Low prevalence and independent prognostic role of del(11q) in Chinese patients with chronic lymphocytic leukemia

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A B S T R A C T

The 11q deletion (del(11q)) is a conventional cytogenetic aberration observed in chronic lymphocytic leukemia (CLL) patients. However, the prevalence and the prognostic value of del(11q) are still controversial. In this research, we retrospectively explored the prevalence, association, and prognostic significance of del(11q) in 352 untreated and 99 relapsed/refractory Chinese CLL patients. Totally 11.4% of untreated and 19.2% of relapsed/refractory patients harbored del(11q). Del(11q) was more common in patients with β2-microglobulin > 3.5 mg/L, positive CD38, positive zeta-chain associated protein kinase 70, unmutated immunoglobulin heavy variable-region gene and ataxia telangiectasia mutated mutation. Kaplan-Meier method and univariate Cox regression indicated that del(11q) was an independent prognostic factor for overall survival (OS). Based on the results of univariate Cox regression analysis, two nomograms that included del(11q) were established to predict survival. Desirable area under curve of receiver operating characteristic curves was obtained in the training and validation cohorts. In addition, the calibration curves for the probability of survival showed good agreement between the prediction by nomogram and actual observation. In summary, the prevalence of del(11q) is relatively low in our cohort and del(11q) is an unfavorable prognostic factor for untreated CLL patients. Besides, these two nomograms could be used to accurately predict the prognosis of untreated CLL patients.

Introduction

Chronic lymphocytic leukemia (CLL) is a common type of mature B-cell malignancy in adults, with heterogeneous clinical courses. Some patients can “watch and wait” for a long time, while some patients need treatment immediately after diagnosis. Previous studies reported that many factors could indicate the clinical course of CLL, including clinical as well as laboratory (age, stage, β2-microglobulin (β2-MG), thymidine kinase 1 (TK-1), etc.), immunophenotypic (CD38, zeta-chain associated protein kinase 70 (ZAP-70), CD49d, etc.), cytogenetic (chromosome, fluorescence in situ hybridization (FISH), etc.) and molecular (immunoglobulin heavy variable-region gene (IGHV) status, gene mutations, etc.) biomarkers. 11q deletion (del(11q)), an important cytogenetic aberration, occurs in nearly 20% of previously untreated European CLL patients and is often accompanied by unmutated IGHV [1–3]. In Asian countries, the prevalence of del(11q) is relatively low, ranging from

Abbreviations: Del(11q), 11q deletion; CLL, chronic lymphocytic leukemia; β2-MG, β2-microglobulin; TK-1, thymidine kinase 1; ZAP-70, zeta-chain associated protein kinase 70; IGHV, immunoglobulin heavy variable-region gene; ATM, ataxia telangiectasia mutated; BIRC3, baculoviral IAP repeat containing 3; NF-κB, nuclear factor-κB; CLL-IPI, chronic lymphocytic leukemia-international prognostic index; TP53, tumor protein 53; ALC, absolute lymphocyte count; LDH, lactate dehydrogenase; ESR, erythrocyte sedimentation rate; CA-125, carbohydrate antigen 125; 25VitD, 25 hydroxyvitamin D; TFS, treatment-free survival; OS, overall survival; C-index, concordance index; AUC, area under curve; ROC, receiver operating characteristic.

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6.9% to 12.5% according to previous studies [4–6]. Del(11q) affects many genes, such as ataxia telangiectasia mutated (ATM) and baculoviral IAP repeat containing 3 (BIRC3) gene [7]. ATM gene is involved in the cellular response to DNA damage and BIRC3 gene is a negative regulator of the non-canonical nuclear factor-xB (NF-xB) pathway [3].

To date, the exact role of del(11q) in CLL patients remains controversial. Dohner et al. [2] compared the survival of CLL patients with del (17p), del(11q), trisomy 12, normal karyotype, and sole del(13q) and found that del(17p) and del(11q) were independent adverse prognostic factors for CLL patients. While Huang et al. [4] failed to validate the value of del(11q) in their cohort. Many other studies also explored the role of del(11q) in different situations [7]. Most of the studies found that del(11q) was associated with shorter survival, while some studies failed to find the relationship between del(11q) and unfavorable prognosis. Tsimberidou et al. [8] even found that del(11q) was associated with high rates of response, survival, and relapse-free survival when treated with chemotherapy.

Therefore, it is necessary to confirm the effects of del(11q) on survival.

Nomograms have been developed to estimate individual survival probability in many kinds of diseases in recent years. Most can be used to accurately predict prognosis and their efficacy is as good as that of traditional prognostic systems [9–11]. In CLL, the most classic model is chronic lymphocytic leukemia-international prognostic index (CLL-IPI) [12]. Previous researches also established several nomograms to predict probability in many kinds of diseases in recent years. Most can be used to find the relationship between del(11q) and unfavorable prognosis.

Materials and methods

Patients

This was a single-center retrospective study. A total of 546 patients were diagnosed with CLL between January 2011 and December 2019 in the department of hematology, the First Affiliated Hospital of Nanjing Medical University, Jiangsu Province Hospital. Four hundred and fifty-one patients (451/546, 82.6%) who did del(11q) test were included in this study. Diagnostic criteria were referred to the International Workshop on CLL-National Cancer Institute criteria. This study was approved by the hospital ethics committee (2018-SRFA-087) and all patients provided informed consent according to the Declaration of Helsinki.

Detection of clinical, cytogenetic, molecular, and immunophenotypic aberrations

Laboratory examination data such as absolute lymphocyte count (ALC), platelet count, hemoglobin concentration, lactate dehydrogenase (LDH) concentration, TK-1 concentration, j2-MG concentration, erythrocyte sedimentation rate (ESR), ferritin concentration, carbohydrate antigen 125 (CA125) concentration, and 25 hydroxyvitamin D (25VitD) concentration were collected in our study [19]. We used peripheral blood/bone marrow samples to detect cytogenetic, molecular, and immunophenotypic aberrations. FISH was conducted to detect del(17p), del(11q), del(13q), and trisomy 12 according to the procedures described previously [20]. FISH probes included: LSI D13S319 for detection of del(13q14), LSI ATM for detection of del(11q22.3), CEP12 (centromere 12) for detection of trisomy 12 and LSI p53 for detection of del(17p13). Gene mutations were detected by Sanger sequencing or next-generation sequencing. The primer sequences of Sanger sequencing for mutation detection (TP53, NOTCH1, SF3B1, and MYD88) were reported in previous papers [21]. IGHV mutational status, CD38, ZAP-70, and CD49d were detected according to corresponding protocols [21], and the cut-off values for mutation or positivity were 98%, 30%, 20%, and 30%, respectively. All data were collected at the same time or the same disease state.

Statistical analyses

SPSS 23 (IBM Corporation, Armonk, NY, USA) was used to analyze data. Categorical variables were analyzed by y2 test. Methods were selected according to the following principles: 1. Total count ≥ 40 and minimum expected count ≥ 5, we used Pearson Chi-Square. 2. Total count ≥ 40 and 1 ≤ minimum expected count < 5, we used continuity correction. 3. Total count < 40 or minimum expected count < 1, we used Fisher’s exact test. Continuous variables were analyzed by Mann–Whitney U test because of skewed distribution. Treatment-free survival (TFS) was calculated as the time from del(11q) detection to first-line treatment or indications appearance (if patients refused to receive the treatment). Overall survival (OS) was defined as the time from del (11q) detection to death or last follow-up. Survival curves were constructed by the Kaplan-Meier method, and the log-rank test was used to examine statistical associations. The Cox proportional hazards model was established to evaluate different factors affecting survival by univariate and multivariate analyses. For the multivariate analysis, we included variables whose P value was less than 0.2 during the univariate analysis.

Patients were randomly divided into training (70%) and validation (30%) cohorts by setting seed in R software version 4.0.1. Nomograms were formulated based on the results of univariate analysis (P < 0.2) and by using the rms package [10]. The performance of the nomograms was measured by concordance index (C-index), receiver operating characteristic (ROC) curves, and calibration plots. ROC curves and the corresponding area under the curve (AUC) were constructed to assess the predictive accuracy of each model by using survivalROC package. Calibration plots were drawn with predicted probability of survival as X axis and corresponding actual probability of survival as Y axis. The validation cohort was used to assess C-index, ROC curves, and calibration plots in order to validate the performance of the models generated depending on the data in the training cohort. P < 0.05 was defined as a statistically significant value. A Circos plot was drawn by using Circos Table Viewer (http://mktweb.bcgsc.ca/tableviewer/) to present the pairwise co-occurrence of del(11q) and other mutations as well as cytogenetic lesions in untreated CLL patients. Graphs were made by R software version 4.0.1 and GraphPad Prism 8.0 (GraphPad Software, Inc., La Jolla, CA, USA).

Results

Patient characteristics and del(11q) frequency

A total of 352 previously untreated and 99 relapsed/refractory CLL patients were enrolled in our study. The characteristics of untreated patients were presented in Table 1. The median age was 61 years (16–86 years), with a male/female ratio of 2.26:1. The percentage of CD38 mutation, ZAP-70 mutation, and mutation were 14.7%, 29.2%, 16.4%, 30.7%, 20.2%, 10.0%, 2.2%, and 17.5%, respectively. In Table 1, median follow-up time was 42 months (2–111 months), and 209 patients received treatment or had treatment indications during the follow-up period. Treatment regimens included: fludarabine/cyclophosphamide ± rituximab (N = 53), bendamustine ± rituximab (N = 30), chlorambucil ± rituximab (N = 28), rituximab (N = 18), high-dose methylprednisolone ± fresh frozen plasma + rituximab (N = 5), hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) ± rituximab (N = 3), ibritinib (N = 19), ibritinib + fludarabine/cyclophosphamide + rituximab (N = 13), ibritinib ± rituximab (N = 7), other treatment (N = 2), and not available (N = 2).
Table 1
Baseline characteristics of 352 untreated chronic lymphocytic leukaemia patients.

| Variables (N = 352) | N (%) |
|---------------------|-------|
| Age > 65 years      | 114 (32.4) |
| Male                | 244 (69.3) |
| Rai I-IV or Binet B/C | 313 (88.9) |
| ALC > 50 x 10^9/L   | 89 (25.3) |
| Platelets < 100 x 10^9/L | 93 (26.4) |
| Hemoglobin > 100 g/L | 61 (17.3) |
| LDH > ULN (N = 343) | 69 (20.1) |
| TK-1 > ULN (N = 316) | 38 (12.0) |
| β2-MG > 3.5 mg/L (N = 332) | 135 (40.7) |
| ESR ≥ 38 mm/h (N = 303) | 45 (14.9) |
| Ferritin > ULN (N = 314) | 19 (6.1) |
| CA125 > ULN (N = 294) | 19 (5.5) |
| 25ViD < LLN (N = 150) | 57 (38.0) |
| Light chain (N = 292) | 187 (64.0) |
| CD33 (≥30%) (N = 268) | 63 (23.1) |
| ZAP-70 (>20%) (N = 218) | 91 (41.7) |
| CD49d (>30%) (N = 125) | 27 (21.6) |
| Del(11q) | 40 (11.4) |
| Del(13q) (N = 269) | 124 (46.1) |
| Trisomy 12 (N = 267) | 43 (16.1) |
| Unmutated IGHV (N = 291) | 119 (40.9) |
| SFB1 mutation (N = 265) | 13 (4.9) |
| NOTCH1 mutation (N = 294) | 26 (8.8) |
| MTD88 mutation (N = 259) | 26 (10.0) |
| BIRC3 mutation (N = 216) | 5 (2.1) |
| ATM mutation (N = 220) | 38 (17.3) |

Abbreviations: 25ViD: 25 hydroxyvitamin D; ALC: absolute lymphocyte count; ATN: ataxia telangiectasia mutated; β2-MG: β2-microglobulin; BIRC3: baculoviral IAP repeat containing 3; CA125: carbohydrate antigen 125; ESR: erythrocyte sedimentation rate; IGHV: immunoglobulin heavy variable-region gene; LDH: lactate dehydrogenase; LLN: lower limit of normal; M: mutated; MYD88: myeloid differentiation factor 88; SFB1: splicing factor 3b subunit 1; TK-1: thymidine kinase 1; ZAP-70: zeta-chain-associated protein kinase 70; TP53: tumor protein 53; ULN: upper limit of normal; UM: unmutated.

Table 2 showed the prevalence of del(11q) in different disease states. In general, del(11q) was detected in 40 untreated (11.4%) and 19 relapsed/refractory (19.2%) patients. Specifically, a total of 7.1%, 13.9%, and 15.2% of patients harbored del(11q) when detected at diagnosis (no indication), between diagnosis and treatment, and before treatment, respectively.

Clinical, immunophenotypic, cytogenetic, and molecular correlations

Del(11q) was more common in untreated patients with β2-MG > 3.5 mg/L (17.8% vs 8.1%, P = 0.008), positive CD38 (23.8% vs 5.5%, P = 0.001), positive ZAP-70 (17.6% vs 7.9%, P = 0.029), unmutated IGHV (27.7% vs 2.3%, P < 0.001), and ATM mutation (31.6% vs 8.8%, P < 0.001) (Table 3). The pairwise co-occurrence of del(11q) and other mutations as well as cytogenetic lesions was shown in the Circos plot (Fig. S1). No preferable IGHV gene usage was observed in del(11q) subjects (Table S1). In addition, lower expression of CD19 (median: 206.1 vs 411.5, P = 0.027) and higher expression of CD38 (median: 18.9 vs 6.7, P < 0.001) were found in del(11q) individuals (Table 4).

Table 2
Del(11q) frequency by disease state.

| Disease state                  | Patients number | Del(11q) number (%) |
|--------------------------------|-----------------|---------------------|
| At diagnosis (no indication)   | 155             | 11 (7.1)            |
| Between diagnosis and treatment| 65              | 9 (13.9)            |
| Before treatment               | 132             | 20 (15.2)           |
| Relapsed/refractory            | 99              | 19 (19.2)           |

For untreated patients, by the Kaplan-Meier method and log-rank test, we found that patients with del(11q) had shorter TFS and OS (P = 0.053 and 0.024, Fig. 1). Median TFS for patients with and without del(11q) were 2 and 17 months, respectively. Median OS for patients with and without del(11q) were 75 months and not reached, respectively.

Untreated patients were randomly divided into training (N = 248) and validation cohorts (N = 104) for further research. The baseline patient characteristics of these two cohorts were shown in Table S2, and no significant difference was seen between these two groups. Cox regression analyses were carried out in the training cohort. Univariate Cox regression analysis showed that Rai I-IV or Binet B/C stage (P < 0.001), β2-MG > 3.5 mg/L (P < 0.001), unmutated IGHV (P < 0.001), and TP53 disruption (P = 0.014) had adverse effects on TFS. Age > 65 years (P < 0.001), Rai I-IV or Binet B/C stage (P = 0.048), β2-MG > 3.5 mg/L (P < 0.001), unmutated IGHV (P = 0.001), NOTCH1 mutation (P = 0.029), TP53 disruption (P = 0.002), and del(11q) (P = 0.002) had unfavorable effects on OS. Factors with p value less than 0.2 were included in multivariate Cox regression analysis. Multivariate Cox regression analysis revealed that Rai I-IV or Binet B/C stage (P = 0.004) and β2-MG > 3.5 mg/L (P < 0.001) were independent adverse prognostic factors for TFS, while β2-MG > 3.5 mg/L (P = 0.006), TP53 disruption (P = 0.021) and del(11q) (P = 0.025) were independent adverse prognostic factors for OS (Table 5).

Prognostic nomogram

The prognostic nomograms that integrated all factors with p value less than 0.2 in univariate Cox regression analysis in the training cohort were shown in Fig. 2. The prognostic nomogram for TFS consisted of six factors: stage, β2-MG concentration, IGHV status, NOTCH1 status, TP53 status, and del(11q) status (Fig. 2A). The prognostic nomogram for OS consisted of seven factors: age, stage, β2-MG concentration, IGHV status, NOTCH1 status, TP53 status, and del(11q) status (Fig. 2B). Three-year and five-year survival probabilities were presented in corresponding figures.

The C-index for TFS and OS prediction in the training cohort were 0.761 (95% CI, 0.753–0.769) and 0.791 (95% CI, 0.780–0.802), respectively. ROC curves were conducted to analyze the power of these two prognostic models in predicting TFS and OS of CLL patients. The AUCs were 0.889 and 0.838 for predicting 3-year and 5-year TFS (Fig. 3A), respectively. The AUCs were 0.782 and 0.922 for predicting 3-year and 5-year OS (Fig. 3B), respectively. In the validation cohort, the C-index for TFS was 0.691 (95% CI, 0.668–0.714), and that for OS was 0.789 (95% CI, 0.751–0.827). The associated AUCs were 0.795 and 0.735 for 3-year and 5-year TFS (Fig. 3C), respectively. The AUC was 0.732 for 3-year and 5-year OS (Fig. 3D). In addition, we compared our nomogram models with the golden standard CLL-IPI. No significant difference was seen between these two models (Fig. S2). Whether in the training (Fig. 4A) or validation (Fig. 4B) cohort, the calibration plots for the probability of survival at 3- and 5-year showed an optimal agreement between the prediction by the nomogram and actual observation.

We calculated the risk points of each patient according to the formula presented in the nomograms, and eventually divided patients into high risk (risk points > median) and low risk (risk points ≤ median) groups. In the training cohort, high risk patients had inferior TFS (P < 0.001) and OS (P < 0.001) than low risk patients (Fig. 5A). Similar results were seen in the validation cohort (Fig. 5B), although the p value for OS was not less than 0.05.

Discussion

CLL, a heterogeneous B-cell chronic lymphoproliferative disorder, is often accompanied by cytogenetic aberrations, one of which is del(11q). In western countries, nearly 20% of untreated CLL patients harbor this...
only 6.9% of newly diagnosed CLL patients had del(11q), and in Asian countries, the prevalence of del(11q) is relatively low, and its role remains unclear. Kaplan-Meier analysis indicated that patients with del(11q) had longer TFS and OS than those without del(11q). However, the specific mechanisms remained unclear. Kaplan-Meier analysis showed that del(11q) had a favorable effect on TFS and OS, while del(11q) failed to be an independent adverse factor. In our study, they took del(11q) and del(17p) into account at the same time, which would influence the judgment of sole del(11q), and thus, their results were unable to illustrate the real role of del(11q) in CLL.

We retrospectively analyzed the clinical data of 352 previously untreated and 99 relapsed/refractory CLL patients in order to explore the role of del(11q). Totally 11.4% of untreated and 19.2% of relapsed/refractory patients had del(11q). The prevalence of del(11q) in our study was lower than that reported by western countries. Besides, the frequency of del(11q) increased with the progression of the disease. Most of the patients with del(11q) harbored high concentrations of J2-MG, positive CD38 as well as ZAP-70, lower expression of CD19 and unmutated IGHV. In our study, they considered del(11q)/del(17p) as an unfavorable factor. However, in this study, they took del(11q) and del(17p) into account at the same time, which would influence the judgment of sole del(11q), and thus, their results were unable to illustrate the real role of del(11q) in CLL.

We retrospectively analyzed the clinical data of 352 previously untreated and 99 relapsed/refractory CLL patients in order to explore the role of del(11q). Totally 11.4% of untreated and 19.2% of relapsed/refractory patients had del(11q). The prevalence of del(11q) in our study was lower than that reported by western countries. Besides, the frequency of del(11q) increased with the progression of the disease. Most of the patients with del(11q) harbored high concentrations of J2-MG, positive CD38 as well as ZAP-70, unmutated IGHV, and mutated TP53. Previous research suggested that del(11q) and del(17p) had unfavorable effects on TFS, while del(11q) failed to be an independent prognostic factor for TFS in multivariate Cox regression analysis. This may be because, in our cohort, patients with del(11q) also harbored other adverse prognostic factors such as unmutated IGHV and J2-MG > 3.5 mg/L. In addition, as reported by Huang et al. [4], no standard protocol or guideline was available in the early years in China, so some physicians recommended asymptomatic patients to receive...
Table 5
Univariable and multivariate Cox regression analysis of treatment-free survival and overall survival in training cohort.

| Characteristic | Treatment-free survival Univariate analysis | Multivariate analysis | Overall survival Univariate analysis | Multivariate analysis |
|----------------|-------------------------------------------|----------------------|-------------------------------------|----------------------|
|                | HR (95% CI)                               | P value              | HR (95% CI)                         | P value              |
| Age > 65 years | 1.22 (0.87-1.71)                          | 0.247                |                                    |                      |
| Rai I-IV or Binet B/C | 6.15 (2.51-15.05)                  | <0.001               | 4.58 (1.64-12.81)                   | 0.004                |
| TK-1 > ULN     | 1.09 (0.67-1.77)                          | 0.731                |                                    |                      |
| β2-MG > 3.5 mg/L| 3.30 (2.32-4.69)                          | <0.001               | 3.16 (2.05-4.88)                    | <0.001               |
| Unmutated IGHV | 2.06 (1.44-2.95)                          | <0.001               |                                    |                      |
| NOTCH1 mutation| 1.45 (0.83-2.52)                          | 0.194                |                                    |                      |
| MYD88 mutation | 1.07 (0.54-2.11)                          | 0.851                |                                    |                      |
| SF3B1 mutation | 1.54 (0.75-3.17)                          | 0.240                |                                    |                      |
| TP53 disruption | 1.74 (1.12-2.70)                         | 0.014                |                                    |                      |
| Del(11q)       | 1.52 (0.66-2.98)                          | 0.065                |                                    |                      |

Abbreviations: β2-MG: β2-microglobulin; CI: confidence interval; HR: hazard ratio; IGHV: immunoglobulin heavy variable-region gene; MYD88: myeloid differentiation factor 88; SF3B1: splicing factor 3b subunit 1; TK-1: thymidine kinase 1; TP53: tumor protein 53; ULN: upper limit of normal.
therapy, which would shorten patients’ TFS and interfere with the accuracy of the analysis. While for OS, del(11q) was an independent prognostic factor.

Several prognostic nomograms were constructed to predict the survival of CLL patients in previous researches. Wierda et al. [13] designed a prognostic nomogram consisting of age, sex, β2-MG concentration, ALC, Rai stage, and lymph nodes groups. This nomogram could effectively estimate the OS of untreated CLL patients according to the index score. In 2009, Wierda et al. [14] updated some prognostic factors and constructed two other prognostic nomograms. One included age, β2-MG concentration as well as treatment, and the other consisted of age, β2-MG concentration as well as alkaline phosphatase concentration. These two models also showed excellent performance for the prediction of OS. However, these three nomograms only took clinical and laboratory examination data into consideration and ignored the importance of cytogenetic as well as molecular aberrations. A new nomogram, which included the largest lymph node size in the neck, LDH concentration, number of lymph node sites in involved and FISH, was established again in 2011 to accurately predict TFS [16]. Nonetheless, this model excluded some classical prognostic factors such as age, β2-MG concentration, stage, and molecular aberrations. Therefore, we constructed two new nomograms to respectively predict the TFS and OS of untreated CLL patients in this research. The selection standards of factors involved in nomograms were based on the results of univariate Cox regression analysis. The good performance of these two nomograms was verified by calculating the C-index as well as the AUC of ROC curves, drawing calibration plots, and conducting internal validation. Besides, Kaplan-Meier curves showed that these two nomograms could stratify the prognosis of patients completely according to the prognostic points.

In summary, we retrospectively analyzed the prevalence, association, and outcomes of del(11q) in 352 previously untreated and 99 relapsed/refractory CLL patients in this study. Moreover, we established prognostic nomograms including del(11q) based on our data and validated their performance. Admittedly, there were some limitations in our study, such as small sample size, short follow-up time and lack of some patients’ information. All these limitations would lead to bias and

Fig. 4. The calibration curves for predicting patient treatment-free survival and overall survival at 3-year and 5-year in the training (A) and validation cohort (B). X axis was predicted probability of survival and Y axis was corresponding actual probability of survival.
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Yi-Xin Zou: Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization. Ha-Ning Tang: Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization. Jing Zhang: Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization. Xiao-Lu Tang: Resources, Data curation. Shu-Chao Qin: Resources, Data curation. Yi Xia: Resources, Data curation. Hua-Yuan Zhu: Resources, Data curation. Chun Qiao: Formal analysis. Li Wang: Formal analysis. Investigation. Lei Fan: Formal analysis, Investigation, Writing – review & editing. Wei Xu: Formal analysis, Investigation, Writing – review & editing. Jian-Yong Li: Conceptualization, Methodology, Validation, Writing – review & editing. Supervision. Yi Miao: Conceptualization, Methodology, Validation, Writing – review & editing. Supervision.

Declaration of Competing Interest

The authors declare no conflict of interest.

Authors’ contributions

Y.M. and J.Y.L. designed the research study. Y.X.Z., H.N.T., J.Z., X.L.T., S.C.Q., Y.X. and H.Y.Z. performed the research. Y.X.Z., H.N.T., J.Z., C.Q., L.W., L.F. and W.X. analyzed the data. Y.X.Z., H.N.T. and J.Z. wrote the paper. L.F., W.X., J.Y.L. and Y.M. revised the manuscript and finalized the last version of the article. All authors checked and approved the submitted version.

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Fig. 5. Kaplan-Meier curves of survival for patients with different risk levels. (A) Kaplan-Meier curves of treatment-free survival and overall survival in training cohort. (B) Kaplan-Meier curves of treatment-free survival and overall survival in validation cohort.

should be taken into consideration in further studies. More researches are needed to further confirm the role of del(11q) in CLL patients.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tranon.2021.101176.

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