFT), defined as the time between presentation and start of first treatment of CLL because of progression to symptomatic disease according to the National Cancer Institute-Working Group-International Workshop on Chronic Lymphocytic Leukemia guidelines [2].

Sixteen baseline biomarkers, assessed within 1 month from initial presentation, were analyzed. These covariates were clinical characteristics (age, sex, >1 palpable lymph node with a diameter >1 cm and palpable spleen by investigator's physical examination) [9] laboratory values (hemoglobin level, platelet count, absolute lymphocyte count, and B2-microglobulin), cytogenetic abnormalities as assessed by Multiplex-ligation dependent probe amplification (MLPA) performed by the Center for Biomolecular Pharmaceutical Analyses at the Faculty of Pharmacy, Skopje, Republic of Northern Macedonia: del(17p), del(11q), trisomy 12, del(13q), and gene mutations (immunoglobulin heavy variable gene (IGHV), MYD88, NOTCH1, SF3B1.

On table 2 we present patients clinical and laboratory characteristics.

IPS-E groups	Low risk score 0 N.	Low risk score o %	Intermediate risk, score 1 N.	Intermediate risk score 1 %	High risk score 2.3 N.	High risk score 2,3 %
Age >65 years	2	22%	23	43%	27	45%
Male gander	2	22%	31	58%	35	59%
Palpable lympodenopathy>1sm	0	0%	4	7,5%	27	45%
Palpable spleen	0	0%	2	3,7%	12	20%
Lymphocyte > 15x 10^9 /L	0	0%	42	80%	55	93%
Hgb<120g/d at female Hgb <130gr/d at male	2	22%	5	9,4%	8	13,5%
Platelets <150x 10^9 /L	0	0%	3	5,6%	7	11,8%
B2M>3,5 mg/L	1	11%	4	7,5%	7	11,8%

Table 2. Patients clinical and laboratory characteristics.

On table 3 we present patients cytogenetic abnormalities.

IPS-E groups	Low risk score 0 N.	Low risk score o %	Intermediate risk, score 1 N.	Intermediate risk score 1 %	High risk score 2.3 N.	High risk score 2,3 %
Del(13q)	2	22%	18	34%	7	11,8%
Trisomy 12	2	22%	4	7,5%	7	11,8%
Del(11q)	0	0%	1	1,8%	12	20%
Del(17p)	0	0%	0	0%	9	15,2%
Unmutated IGHV	0	0%	10	18,8%	50	84%
MYD88 mutation	0	0%	0	0%	1	1,69%
NOTCH1 mutation	0	0%	1	1,8%	1	1,69%
SF3B1 mutation	0	0%	0	70%	3	5%

Table 3. Patients cytogenetic abnormalities.

We used validated IPI score for patients with Binet A stage distribution, data are presented on table 3.

CLL-IPI	IPS-E low risk N.	%	IPS-E intermediate risk N.	%	IPS-E high risk N.	%
Low risk	5	55%	38	71,6%	9	15%
Intermediate risk	4	44%	17	32%	37	63%
High risk	0	0%	0	0%	4	6,7%
Very high risk	0	0	0	0	9	15,2%

Table 3. Distribution of patients according to IPS-E and IPI score.

On figure 1 we presented percent distribution of palpable lymphadenopathy among risk IPS-E groups, and we found statistical significant difference in distribution of palpable lymphadenopathy among IPS-R intermediate and high risk groups(p=0.0004) and among IPS-R low and high risk groups(p=0.0008).

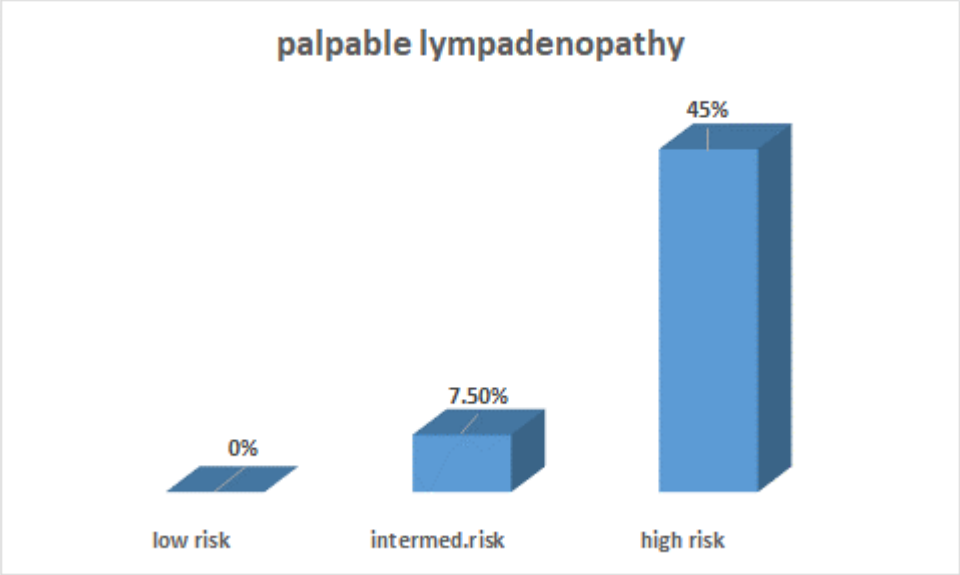

Figure 1. Palpable lymphadenopathy among risk IPS-E groups

On figure 2 we present percent distribution of lymphocythosis > $15x10^{9}/L$ among risk IPS-E groups. We found statistical significant difference in distribution of lymphocythosis >$15x10^{9}/L$ among IPS-R low and high risk groups(p=0.0006).

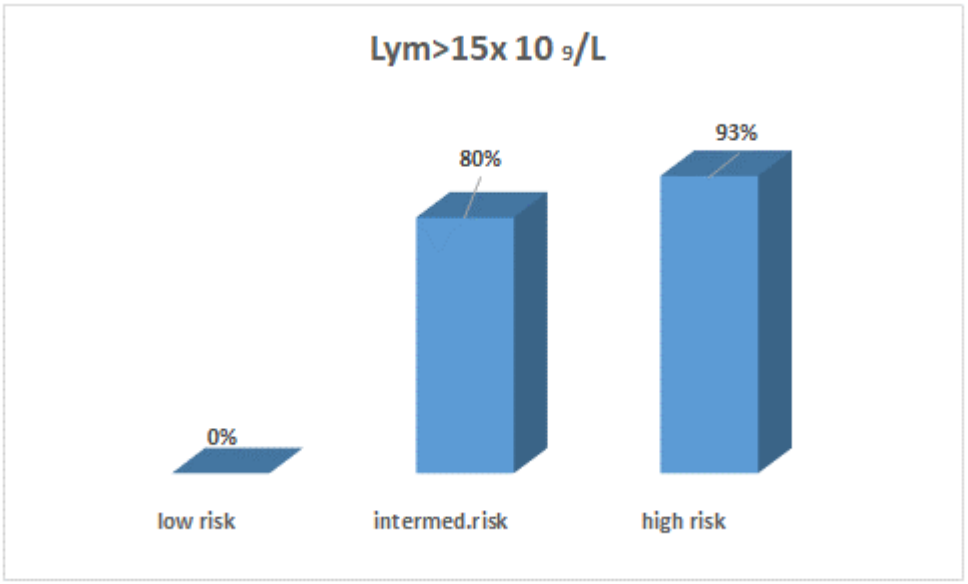

Figure 2. Distribution of lymphocytosis > 15x10 ^{9}/L among risk IPS-E groups.

On figure 3 we presented percent distribution of UnM IGHV among risk IPS-E groups, and we found statistical significant difference in distribution of UnM IGHV among IPS-E intermediate and high risk groups(p=0.00001).

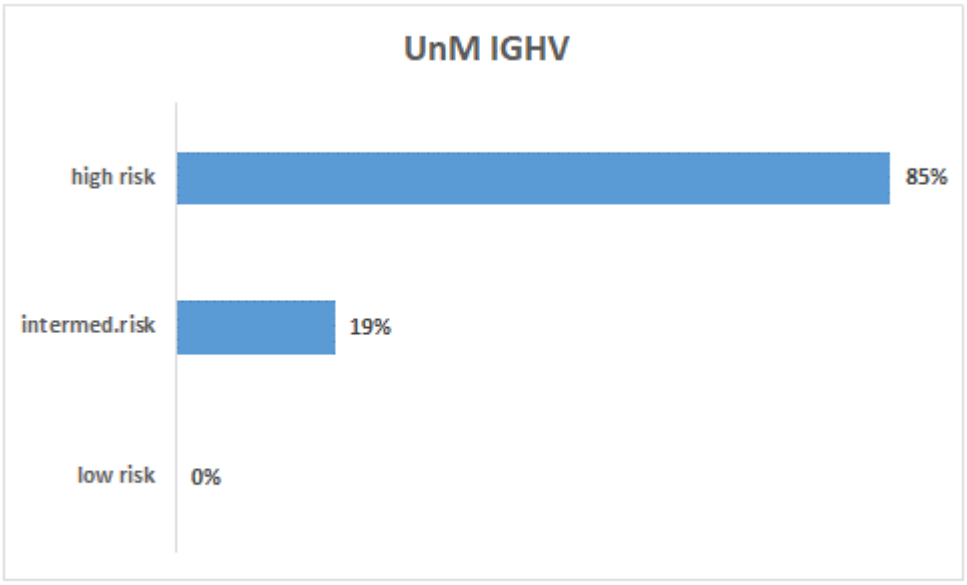

Figure 3. Distribution of UnM IGHV among risk IPS-E groups.

The average TFS at low risk CLL-Ips-E (n=9), intermediate CLL-IPS-E (n=53), high risk CLL-IPS-E (n=59), according to the CLL-IPS-E scoring system was 29.3, 28.6, 27 months respectively (figure 4). The average OS at low risk CLL-Ips-E (n=9), intermediate CLL-IPS-E (n=53), high risk CLL-IPS-E

(n=59), according to the CLL-IPS-E scoring system was was 52.7, 51.1 and 50 months, respectively (figure 5).

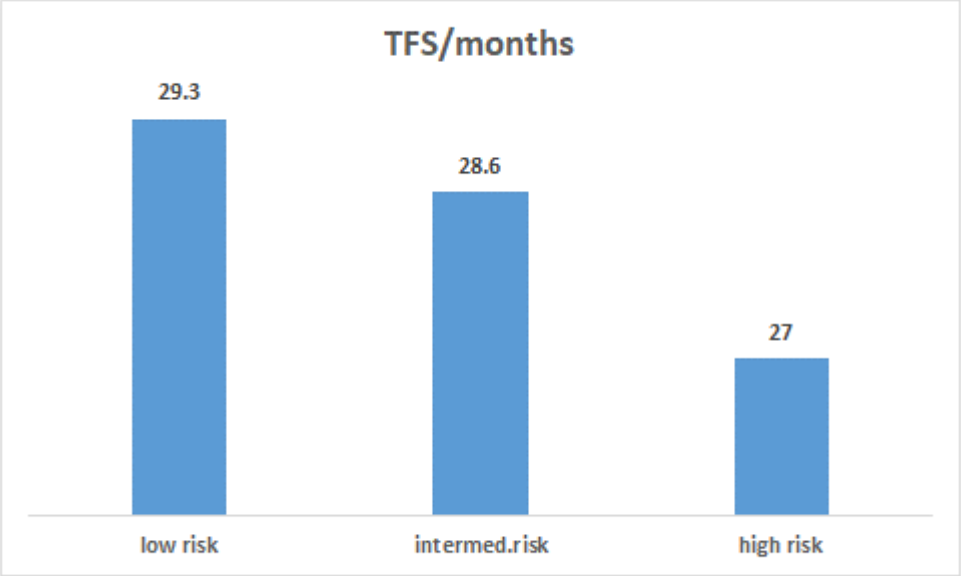

Figure 4. Average TFS among IPS-E risk groups in months.

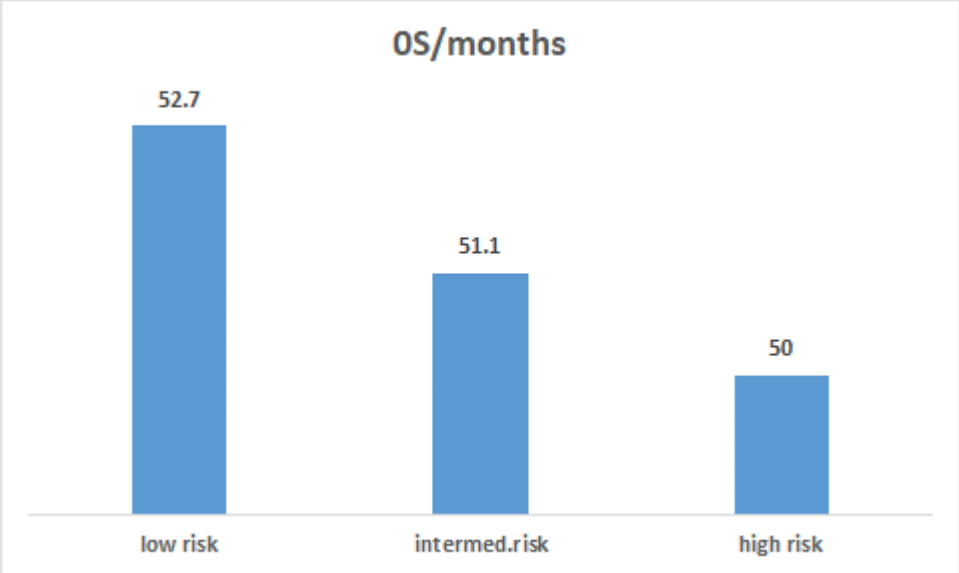

Figure 5. Average OS among IPS-E risk groups in months.

Using Prognostic Nomogram we calculate estimated 5-year OS (figure 6) [8)].The estimated 5-year OS rate was 73 %, 72%, 70% respectively for low, intermediate and high IPS-E risk groups.

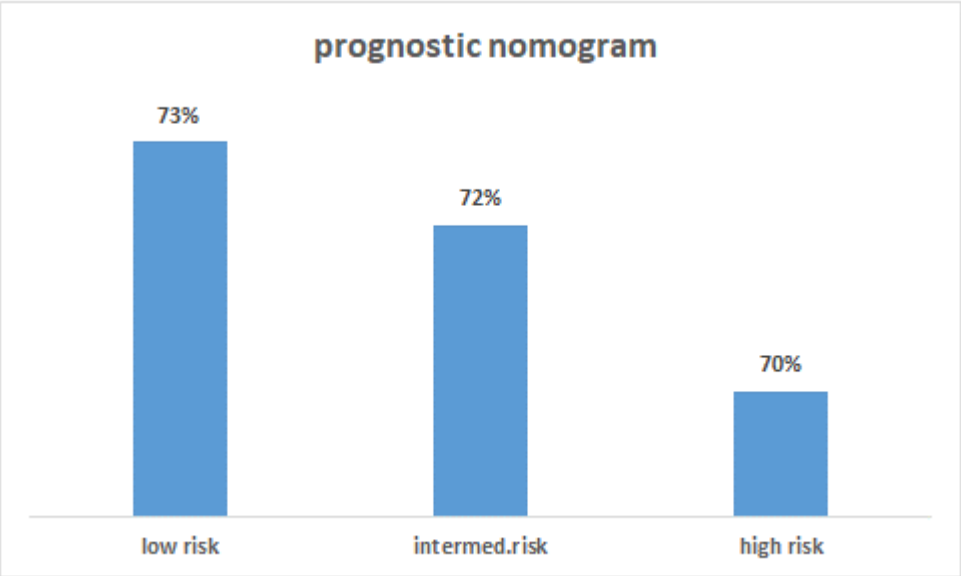

Figure 6. Estimated 5-year OS rate in different risk CLL-IPS-E groups.

We also calculated projected median survival (8) in years among three IPS-E risk groups (figure 7).

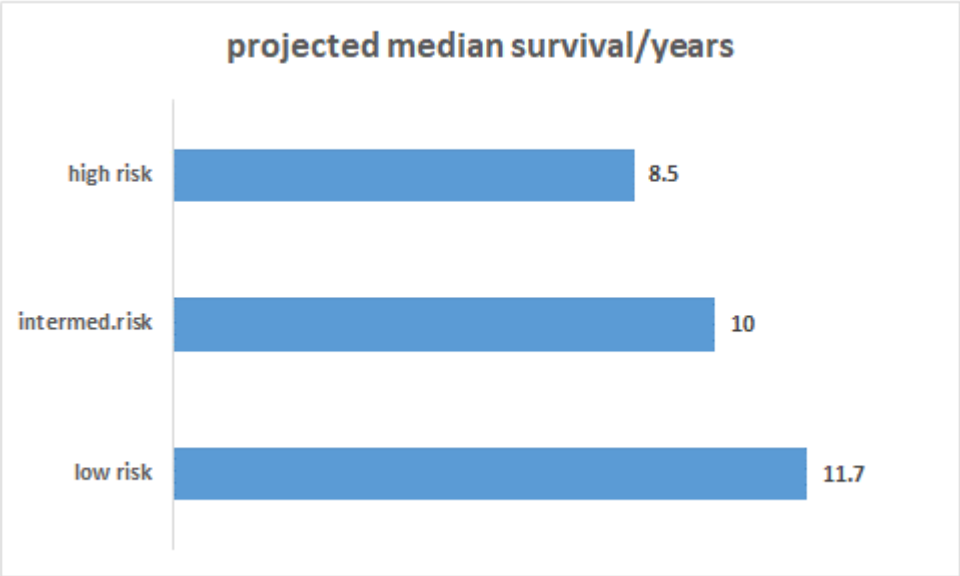

Figure 7. Projected median survival in different risk CLL-IPS-E groups.

Survival analysis for patients stratified according to CLL-IPS-E, Time to first treatment and OS analysis for different risk groups are presented on figure 8,9.

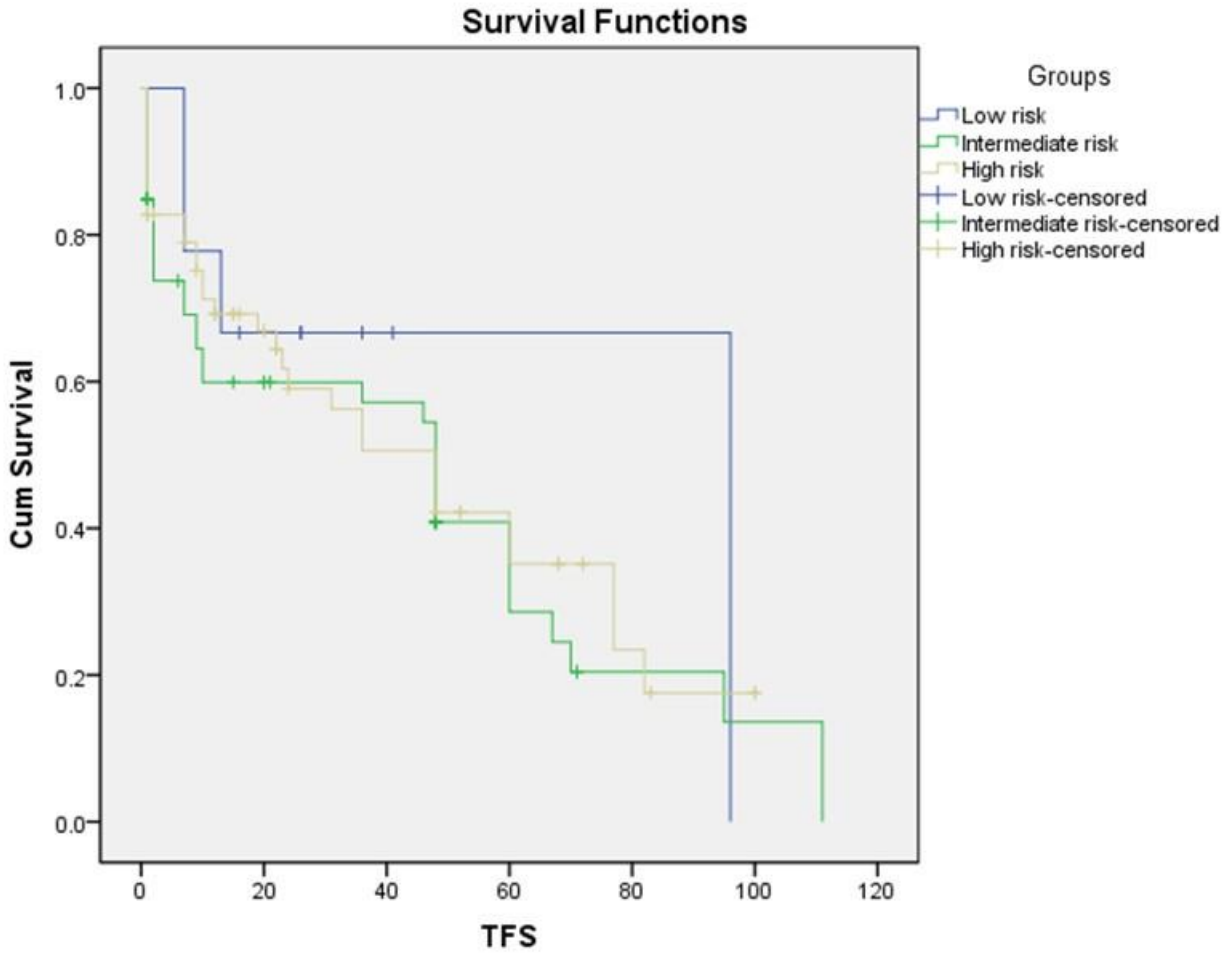

Figure 8. *Kaplan-Meier* curve of TFS in IPS-E risk groups

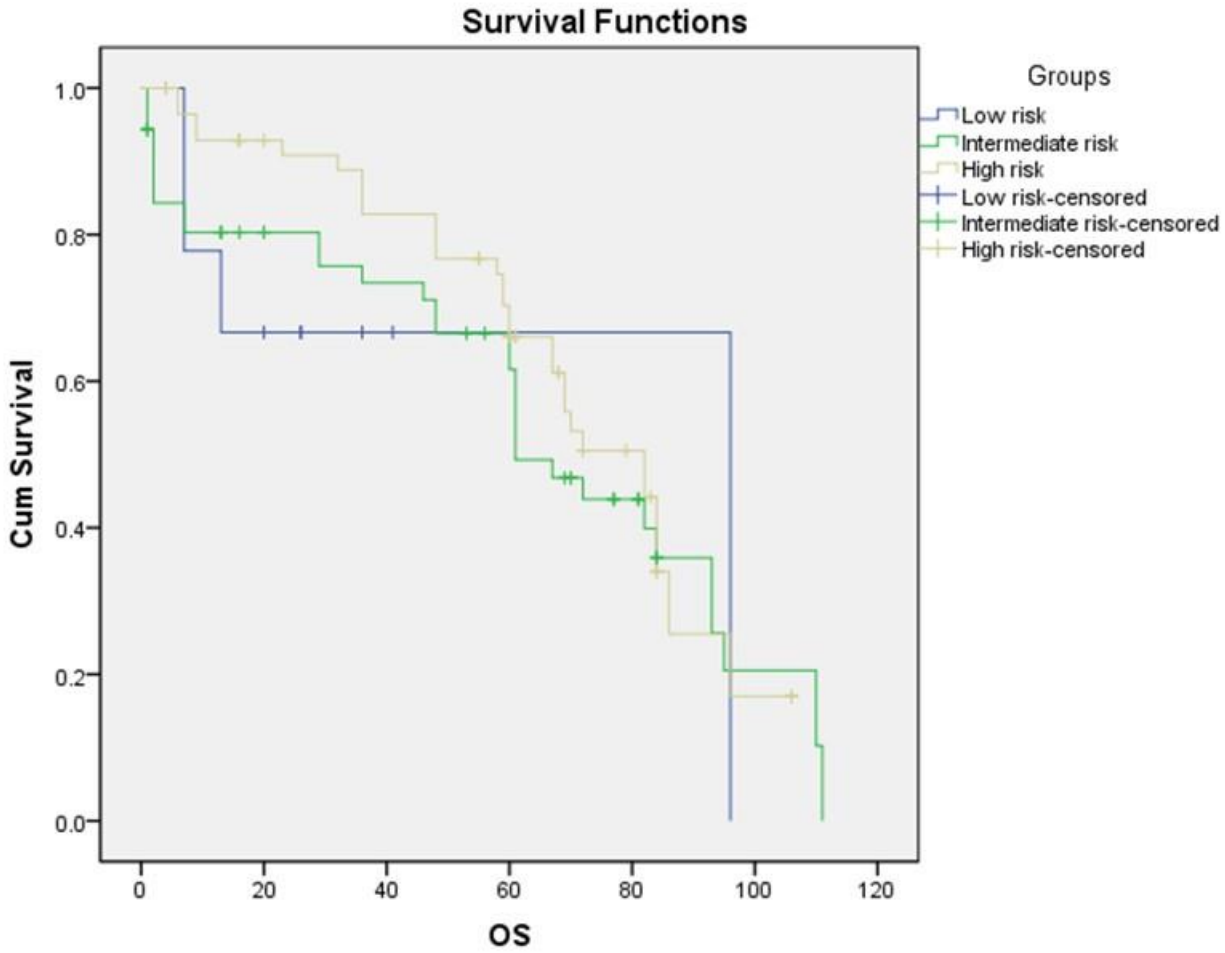

Figure 9. *Kaplan-Meier* curve of OS in IPS-E risk groups.

Discussion

The greater part of patients with CLL are diagnosed in asymptomatic, early phases of the disease and are followed with no need for therapy [9]. The clinical development of the disease is heterogeneous and difficult to predict. Although some patients display a inactive disease never requiring therapy, others present active disease after diagnosis and have need of therapy.

Despite the conventional advance on the outcome of patients with CLL, the survival of early-stage patient ((Binet stage A) has not significantly changed during the last decades [10,11].

Risk-tailored strategy should be made for best treatment management of these patients. In our everyday work we implemented several prognostic models that can be used to separate patients with different outcome within the whole population of subjects with CLL [12].

But all these prognostic models are not focused on the outcome of patients with early-stage asymptomatic CLL patients. They are based on analyzing the overall survival like end point [13]. In our study we used CLL-IPI patient differentiation and we made correlation with IPS-E patients segregation. We found nearly equal distribution of patients between groups in two models.

The distinctiveness of patients with asymptomatic early stage disease presented subpopulation of CLL patients with need for specific prognostic model with Time to treatment failure as a main end point. Daily work with patients in the early asymptomatic stage of the disease imposes the need to distinguish patients in need of treatment from those to be followed not requiring intuition of therapy.

A powerful tool in monitoring this group of patients is the IGHV unmutated status, a biomarker with the strongest effect on TFT prognostication. It is an integral part of the applied prognostic IPS-E

model. But the remaining prognostic parameters associated with inferior survival as del 17p/ TP53 abnormalities, NOTCH1 mutations did not enter into the IPS-E model. The reason is the heterogeneity of this disease where the carriers of 17p/ TP53 aberrations, but mutated IGHV genes, may have a prolonged TFT and a relatively benign clinical course under observation [14]. Patients having NOTCH1 mutations are highly associated with unmutated IGHV genes. Still, some of IGHV unmutated patients does not have NOTCH1 mutation [15,16].

Therefore IGHV unmutated status has a greater prognostic significance than NOTCH1 abnormalities In line with TTF prognosis.

The IPS-E presented in this study is a robust prognostic tool based on routine clinical and laboratory variables that informs at the time of diagnosis about the probability that a given patient with CLL in early-stage disease progresses and needs treatment.

The cumulative risk for need of treatment after 1 and 5 years of observation was 14.1% and 61.2%, respectively, for an IPS-E high-risk patient, whereas it was 2.1% and 28.4%, for intermediaterisk patients and less than 0.1% and 8.4% for low-risk patients [7] .

In everyday practice hematologists should followed more closely IPS-E high-risk patients than low- and intermediate-risk patients because of the possibility of requiring treatment earlier.

Calculation in IPS-E model is simple, being the sum of 3 variables. Compared with other scores, IPS-E calculation needs the assessment of only 1 molecular variable namely, the IGHV mutation status, it has been accepted by the current guidelines as a predictive marker for treatment adjusting [17].

Furthermore, as IGHV status never changes during the course of disease, it might be evaluated at the time of first diagnosis to provide an estimate of TFT to the patient and to the hematologist. The results of Condoluci at all. study also support that FISH analysis and molecular testing for TP53 has no clinical utility when performed at CLL presentation in early-stage asymptomatic patients. Del 17p/TP53 abnormalities have a predictive role at time of therapy, but no prognostic role in an early-stage setting when determining TFT. Also, they can change during the course of disease.

Therefore, TP53 status may not be routinely evaluated in early stage asymptomatic patients requiring treatment indication.

Regarding the prognosis of the three groups of patients from IPS-E prognostic model, we also applied the prognostic nomogram which showed 5 years of probable survival, and projected median survival of three groups.

Namely patients from high risk group are associated with shorter estimated median survival and only 70% of them have projected 5-years OS. That subgroup of patients need more careful monitoring.

Although this prognostically simple model validated by several leading CLL centers requires prospective application and discovery of new prognostic parameters for management of this group of patients at an early stage of the disease.

Conclusions

The IPS-E is a simple prognostic model that predicts the probability of treatment necessity in patients with early-stage CLL.

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