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Identification of promising prognostic genes for relapsed acute lymphoblastic leukemia

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ABSTRACT

Purpose: The present study aimed to identify the molecular mechanism of acute lymphoblastic leukemia (ALL), and explore valuable prognostic biomarkers for relapsed ALL.
Methods: Gene expression dataset including 59 samples from ALL survivals without recurrence (good group) and 114 samples from dead ALL patients died of recurrence (poor group) was downloaded from TCGA database. The differentially expressed genes (DEGs) were identified between good and poor groups, followed by pathway and functional enrichment analyses. Subsequently, logistic regression model and survival analysis were performed.
Results: In total, 637 up- and 578 down-regulated DEGs were revealed between good and poor groups. These DEGs were mainly enriched in functions including transcription and pathways like focal adhesion. Genes including alpha-protein kinase 1 (*ALPK*1), zinc finger protein 695 (*ZNF695*), actinin alpha 4 (*ACTN4*), calreticulin (*CALR*), and F-Box and leucine rich repeat protein 5 (*FBXL5*) were outstanding in survival analysis.
Conclusion: Transcription and focal adhesion might play important roles in ALL progression. Furthermore, genes including *ALPK1*, *ZNF695*, *ACTN4*, *CALR*, and *FBXL5* might be novel prognostic genes for relapsed ALL.

1. Introduction

Acute lymphoblastic leukemia (ALL) is characterized by the development of large numbers of immature lymphocytes [1,2]. It is estimated that ALL affects 876,000 people and results in 111,000 deaths in a year [3]. Even though most patients with ALL can be cured, the prognosis is dismal due to disease relapse after treatment [4]. Thus, exploration of effective prognostic biomarkers is pivotal for improve the clinical outcomes of ALL.

A previous study has shown that the different expression levels of certain genes are associated with relatively poorer outcomes in patients with ALL [5]. Preferentially expressed antigen of melanoma (*PRAME*) that is found dysregulated in ALL is considered as a target for immunotherapy for the monitoring the outcome of ALL [6]. Jiang et al. showed that BCL2 Like 11 (*BIM*) was a potential prognostic biomarker for early prednisolone response in pediatric ALL [7]. Although multidrug resistance protein 1 (MDR1) is commonly used as anti-cancer drugs and contributes to multi-drug resistance phenotype in adult ALL, MDR1 is not a useful prognosticator in adult ALL [8]. Thus, the relationship between the existing differentially expressed genes (DEGs) and ALL prognosis is still controversial. Actually, the regulation of DEGs in the progression of ALL is typically based on certain biological functions or pathways. Mullighan et al. indicated that the CREB Binding Protein (CREBBP) played a vital role in ALL process via Ras signaling pathway and histone modification function [9]. Nevertheless, the prognostic biomarker for relapsed ALL is lacking. Thus, identification of new biomarkers for ALL prognosis is urgently needed.

In the present study, a gene expression profile including 59 samples from ALL survivals without recurrence and 114 samples from dead ALL patients died of recurrence were downloaded from the cancer genome atlas (TCGA) database. The DEGs were revealed between two sample groups. Then, the pathway and functions enriched by DEGs were investigated. Finally, logistic regression (LR) and survival analysis was conducted to identify potential biomarkers for relapsed ALL. We aimed to identify the molecular mechanism of ALL, and explore valuable prognostic biomarkers for relapsed ALL.

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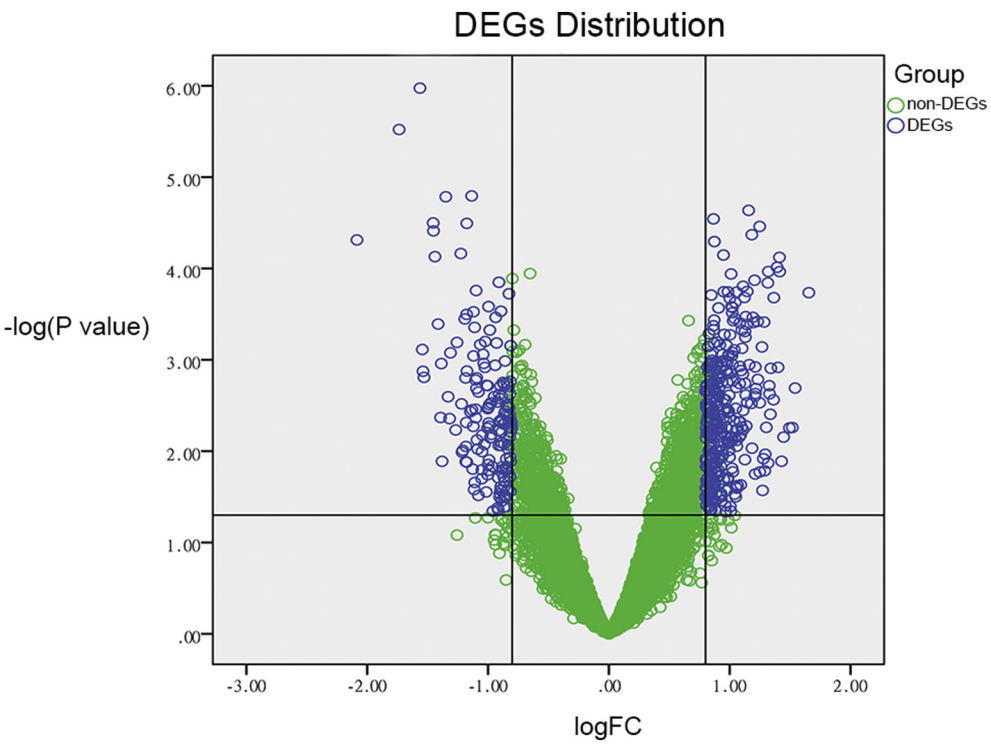

Fig. 1. The distribution of differentially expressed genes. The horizontal axis represents $\log_2|FC|$ and the vertical axis represents negative denary logarithm of *P*-value. Blue nodes represent the differentially expressed genes and green nodes represent the non-differentially expressed genes. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

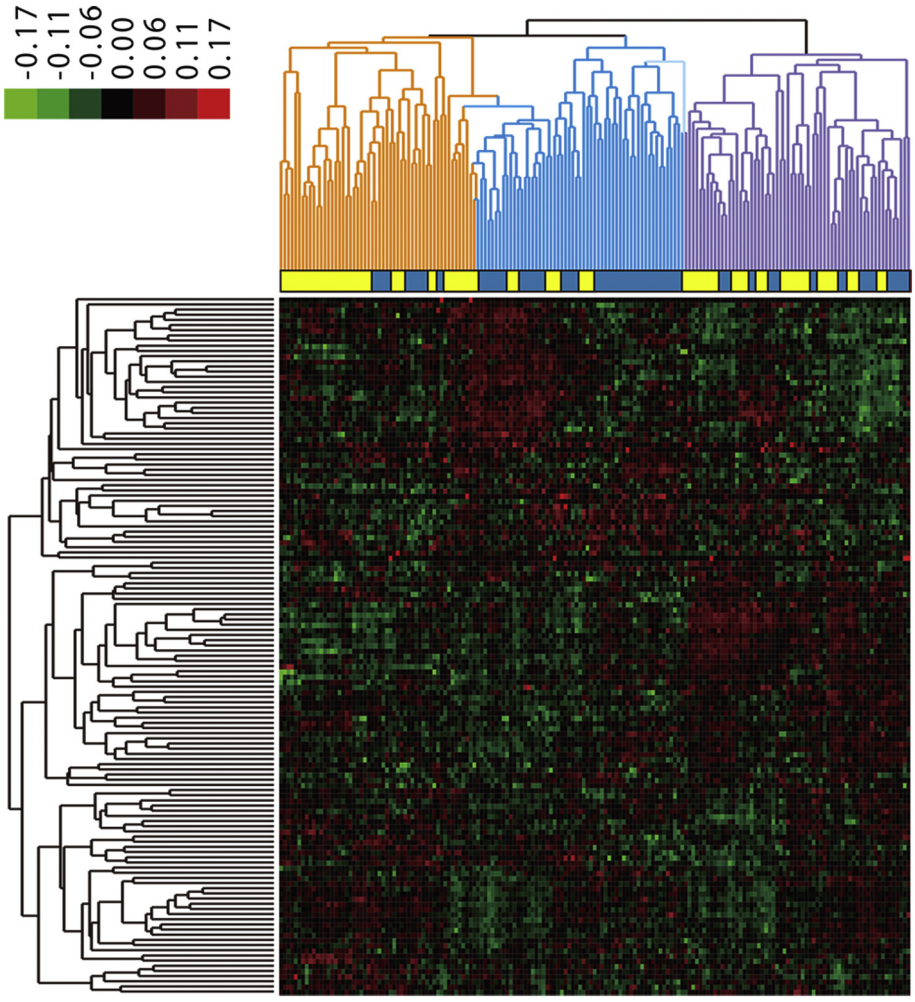

Fig. 2. Hierarchical clustering analysis of the 59 survival samples and 114 carcass sample. For the horizontal axis, yellow represents survival samples and blue represents carcass sample. Red represents high expression level and green represents low expression level. The 173 samples were divided into three clusters represented by orange, blue and purple cluster, respectively. The orange and purple clusters were mainly dominated by good group samples (yellow), while the blue cluster was mainly dominated by poor group samples (blue). Samples with similar gene expression profiles were hierarchically clustered into the same group, indicating that the screened DEGs can well distinguish different samples. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

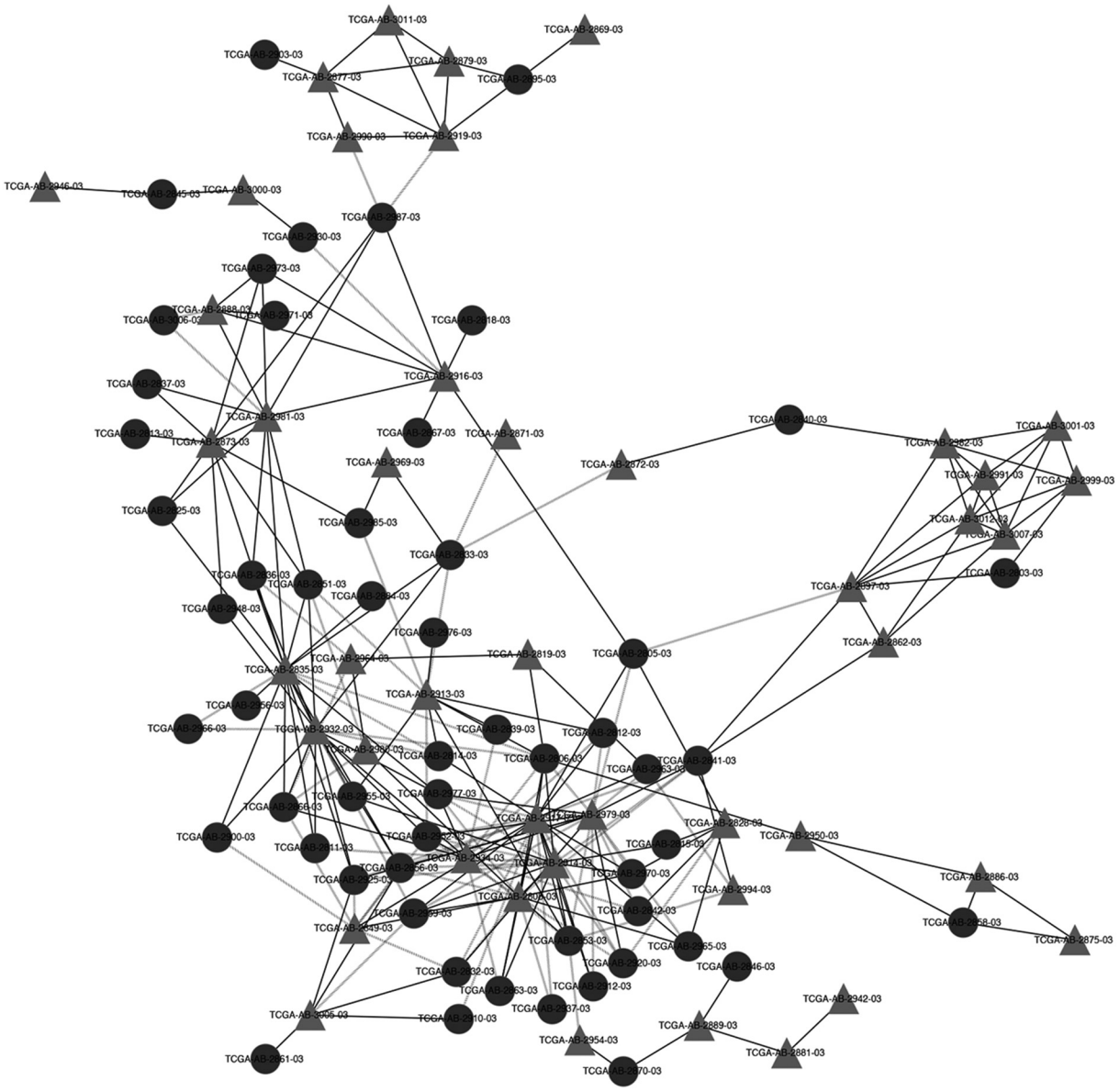

Fig. 3. Correlated network analysis of the 59 survival samples and 114 carcass sample. Triangle nodes with light colored represent survival samples and circle nodes with dark node represent carcass sample. The solid lines between nodes represent samples with the correlation coefficient > 0.5. The dashed lines between nodes represent samples with the correlation coefficient < -0.5.

2. Material and methods

2.1. Microarray data

The gene expression dataset including 59 samples from ALL survivals without recurrence (good group) and 114 samples from dead ALL patients died of recurrence (poor group) were downloaded from TCGA database (https://cancergenome.nih.gov/). The platform used here was TCGA_LAML_exp_HiSeqV2_PANCAN-2014-08-22.

2.2. Data preprocessing and DEGs screening

The normalization of original data was conducted using *Z*-score transformation [10,11]. Subsequently, expression matrix was obtained, in which each row represented expression gene, and each column represented samples. Next, the DEGs between good and poor groups were identified using limma package of R/Bioconductor with multiple testing correction based on Benjamini and Hochberg (BH) [12] method. We defined *P*-value < 0.05 and $\log_2|\text{fold change (FC)}| > 1$ as the statistical thresholds. To verify whether DEGs could be used for distinguishing samples between good and poor groups, hierarchical clustering [13] was then performed on 173 samples based on the screened DEGs, followed by visualization by heatmap using pheatmap package [14] of R/Bioconductor.

2.3. Correlation network construction

According to gene expression level, the correlation between samples in good and poor groups was evaluated using Pearson correlation coefficient [15]. Network visualization was performed by using Cytoscape [16] and $|\text{correlation coefficient}| > 0.5$ was set as the threshold.

2.4. Functional enrichment analysis of DEGs

Gene Ontology (GO) functional annotation as well as the Kyoto Encyclopedia of Gene and Genomes (KEGG) pathway enrichment

Table 1
The result of the most outstanding GO functional analysis assembled with differentially expressed genes.

	Category	GO term	Count	*P*-value
Up-regulation	BP	GO:0002474 antigen processing and presentation via MHC class I	29	9.15E−58
		GO:0044419 interspecies interaction between organisms	35	7.23E−51
		GO:0019882 antigen processing and presentation	29	2.23E−49
	CC	GO:0044419 interspecies interaction between organisms	35	7.23E−51
		GO:0005737 cytoplasm	174	2.86E−139
		GO:0016020 membrane	167	3.35E−129
	MF	GO:0019882 antigen processing and presentation	29	2.23E−49
		GO:0000166 nucleotide binding	67	1.78E−60
		GO:0008270 zinc ion binding	66	1.61E−55
Down-regulation	BP	GO:0006350 transcription	63	1.29E−55
		GO:0006355 regulation of transcription, DNA-dependent	60	4.50E−54
		GO:0019941 modification-dependent protein catabolism	25	3.88E−29
	CC	GO:0005634 nucleus	174	3.86E−184
		GO:0005737 cytoplasm	155	7.91E−134
		GO:0016020 membrane	81	4.38E−46
	MF	GO:0005515 protein binding	152	6.85E−127
		GO:0008270 zinc ion binding	85	5.92E−90
		GO:0046872 metal ion binding	84	3.28E−68

Notes: GO, gene ontology; Count, the number of genes assembled in target function; BP, biological process; CC, cellular component; MF, molecular function.

Table 2
The result of KEGG pathway analysis enriched by differentially expressed genes (top 5 listed).

	Pathway	Count	*P*-value
Up-regulation	Focal adhesion	10	9.48E−06
	Chronic myeloid leukemia	6	3.90E−05
	Phosphatidylinositol signaling system	6	4.20E−05
	Leukocyte transendothelial migration	7	7.18E−05
	Prostate cancer	6	9.58E−05
Down-regulation	Ubiquitin mediated proteolysis	13	9.80E−12
	Small cell lung cancer	7	1.66E−06
	Wnt signaling pathway	8	8.00E−06
	Cell cycle	7	1.44E−05
	Prostate cancer	6	2.59E−05

Notes: KEGG, Kyoto Encyclopedia of Gene and Genomes; Count, the number of genes enriched in target pathway.

analysis were performed based on molecule annotation system (MAS) (version: 3) [17]. GO functional categories included molecular function (MF), biological process (BP), and cellular component (CC) [18]. $P < 0.05$ was set as the threshold value.

2.5. LR model analysis

In order to identify prognostic biomarkers for ALL, LR model [19,20] was used to identify the significant feature genes from DEGs enriched in GO term. The classification was performed on patients with different prognosis in two groups. All genes with $P < 0.05$ were regarded as significant feature genes. Then, the discrimination accuracy was calculated according to significant feature genes. In terms of genes, all samples were classified into two groups (good and poor) according to the sample label. LR model was implemented in SPSS 19.0. $P < 0.05$ was set as the threshold value.

2.6. Survival analysis

To confirm whether significant feature genes could be used as prognostic biomarkers for ALL, based on the information of cbioportal database [21], survival analysis for these 179 samples from TCGA database was performed to evaluate the overall survival and disease-free survival difference. The results are displayed as Kaplan-Meier plots with *P* values from a log-rank test.

3. Results

3.1. DEGs screening

With $P < 0.05$ and $\log_2|FC| > 1$, a total of 1215 DEGs (637 up-regulated and 578 down-regulated) were identified between good and poor groups (Fig. 1). The results showed that DEGs (blue points) and non-DEGs (green points) were distinctly separated in volcano plot. The results of hierarchical clustering analysis showed these 173 samples were divided into orange cluster, blue cluster and purple cluster. The orange and purple clusters were mainly dominated by samples in good group (yellow), while the blue cluster was mainly dominated by samples in poor group (blue). As showed in Fig. 2, samples with similar gene expression pattern were hierarchically clustered into the same group, indicating that the screened DEGs can well distinguish different samples.

3.2. Correlation network analysis

There were 100 nodes and 246 edges in current correlation network constructed by samples (Fig. 3). The results showed that there were positive correlations among the patients with the same prognosis, or negative correlations between the patients with different prognosis. The results indicated that the DEGs expression levels in ALL patients with two different prognostic phenotypes were significant different. However, we also found that there were positive correlations between some patients with different prognostic phenotypes, or negative correlations between patients with the same prognostic phenotypes, which might be caused by individual differences of samples or heterogeneity of genetic background.

3.3. Functional enrichment analysis

The results showed that the up-regulated DEGs were mainly assembled in GO functions like antigen processing and presentation via MHC class I (BP, GO:0002474, $P = 9.15E-58$), nucleus (CC, GO:0005634, $P = 2.05E-190$) and protein binding (MF, GO:0005515, $P = 1.05E-169$). Meanwhile, the down-regulated DEGs were mainly assembled in GO functions including transcription (BP, GO:0006350, $P = 1.29E-55$), nucleus (CC, GO:0005634, $P = 3.86E-184$) and protein binding (MF, GO:0005515, $P = 6.85E-127$). The most outstanding GO functions assembled with DEGs in BP, CC and MF were listed in Table 1.

The results showed that the up-regulated DEGs were mainly

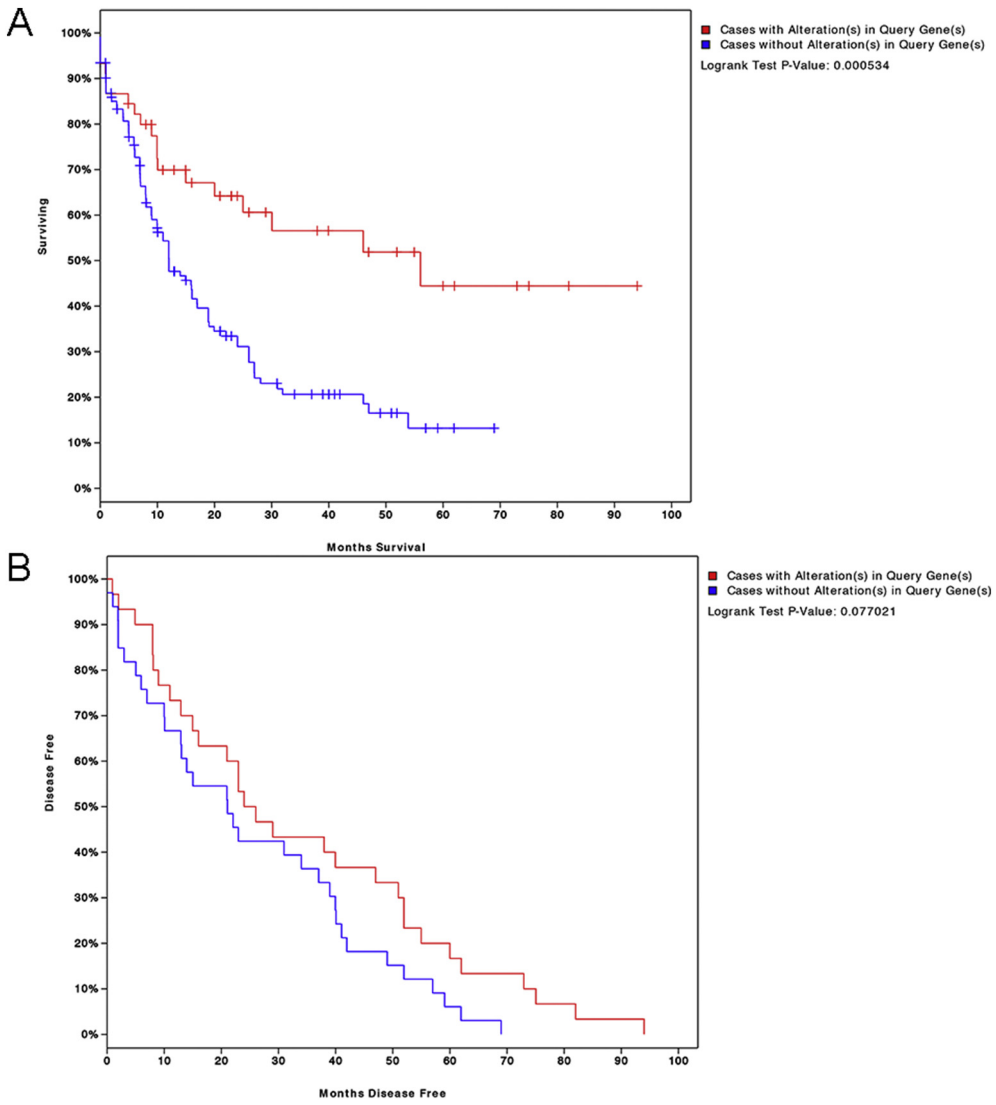

Fig. 4. The results of survival analysis in current study. A, The result of overall survival analysis. B, The result of disease-free survival analysis. The horizontal axis represents survival time and the vertical axis represents the proportion of patients. The red curved line represents patients with alteration in genes ALPK1, ZNF695, ACTN4, CALR and FBXL5. The blue curved line represents patients without alterations in the five genes. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

enriched in KEGG pathways like focal adhesion ($P = 9.48E-06$), chronic myeloid leukemia ($P = 3.90E-05$) and phosphatidylinositol signaling system ($P = 4.20E-05$). Meanwhile, the down-regulated DEGs were mainly enriched in KEGG pathways including ubiquitin mediated proteolysis ($P = 9.80E-12$), small cell lung cancer ($P = 1.66E-06$) and Wnt signaling pathway ($P = 8.00E-06$). The top 3 outstanding pathways enriched by up- and down-regulated DEGs were listed in Table 2.

3.4. LR model and survival analysis

LR model was used to identify the significant feature genes from 254 DEGs enriched in the GO terms. With $P < 0.05$, a total of 13 significant feature genes including alpha-protein kinase 1 (*ALPK*1), ubiquitin conjugating enzyme E2 J1 (*UBE2J1*), zinc finger protein 695 (*ZNF695*), actinin alpha 4 (*ACTN4*), CDC like kinase 3 (*CLK3*), kallikrein B1 (*KLKB1*), calreticulin (*CALR*), mediator complex subunit 12 (*MED12*), N-acylsphingosine amidohydrolase 2 (*ASAH2*), phosphoinositide-3-kinase regulatory subunit 5 (*PIK3R5*), F-Box and leucine rich repeat protein 5 (*FBXL5*), C-X-C motif chemokine receptor 6 (*CXCR6*) and dynein axonemal heavy chain 10 (*DNAH10*) were identified. The classification results showed a significantly better survival in patients without differential expression changes in these genes ($P = 0.0005$). However, the analysis illustrated no significant difference in disease-free survival ($P = 0.07$).

The survival analysis showed that a gene combination, including *ALPK1*, *ZNF695*, *ACTN4*, *CALR*, and *FBXL5* had the highest contribution. The results of overall survival analysis showed that these 5 genes could significantly distinguish patients with different survival time in independent data (Fig. 4A, $P = 0.0005$). However, the difference among patients with different disease-free survival was not significant in disease-free survival analysis (Fig. 4B, $P = 0.07$).

4. Discussion

Despite vast improvements in ALL therapy over the past few decades, the outlook for relapsed leukemia remains dim [22], suggesting a need for innovative treatment approaches. The current analysis was performed to investigate the potential molecular biomarkers for ALL diagnosis. In total, 637 up-regulated DEGs and 578 down-regulated DEGs were revealed between good and poor groups. These DEGs were mainly enriched in functions including transcription and pathways, like

focal adhesion. The survival analysis showed that genes including *ALPK1*, *ZNF695*, *ACTN4*, *CALR*, and *FBXL5* were identified as potential prognostic biomarkers for ALL.

In the present study, the transcription and focal adhesion were most outstanding function and pathway enriched by DEGs, respectively. Transcription plays a pivotal role in ALL via activing signaling cascade in tumor progression [23]. A previous study shows that the transcription-coupled genetic instability marks the structural variation hotspots in ALL [24]. Farrar et al. indicated that B cell transcription factors could define novel tumor suppressor gene network in ALL [25]. Actually, the potential prognostic markers for ALL can be investigated via detecting the gene expression in transcription [26]. Furthermore, focal adhesion is a large macromolecular assembly network [27]. The dynamic assembly and disassembly of focal adhesion network play central roles in cell migration including leukocyte transendothelial migration [28]. A previous study shows that focal adhesion can be used for the ALL treatment [29]. Churchman et al. showed that focal adhesion kinase in focal adhesion pathway contributed to the ALL inhabitation [29]. Thus, we speculate that transcription and focal adhesion may play important roles in the progression of ALL.

ACTN4 takes part in the process of human carcinoma [30]. A previous study indicates that *ACTN4* regulates transcription pathway by controlling tumor cell growth [31]. Noro et al. showed that patients with *ACTN4* gene amplification were much easier to suffer relapse of lung cancer after curative surgery [32]. Actually, *ACTN4* is a candidate oncogene associated with poor patient prognosis [33]. Furthermore, *CALR* is a multifunctional protein which plays a role in promoting macrophages to engulf hazardous cancerous cells [34]. In Chinese, myeloproliferative neoplasms patients carrying *CALR* mutations presented with higher platelet counts and lower hemoglobin levels compared to those in normal [35]. Moreover, *FBXL5* takes part in phosphorylation-dependent ubiquitination via generating F-box/LRR-repeat protein 5 [36]. It is also reported that *FBXL5* plays a vital role in the cells migration of gastric cancer [37]. In addition, *FBXL4* is a pediatric mitochondrial encephalopathy associated with highly aggressive hematological malignancy T-cell ALL [38]. Furthermore, Alpha-protein kinase 1 encodes a newly explored protein kinase [39]. Recently, several studies have proved that ALPK1 plays an important role in inflammation of various diseases [40,41]. ZFP695, a family member of Kruppel-like transcription factors, regulates diverse biological processes of tumor cells [42]. A previous study shows that ZNF695 is a biological marker for ovarian cancer [43]. Unfortunately, the role of genes including *ALPK1*, *ZNF695*, *ACTN4*, *CALR*, and *FBXL5* on ALL has not been fully investigated. In this study, the aforementioned genes were feature genes in survival analysis. Thus, we speculate that these aforementioned genes may be novel prognostic genes for relapsed ALL.

However, there were some limitations in this study such as small sample size and lack of verification test. Further studies with large sample sizes and wide verification analysis are still needed to confirm our findings.

5. Conclusion

In conclusion, our analysis reveals that transcription and focal adhesion may play important roles in the progression of ALL. Furthermore, genes including *ALPK1*, *ZNF695*, *ACTN4*, *CALR*, and *FBXL5* may be novel prognosis genes for relapsed ALL.

Declarations of interest

None.

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