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Evaluation of reproducibility of prognostic index and nomogram in prognosis, and therapeutically approach of patients with Chronic Lymphocytic Leukaemia-single centre experience

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Abstract: At this time staging and prognostication of Chronic lymphocytic leukemia(CLL) is performed by 2 equivalent clinical staging systems developed 30 to 35 years ago by Binet and Rai Both systems use low-cost, simple components such as blood counts and physical examination to identify 3 major prognostic subgroups. Despite these advantages, the clinical staging systems do not reflect the high unpredictability of CLL, nor do they account for known biological characteristics of CLL cells predicting survival and response to therapy. That was the motivation for Mayo Clinic, and Wierda proposed to combine a set of clinical risk factors, to develop a prognostic index (PI) stratifying patients in three risk groups with different expected median survival, and a nomogram, estimating individual patient survivals. Here we report the results from a study designed to evaluate Wierda`s nomogram and prognostic index on Macedonian CLL population. Material and methods: We analyzed medical data of 300 CLL patients diagnosed and treated at University Clinic of Hematology -Skopje Macedonia from a period of 10 years. We used Wierda`s prognostics index and a nomogram, to see 5- and 10-year survival probability and estimated median survival time. Results: There were 300 CLL patients who had traditional and biological prognostic factors evaluated. According to prognostic index a classification tree was built that identified three subsets of patients. Estimated median survival at low risk subset of patients with prognostic nomogram <80 was 68, 7 months, and 37, 5 months respectively at high risk subsets of patients with prognostic nomogram >80. Projected survival in respectively low, intermediate and high-risk groups was 91, 7%, 80%, 50%, and 81, 5%, 60%, 10% at 5-year and10-year, respectively. Conclusion: We use this model to identify patients at high risk for progression to treatment and we are experiencing a paradigm shift toward personalized medicine. This prognostic model may help patients and clinicians in clinical decision making as well as in clinical research and clinical trial design.

Keywords: CLL, Prognostic Index, Nomogram, Prognosis

1. Introduction

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in the Western world. The clinical course is variable, some patients live for decades without ever requiring treatment, whereas others have rapidly progressive disease requiring treatment within months of diagnosis. For more than 30 years the Rai(1,2) and Binet(3) clinical staging systems broadly identify risk groups based on clinical and laboratory characteristics. Overall, stage correlates with survival, however, for each stage there is still heterogeneity, limiting utility in predicting survival. In addition to factors used in clinical staging, several other patient characteristics and laboratory tests have been correlated with overall survival, including age,(4) sex,(4) pattern of bone marrow involvement,(5) lymphocyte doubling time,(6) and the presence of prolymphocytes in blood or bone marrow(7). Other factors that can be measured in the laboratory have also been correlated with poor prognosis, including the presence of chromosome abnormalities such as 17p deletion

and 11q deletion, (8) elevated serum levels of β-2 microglobulin (β-2M), thymidine kinase, soluble CD23, (9) unmutated immunoglobulin heavy chain variable gene (IgV_H), (10) and expression of ZAP-70(11) and CD38 (12) by leukemia cells. Alone, each of these prognostic factors has limited utility in predicting overall survival.

To address this problem, Wierda et al. (13) analyzed the clinical outcomes of a large series of patients cared at The University of Texas M.D Anderson Cancer Center (MDACC) during a period of 25 years to determine whether routinely available clinical and laboratory features could enhance the utility of clinical staging. The MD Anderson analysis identified 6 factors (age, Beta2-microglobulin, clinical stage (Rai), the number of lymph node regions (LNR), absolute lymphocyte count (ALC)) that were independently associated with patient survival and that can be combined in a prognostic index to predict survival. The investigators also developed nomogram to estimate the 5-year survival and 10-years survival probability for every patient. The prognostic index and nomogram were evaluated by Shanafelt et all. at Mayo Clinic Rochester (14). The latter study confirmed the value of the prognostic index as predictor of overall survival.

In the present study, we used the MDACC prognostic index and nomogram in population of 300 CLL patients. We report the initial results from a study designed to evaluate clinical and biological prognostic factors in patients risk stratification.

2. Materials and Methods

2.1. Patient Population

The clinical and biological data of 300 CLL patients were retrospectively analyzed from medical documentation in University Clinic of Hematology in the period of the last 10 years. For all patients complete data on age, Beta2-microglobulin, ALC, sex, Rai staging system and LNR were available.

2.2. Nomogram and Prognostic index

Age, sex, ALC, Beta2-microglobulin, Rai stage, LNR involved were used to calculate the prognostic index score using the method proposed by Wierda et all(13 . Patients total score determined by adding up the scores of the 6 components. Patients with score of 1 to 3 are considered to be at low risk, those with a score of 4 to7 are considered to be at intermediate risk, and those with a score of ≥8 are considered to be at high risk (13).

2.3. Statistical Methods

For each patient total score of the MDACC nomogram was calculated using the score as reported in reference (13). The median total score of the whole patient population was converted in estimated years of median survival, as well as in 5- and 1—year survival probabilities by graphical interpolation using the printed version of the nomogram(figure1).

3. Results

3.1. Patient's Characteristics

We analyzed data of 300 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 prognostic index score.

According to gander distribution there was male predomination (table1).The median age at diagnosis was 65, 1 years, with 37, 3% of patients aged >60years and 30, 7% aged >70 years (table2, figure1). The majority of patients had Rai stage II (34%). Other patient characteristics are shown on table 3.

Table 1. *Gender distribution of CLL patients.*

gender	No.	%
female	106	35.3
male	194	64.7
total	300	100.0

Table 2. *Age distribution of CLL patients.*

Age distribution	No.	%
<50	18	6.0
50 - 59	63	21.0
60 - 69	112	37.3
70 - 79	92	30.7
> 80	15	5.0
total	300	100.0

Table 3. *Patients characteristics at diagnosis.*

Characteristics	No.	%
ECOG-Performance status		
0	82	27.3
1	58	19.3
2	67	22.3
3	79	26.3
4	13	4.3
5	1	0,3
Number of lymph node sites		
>3	140	46.7
≤2	160	53.3
Absolute lymphocyte count($x10^9$/L)		
<20	83	27.7
20-50	109	36.3
>50	108	36.0
RAI stage at diagnosis		
0	98	32.7
I	34	11.3
II	102	34.0
III	26	8.7
IV	40	13.3
BINET stage at diagnosis		
A	133	44.3
B	120	40.0
C	47	15. 7

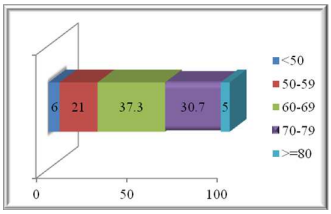

Figure 1. *Age distribution of CLL patients.*

3.2. Nomogram Score

Table 4. *Distribution of CLL patients according to Prognostic Nomogram.*

Prognostuc Nomogram	No.	%
>80	197	65. 7
<80	103	34.3
total	300	100.0

Estimated median survival at low risk subset of patients with prognostic nomogram <80 was 68, 7 months, and 37, 5 months respectively at high risk subsets of patients with prognostic nomogram >80. Projected survival in respectively low, intermediate and high-risk groups was 91, 7%, 80%, 50%, and 81, 5%, 60%, 10% at 5-year and10-year, respectively. (table 6).

Treatment free survival according to prognostic nomogram is presented on figure 4.

The nomogram score was calculated for each patient using the formula published by Wierda et all. (13). Nomogram scores were used to estimate a patient's 5-year and 10-year probability of survival using published methods (13), (table 4, and figure 2). Average data of prognostic nomogram score is presented on table 5.

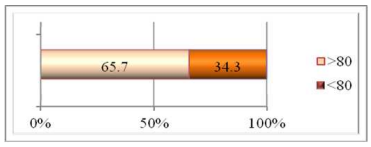

Figure 2. *Distribution of CLL patients according to prognostic nomogram.*

Table 5. *Average data of prognostic nomogram.*

Prognostic nomogram	No.	average	median	min	max	Std. Dev.
	300	87.5	87.0	38.0	136.0	17.90508

Table 6. *Estimated and Projected survival.*

Estimated median survival	Months	
Low risk Prognostic nomogram<80	68,7	
High risk Prognostic nomogram<80	37,5	
Projected survival	5 years	10 years
Low risk	91,7%	81,5%
Intermediate risk	80%	60%
High risk	50%	10%

3.3. Prognostic Index Score

We calculated the prognostic index score for all 300 patients and classified patients as being at low (score of 0-3), intermediate (score 4-7), or high (score of >8) risk using the methods of Wierda at all(13).

According to prognostic index a classification tree was built that identified three subsets of patients who scores were 1-3 (low risk- 51 pts-17%), 4-7 (intermediate risk-232 pts-77, 3%) and >8 (high risk-17 pts-5,7%)(table 7).

Overall survival of CLL patients according to prognostic index and treatment free survival curves are presented on figure 3 and figure 5.

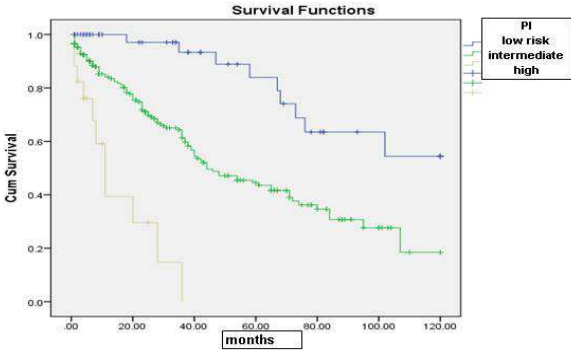

Figure 3. *Overall survival of CLL patients according to prognostic index.*

Overall survival by prognostic index; (No.300). Patients were observed for overall survival Kaplan-Meier estimates of overall survival are shown for each of following categories prognostic index low, intermediate, high risk group.

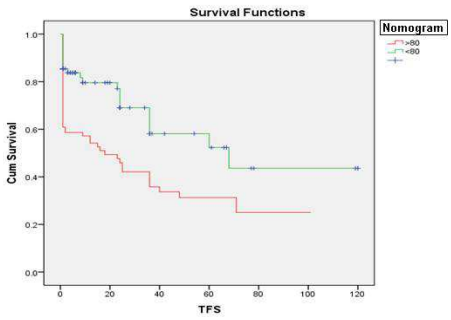

Figure 4. *Treatment free survival according to prognostic nomogram.*

Time to first treatment by prognostic nomogram ;(No.300). Patients were observed for time to first treatment. Kaplan-Meier estimates of treatment-free survival are shown for each of following categories prognostic nomogram>80 and prognostic nomogram<80.

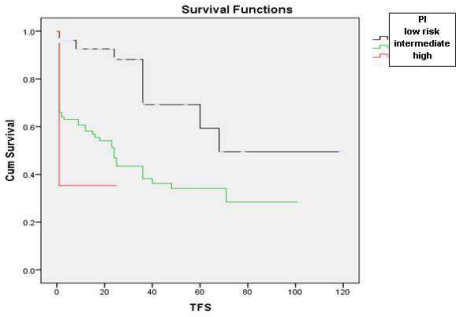

Figure 5. *Treatment free survival according to prognostic index.*

Time to first treatment by prognostic index; (No.300). Patients were observed for time to first treatment. Kaplan-Meier estimates of treatment-free survival are shown for each of following categories prognostic index low, intermediate and high risk group.

Table 7. *Distribution of CLL patients according to Prognostic Index.*

	No.	%
low	51	17.0
intermediate	232	77.3
high	17	5.7
total	300	100.0

Table 8. *Distribution of CLL patients according to immediately started therapy after the diagnose.*

	No.	%
yes	201	67.0
no	99	33.0
total	300	100.0

4. Discussion

According to the updated National Cancer Institute-Working Group (NCI-WG) guidelines, indication for treatment of chronic lymphocytic leukemia (CLL) still depends on clinical stage and disease activity (15). In this context, measurements of biological prognostic markers, namely CD38, ZAP-70, mutational status of immunoglobulin heavy chain variable gene segments (IGHV), are judged as mandatory in the context of clinical trials, but not in general practice, since they fail to influence therapeutic decisions (15). The only exception is represented by analyses of chromosomal aberrations by interphase fluorescence in-situ hybridization (FISH), given the presence of high-risk cytogenetic lesions (del11q and del17p), which may predict resistance to chemotherapy-based treatments (16). Wierda et al. (13) proposed to combine a set of clinical risk factors, i.e. age, gender, Rai staging, absolute lymphocyte count (ALC) and number of involved lymph node regions (LNR), with an inexpensive and widely available serum marker such as beta2-microglobulin (β2 M) to develop a prognostic index (PI) stratifying patients in three risk groups with different expected median survival, and a nomogram, estimating individual patient survivals. This model was subsequently validated in independent patient's series also using time to first treatment as end-point (14, 17-20). A reduction of this model from six to four variables, i.e. age, gender, β_2 M levels and Binet staging, was also shown to predict survival with equal or even better performance (20).

Our analysis based on an observational CLL database assessed the utility of the prognostic index proposed by Wierda et all. (13) to predict time to treatment. The results of our study confirm the ability of a prognostic index to predict survival among patients with untreated CLL. Our study confirms the fact that prognostic index accounts for a least some of the heterogeneity noted within clinical stage categories. The prognostic index is better predictor of patient's survival than Rai or Binet risk. The studies published by Shanafelt at all. (14) et Bulian at all. (20) extended the utility of the index by demonstrating that it is useful at the time of diagnosis, retains prognostic value when applied exclusively to patients with Rai stage 0 diseases and also predict TTT in addition to survival.

The 6 parameters used to calculate the prognostic index score rely on clinical characteristics and laboratory parameters that are available to all CLL patients. The 5-year overall survival rates from the study of Shanafelt at all. (14) are similar to those observed in MDACC study (13) and that proved that the index is reproducible.

We had interesting situation in the beginning, in our study 17% of patients were at low risk group according to prognostic index score and 77% of the patients were at intermediate risk group. When we use Rai risk some of them had 3 or 4 Rai and they were assigned to receive standard chemotherapy by their doctors, but according to prognostic index score they were assigned to watch and wait strategy because they were low or intermediate risk group and still they are on the same strategy. In our study no matter which Rai, Binet stage the patients were, 67% of them received therapy immediately after the diagnose was done.

The prognostic index leads to more precise prediction of patient's outcome than either approach alone.

This model allows us to identify patients with a high likelihood of requiring treatment within few years; these patients would be candidates for interventions to delay time to first treatment with chemoimmunotherapy.

In modern hematology, we are experiencing a model shift toward personalized medicine. This means that patients will be treated with compounds that specifically target the tumor on the basis of its individual molecular characteristics. The new prognostic nomogram proposed by Bulian at all. (20), and Wierda et all. (21) identify the presence of chromosome abnormalities by FISH analysis, which identified high-risk categories, including patients with 17p deletion or 11q deletion, and mutational status of immunoglobulin heavy chain variable gene segments (IGHV), associated with shorter time to first treatment.

New-generation sequencing introduced us to new identified gene mutations affecting:10% to 15% of CLL patients such as NOTCH1,SF3B1 and MYD 88(22). In the reported literature these markers may have prognostic value(23). Prospective clinical trials evaluating the significance of those markers for overall survival and treatment free survival and the additional information in combination with clinical, biological, and genetic markers in CLL are further needed. New prognostic markers will found place in prognostic models, and accurate risk stratification needs to be an evolving process.

5. Conclusions

Using the prognostic index (PI) we stratified patients in three risk groups with different expected median survival, also using the nomogram, we estimated individual patient survivals. The Wierda`s prognostic index appears to be a

powerful tool to help predict risk in patients with untreated CLL. Addition of molecular and biological prognostic parameters will improve this tool and help patients plan their lives, and develop and test risk-adapted treatment strategies. We use this model that incorporates clinical and laboratory prognostic factors to identify patients at high risk for progression to treatment. This prognostic model may help patients and clinicians in clinical decision making as well as in clinical research and clinical trial design.

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