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ORIGINAL ARTICLE

Comparative assessment of prognostic models in chronic lymphocytic leukemia: evaluation in Indian cohort

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Abstract

Prognostic indices combining several clinical and laboratory parameters have been proposed for prognostication in chronic lymphocytic leukemia (CLL). Recently, international consortium on CLL proposed an international prognostic index (CLL-IPI) integrating clinical, molecular, and genetic parameters. The present study was designed to evaluate the reproducibility of CLL-IPI in Indian CLL cohort. The prognostic ability of CLL-IPI in terms of overall survival (OS) and time to first treatment (TTFT) was investigated in treatment-naive CLL patients and also compared with other existing prognostic scores. For assigning scores, clinical and laboratory details were obtained from medical records, and *IGHV* gene mutation status, β2-microglobulin levels, and copy number variations were determined using c-DNA, ELISA, and multiplex ligation-dependent probe amplification (MLPA), respectively. The scores were generated as per the weighted grades assigned to each variable involved in score categorization. The predictive value of prognostic models was assessed and compared using Harrell's C-index and Akaike's information criterion (AIC). Stratification of patients according to CLL-IPI yielded significant differences in terms of OS and TTFT ($p < 0.001$). Comparative assessment of scores for OS suggested better performance of CLL-IPI (C = 0.64, AIC = 740) followed by Barcelona–Brno (C = 0.61, AIC = 754) and MDACC score (C = 0.59, AIC = 759). Comparison of predictive value of prognostic scores for TTFT illustrated better performance of CLL-IPI (C = 0.72, AIC = 726) followed by Barcelona–Brno (C = 0.68, AIC = 743), modified GCLLSG (C = 0.66, AIC = 744), and O-CLL1 index (C = 0.55, AIC = 773). The results suggest better performance of CLL-IPI in terms of both OS and TTFT as compared to other available scores in our cohort.

Keywords Chronic lymphocytic leukemia in India · Prognostic index · CLL-IPI · Time to first treatment

Introduction

Tremendous heterogeneity has been observed in clinical course of patients with chronic lymphocytic leukemia (CLL) and a number of genetic, molecular, biochemical, and clinical prognostic markers have been described that may aid the clinician in defining prognosis of CLL patients. The major challenge in clinical practice is to identify a comprehensive panel of prognostic parameters from the vast array of prognostic markers that best defines the prognosis and is widely available in majority of clinical laboratories worldwide.

Although limited but considerable effort in this field has led to construction of multiple prognostic algorithms for CLL. Initially, M. D. Anderson Cancer Center (MDACC) developed a prognostic index based on six independent prognostic variables, i.e., age, serum β-2-microglobulin (β2M), absolute lymphocyte count (ALC), gender, Rai stage, and the presence of lymphadenopathy [1]. Subsequently, German CLL Study Group (GCLLSG) proposed GCLLSG index for prognostication in CLL based on age, gender, Eastern Cooperative Oncology Group (ECOG) performance status, immunoglobulin heavy chain variable region (*IGHV*) gene mutational status, del(17p), del(11q), serum β2M, and serum thymidine kinase (TK) levels [2]. Since serum TK, one of the major component of the GCLLSG index, is not routinely investigated at all centers,

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implementation of this score became challenging [3]. Molica et al. later modified the GCLLSG index [2] by excluding serum TK levels and compared it with MDACC score [1]. The comparative assessment confirmed the prognostic ability of modified GCLLSG index as well as its superiority over MDACC score for TTFT [4]. However, on excluding serum TK from the GCLLSG index, the prognostic association of the model for OS was lost [2]. Later, Gentile et al. demonstrated prognostic utility of an index based on Rai stage, β2M, ALC, and *IGHV* mutation status in terms of TTFT [5].

With the availability of so many scores, dissimilar applicability in different populations and simultaneous emergence of newer prognostic markers, the prognostic ability of 27 well-established prognostic markers was evaluated by the international consortium on CLL in a cohort of 3472 patients enrolled in phase 3 trials from France, Germany, Poland, UK, and USA. Based on five most significant parameters, i.e., clinical Rai stage, age, β2M, *IGHV* mutational status and TP53 deletion and/or mutation, the international consortium on CLL proposed a comprehensive international prognostic index (CLL-IPI; International CLL-IPI working group, 2016) [6]. CLL-IPI was initially designed for prediction of OS, but later validation studies extended its utility in prediction of TTFT, as well in early-stage CLL patients [7, 8]. Delgado et al. recently proposed a simplified version of CLL-IPI, i.e., Barcelona–Brno index comprising of only two biomarkers: *IGHV* mutation status and FISH cytogenetics [9]. However, a comparison between CLL-IPI and the Barcelona–Brno prognostic indices on an Italian–American cohort of patients suggested better prognostic ability of CLL-IPI for progression as well as survival [10].

The ethnic differences and population-based variability and the populations on which these scores have been developed stipulate validation of the CLL-IPI prior to its broader implementation on Indian population. The present study was thus designed to evaluate the applicability and reproducibility of this score in Indian CLL cohort.

Materials and methods

Patients

A total of 198 treatment-naive CLL patients were evaluated to generate the prognostic scores. The diagnosis was established as per the International Workshop on CLL (IWCLL) criteria for diagnosis of CLL [11]. The informed consent was obtained from all the participants as per the guidelines of Institute's Ethics Committee.

Clinical and laboratory parameters

Information regarding clinical and laboratory parameters including performance status, gender, age, Rai stage, number of palpable lymph node sites, and ALC were obtained from medical records of the patients. Serum β2M levels were estimated using human ELISA kits (R&D systems, Minneapolis, MN, USA) with assay range (0–12.5 μg/mL). The *IGHV* gene mutation status was determined using c-DNA as outlined previously [12].

Copy number variations

Copy number variations at loci frequently aberrant in CLL were investigated using multiplex ligation-dependent probe amplification (MLPA). The P040 CLL probe mix consisting of probes against the genomic regions 17p13, the RB1/DLEU/MIR15A-16 region on 13q14, 11q22 (ATM gene), and chromosome 12 was used. Samples were processed as per the manufacturer's instructions (MRC Holland, The Netherlands) and data was interpreted using the Coffalyser.Net software (MRC Holland, The Netherlands). Relation dosage quotient values < 0.8 were used to determine deletion of TP53 region at 17p13, the RB1/DLEU/MIR15A-16 region on 13q14 and 11q22 (ATM gene), and values > 1.2 indicated amplification of chromosome 12 in patient samples.

Prognostic index scoring

Using the weighted grades assigned to involved variables as per different prognostic indices, scores were generated for each patient $n = 198$. The prognostic ability of CLL-IPI for TTFT and OS was compared with other available indices.

Survival analysis

TTFT was defined as the time from the date of diagnosis to date of commencement of first therapy, and OS was defined as the time from the date of diagnosis to date of death or date of last follow-up. The Kaplan–Meier method of survival analysis including the log rank test was used for estimations and comparisons of TTFT and OS. Hazard ratios (HRs) and confidence intervals (CIs) for HR were calculated according to the Cox proportional hazard model. The predictive power of prognostic models was assessed using the Harrell's C-index where a value ≥ 0.7 was considered significant, and the Akaike's information criterion (AIC), where lower AIC values indicated higher prognostic accuracy of the predictive model. All the statistical tests were carried out using the STATA/SE software ver 14.2 (StataCorp LP, College Station, TX, USA), and results were considered statistically significant at $p \leq 0.05$.

Results

Baseline clinical and laboratory characteristics of patients, IGHV mutational status, and copy number variations at

various loci are listed in Table 1. During the follow-up period, 138/198 (70%) required initiation of therapy of which 62 (45%) received chlorambucil-based therapy, 56 (41%) received rituximab-based therapy, and 20 (14%) received other therapies. As per Rai staging criteria [13], 71% patients were categorized as early-stage CLL (Rai 0–2), and 89 (63.5%) of these required initiation of therapy during the course of follow-up. The median follow-up time was 40.5 months (range, 1–215 months). During the study period, 86 patients died of which 78 died due to disease progression.

Patients were risk stratified as per CLL-IPI, Barcelona–Brno index, O-CLL1 score, modified GCLLSG index, and MDACC score (Table 2). On univariate analysis of nine parameters involved in designing of various scores including gender, lymph node groups, ALC, ECOG PS, age, Rai stage, copy number variations, β2M, and *IGHV* mutational status, all parameters except gender and age were statistically significantly associated with OS ($n = 198$; gender: $p = 0.38$, age: $p = 0.8$; Supplementary Table 1 and Supplementary Fig. 1) and TTFT ($n = 140$; gender: $p = 0.72$, age: $p = 0.8$; Supplementary Table 1 and Supplementary Fig. 2). Upon subjecting parameters with $p \leq 0.05$ to multivariate analysis, Rai stage, del(17p), and *IGHV* mutational status retained independent prognostic association with OS, and Rai stage 2, del(17p), *IGHV* mutational status, performance status, and β2M retained independent prognostic association with TTFT.

Table 1 Clinical and laboratory features of CLL patients ($n = 198$)

Parameter	Numbers (%)
Gender	
Male	153 (77%)
Female	45 (23%)
Median age	60
≤ 65 years	148 (75%)
> 65 years	50 (25%)
Rai stage	
Stage 0/I/II	29/42/69
Stage III/IV	28/30
Beta-2-microglobulin	
≤ 3.5	45 (23%)
> 3.5	153 (77%)
IGHV mutational status	
Mutated	101 (51%)
Unmutated	97 (49%)
Genetic abnormality	
No abnormality	73 (37%)
Del(13q)+	47 (24%)
Del(11q)+	19 (9%)
Del(17p)+	38 (19%)
Trisomy12	21 (11%)
Treatment received	138 (70%)
Chlorambucil-based therapy	62 (45%)
Rituximab-based therapy	56 (41%)
Other therapies	20 (14%)

On stratifying the patients according to CLL-IPI score, significant differences were observed in OS and the median OS was 28, 62, and 190 months and not reached for very high-, high-, intermediate-, and low-risk groups, respectively ($p < 0.001$; Fig. 1a). The multiple pairwise comparison demonstrated significant differences in all the pairs except high vs. intermediate group. As compared to low-risk group, the HR for death for intermediate risk was 5.5 (95% CI = 1.25–24.21, $p = 0.024$), for high risk was 8.7 (95% CI = 2.09–36.3, $p = 0.003$) and for very high risk group was 17.2 (95% CI = 3.9–74.7, $p < 0.001$). The comparisons for OS for other scores are shown in Fig. 1 and Supplementary Table 2.

Since the major challenge faced by the clinicians is management of early-stage CLL patients, we analyzed the TTFT for early stage (Rai stage 0–2, $n = 140$) CLL patients. Comparison of median TTFT among the four risk groups in CLL-IPI revealed a significant association between TTFT and risk groups ($p < 0.001$). Median TTFT for very high-, high-, and intermediate-risk groups was 1, 9, and 51 months, respectively, while for low-risk group, median TTFT could not be reached (Fig. 2a). The COX PH model suggested that as compared to low-risk group, the HR for treatment for intermediate risk was 4.1 (95% CI = 1.39–12.04, $p = 0.010$), for high risk was 9.7 (95% CI = 3.45–27.3, $p < 0.001$), and for very high risk group was 25.10 (95% CI = 8.06–78.13, $p < 0.001$).The TTFT for other risk categories of scores compared is shown in Fig. 2 and supplementary Table2.

The TTFT and OS were also compared in patient groups with copy number variations at 17p13, 13q14, 11q22, and chromosome 12. As compared to patients with no genomic aberrations, median OS was significantly shorter for patients harboring del(17p) (HR 2.12, 95% CI 1.20–3.76, $p = 0.009$; Fig. 3a), and median TTFT was significantly lower for patients harboring del(17p) (HR 2.25, 95% CI 1.28–3.9, $p = 0.005$) and del(11q) (HR 2.13, 95% CI 1.05–4.3, $p = 0.03$; Fig. 3b).

The prognostic value of CLL-IPI was then compared with MDACC and Barcelona–Brno score for OS (Table 3). Harrell's C-value of 0.70, necessary threshold to have a model prognostic value at individual patient level, could not be reached for any of the model for OS. Harell's C-value was highest for CLL-IPI (C = 0.64) followed by Barcelona–Brno index (C = 0.61) and MDACC score (C = 0.59). The AIC values were lowest for CLL-IPI (AIC = 740), followed by Barcelona–Brno index (AIC = 754) and MDACC score (AIC = 759).

The prognostic value of CLL-IPI was then compared with Barcelona–Brno score, modified GCLLSG score and O-CLL1 score for TTFT (Table 3). Harrell's C-value was highest

Table 2 Distribution of patients according to CLL prognostic scores

Prognostic index	Score categorization	Patient stratification ($n = 198$)	Patient stratification (Rai 0–II, $n = 140$)
IPI [6]	Low (score 0–1)	21 (11%)	20 (14%)
	Intermediate (score 2–3)	50 (25%)	40 (29%)
	High (score 4–6)	96 (48%)	62 (44%)
	Very high (score 7–10)	31 (16%)	18 (13%)
Barcelona–Brno [9]	Low (score 0)	78 (39.4%)	62 (44%)
	Intermediate (score 1)	88 (44.4%)	61 (44%)
	High (score 2)	32 (16.2%)	17 (12%)
O-CLL1 [5]	Low (score 0–2)	Not designed for stage III–IV	7 (5%)
	Intermediate (score 3–5)		80 (57%)
	High (score 6–7)		53 (38%)
GCLLSG (modified) [2, 4]	Low (score 0–2)	Not evaluated	7 (5%)
	Intermediate (score 3–5)		86 (61%)
	High (score 6–10)		34 (24%)
	Very high (score 11–14)		7 (5%)
MDACC [1]	Low (score 1–3)	6 (3%)	7 (5%)
	Intermediate (score 4–7)	147 (74%)	120 (86%)
	High (score ≥ 8)	45 (23%)	13 (9%)

for CLL-IPI (C = 0.72), followed by Barcelona–Brno (C = 0.68), modified GCLLSG (C = 0.66), and O-CLL1 index (C = 0.53). The AIC values also followed the same trend, and the AIC was lowest for CLL IPI (AIC = 726) as compared to Barcelona–Brno (AIC = 743), modified GCLLSG (AIC = 751), and O-CLL1 index (AIC = 773).

Discussion

Since CLL is largely heterogeneous disease, prognostic assessment of patients is essential from clinical perspective. The initial MDACC prognostic index designed to predict OS in CLL patients was validated by several groups [1, 14–16]. In the last decade, a number of prognostic scores have also been proposed by other groups working in different regions of the world. The latest in the series is the score developed by the international consortium on CLL (CLL-IPI; International CLL-IPI working group, 2016) [5]. The score was initially designed in terms of OS, but later validation studies extended its utility for TTFT as well [7, 8]. The present study thus aimed to assess the reproducibility and validity of recently developed CLL-IPI in Indian CLL cohort. An additional aim of the present study was to compare the efficiency of CLL-IPI with other available prognostic scores. The data available to us for the variables associated with the existing indices restricted the comparison of CLLIPI with MDACC [1] and Barcelona–Brno score [9] for OS and Barcelona–Brno

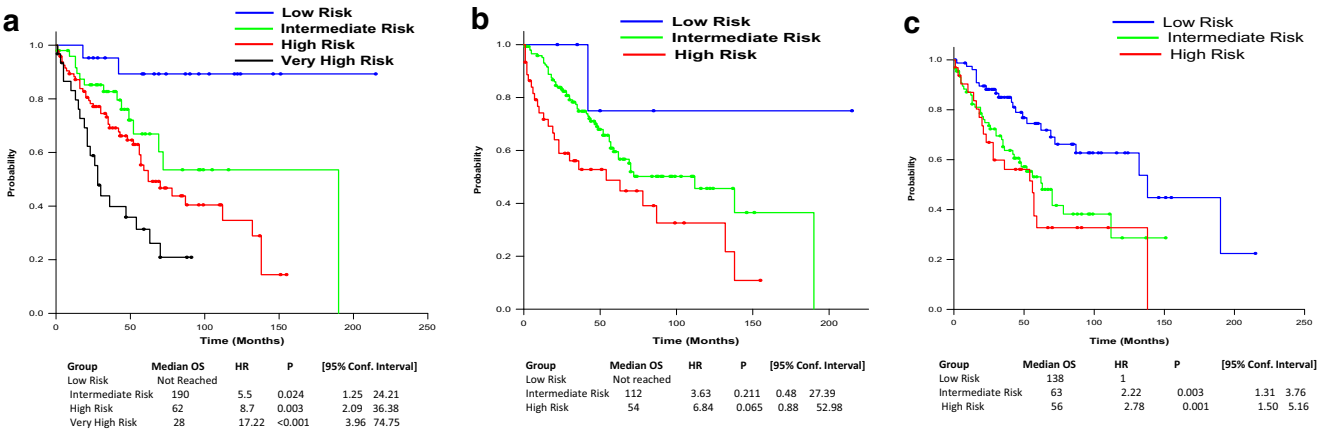

Fig. 1 Overall survival according to prognostic index, **a** CLL-IPI, **b** MDACC score, and **c** Barcelona–Brno index, in chronic lymphocytic leukemia patients ($n = 198$)

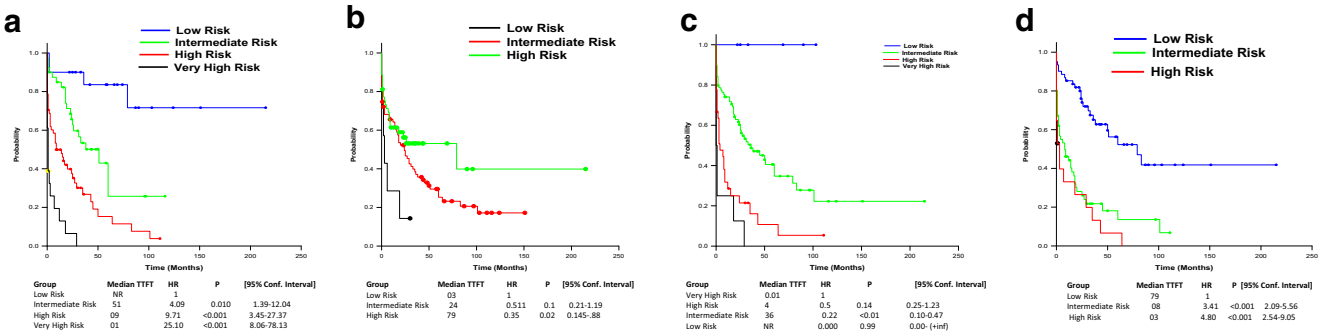

Fig. 2 Time to first treatment according to prognostic index, **a** CLL-IPI, **b** O-CLL1, **c** GCLLSG score, and **d** Barcelona–Brno index, in chronic lymphocytic leukemia patients ($n = 140$)

score [9], modified GCLLSG score [4], and O-CLL1 score [5] for TTFT.

Of the nine parameters involved in categorization of different risk scores, all parameters except age and gender were significantly associated with OS and TTFT in univariate analysis. Although the median age of the patients analyzed in our series was almost similar to the patients evaluated for CLL-IPI, age was not significantly associated with OS and TTFT. In multivariate analysis also, only Rai stage, del(17p) and *IGHV* mutational status retained independent prognostic association with OS, and del(17p), Rai stage 2, *IGHV* mutational status, performance status, and β2M retained independent prognostic association with TTFT. The differences in the results obtained in our series could be due to lower number of patients in our study as compared to other studies performed, and due to short follow-up, there are not enough events in our cohort.

Even if Harrell's C-value of 0.7 could not be reached, the risk groups categorized according to CLL-IPI have distinct and significantly different overall survival. The AIC values obtained for the scores compared for OS in the present study suggest better performance of CLL-IPI.

The prognostic scores were further compared using TTFT as end point which is more suitable than OS for patients with early CLL as it is not affected by competing risks of death due to unrelated conditions, relapses, and impact of new therapies. In a country like India, several patients opt for conventional therapies due to financial constraint. This is clearly evident in present study as well as previous study by our group [17] where 45% and 68% patients, respectively, received chlorambucil-based therapy as first-line treatment. Significant Harrell's C-value and lower AIC validate robust discriminatory value of CLL-IPI score for Indian CLL patients for TTFT too. Delgado et al. evaluated all possible combinations of five variables involved in CLL-IPI to identify the simplest model with minimum number of variables and developed a prognostic model based on *IGHV* mutational status + FISH [del(17p) and/or del(11q)] which was further validated on Barcelona–Brno patient series. However, comparison of Barcelona–Brno score with CLL-IPI demonstrated the

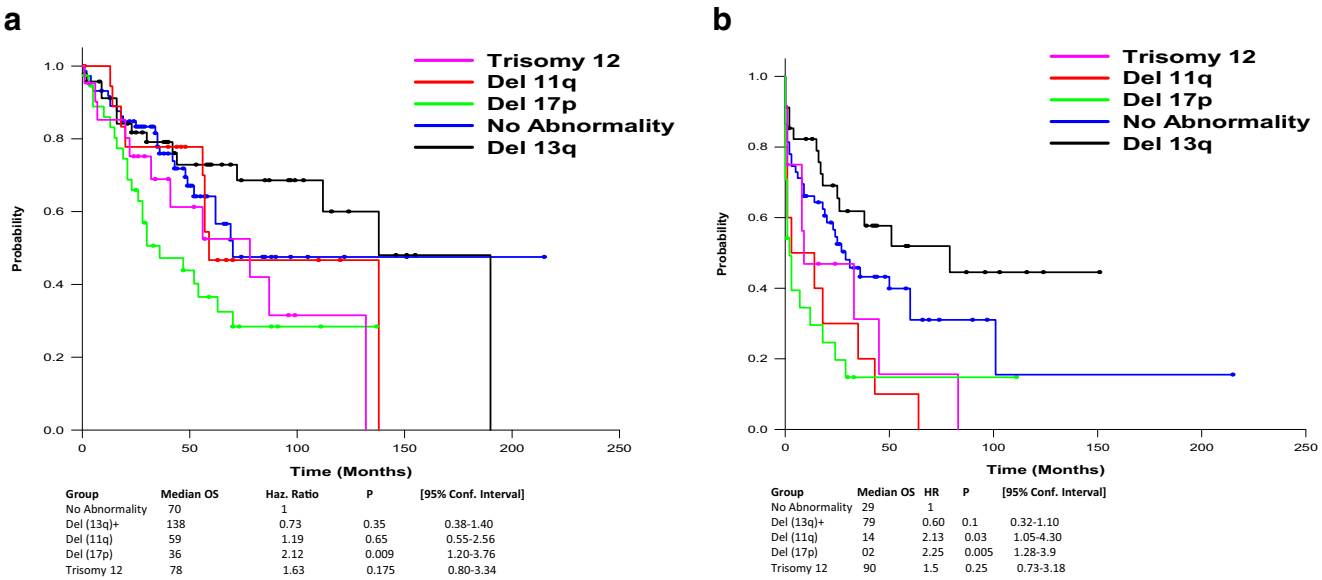

Fig. 3 Kaplan–Meier curves for **a** OS ($n = 198$) and **b** TTFT ($n = 140$) according to genetic abnormalities as assessed by MLPA in chronic lymphocytic leukemia. OS overall survival, TTFT time to first treatment, MLPA multiplex ligation-dependent probe amplification

Table 3 Ability of prognostic models to predict OS ($n = 198$) and TTFT ($n = 140$) in terms of Harell's C-index and Akaike's information criteria (AIC)

Sr. no.	Model	Overall survival		Time to first treatment	
		Harrell's C-index (95% CI)	AIC	Harrell's C-index (95% CI)	AIC
1	CLL-IPI	0.64 (0.58–0.70)	740	0.72 (0.68–0.78)	726
2	MDACC (2007)	0.59 (0.53–0.64)	759	Not evaluated	
3	Barcelona–Brno	0.61 (0.55–0.67)	754	0.68 (0.63–0.74)	743
4	Modified GCLLSG	Not evaluated		0.66 (0.61–0.71)	744
5	O-CLL1	Not evaluated		0.55 (0.49–0.60)	773

superiority of the CLL-IPI score [10]. The present results also suggest CLL-IPI to be better than Barcelona–Brno index. The results from the present study demonstrated that among all the scores evaluated, CLL-IPI possess highest discriminatory value for TTFT in early-stage CLL patients. A comparative study by Molica et al., however, revealed better performance of O-CLL1 score as compared to CLL-IPI and GCLLSG scores for TTFT [18]. Low performance of O-CLL1 score in the present study could be explained by exclusion of del(17p) status from O-CLL1 score, which retained independent prognostic value and high risk in multivariate analysis for Indian population. The present results thus support the notion that scores involving CNV (CLL-IPI, Barcelona–Brno, and GCLLSG) perform better than others (O-CLL1 score). Although the present study evaluated patients at the time of diagnosis, a recent meta analysis of all published studies that have used CLL-IPI has revealed applicability of CLL-IPI at different time points such as at the time of diagnosis and at the time of therapy or relapse, thus confirming its utility in CLL prognostication [19].

The present study has certain limitations. In the present study, only TP53 deletions were used to document TP53 aberrations because of unavailability of TP53 mutation status for all the patients. As TP53 mutation status using Sanger sequencing or next-generation sequencing is labor intensive and costly affair, the results of the present study indicate that the modified CLL-IPI which is based on TP53 deletion instead of TP53 deletion/mutation can also be applied in settings where TP53 mutation status cannot be investigated. Unlike other studies, the CNVs in the present study were assessed by MLPA instead of FISH. Alhourni et al. have already shown that both MLPA and iFISH have comparable detection rates for genomic aberrations typically associated with CLL [20]. Since the study cohort consisted of the patients treated with chemotherapy or chemoimmunotherapy, the results of the present study may not be applicable to the patients treated with novel agents such as Bruton tyrosine kinase inhibitor, phosphoinositide 3-kinase inhibitor, and bcl2 inhibitor [21]. The introduction of these novel agents have altogether changed the therapeutics in CLL. Moreover, the present study shows moderate prognostic value of all the prognostic models which could be due to small number of patients. The results support the notion that in clinical practice, CLL patients should only be treated in presence of active disease and that prognostic models can complement but not replace clinical expertise.

In conclusion, CLL-IPI is a simplified index composed of robust and easily available prognostic markers with a better prognostic potential than other existing scores in Indian cohort. The implication of this score would lead to execution of common criteria of prognostication worldwide which will allow multicentric comparisons and collaborations.

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Compliance with ethical standards

This study was carried out according to the Helsinki declaration. The informed consent was obtained from all the participants included in this study as per the guidelines of Ethics Committee of All India Institute of Medical Sciences.

Conflict of interest The authors declare that they have no conflict of interest.

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