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ORIGINAL ARTICLE

A Peripheral Blood Circular Ribonucleic Acid-Based Nomogram for Risk Stratification in Chronic Myeloid Leukemia

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ABSTRACT

Background: **Current prognostic tools for chronic myeloid leukemia (CML) rely primarily on clinical parameters and lack reliable molecular biomarkers for dynamic risk assessment. Circular RNAs (circRNAs) have emerged as promising liquid biopsy biomarkers because of their stability in peripheral blood. However, their prognostic value in CML remains underexplored.**
Methods: **In this retrospective cohort study, peripheral blood samples were collected from 417 patients newly diagnosed with CML and 45 healthy controls. Differentially expressed circRNAs were identified by high-throughput sequencing and validated by quantitative real-time PCR. The patients were randomly divided into training (n = 292) and validation (n = 125) cohorts. A prognostic nomogram incorporating circRNAs and clinical variables was developed using multivariate Cox regression, with model performance assessed using the area under the curve (AUC), calibration, and decision curve analysis.**
Results: **Two circRNAs (hsa_circ_0001523 and hsa_circ_0000095) were significantly dysregulated in patients with advanced-phase CML ($p < 0.0001$). The nomogram combining the expression patterns of two circRNAs with basophil%, blast%, and hemoglobin levels achieved an AUC of 0.920 (95% CI: 0.873 - 0.968) for survival prediction. High-risk patients (score > 122.5) had a significantly shorter median survival (22 vs. 83 months, $p < 0.0001$).**
Conclusions: **This circRNA-based nomogram is a clinically applicable, non-invasive tool for dynamic risk stratification in CML. The integration of molecular and hematological markers may guide personalized therapy decisions and address the limitations of existing prognostic systems.**
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Supplementary Data

Table S1. Baseline clinical characteristics of the training and validation set.

Variable	Training set (n = 292)	Validation set (n = 125)	p-value
Age (years)			
≤ 34	46 (15.8%)	19 (15.2%)	0.724
35 - 58	158 (54.1%)	69 (55.2%)	
59 - 89	88 (30.1%)	37 (29.6%)	
Gender			
Male	160 (54.8%)	67 (53.6%)	0.492
Female	132 (45.2%)	58 (46.4%)	
CML Phase			
Chronic Phase	242 (82.9%)	97 (77.6%)	0.137
Advanced Phase	50 (17.1%)	28 (22.4%)	
hsa_circ_0000095 Expression			
≤ 0.69	28 (9.6%)	14 (11.2%)	0.267
0.69 - 2.85	60 (20.5%)	22 (17.6%)	
> 2.85	204 (69.9%)	89 (71.2%)	
hsa_circ_0001523 Expression			
≤ 2.10	200 (68.5%)	86 (68.8%)	0.832
2.10 - 5.99	60 (20.5%)	24 (19.2%)	
> 5.99	32 (11%)	15 (12%)	
WBC (10^9/L)			
≤ 60.22	186 (63.7%)	79 (63.2%)	0.878
60.22 - 176.31	66 (22.6%)	29 (23.2%)	
> 176.31	40 (13.7%)	17 (13.6%)	
Neutrophil%			
≤ 0.46	60 (20.6%)	24 (19.2%)	0.617
0.46 - 0.63	132 (45.2%)	55 (44%)	
> 0.63	100 (34.2%)	46 (36.8%)	
Eosinophil%			
≤ 0.02	154 (52.7%)	68 (54.4%)	0.625
0.02 - 0.03	58 (19.9%)	24 (19.2%)	
> 0.03	80 (27.4%)	33 (26.4%)	
Basophil%			
≤ 0.01	152 (52.1%)	63 (50.4%)	0.691
0.01 - 0.04	64 (21.9%)	30 (24%)	
> 0.04	76 (26%)	32 (25.6%)	
Blast%			
0	184 (63%)	79 (63.2%)	0.905
0 - 0.03	64 (21.9%)	28 (22.4%)	
> 0.03	44 (15.1%)	18 (14.4%)	
Hemoglobin (g/L)			
≤ 85	32 (11%)	15 (12%)	0.827
85 - 108	100 (34.2%)	41 (32.8%)	
> 108	160 (54.8%)	69 (55.2%)	

Table S1. Baseline clinical characteristics of the training and validation set (continued).

Variable	Training set (n = 292)	Validation set (n = 125)	p-value
RBC (10^{12}/L)			
≤ 2.79	36 (12.3%)	16 (12.8%)	0.633
2.79 - 3.55	76 (26%)	33 (26.4%)	
> 3.55	180 (61.7%)	76 (60.8%)	
RDW-CV (%)			
≤ 15.7	176 (60.3%)	73 (58.4%)	0.484
15.7 - 18.2	68 (23.3%)	31 (24.8%)	
> 18.2	48 (16.4%)	21 (16.8%)	
PLT (10^9/L)			
≤ 207	130 (44.5%)	52 (41.6%)	0.527
207 - 290	70 (24%)	34 (27.2%)	
> 290	92 (31.5%)	39 (31.2%)	
Splenomegaly	140 (47.9%)	60 (48%)	0.885

Table S2. Primer sequences used for qPCR.

Gene	Primer type	Primer sequences（5′′-3′′）
hsa_circ_0001523	F	GTGTGGCATGAAACAGAAGAAGGTT
	R	GTAGAATCTGAGGCGTGAGACTGCT
hsa_circ_0000095	F	GCATACTACCTTGTACTGGTTGAAG
	R	AACCTGGAGAAACTTTTGCTGA
GAPDH	F	GAGTCAACGGATTTGGTCGT
	R	TTGATTTTGGAGGGATCTCG

F: forward primer, R: reverse primer.

Table S3. Univariate and multivariate Cox regression analyses of prognostic factors in the training set.

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (years)				
≤ 34	1			
35 - 58	0.275 (0.131 - 1.182)	0.946		
59 - 89	0.252 (0.093 - 0.684)	0.007		
Sex				
Male	1			
Female	1.003 (0.529 - 1.901)	0.993		
CML Phase				
Chronic Phase	1			
Advanced Phase	3.619 (1.275 - 6.449)	< 0.001		

Table S3. Univariate and multivariate Cox regression analyses of prognostic factors in the training set (continued).

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
hsa_circ_0000095 Expression				
> 2.85	1			
0.69 - 2.85	5.105 (0.092 - 10.906)	< 0.001	1.095 (0.681 - 2.116)	0.413
≤ 0.69	5.573 (0.099 - 10.135)	< 0.001	5.469 (0.912 - 11.891)	0.005
hsa_circ_0001523 Expression				
≤ 2.10	1			
2.10 - 5.99	1.039 (0.460 - 2.173)	< 0.001	1.103 (0.176 - 6.899)	0.917
> 5.99	3.209 (0.131 - 7.657)	< 0.001	3.355 (1.561 - 6.950)	0.027
WBC (10^9/L)				
≤ 60.22	1			
60.22 - 176.31	1.411 (0.889 - 1.853)	< 0.001		
> 176.31	1.816 (1.049 - 2.909)	< 0.001		
Eosinophil%				
≤ 0.02	1			
0.02 - 0.03	1.662 (0.727 - 3.799)	0.229		
> 0.03	2.045 (0.985 - 4.245)	0.055		
Basophil%				
≤ 0.01	1			
0.01 - 0.04	1.839 (1.472 - 2.792)	< 0.001	0.826 (0.601 - 2.255)	0.031
> 0.04	1.374 (0.853 - 2.325)	< 0.001	1.031	0.016
Blast%				
0	1			
0 - 0.03	4.893 (2.130 - 7.269)	< 0.001	3.059 (1.734 - 5.865)	0.015
> 0.03	5.375 (3.866 - 8.458)	< 0.001	6.655 (1.159 - 21.218)	0.004
Hemoglobin (g/L)				
85 - 108	1			
> 108	0.332 (0.162 - 0.682)	0.003	0.576 (0.025 - 1.285)	0.047
≤ 85	0.069 (0.027 - 0.174)	< 0.001	0.738 (0.052 - 1.553)	0.023
RDW-CV (%)				
≤ 15.7	1			
15.7 - 18.2	1.725 (0.887 - 3.597)	< 0.001		
> 18.2	1.452 (0.889 - 2.661)	< 0.001		
PLT (10^9/L)				
≤ 207	1			
207 - 290	1.038 (0.384 - 2.807)	0.942		
> 290	3.335 (1.606 - 6.925)	0.001		
Splenomegaly				
No	1			
Yes	1.402 (1.261 - 1.559)	< 0.001		

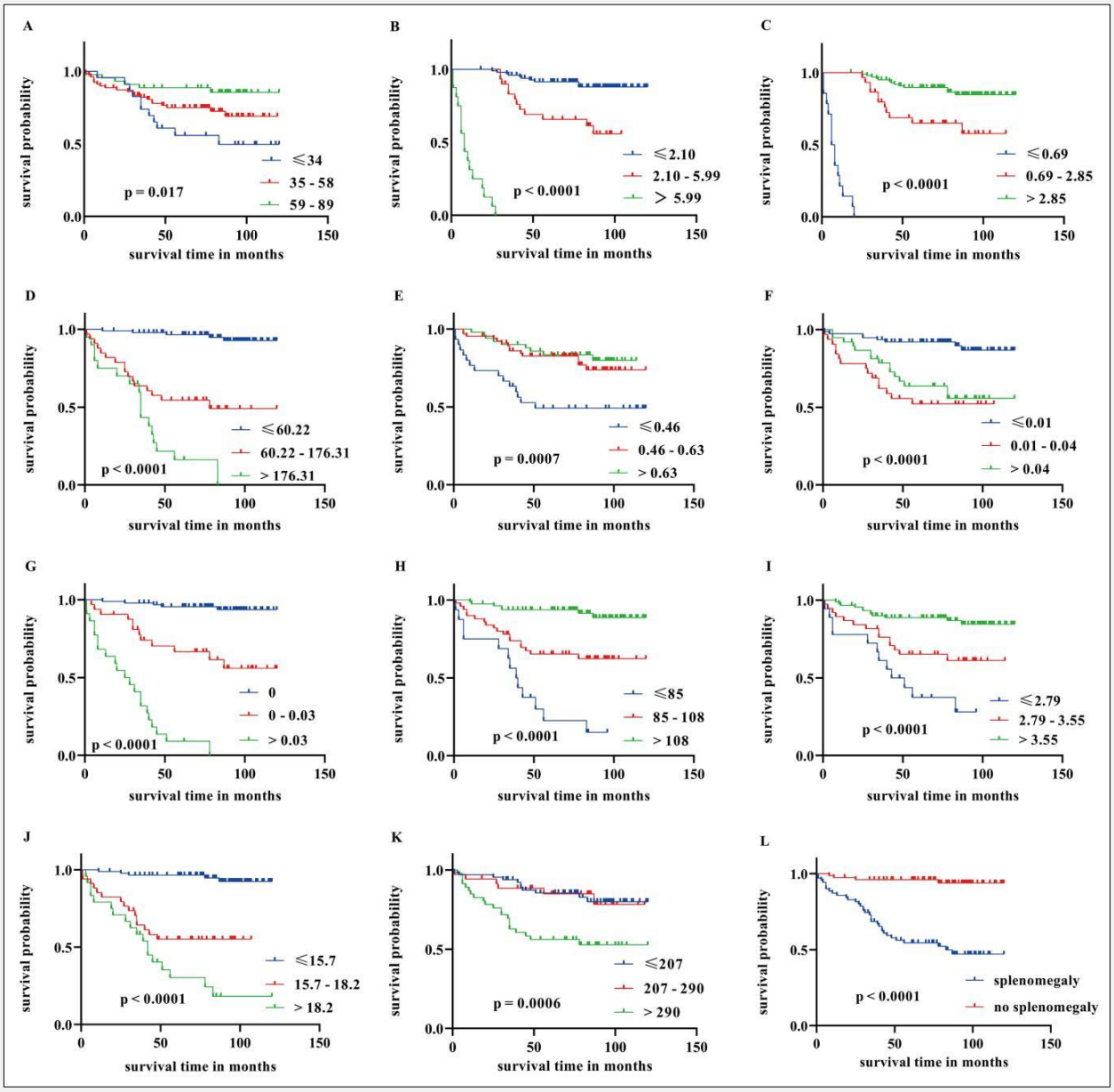


Figure 1. Kaplan-Meier survival curves for different prognostic factors in CML patients.

A: Survival curves by age, B: Survival curves by hsa_circ_0001523 expression, C: Survival curves by hsa_circ_0000095 expression, D: Survival curves by WBC, E: Survival curves by neutrophil%, F: Survival curves by basophil%, G: Survival curves by blast%, H: Survival curves by hemoglobin, I: Survival curves by RBC, J: Survival curves by RDW-CV, K: Survival curves by PLT, L: Survival curves by splenomegaly. The x-axis represents survival time, and the y-axis represents survival probability.