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Original Research Article

Use of chronic lymphocytic leukemia-international prognostic index in patient risk stratification-single center experience

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ABSTRACT

Background: Several prognostic factors have been identified to predict the outcome of patients with chronic lymphocytic leukemia (CLL). To predict the time to first treatment (TFT) we integrated the data of clinical and biological markers in CLL-International prognostic index (CLL-IPI). Aim of the study was the determination of the impact of CLL-IPI in prediction of TFS in CLL patents.
Methods: The study was set up retrospectively and included 90 patients with CLL diagnosed and treated at the university clinic of hematology for a period of time from January 2012 to January 2020. We incorporated the data of Binet staging system, most adverse cytogenetic marker and mutational status of immunoglobulin heavy chain in CLL-IPI.
Results: The statistical data of the 90 patients showed that the median TFS for low CLL-IPI (N=24), intermediate CLL-IPI (N=40), high risk CLL-IPI (N=17) and very high risk group (N=9) according to the CLL-IPI scoring system was 20.1, 17.6, 7.1 and 5.8 months, respectively. Multivariate analysis indicated that del 17p ($p<0.008$) was independent prognostic factors of TFS.
Conclusions: CLL-IPI is a powerful risk stratification tool for CLL patients and this system has also provided treatment recommendations for different patient risk subgroups.

Keywords: CLL-IPI, Risk stratification, Survival

INTRODUCTION

CLL is a heterogeneous clonal lymphoproliferative disease derived from activated B lymphocytes that have experienced antigen.[1] This type of leukemia is characterized by the accumulation of circulating long-lived circulating clonal leukemic B cells as a result of the complex balance between cell proliferation and apoptotic death. Most tumor cells are confined in the G0/G1 stage of the cell cycle, while only a small fraction of the clone exhibits proliferative activity, with about 2% of the cells being re-generated daily.[2] CLL is the most common type of leukemia in adults in the United States and European countries.[3] In the Republic of Northern Macedonia, with the better quality of life, the percentage of adult population increases proportionally and thus the incidence rate of CLL increases. The clinical course is very diverse. Some patients never look for treatment as

opposed to others who live and die with an aggressive illness. This clinical heterogeneity is likely a reflection of molecular and cellular heterogeneity, on the basis of which patients with CLL can be divided into subgroups with different clinical-biological characteristics. Traditional Rai and Binet clinical staging systems, based exclusively on physical examination and laboratory findings, do not reflect the biologic diversity of the disease nor predict response to therapy, which ultimately profile patients' outcome.[4] Old systems do not enter in biology of leukemic cells and some new prognostic markers such as the TP53 deletion and mutational status of the heavy immunoglobulin chain variable genes (IGHV) are not part of that prognostic systems. Mutation status of IGHV and molecular markers have a strong prognostic value for patients with CLL.[5,6] According to the knowledge of the biology of the disease, especially in patients who are at the time of diagnosis when we need to think about the prognosis of those patients, we found that the clinical systems of Rai and Binet became incomplete and insufficient. Therefore, a new prognostic system was needed for accurate prognostic stratification of patients with CLL.

An international team of researchers analyzed data from patients who participated in eight randomized clinical trials in Europe and the United States to develop a prognostic index that included widely available clinical, biological and genetic prognostic parameters.[7]

The results of this international project have created a relatively easy-to-use prognostic model called the CLL-IPI. This prognostic model used 5 parameters (age, clinical stage, TP53 status, normal versus fraction (17p) and/or TP53 mutation), IGHV mutation status, serum β2-microglobulin. Creating four different groups for stratification of patients with different survival. The CLL-IPI is a risk-weighted scoring system consisting of 5 adverse prognostic factors, including age >65 (1 point), Rai I-IV or Binet B/C (1 point), β2-microglobulin (B-2M) >3.5 mg/l (2 points), IGHV unmutated (2 points) and del17p and/or TP53M (4 points), which separated patients into 4 CLL-IPI risk groups: low (score 0-1), intermediate (score 2-3), high (score 4-6) and very high (score 7-10).[7]

The prognostic applicability of CLL-IPI was subsequently confirmed by two independent groups from the Mayo clinic and the Swedish CLL registry.[7] Although CLL-IPI was originally developed to predict overall survival, the index had also been shown to predict the TFT of CLL patients.

With this in mind, we used a data from newly diagnosed CLL patients from our daily practice to confirm the utility of CLL-IPI in predicting TFT and overall survival (OS) and to optimize CLL-IPI outcomes in our population.

METHODS

Study design, setting and ethics

This was a retrospective study that included 90 patients with CLL diagnosed and treated at the university clinic of hematology for a period of time from January 2012 to January 2020. The median follow up was 48 months (1-96 months). The diagnosis of patients with CLL was established according to the recommendations of the international working group on CLL (IWCLL).[8]

All the patients were evaluated for traditional clinical and laboratory prognostic factors and newer prognostic factors including IGHV mutation status and deletion 17p/TP53 mutation. 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, B-2M. IGHV mutation status and deletion 17p/TP53 mutation were characterized by the direct sequencing method. Patients were categorized as unmutated (IGHV ≥98% germline homology) or mutated (<98% homology). IGHV mutation status and detection of deletion 17p/TP53 mutation performed by the center for biomolecular pharmaceutical analyses at the faculty of pharmacy, Skopje, Republic of Northern Macedonia. Ethical approval was obtained from the ethics committee of university clinic of hematology. Only patients who gave informed consent to participate in this study were enrolled. All procedures were carried in line with WHO Helsinki declaration on human research.

We recognized the prognostic markers of TFT, in line of definition that prognostic markers we incorporated the data of Binet staging system, most adverse cytogenetic marker and mutational status of immunoglobulin heavy chain.

Statistical analysis

Statistical analysis was performed using the SPSS software package version 21.0. OS was calculated from the time of diagnosis to death or last follow up and 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. Cox regression was used for univariate and multivariate analyses of the impact of variables on OS. 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 90 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 gender distribution there was male predomination, with a median age of 65.5 (41-85) years old (Figure 1).

To validate the prognostic value of CLL-IPI in Macedonian CLL patients we incorporated the data of Binet staging system, most adverse cytogenetic marker and mutational status of immunoglobulin heavy chain. On Table 1 are presented patient's characteristics according to IPI group.

The distribution of patients according to presence of unmuteted IGHV and adverse prognostic marker 17p deletion is presented on Figure 2. There was significant predominance of UM gene in IPI intermediate risk group in correlation with IPI low risk group ($p<0.0001$).

The median TFS at low CLL-IPI (N=24), intermediate CLL-IPI (N=40), high risk CLL-IPI (N=17) and very high risk group (N=9) according to the CLL-IPI scoring system was 20.1, 17.6, 7.1 and 5.8 months, respectively (Figure 3). The median OS for low risk group was 52.2 for intermediate, high and very high risk group was 32.7, 25.2 and 18.8 months, respectively (Figure 4). Patients with low CLL-IPI have the longest TFS and OS.

Table 1: Patients characteristics according to IPI group.

CLL-IPI risk groups	Low risk (0-1 score); 24 pts	Intermediate risk (2-3 score); 40 pts	High risk (4-6 score); 17 pts	Very high risk (7-10 score); 9 pts
Hgb	129.6	133.5	100	131.8
WBC	78.8	65.9	91.1	48
PL	228	181	181.8	203
ALC	71.7	52	72.6	37
% of Lym	82.4	82.3	84.8	77
CD38±	4/20	11/29	12/5	8/1
B2 microglobulin mg/l	2.1	2.2	4.3	4.6
Binet B/C	9	10	12	8
IGHV M/UnM	24/0	9/31	6/11	0/9
Del 17p	0	0	3	9
WW/therapy	17/7	22/18	5/12	1/8

*Lym-lymphocyte, IGHV M-mutated UnM-unmutated, ALC-apsolute lymphocyte count, WW-watch and wait.

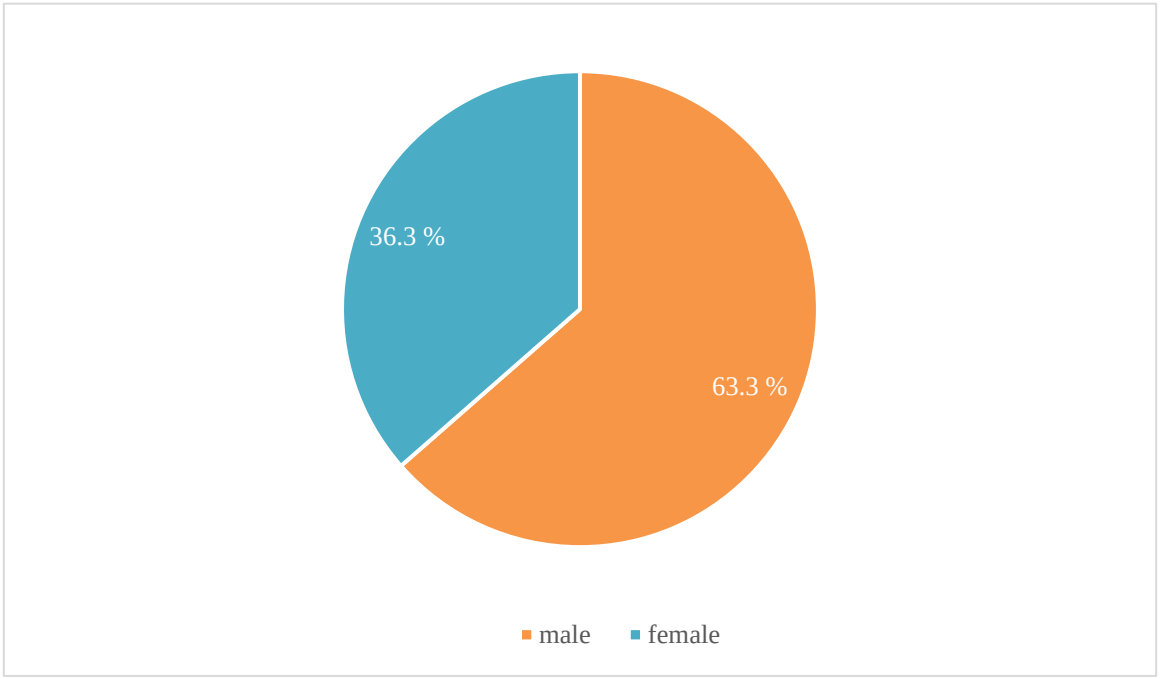

Figure 1: Distribution of patients according to gender distribution.

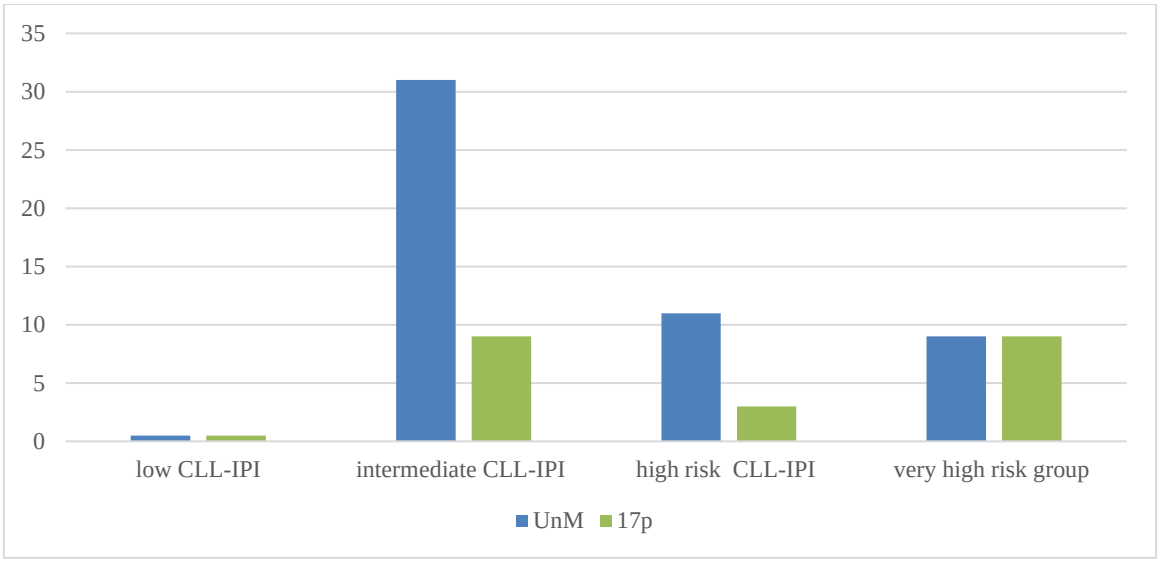

Figure 2: Distribution of patients according to presence of unmuteted IGHV and 17p deletion.

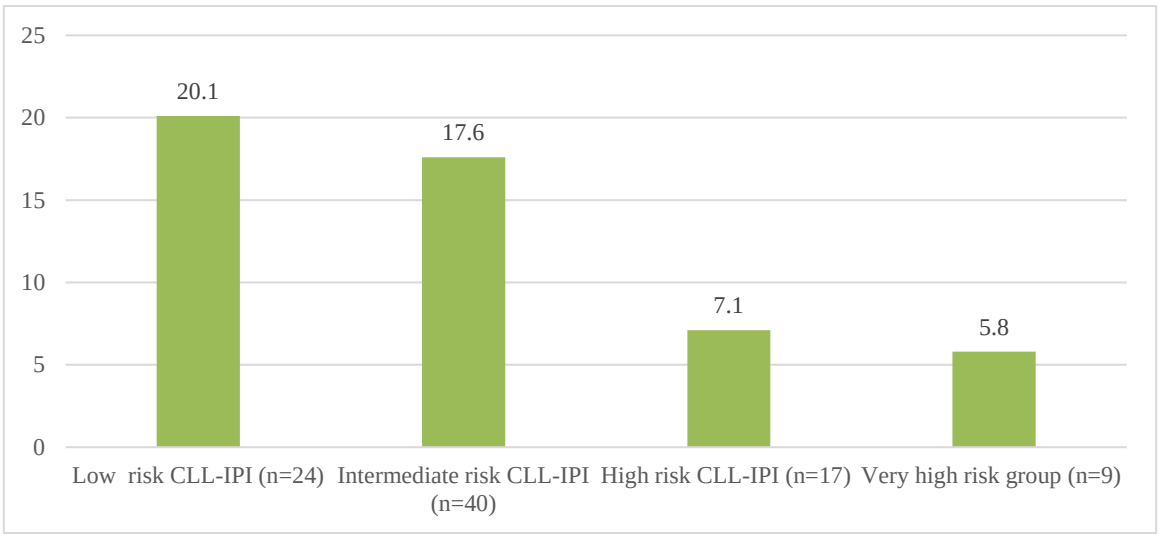

Figure 3: Median TFS in months in different risk CLL-IPI groups.

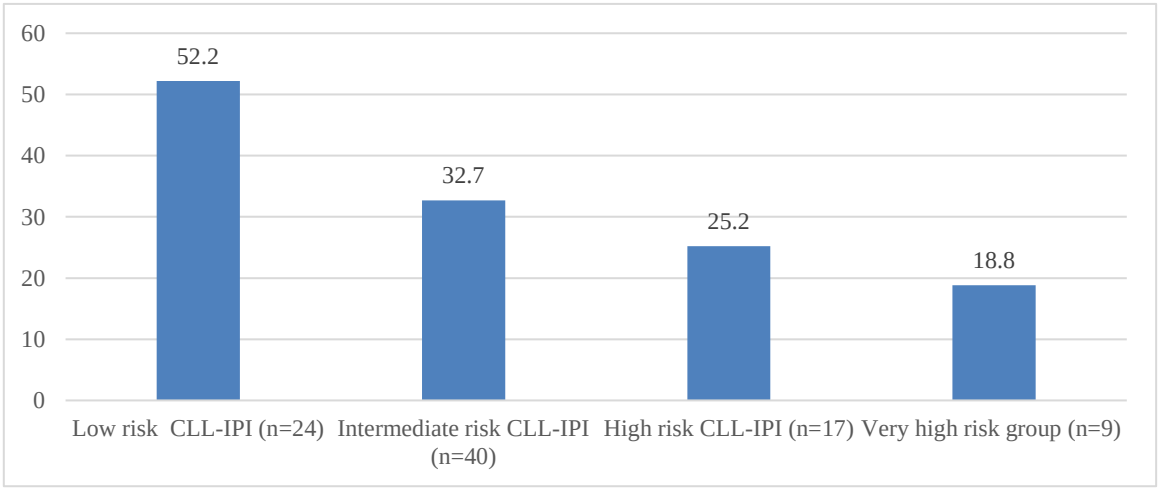

Figure 4: Median OS in months in different risk CLL-IPI groups.

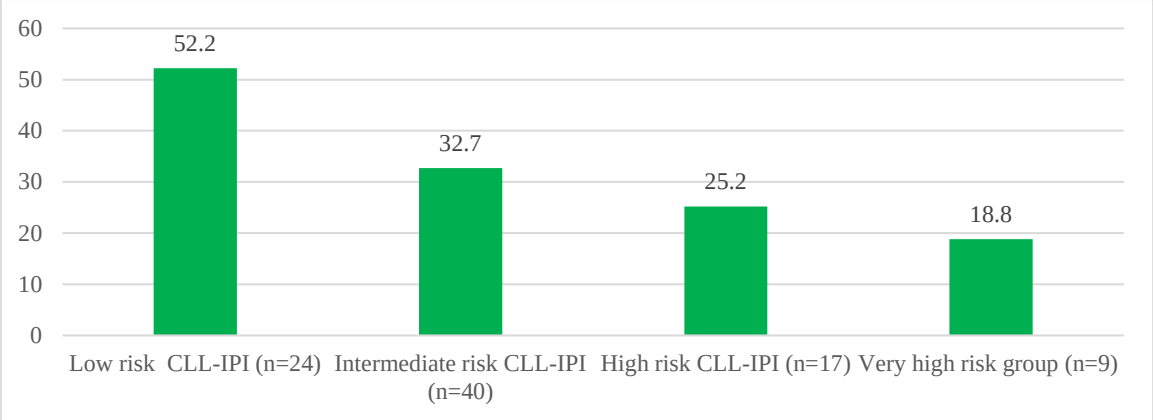

Figure 5: Estimated 5-year OS rate in different risk CLL-IPI groups.

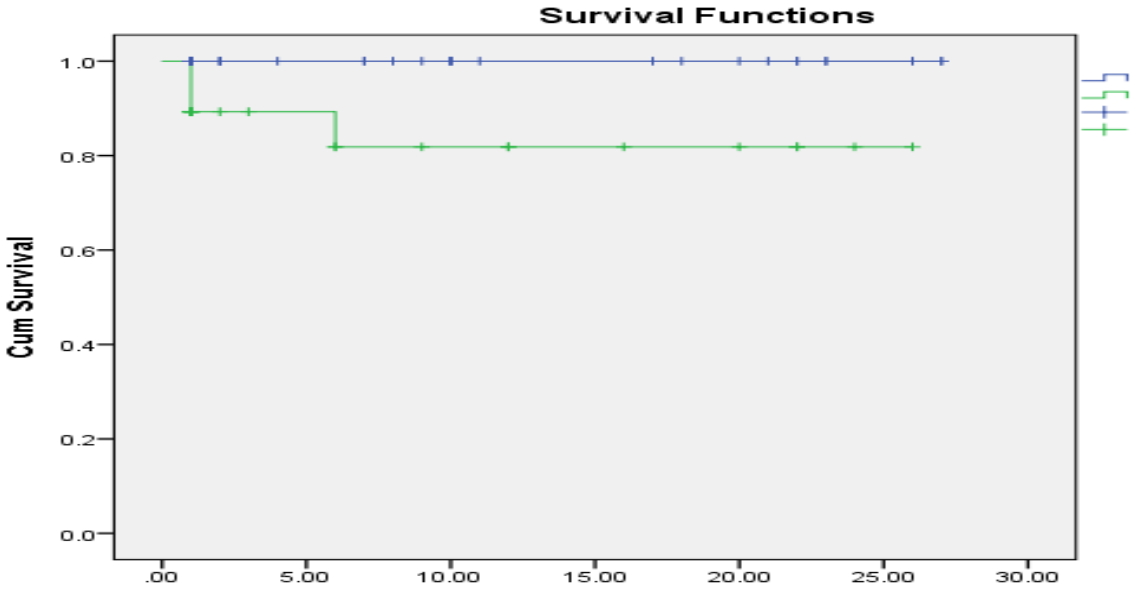

Figure 6: Survival of CLL patients according to molecular prognostic markers with different prognostic significance; good prognostic molecular markers, adverse prognostic molecular markers (del17p).

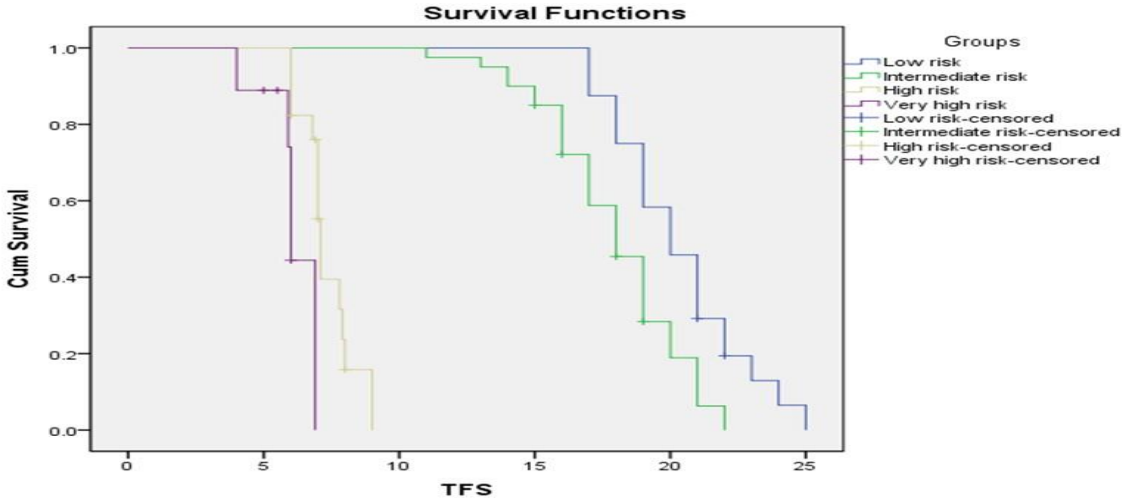

Figure 7: Survival analysis for patients stratified according to CLL-IPI, time to first treatment analysis for all risk CLL-IPI groups (months).

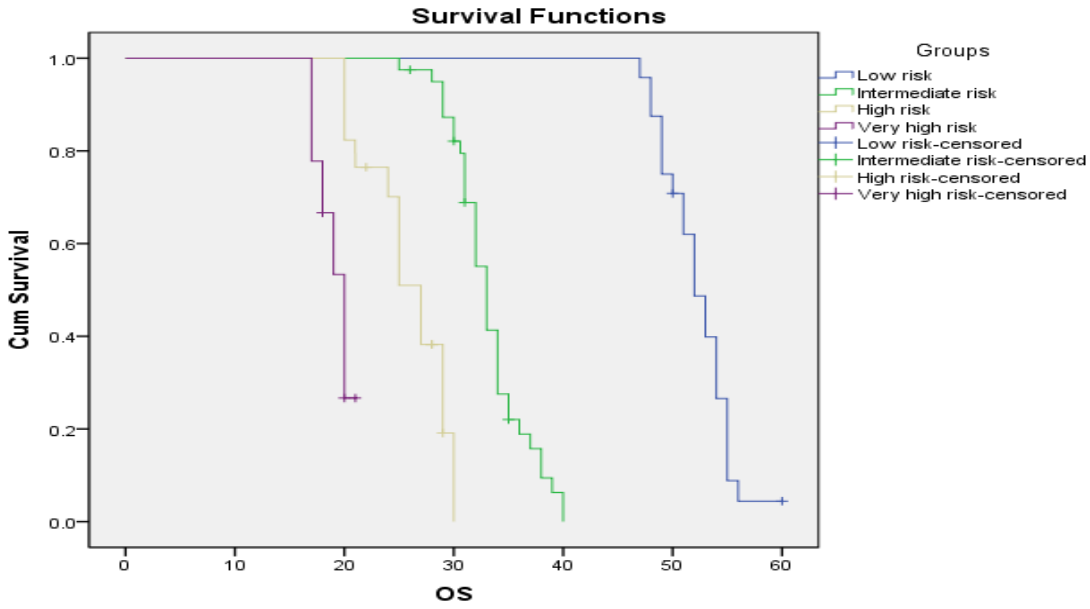

Figure 8: Survival analysis for patients stratified according to CLL-IPI, OS analysis for all risk CLL-IPI groups (months).

Using prognostic nomogram we calculate estimated 5-year OS (Figure 5).[9] The estimated 5-year OS rate was 96%, 89%, 41% and 30%, respectively for low risk group intermediate, high and very high risk group. Using another prognostic algorithm, it was confirmed that patients placed in a low-risk group have the longest expected 5-year survival.

Multivariate analysis indicated that del 17p ($p<0.008$) was independent prognostic factors of TFS (Figure 6). Our study also confirmed the prognostic significance of del 17p as an inferior prognostic marker in terms of survival of patients with CLL.

Survival analysis for patients stratified according to CLL-IPI, TFT and OS analysis for different risk groups are presented on Figure 7 and 8. With the longest OS and TFS in patients stratified in the low risk group (Figure 7 and 8).

DISCUSSION

CLL is a disease characterized by B cell heterogeneity and amplified cellular proliferation. Heterogeneity of the disease displays several genetic abnormalities that are associated with different prognosis and therapeutic implications.[1]

An average survival of CLL patients was about 10 years, but the prognosis was diverse in different groups of patients with the same diagnosis. For the past half century, both Rai and Binet's clinical staging systems had been used to assess patient prognosis. As we mentioned they were based only on physical examination and laboratory analysis. The development of science had made it possible to infiltrate in to the biology of this disease and new prognostic and predictor factors had been discovered. Mutations in the IGHV gene, combined with del (17p) and/or TP53 were the strongest prognostic and predictor factors. Next-generation sequencing revealed some new mutations related to CLL prognosis for personalized management of CLL patients in clinical practice.[10] Following scientific advances, both Rai and Binet clinical systems had been suppressed and the clinician needed a new risk stratification system for patients with CLL.

CLL-IPI was developed using patient data of eight phase-III clinical trials from France, Germany, UK, USA and Poland comprising 3472 treatment-naive patients and validated in multiple independent COHORTs of CLL patients from Mayo clinic and Sweden. The proposal and validation was conducted by the International CLL-IPI working group.

This risk score separated four risk groups with significantly different OS at five years: low (93.2%), intermediate (79.3%), high (63.3%) and very high risk (23.3%).[7] Using Prognostic nomogram (3) our study presented data that 96% of patients with low CLL-IPI group had 5 years OS, 89% of patients from intermediate CLL-IPI group had 5 years OS, only 41% of patients from high risk group had 5 years OS and 30% of patients from very high risk group had 5 years OS, data that were compatible with those published in Lancet.[7] This estimation of OS was constructed in the past before application of targeted therapy so we used them with

vigilance especially in the era of targeted signaling inhibitors.

Kutsch provided treatment recommendations for the different patient risk subgroups emphasizing that treatment should be initiated in patients with symptoms especially in patients from high and very high risk groups, by avoiding chemo or immunochemotherapy and highlighting new experimental targeted drugs.[11] In our study in low and intermediate risk IPI groups very high percent of patients were on observation on watch and wait strategy, but in high and very high risk groups most of the patients were initially treated with or immunochemotherapy associated with short TFS.

Our study included patients diagnosed between 2012 and 2020, a period of abundant developments in the treatment of the disease. In this context, these prognostic index was used with patients treated with chemotherapy or chemoimmunotherapy, so results cannot be generalized to patients treated with the new inhibitors of B cell receptor and Bcl-2 antagonists. These novel therapies have transformed the treatment for patients with CLL, especially in patients with higher risk, whom treatment individualization is needed. In our study presence of 17p deletion was statistically significant associated with inferior prognosis ($p<0.008$) .That group of patients from high CLL-IPI risk group were candidates for novel therapy modalities.

The TFS time of the patients in the very high-risk group from our study was similar to that in the West Europe, suggesting that the TFS time of these patients was extremely short. The timing of treatment should be determined carefully and in a timely manner and the CLL-IPI scoring system can also examine patients who really need treatment.

Use of this score had been shown to be limited in patients with relapsing and refractory disease treated with targeted therapy such as idelalisib where a modified score of one point was used for each adverse prognostic factor.[12] There multivariate analyses recommended that the relative contribution of each adverse risk factor might be different in the relapsed or refractory setting. A modified CLL-IPI partially addresses these borders but this approach was restricted to the CLL-IPI variables and did not account for alternative baseline factors which might be critical in this setting. Therefore, a more comprehensive analysis of candidate prognostic factors for OS were required.

There were some limitations with our study we did not incorporate novel molecular mutations affecting NOTCH1, SF3B1, MYD88 and BIRC3 genes in this study, further studies were required to determine whether their applicability in future clinical practice was achievable. But we could conclude that incorporation of molecular variables such as 17p deletion and the mutational state of IGHV added an evident predictive advantage.

CONCLUSION

CLL-IPI is a powerful risk stratification tool for CLL patients and this system has also provided treatment recommendations for different patient risk subgroups. However, additional studies on our population are needed for the application of this system when using the new targeted CLL therapies. And perhaps this staging system will need to be revised when inserting newly identified molecular mutations.

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