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A Multi-Gene Expression-Based Prognostic Model for Risk Stratification in Chronic Lymphocytic Leukemia (CLL)

Anantharamanan Rajamani[1], Henrik Himmelreich[1], Florian Simon[1], Jasmin Schulz[1], Sandra Robrecht[1], Can Zhang[1], Eugen Tausch[2], Christof Schneider[2], Matthias Ritgen[3], Karl Anton Kreuzer[1], Brenda Chyla[4], Hyun Yong Jin[5], Yanwen Jiang[5], John F Seymour[6], Arnon Kater[7], Stephan Stilgenbauer[2], Barbara Eichhorst[1], Michael Hallek[1],Kirsten Fischer[1], Othman Al-Sawaf[1]

[1]University of Cologne, Faculty of Medicine and University Hospital Cologne, Department I of Internal Medicine, Köln, Germany, [2]Department III of Internal Medicine, Ulm University, Ulm, Germany, [3]Department II of Internal Medicine, University of Schleswig Holstein, Kiel, Germany, [4]AbbVie Inc, Illinois, United States, [5]Genentech Inc, San Francisco, United States, [6]Peter MacCallum Cancer Centre, University of Melbourne, Melbourne, Australia, [7]Amsterdam University Medical Centers, Cancer Center Amsterdam, University of Amsterdam, Amsterdam, Netherlands

OBJECTIVES

- Current prognostic features, such as deletion 17 (del17p)/*TP53* or IGHV status, only partly explain high and low-risk disease groups in CLL, as some subgroups of patients with genetic high-risk features still experience favorable outcomes, and patients with low-risk disease can still experience early disease progression.
- To address these limitations, we developed a composite gene signature-based risk stratification model leveraging transcriptomic data from RNA-Seq of over 1,100 patients treated with chemotherapy or targeted therapy.

CONCLUSIONS

- The multi-gene prognostic model reproducibly identifies clinically relevant subgroups with distinct prognoses, facilitating refined risk stratification in both frontline and relapsed CLL.

INTRODUCTION

- Aberrant gene expression impacts disease biology and correlates with patient outcomes in CLL, but expression-based prognostic models have had limited clinical applicability to date.

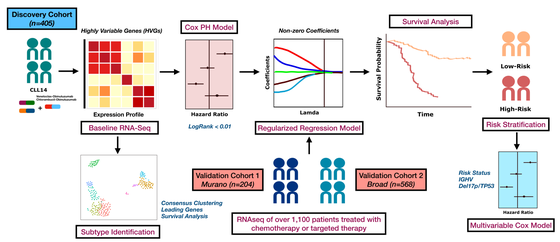
METHODS

- Transcriptomic profiles of 405 CLL patients with available samples from the first-line phase 3 CLL14 trial (Ven-Obi vs. Clb-Obi) were used to train a prognostic model for progression-free survival (PFS).
- Univariable Cox proportional hazards regression and cross-validated LASSO models were applied subsequently to highly variable genes (HVGs) to identify those associated with PFS.
- A risk score was derived by applying nonzero model coefficients to normalized expression values.
- Risk status was assessed using a multivariable Cox model adjusted for genetic markers.
- The model was subsequently validated in cohorts from the *MURANO* relapse trial (BR vs. Ven-Rit; n=204) and the *Broad* (cllmap.org; n=568) dataset.

RESULTS

- A total of 107 of 251 HVGs were significantly associated with PFS (p<0.01).
- An eight-gene (*BCAT1, LHFPL6, C10orf10, ZNF471, PLD1, DNAH14, KLK4*, and *IL15*) derived risk score stratified patients into high-risk (n=251) and low-risk (n=154) classes (Fig 2,3).
- Risk status correlated with PFS (hazard ratio [HR]=3.12 [95% CI 2.05–4.75], p<0.001), independent of IGHV mutation and del17p/*TP53* alterations (Fig 4).
- Both high-risk IGHV-mutated and unmutated patients had shorter PFS compared to their respective low-risk counterparts (HR=3.68 [95% CI 2.16–6.29], p<0.001 for IGHV-mutated; HR=0.40 [95% CI 0.22–0.73], p=0.002 for IGHV-unmutated, comparing low- vs. high-risk) (Fig 5).
- Among del17p/*TP53* subgroups, low-risk patients with or without del17p/*TP53* exhibited longer PFS than high-risk patients (HR=0.10 [95% CI 0.023–0.44], p=0.002 for mutated; HR=3.02 [95% CI 2.20–4.13], p<0.001 for wild-type, comparing high- vs. low-risk) (Fig 5).
- C-statistics of 0.62 and 0.63 from the two validation cohorts supported the model's prognostic performance.

Figure 1. Prognostic Model for Risk Stratification



Analysis Workflow

Figure 2. Gene Expression Profile of Top Features

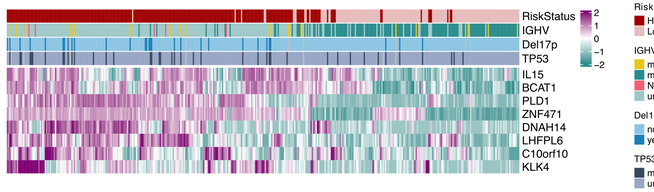


Figure 3. Progression Free Survival

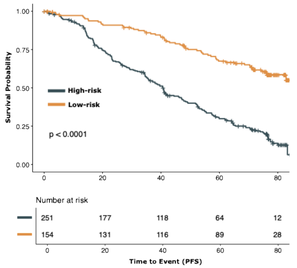
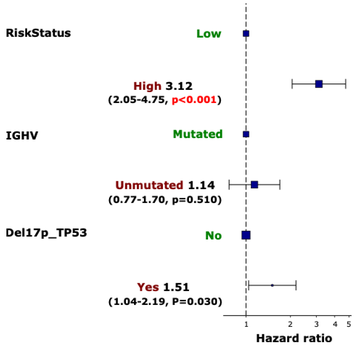


Figure 4. Multivariable Analysis



Risk-status correlated with PFS independent of IGHV mutation and del17p/*TP53* alterations

Figure 5. Risk Status with IGHV and Del17p/*TP53*

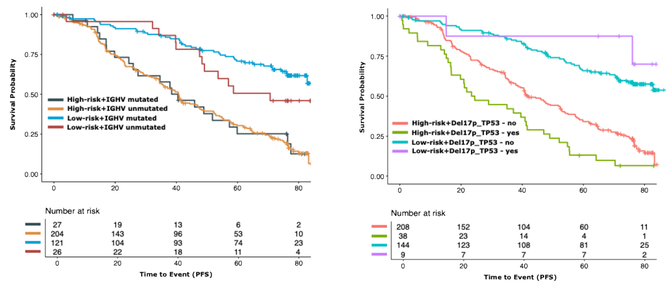


Figure 6. Validation Cohorts: *Murano* and *Broad*

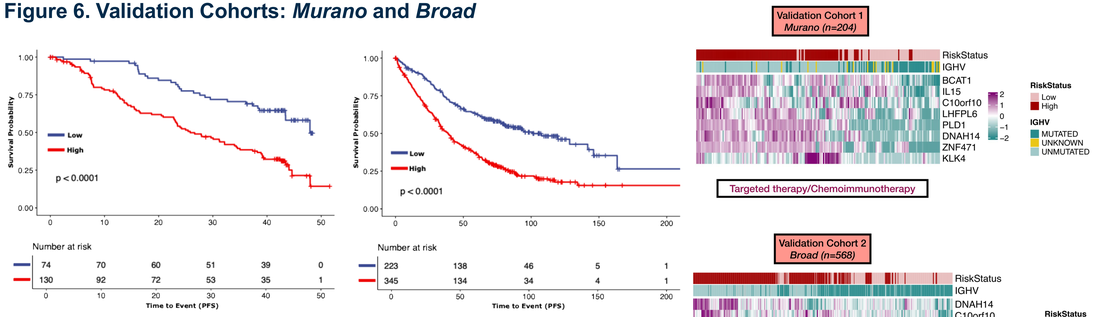
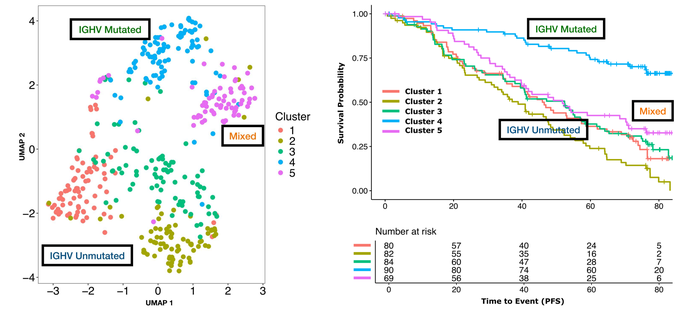


Figure 7. CLL14: Transcriptional Subtypes



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for correspondence: othman.al-sawaf@uk-koeln.de, anantharamanan.rajamani@uk-koeln.de