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# MULTIVARIABLE MODEL CONSISTING OF CLINICAL AND BIOLOGICAL MARKERS FOR TIME TO FIRST TREATMENT IN CLL PATIENTS: PRELIMINARY RESULTS FROM SINGLE CENTRE EXPERIENCE

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**Abstract**

*Introduction:* The clinical course for patients with chronic lymphocytic leukaemia (CLL) is extremely heterogeneous; one of the most important challenges in the clinical management of these patients is the decision on initiating their treatment, but there is no available prognostic system that will resolve this issue. Usually, criteria for active disease are used to initiate therapy. Recently, some authors have proposed prognostic models, scoring systems involving a set of clinical and biological risk factors and estimates of individual patient survivals. Here, we report our initial results from a study designed to evaluate the statistical association of the distinct clinical and biological parameters with the prognosis and time to initiating treatment for patients with CLL.

*Material and methods:* Our study incorporated 100 consecutive, treatment naïve CLL patients. In each patient all traditional laboratory, clinical and biological prognostic factors were evaluated at their first visit to our Institution. We then combined the following independent characteristics: age, β-2 microglobulin, absolute lymphocyte count, sex, Rai stage, and number of involved lymph node groups, which are included in some of the already published CLL prognostics index, in association with the CD38 expression and mutational status of the immunoglobulin heavy chain gene variable region (IGVH). Further, we correlated those factors by multivariable analysis with time to first treatment. This multivariable model was used to develop a nomogram-a weighted tool to calculate 5- and 10-year survival probability and estimate median time to first treatment (TFT).

*Results:* According to the prognostic index, a classification tree was built that identified three subsets of patients whose scores were 1–3 (low risk – 32 pts – 32%), 4–7 (intermediate risk – 48 pts – 48%) and > 8 (high risk – 20 pts – 20%). Estimated median survival in the low risk subset of patients is 141 years, and 10.7 and 4.6 years respectively in the intermediate and high risk subsets of patients. Projected survival in respectively low, intermediate and high-risk groups are 100%, 100%, 25%, and 43%, 34%, 25% at 5 years and 10 years, respectively. Also, statistical analyses showed that among other things CD38 expression and unmutated IGHV mutation status are associated with a shorter time to first treatment.

*Conclusion:* Our prognostic model that combines and correlates the distinct clinical and biological markers of CLL patients enables identification of patients who are at high risk of progression. This prognostic model may facilitate the clinical decision for initiating treatment.

**Key words:** chronic lymphocytic leukaemia, prognosis, time to first treatment.

## Introduction

The clinical course for patients with chronic lymphocytic leukaemia (CLL) is extremely heterogeneous in its clinical and biological aspects. One of the most important challenges in the clinical management of these patients is the decision on initiating their treatment, but there is no available prognostic system that will resolve this issue. Usually the criteria for active disease are used to initiate therapy. Recently some authors have proposed prognostic models, scoring systems involving a set of clinical and biological risk factors and estimates of individual patients survival.

Wierda et al. [1] developed a prognostic index (PI) and nomogram consisting of clinical risk factors, i.e age, gender, number of involved lymph node sites, Rai system, absolute lymphocyte count (ALC), widely used serum marker Beta-2 microglobulin (β2 M). According to PI patients with CLL could be stratified into three risk groups with different expected median survivals. Using the nomogram, clinical doctors could estimate -5 and -10 years of patient survival. This model was subsequently validated in independent patients series also using time to first treatment as an end-point followed at the Mayo Clinic [2]. Bulian et al. [3] improved a prognostic model for overall survival based on clinical variables and biological risk factors such as immunoglobulin, heavy chain gene variable region (IGHV), mutational status and chromosomal abnormalities such as deletion 17 p.

But the father of prognostic CLL models and nomograms, Wierda et al. [4], developed a weighted multivariable model and nomogram for the time to first treatment as an end point, developing a tool for identifying high risk patients with a shorter time to first treatment.

The aim of the present study was to evaluate the statistical association of the distinct clinical and biological parameters with the prognosis and time to initiating treatment for our patients with CLL.

## Patients and Methods

*Patients*

Our study incorporated 100 consecutive-treatment naïve CLL patients. All the patients were evaluated for traditional clinical and laboratory prognostic factors and one or more of the newer prognostic factors including IGHV mutation status and CD38 expression by flow cytometry. Prognostic factors were evaluated at patients' first visit to the University Clinic for Haematology between September 2011 and March 2013.

At the initial evaluation, date of CLL diagnosis was recorded, and the time-to-event end point was defined as the time from first visit to the University Haematology Clinic to first CLL treatment. There was no restriction of time from diagnosis to presentation at the University Haematology Clinic.

All patients had more than 1 month of treatment-free follow-up from the initial evaluation at the University for Haematology Clinic, and physicians were to conform to 1996 NCI-WGguidelines for initiating treatment. This was done to develop a model that best correlated with time to first treatment for patients who do not have an indication for treatment at the time of evaluation. Clinical and laboratory evaluation at the first visit to the University Haematology Clinic included history and physical examination, standard clinical laboratory evaluation, and evaluation for CD38 by flow cytometry was performed on peripheral blood at the University Haematology Clinic. Traditional prognostic factors and clinical and laboratory variables included sex; age, Rai stage, Eastern Cooperative Oncology Group performance status, 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), haemoglobin level, platelet count, Beta-2 microglobulin (B-2M), lactate dehydrogenase (LDH), creatinine, albumin, and quantitative immunoglobulin (Ig) levels (IgG, IgA, and IgM). Peripheral blood was taken to confirm the diagnosis by flow cytometry and characterization of CD38 expression.

*IGHV* mutation status was characterized by the direct sequencing method, and patients were categorized as unmutated (*IGHV* ≥ 98% germline homology) or mutated (< 98% homology) [5]. There were 100 patients who had IGHV mutation status performed by the Center for Biomolecular Pharmaceutical Analyses at the Faculty of Pharmacy.

CD38 measurements were performed at the University Haematology Clinic, as reported [6], using a threshold at 30% expression to define positive cases.

**Statistical methods**

All analyses were performed in an open source statistical package (http://www.statsoft.com). Median follow-up was computed using the reverse censoring method. The primary end points was the time to first treatment (TFT). TFT was estimated using Kaplan-Meier plots and compared between groups by log-rank test. Univariate and multivariate Cox models were used to verify the independent prognostic power of each parameter. Model minimization was performed by stepwise backward elimination. A p value < 0.05 was considered to be statistically significant

**Results**

100 patients were included in the analyses, with a median age of 64.8 years (range 47 to 78 years); 63% were male; 41% had unmutated IGHV status; 61% had > 30% CD38 expression (Table1).

Table 1

*Baseline patient characteristics*

| Age at diagnosis | | IgG g/L | |
|---|---|---|---|
| Median | Range | Median | Range |
| 64.8 | (47-78) | 12.27 | (7.24-18.2) |
| Gender | | IgM g/L | |
| male | 20% | Median | Range |
| female | 80% | 1.03 | (0.23- 3.42) |
| ECOG- Performance Status | | IgA g/L | |
| 0 | 48% | Median | Range |
| 1 | 21% | 2.43 | (0.7- 3.9) |
| 2 | 26% | Lactate dehydrogenase IU/L | |
| 3 | 5% | Median | Range |
| No. of lymph node sites | | 586.2 | (322-903) |
| 0 | 54% | Beta-2 microglobulin mg/L | |
| 1 | 6% | Median | Range |
| 2 | 10% | 2.7 | (1.57- 4.9) |
| ≥3 | 30% | | |
| ALC(x10⁹/L) | | Albumin level gr/L | |
| Median | Range | Median | Range |
| 54.1 | (7.1-130) | 39.1 | (30- 45) |
| Hemoglobin level gr/L) | | Alkaline phosphatase IU/l | |
| Median | Range | Median | Range |
| 129.2 | (77-164) | 85.5 | (45-205) |
| White blood cells(x10⁹/L) | | Liver size,sm | |
| Median | Range | Median | Range |
| 68.1 | (22.1-299.8) | 6.5 | (0- 5) |
| Platelet K/mL | | Spleen size,sm | |
| Median | Range | Median | Range |
| 210.95 | (93-354) | 5.9 | (0-20) |
| RAI stage | | IGHV mutation status | |
| 0 | 54% | Unmutated | 41% |
| I | 5% | Mutated | 59% |
| II | 32% | CD38 expression | |
| III | 5% | positive(>30%) | 61% |
| IV | 4% | negative(<30%) | 39% |

According to the prognostic index (1) a classification tree was built that identified three subsets of patients whose scores were 1–3 (low risk – 32 pts – 32%), 4–7 (intermediate risk – 48 pts – 48%) and > 8 (high risk – 20 pts – 20%) (Figure 1). According to the nomogram (1) estimated median survival in the low-risk subset of patients was 14.1 years, and 10.7 and 4.6 years respectively in intermediate and high risk subsets of patients. Projected survivals in respectively low, intermediate and high-risk groups are 100%, 100%, 25%, and 43%, 34%, 25% at 5 years and 10 years, respectively (Table 2).

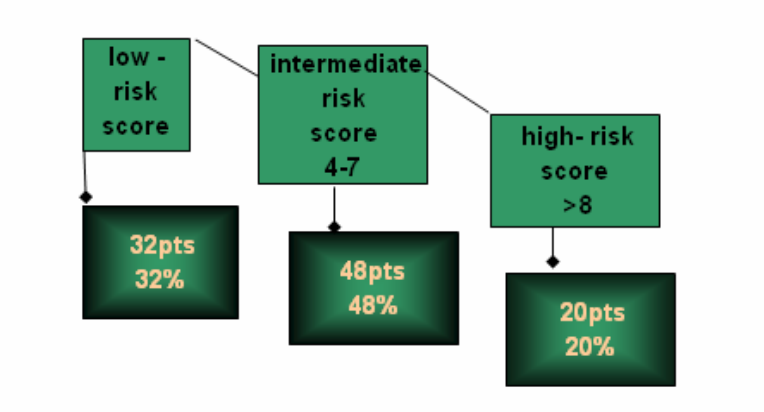


*Figure 1 – Classification tree according to Wierda's prognostic index*

Table 2

*Estimated and Projected survival according to Wierda`s nomogram*

| Estimated median survival | years | |
|---|---|---|
| low risk | 14,1 | |
| intermediate risk | 10,7 | |
| high risk | 4,6 | |
| Projected survival | 5-years | 10-years |
| low risk | 100% | 43% |
| intermediate risk | 100% | 34% |
| high risk | 25% | 25% |

All the patients were alive at the last follow-up, 59 patients were treatment-free and censored. Median time to treatment-free was 8.3 months (range 0–18 months), 41 patients were to be given therapy at the University Haematology Clinic according to 1996NCI-WG guidelines for initiating treatment.

Univariable analyses identified both traditional and new prognostic factors associated ($P < .05$) with shorter time to first treatment, including the following: age, higher absolute lymphocyte count, lower haemoglobin, platelet count, white blood cells count, IgG level, higher beta-2 microglobulin and LDH and number of lymph node sites involved, increased spleen, liver, and a high level of alkaline phosphatase (Table 3).

Table 3

*Univariable analyses for Time to First Treatment*

| Variable | Statistical test | p-value |
|---|---|---|
| TFS | -8.32935 | 0.000000 |
| Age | 5.60313 | 0.000000 |
| ALC | 6.78402 | 0.000000 |
| Hgb | -3.48662 | 0.000471 |
| WBC | 6.39857 | 0.000000 |
| Plt | 4.73760 | 0.000002 |
| L.gl | 3.14322 | 0.000496 |
| Lien | 3.79849 | 0.000008 |
| Hepar | 2.72973 | 0.000011 |
| IgG | -3.32543 | 0.000860 |
| IgM | -0.14017 | 0.888212 |
| IgA | -1.17739 | 0.238398 |
| LDH | 4.35916 | 0.000012 |
| B2 microglobulin | 4.44676 | 0.000008 |
| Alb | 0.69732 | 0.477590 |
| AP | 2.13753 | 0.031565 |

There were 100 patients who had IGHV mutation status determined, and this was correlated with time to first treatment (Table 4). Patients with unmutated IGHV had a shorter

time to first treatment, associated with these prognostic factors: higher absolute lymphocyte count, platelet count, white blood cell count, number of lymph node sites involved, increased spleen, advanced Rai and > 30% CD38 expression.

CD38 expression was correlated with time to first treatment (Table 5).

Table 4

*IGHV mutation status and Time to First Treatment*

| Variables | Statistical test | p-value |
|---|---|---|
| TFS | -1.79275 | 0.073014 |
| Age | 1.44799 | 0.147620 |
| ALC | 1.96513 | 0.049400 |
| Hgb | -1.41352 | 0.157505 |
| WBC | 2.37884 | 0.017368 |
| Plt | -4.26813 | 0.000020 |
| L.gl | 4.45775 | 0.000008 |
| Lien | 2.46159 | 0.013833 |
| Hepar | 0.72055 | 0.471188 |
| Gender | -1.33077 | 0.183265 |
| ECOG | 0.95499 | 0.339586 |
| RAI | 4.49222 | 0.000007 |
| CD38 expression | -3.40623 | 0.000659 |
| Renal function | -1.05152 | 0.293022 |

Table 5

*CD38 expression and Time to First Treatment*

| Variable | Statistical test | p-value |
|---|---|---|
| TFS | 0.23321 | 0.815599 |
| Age | 0.66429 | 0.506502 |
| ALC | 0.00000 | 1.000000 |
| HB | -0.80563 | 0.420455 |
| WBC | -0.42402 | 0.671553 |
| Plt | 3.80909 | 0.000140 |
| L.gl | -4.28611 | 0.000018 |
| Lien | -2.69958 | 0.006943 |
| Hepar | -0.47349 | 0.635867 |
| Gender | 2.67131 | 0.007556 |
| ECOG | -1.19078 | 0.233740 |
| RAI | -3.84443 | 0.000121 |
| IGHV mutation status | -3.49108 | 0.000481 |
| Renal function | 1.28972 | 0.197149 |

A multivariable model for time to first treatment was developed with 100 patients (100%), who had complete data available for the fitted covariates (Table 6). The following patient characteristics were independently associated with shorter time to first treatment: d age, higher absolute lymphocyte count; lower haemoglobin, platelet count, white blood cell count, IgG, IgM, IgA level, three involved lymph node sites, elevated serum LDH, higher beta-2 microglobulin, increased spleen, liver, high level of alkaline phosphatase and albumine, impairment of renal function, > 30% CD38 expression and unmutated IGHVgene.

Patients with unmutated IGHVgene, > 30% CD38 expression, male gender, advanced Rai stage, advanced ECOG performance status, had shorter time to first treatment (Figure 2).

Table 6

*Multivariable model for Time to First Treatment*

| N = 100 | Regression Summary for Dependent Variable: TFS (Multipna regresiona Spreadsheet17.sta)<br>R = .95147613 R² = .90530683 Adjusted R² = .88839733<br>F(15,84) = 53.538 p < 0.0000 Std. Error of estimate: 2.3475 | | | | | |
|---|---|---|---|---|---|---|
| | b* | Std.Err. of b* | b | Std.Err. of b | t(84) | p-value |
| Intercept | | | 195.3726 | 12.64141 | 15.4550 | 0.000000 |
| Age | -1.95715 | 0.115066 | -1.6669 | 0.09800 | -17.0089 | 0.000000 |
| ALC | 1.12751 | 0.148885 | 0.1751 | 0.02313 | 7.5731 | 0.000000 |
| HB | -1.46552 | 0.105605 | -0.4142 | 0.02985 | -13.8774 | 0.000000 |
| WBC | -2.38388 | 0.188089 | -0.2594 | 0.02047 | -12.6742 | 0.000000 |
| Plt | 1.15139 | 0.096863 | 0.0967 | 0.00814 | 11.8868 | 0.000000 |
| L.gl | -0.21375 | 0.094444 | -1.1095 | 0.49022 | -2.2633 | 0.026197 |
| Lien | 0.48220 | 0.149584 | 0.4114 | 0.12763 | 3.2236 | 0.001803 |
| Hepar | 0.46612 | 0.092019 | 2.0499 | 0.40469 | 5.0654 | 0.000002 |
| IgG | -0.18977 | 0.076483 | -0.4508 | 0.18171 | -2.4812 | 0.015089 |
| IGM | -1.07336 | 0.095451 | -7.3362 | 0.65239 | -11.2451 | 0.000000 |
| IgA | -0.47062 | 0.062423 | -2.8625 | 0.37969 | -7.5391 | 0.000000 |
| LDH | 0.83053 | 0.083173 | 0.0336 | 0.00336 | 9.9856 | 0.000000 |
| B2 | 0.31442 | 0.052399 | 1.8441 | 0.30732 | 6.0005 | 0.000000 |
| Alb | -0.60604 | 0.059530 | -1.0702 | 0.10512 | -10.1803 | 0.000000 |
| AP | -0.22775 | 0.082813 | -0.0445 | 0.01620 | -2.7501 | 0.007294 |
| Intercept | | | 17.55133 | 3.061216 | 5.73345 | 0.000000 |
| Gender | 0.406747 | 0.081493 | 5.89036 | 1.180147 | 4.99121 | 0.000003 |
| ECOG | -0.533311 | 0.085596 | -3.87576 | 0.622053 | -6.23060 | 0.000000 |
| RAI | -0.036958 | 0.093607 | -0.21101 | 0.534451 | -0.39482 | 0.693879 |
| IGHV mutatiation status | -0.172195 | 0.087495 | -2.40838 | 1.223734 | -1.96806 | 0.050000 |
| CD38 expression | -0.196442 | 0.085186 | -2.81596 | 1.221122 | -2.30604 | 0.023330 |
| Gender | 0.406747 | 0.081493 | 5.89036 | 1.180147 | 4.99121 | 0.000003 |

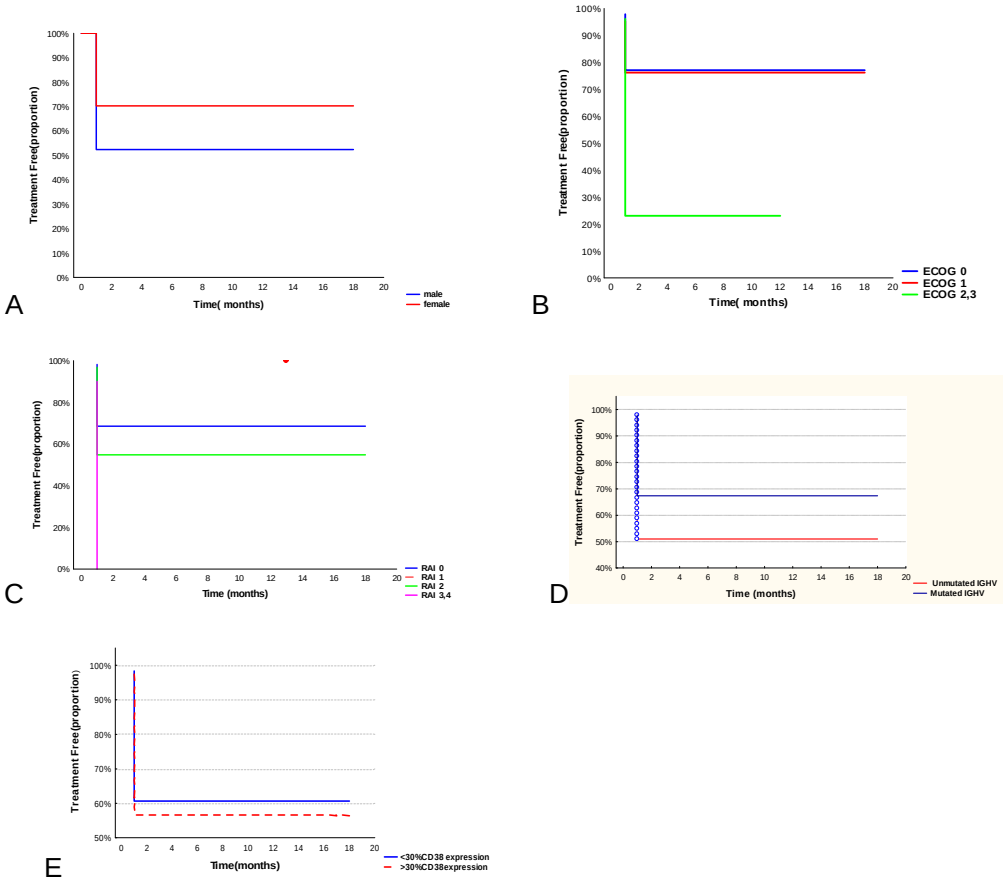


*Figure 2 – Time to first treatment by (A-E) gender (A), ECOG performance status (B), Rai stage (C), IGHV mutation status (D), CD38 expression (E). Patients were observed for time to first treatment, Kaplan Meier estimates of treatment-free survival are shown (D; red) unmutated versus mutated D; blue) IGHV status (E; red) or positive versus negative (E; blue) CD38 expression*

**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 [7]. 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 [7]. 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 (del 11q and del 17p), which may predict resistance to chemotherapy-based treatments [8].

FISH analysis is not available in our country, so at this moment the need to explore the influence of new home set prognostic factors such as CD38 expression and the mutational status of IGHV on treatment-free survival is necessary.

Until now we have used Wierda`s prognostic index and nomogram to stratify patients into risk groups and to estimate median survival and project 5- and 10-year survival in line to overall survival. But this present analysis is based on a treatment naive CLL database assessing the utility of the prognostic index proposed by Wierda et al. [1, 4] to predict TFT in patients with early disease. 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 a better predictor of patients' survival than Rai or Binet risk. Our multivariable model for Time to First Treatment revealed that the Rai stage has no statistical significance in TFT, so we could not rely on this system.

The 6 parameters used to calculate the prognostic index score, from Wierda`s first model (1), are based 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 al. (2) are similar to those observed in the MDACC study (1) and that proved that the index is reproducible.

Our analyses were limited to newly diagnosed patients, the time at which risk stratification is needed. Other analyses have attempted to evaluate the relative contribution of multiple prognostic factors to time to first treatment. This model was possible only with prolonged follow-up and is relevant particularly for early-stage patients who did not have NCI-WG9 or IWCLL10 indications for initial therapy (4). The median time from initial CLL diagnosis to prognostic factor evaluation was 8.3 months, this model incorporated both fixed characterristics such as IGHV mutation status and features that evolve with the progression of disease, such as number of nodal sites involved, LDH, Beta 2 microglobuline and Rai status.

Our multivariable model identified more than 10 independent characteristics from a total of 100 patients in the final model, and of whom 41 patients required treatment. But from the identified more than 10 independent characteristics, there is a contribution from some new prognostic factors to time to first treatment which are not included in Wierda`s first nomogram and prognostic index (1), which is part of our every day work. Results from this study confirm that patients with unmutation status of IGHV, > 30% CD38 expression are associated with shorter treatment free survival. So, we would propose that CD38 expression and mutational status of IGHV be incorporated in the nomogram and prognostic index named for stratifying patients into risk groups, and for the most important making of the decision to start treatment.

This analysis has some weaknesses. The first weakness is that it is a single-centre study, and there are likely unknown prognostic factors affecting the outcome not accounted for in this analysis. At the moment we are not in a position to identify the presence of chromosome abnormalities by FISH analysis, which identifies high-risk categories, including patients with 17p deletion or 11q deletion, associated with shorter time to first treatment. Further evaluation of this model will require validation in an independent population.

But there are some potential applications for this model, particularly in identifying patients at high risk of early progression. This mo-

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

**Conclusions**

In the present study we have shown that the survival of untreated CLL patients may be estimated by a limited set of clinical and biological variables, integrated in a prognostic index and in a nomogram, allowing group and individual estimation, respectively. CD38 and unmutated IGHV gave redundant prognostic information.

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Резиме

## МУЛТИВАРИЈАБИЛЕН МОДЕЛ СОСТАВЕН ОД КЛИНИЧКИ И БИОЛОШКИ МАРКЕРИ ЗА ОДРЕДУВАЊЕ НА ВРЕМЕ ЗА ПРВ ТРЕТМАН КАЈ ПАЦИЕНТИ СО ХРОНИЧНА ЛИМФОЦИТНА ЛЕУКЕМИЈА: ПРЕЛИМИНАРНИ РЕЗУЛТАТИ ОД ИСКУСТВА НА ЕДЕН ЦЕНТАР


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*Вовед:* Клиничкиот тек на пациентите со хронична лимфоцитна леукемија (ХЛЛ) е многу хетероген, една од најважните предизвици во клиничкото водење на овие пациенти е одлуката за започнување на нивниот третман, но сè уште нема достапни прогностички системи кои би го разрешиле ова прашање. Вообичаено, критериумот активна болест се користи за започнување на терапија. Неодамна некои автори предложија прогностички модел, систем за степенување составен од сет на клинички и биолошки фактори на ризик со цел да се процени индивидуалното преживување на пациентите. Тука, ние ги прикажуваме иницијалните резултати од студијата, дизајнирана да ја евалуира статистичката асоцијација на одредени клинички и биолошки параметри со прогнозата и времето да се започне третман за пациентите со хронична лимфоцитна леукемија.

*Материјал и методи:* Во нашата студија беа вклучени 100 последователни пациенти, кои не беа третирани со ХЛЛ. Кај секој пациент беа евалуирани традиционалните лабораториски, клинички и биолошки прогностички фактори на првата посета во нашата

институција. Потоа ние ги комбинираме според следниве независни карактеристики: возраст, β-2 микроглобулин, апсолутен лимфоцитен број, пол, Rai stage, број на региони на зафатени лимфни жлезди, некои кои веќе се вклучени во публикувани прогностички системи за ХЛЛ, во асоцијација со CD38 експресија и мутациониот статус на варијабилниот регион на имуноглобулинскиот тежок ланец. Понатаму ги споредуваме овие фактори со мултиваријабилна анализа со времето на првиот третман. Овој мултиваријабилен модел го користевме да создадеме номограм – алатка за мерење на веројатноста за 5 и 10-годишно преживување и да се процени средното време за првиот третман.

*Резултати:* Според прогностичкиот индекс создадовме класификационо стебло кое идентификуваше три подгрупи на пациенти со поени 1–3 (низок ризик – 32 пациенти – 32%), 4–7 (среден ризик – 48 пациенти – 48%) и > 8 (висок ризик – 20 пациенти – 20%). Проценето средно преживување кај пациенти со низок ризик е 14,1 години, 10,7 и 4,6 години кај пациентите со среден и висок ризик. Проектирано преживување кај пациенти со низок, среден и висок ризик е 100%, 100%, 25%, и 43%, 34%, 25% за 5 и 10 години. Понатаму, статистичката анализа покажа дека меѓу другите екстресијата на CD38 и немутирани IGVT се асоцирани со пократко време за првиот третман.

*Заклучок:* Нашиот прогностички модел кој комбинира и споредува клинички и биолошки маркери за пациенти со ХЛЛ овозможува идентификација на пациенти кои имаат висок ризик од прогресијата. Овој прогностички модел може да влијае на клиничката одлука за започнување на третманот.

**Клучни зборови:** хронична лимфоцитна леукемија, прогноза, преживување без терапија.

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| Variable | Statistical test | p-value |
|---|---|---|
| TFS | -8.32935 | 0.000000 |
| Age | 5.60313 | 0.000000 |
| ALC | 6.78402 | 0.000000 |
| Hgb | -3.48662 | 0.000471 |
| WBC | 6.39857 | 0.000000 |
| Plt | 4.73760 | 0.000002 |
| L.gl | 3.14322 | 0.000496 |
| Lien | 3.79849 | 0.000008 |
| Hepar | 2.72973 | 0.000011 |
| IgG | -3.32543 | 0.000860 |
| IgM | -0.14017 | 0.888212 |
| IgA | -1.17739 | 0.238398 |
| LDH | 4.35916 | 0.000012 |
| B2 microglobulin | 4.44676 | 0.000008 |
| Alb | 0.69732 | 0.477590 |
| AP | 2.13753 | 0.031565 |

Table3.Univariable analyses for Time to first Treatment

| Variables | Statistical test | p-value |
|---|---|---|
| TFS | -1.79275 | 0.073014 |
| Age | 1.44799 | 0.147620 |
| ALC | 1.96513 | 0.049400 |
| Hgb | -1.41352 | 0.157505 |
| WBC | 2.37884 | 0.017368 |
| Plt | -4.26813 | 0.000020 |
| L.gl | 4.45775 | 0.000008 |
| Lien | 2.46159 | 0.013833 |
| Hepar | 0.72055 | 0.471188 |
| Gender | -1.33077 | 0.183265 |
| ECOG | 0.95499 | 0.339586 |
| RAI | 4.49222 | 0.000007 |
| CD38 expression | -3.40623 | 0.000659 |
| Renal function | -1.05152 | 0.293022 |

Table 4. IGHV mutation status and Time to first Treatment

| Variable | Statistical test | p-value |
|---|---|---|
| TFS | 0.23321 | 0.815599 |
| Age | 0.66429 | 0.506502 |
| ALC | 0.00000 | 1.000000 |
| HB | -0.80563 | 0.420455 |
| WBC | -0.42402 | 0.671553 |
| Plt | 3.80909 | 0.000140 |
| L.gl | -4.28611 | 0.000018 |
| Lien | -2.69958 | 0.006943 |
| Hepar | -0.47349 | 0.635867 |
| Gender | 2.67131 | 0.007556 |
| ECOG | -1.19078 | 0.233740 |
| RAI | -3.84443 | 0.000121 |
| IGHV mutation status | -3.49108 | 0.000481 |
| Renal function | 1.28972 | 0.197149 |

Table5.CD38 expression and Time to first Treatment

| N = 100 | Regression Summary for Dependent Variable: TFS (Multipna regresiona Spreadsheet17.sta)<br>R = .95147613 R² = .90530683 Adjusted R² = .88839733<br>F(15,84) = 53.538 p < 0.0000 Std. Error of estimate: 2.3475 | | | | | |
|---|---|---|---|---|---|---|
| | b* | Std.Err. of b* | b | Std.Err. of b | t(84) | p-value |
| Intercept | | | 195.3726 | 12.64141 | 15.4550 | 0.000000 |
| Age | -1.95715 | 0.115066 | -1.6669 | 0.09800 | -17.0089 | 0.000000 |
| ALC | 1.12751 | 0.148885 | 0.1751 | 0.02313 | 7.5731 | 0.000000 |
| HB | -1.46552 | 0.105605 | -0.4142 | 0.02985 | -13.8774 | 0.000000 |
| WBC | -2.38388 | 0.188089 | -0.2594 | 0.02047 | -12.6742 | 0.000000 |
| Plt | 1.15139 | 0.096863 | 0.0967 | 0.00814 | 11.8868 | 0.000000 |
| L.gl | -0.21375 | 0.094444 | -1.1095 | 0.49022 | -2.2633 | 0.026197 |
| Lien | 0.48220 | 0.149584 | 0.4114 | 0.12763 | 3.2236 | 0.001803 |
| Hepar | 0.46612 | 0.092019 | 2.0499 | 0.40469 | 5.0654 | 0.000002 |
| IgG | -0.18977 | 0.076483 | -0.4508 | 0.18171 | -2.4812 | 0.015089 |
| IGM | -1.07336 | 0.095451 | -7.3362 | 0.65239 | -11.2451 | 0.000000 |
| IgA | -0.47062 | 0.062423 | -2.8625 | 0.37969 | -7.5391 | 0.000000 |
| LDH | 0.83053 | 0.083173 | 0.0336 | 0.00336 | 9.9856 | 0.000000 |
| B2 | 0.31442 | 0.052399 | 1.8441 | 0.30732 | 6.0005 | 0.000000 |
| Alb | -0.60604 | 0.059530 | -1.0702 | 0.10512 | -10.1803 | 0.000000 |
| AP | -0.22775 | 0.082813 | -0.0445 | 0.01620 | -2.7501 | 0.007294 |
| Intercept | | | 17.55133 | 3.061216 | 5.73345 | 0.000000 |
| Gender | 0.406747 | 0.081493 | 5.89036 | 1.180147 | 4.99121 | 0.000003 |
| ECOG | -0.533311 | 0.085596 | -3.87576 | 0.622053 | -6.23060 | 0.000000 |
| RAI | -0.036958 | 0.093607 | -0.21101 | 0.534451 | -0.39482 | 0.693879 |
| IGHV mutatiation status | -0.172195 | 0.087495 | -2.40838 | 1.223734 | -1.96806 | 0.050000 |
| CD38 expression | -0.196442 | 0.085186 | -2.81596 | 1.221122 | -2.30604 | 0.023330 |
| Gender | 0.406747 | 0.081493 | 5.89036 | 1.180147 | 4.99121 | 0.000003 |

Table 6.Multivariable model for Time to first Treatment