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Original Article

Extracellular Immune Signatures as Prognostic Biomarkers and Liquid-Biopsy Candidates in AML

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Abstract

Background: Acute myeloid leukemia (AML) has poor long-term survival, necessitating robust prognostic biomarkers. While conventional markers focus on cytogenetics and mutations, immune-extracellular genes suitable for liquid biopsy remain understudied.

Methods: RNA-sequencing data from 200 AML patients were analyzed from The Cancer Genome Atlas (TCGA). Univariate Cox regression identified survival-associated genes. Gene Ontology enrichment analysis selected immune and extracellular genes, with Kaplan-Meier analysis validating prognostic significance. REACTOME pathway enrichment revealed biological mechanisms. External validation used GEPIA2.

Results: Cox regression identified 201 survival-associated genes ($p<0.05$): 149 favorable prognosis (*HR<1*) and 52 poor prognosis (HR>1). Gene Ontology enrichment revealed 29 immune-associated and 9 extracellular genes, with 5 overlapping candidates. Kaplan-Meier analysis confirmed four genes; *EPHA10*, *CD160*, *BTN2A2*, and *KLRK1* as significant protective prognostic markers ($p<0.05$, *HR<1*). REACTOME analysis highlighted immune signaling pathways including adaptive immune response, natural killer cell-mediated cytotoxicity, and cell surface interactions. External validation demonstrated differential expression in AML versus normal tissues.

Conclusion: This study identified *EPHA10*, *CD160*, *BTN2A2*, and *KLRK1* as novel immune-extracellular prognostic biomarkers in AML. These genes represent promising candidates for liquid biopsy applications and personalized immunotherapy strategies, offering new perspectives for monitoring immune surveillance and overcoming AML immune evasion.

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1. INTRODUCTION

Acute myeloblastic leukemia (AML) is a hematological malignancy resulting from accumulation of a large number of myeloblasts in the bone marrow and peripheral blood. AML is ranked as the second most common type of hematologic malignancy among adults and also it is responsible for 80% of adult cases diagnosed with acute leukemia [1]. Based on the statistics published by the American Cancer Society, approximately 59,610 new cases and 23,710 deaths due to AML were reported in the USA in 2023. According to reports, the 5-year survival rate for AML is 30.5% [2]. Although AML is present worldwide, its incidence and mortality rates are greater in developed nations. It is shown that men have a slight predominance, and the average lifetime risk is 0.5% [3].

The main etiology of AML consists of malignant clonal expansion and maturation arrest of myelopoiesis. Confirmation of the diagnosis is based on finding ≥20% blasts in the peripheral blood or bone marrow, or by specific genetic abnormalities in the bone marrow, regardless of blast count [4]. While the French-American-British (FAB) system has been utilized for the AML classification for decades, the WHO 2016 classification system is currently preferred for categorization. This system allows clinicians to organize the cases regarding clinical features, leukemic cell morphology, immunophenotypes, and cytogenetics [5]. The traditional chemotherapy regimen for AML, also known as 7+3, is an intensive remission induction therapy containing a 7-day continuous infusion of cytarabine followed by anthracycline treatment for the next three days.

Conventional AML biomarkers are mainly categorized into cytogenetic and gene mutations. For example, t(15;17), t(8;21), and inv(16;16) are associated with better prognosis, while deletion of chromosome 5 or 7 and some other chromosomal rearrangement lead to poor prognosis. Moreover, mutations in several genes, including Fms-like Tyrosine Kinase 3 (*FLT3*), Nucleophosmin 1 (*NPM1*), CCAAT Enhancer Binding Protein (*CEBPA*), and KIT were known to be useful in risk stratification of patients with AML [6].

During the recent decade, by using bioinformatic technology, including next-generation sequencing and microarray analysis, researchers have reached a valuable source of different mutations and transcriptions of cancers. The Cancer Genome Atlas (TCGA) online database provides extensive information on 30 types of human cancers. This database presents omics data and clinicopathological features of patients to accelerate access to data and help to find novel approaches for diagnosis, treatment, and prevention.

In this study, we identified AML biomarkers through bioinformatics approaches. The survival analysis employed the Kaplan-Meier method and Cox proportional hazard to predict prognostic biomarkers. Moreover, we assessed disease ontology, molecular pathways between candidate genes and AML disease.

2. MATERIALS AND METHODS

2.1. Data collection

RNA-sequencing data and corresponding clinico-pathological information for acute myeloid leukemia were obtained from the TCGA database (https://portal.gdc.cancer.gov/). A total of 200 patients with available overall survival (OS) data were included. Clinical variables (e.g., sex, race/ethnicity, and vital status) were taken from the TCGA clinical tables. The majority of patients were White (128 patients, 84.8%), followed by Black or African American (13 patients, 8.6%), Asian (5 patients, 3.3%), and unknown race (5 patients, 3.3%). Ethnicity was predominantly not Hispanic or Latino (142 patients, 94%), with 6 patients (4%) identified as Hispanic or Latino and 3 patients (2%) unknown. Detailed clinico-pathological characteristics are summarized in **Table 1**.

Table 1. The Clinicopathological characteristics of AML patients.

Clinicopathological Variables	No. of patients (%)/mean ± SD
Patients	200
Mean age (Years, mean ± SD)	55.03±1.13
Gender	
Male	109
Female	91
Vital status	
Alive	67
Dead	133
Race	
Asian	2
Withe	181
Black	15
Not Available	2
Ethnicity	
Not Hispanic or latino	3
Hispanic or latino	194
Not Available	3
Prior hematologic disorder	
Yes	192
No	8

2.2 Data Preprocessing and Univariate Cox Regression Analysis

Raw RNA-sequencing data (FPKM normalized) were processed using R software (version 4.2.0). Samples with null expression values, duplicates, or missing annotations were excluded. Low-expression genes (defined as counts per million <1 across all samples) were filtered out to focus on reliably expressed transcripts. Univariate Cox proportional hazards regression analysis was performed on the preprocessed gene expression data against overall survival (OS) outcomes using the survival package in R. Genes were selected as significant candidates if they met predefined criteria: *p-value* <0.05 and hazard ratio (HR) ≠1, indicating a prognostic association with AML survival.

2.3 Functional Enrichment Analysis

To identify immune-related and extracellular genes suitable as biomarkers for the immune microenvironment and liquid biopsy applications in AML, functional enrichment analysis was conducted on the significant genes from Cox regression using the Database for Annotation, Visualization, and Integrated Discovery (DAVID) online functional enrichment analysis tool. Gene Ontology (GO) analysis focused on biological process (BP) terms to select immune-associated genes (e.g., those enriched in immune cell compartments or structures). From BP terms, immune-associated genes were identified. Similarly, cellular componet (BP) terms were used to select genes linked to extracellular localization or secretion, yielding extracellular genes. Overlap between immune-associated (BP) and extracellular (CC) gene sets was determined using Venn diagram analysis, identifying mutual genes as candidate biomarkers. Additionally, REACTOME pathway enrichment analysis was performed to uncover significant signaling pathways associated with these genes.

2.4 Identification of Prognostic Biomarkers

To assess the association of candidate genes with OS, Kaplan-Meier survival analysis was conducted using the Kaplan-Meier Plotter online tool (https://kmplot.com/analysis/), which integrates TCGA and GEO datasets. High- and low-expression groups were defined by median expression thresholds, with survival curves generated for a 5-year (60-month) follow-up period. Genes with *p-value* <0.05 (log-rank test) were selected as prognostic biomarkers correlated with survival outcomes.

2.5 External Validation

External expression validation of the final prognostic biomarkers was performed using GEPIA2 (Gene Expression Profiling Interactive Analysis, version 2), a web-based platform that integrates RNA-sequencing expression data. The expression analysis module was used to compare transcript levels between AML samples and available normal reference samples. Expression values were presented as log2-transformed transcripts per million values, and the results were visualized as boxplots to assess differences in expression distribution between tumor and normal groups. This validation step was performed to determine whether the biomarkers identified through survival and functional enrichment analyses also showed disease-associated expression patterns in an independent database-based expression comparison.

3. Results

3.1 Univariate Cox Regression Analysis

Univariate Cox regression analysis identified 201 genes significantly associated with OS in AML ($p<0.05$). Among these, 52 genes were linked to poor prognosis ($HR>1$), while 149 genes were associated with favorable prognosis ($0<HR<1$).

3.2 Functional Enrichment Analysis

GO analysis of the 201 significant genes revealed enrichment in immune-related processes within BP terms, from which 29 immune-associated genes were selected as candidates relevant to the AML immune microenvironment. CC terms highlighted extracellular processes, yielding 9 genes suitable for liquid biopsy detection due to their secreted or cell-surface localization. GO enrichment results for CC and BP terms are shown as bar charts in **Figure 1A.** Venn diagram analysis of these sets identified 5 overlapping genes as dual immune-extracellular candidates (**Figure 1B**). REACTOME pathway analysis further demonstrated enrichment in key pathways, such as immune signaling and extracellular matrix interactions, visualized in **Figure 1C**.

3.3 Discovery of Genes Linked to Overall Survival Dysregulation in AML

Kaplan-Meier survival analysis of the five candidate genes revealed that four genes, *EPHA10*, *CD160*, *BTN2A2*, and *KLRK1*, exhibited significant associations with OS ($p<0.05$). Individual Kaplan-Meier plots for these genes are

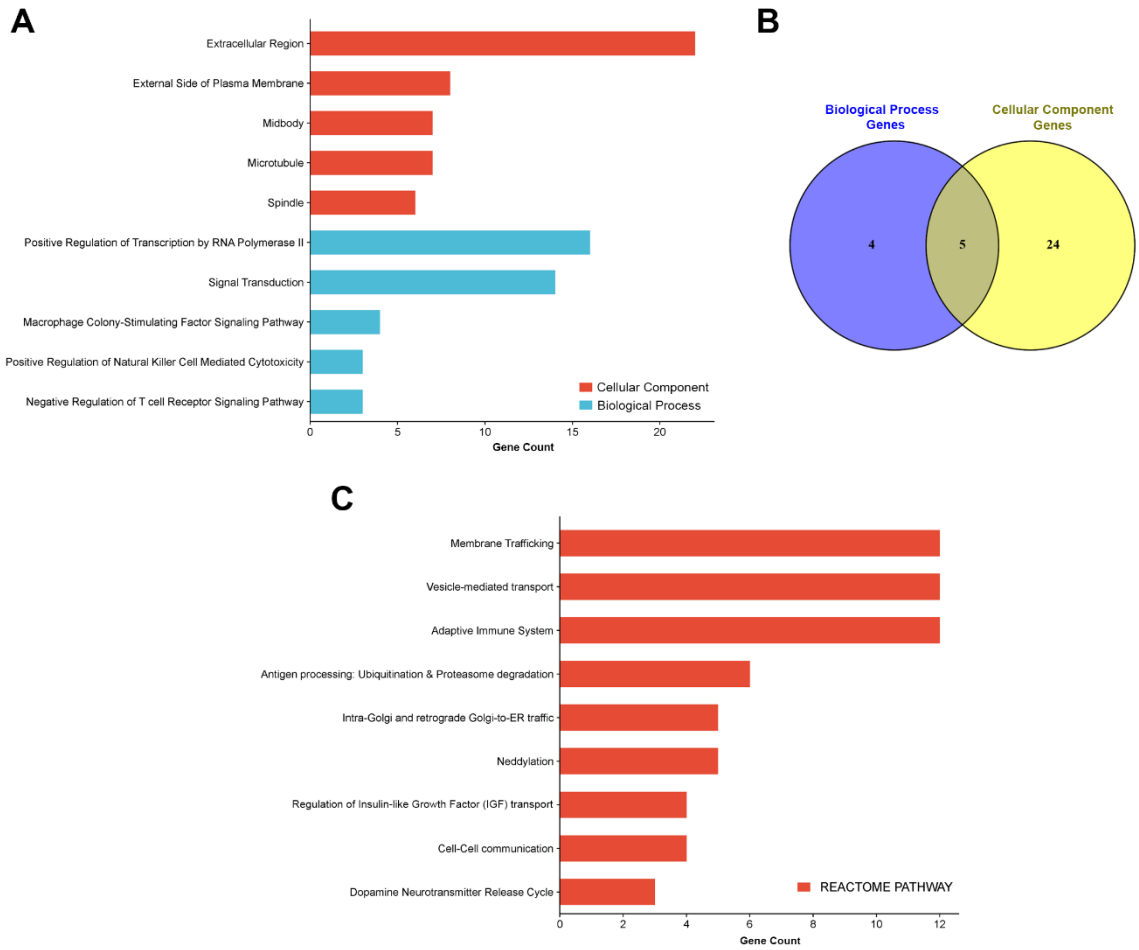

Figure 1. Functional enrichment analysis of survival-associated genes in AML. **(A)** Gene Ontology enrichment of the 201 survival-associated genes identified by univariate Cox regression, showing selected cellular component terms in red and biological process terms in blue. **(B)** Venn diagram showing the overlap between biological process-derived and cellular component-derived gene sets, identifying five shared candidate genes. **(C)** Reactome pathway enrichment of the survival-associated genes, highlighting pathways related to membrane trafficking, vesicle-mediated transport, adaptive immunity, antigen processing, and cell-cell communication.

presented in **Figure 2.** All 4 genes correlated with favorable prognosis ($0 < HR < 1$), indicating their potential as protective prognostic markers in AML. Forest plot summarizing HRs and p-values is shown in **Figure 3**.

3.4 Validation of Dysregulated Genes

The expression profiles of the final prognostic biomarkers were further examined using GEPIA2. Tumor-normal boxplot analysis was used to compare RNA expression levels between AML samples and available normal reference samples. This analysis showed disease-associated expression differences for the selected biomarkers, providing additional database-based support for their relevance in AML. Pan-cancer boxplots were also generated to contextualize their expression patterns across other malignancies. The resulting validation plots are shown in **Figure 4**.

4. DISCUSSION

Acute myeloid leukemia remains a challenging hematologic malignancy with high relapse rates and poor long-term survival, underscoring the need for robust prognostic biomarkers that integrate molecular and immunological insights [7], [8]. In this study, we employed a systematic bioinformatics approach using TCGA-AML data to identify prognostic genes linked to the immune microenvironment and extracellular localization, ideal for liquid biopsy applications. Univariate Cox regression identified 201 survival-associated genes, from which functional enrichment analysis via Gene Ontology (GO)

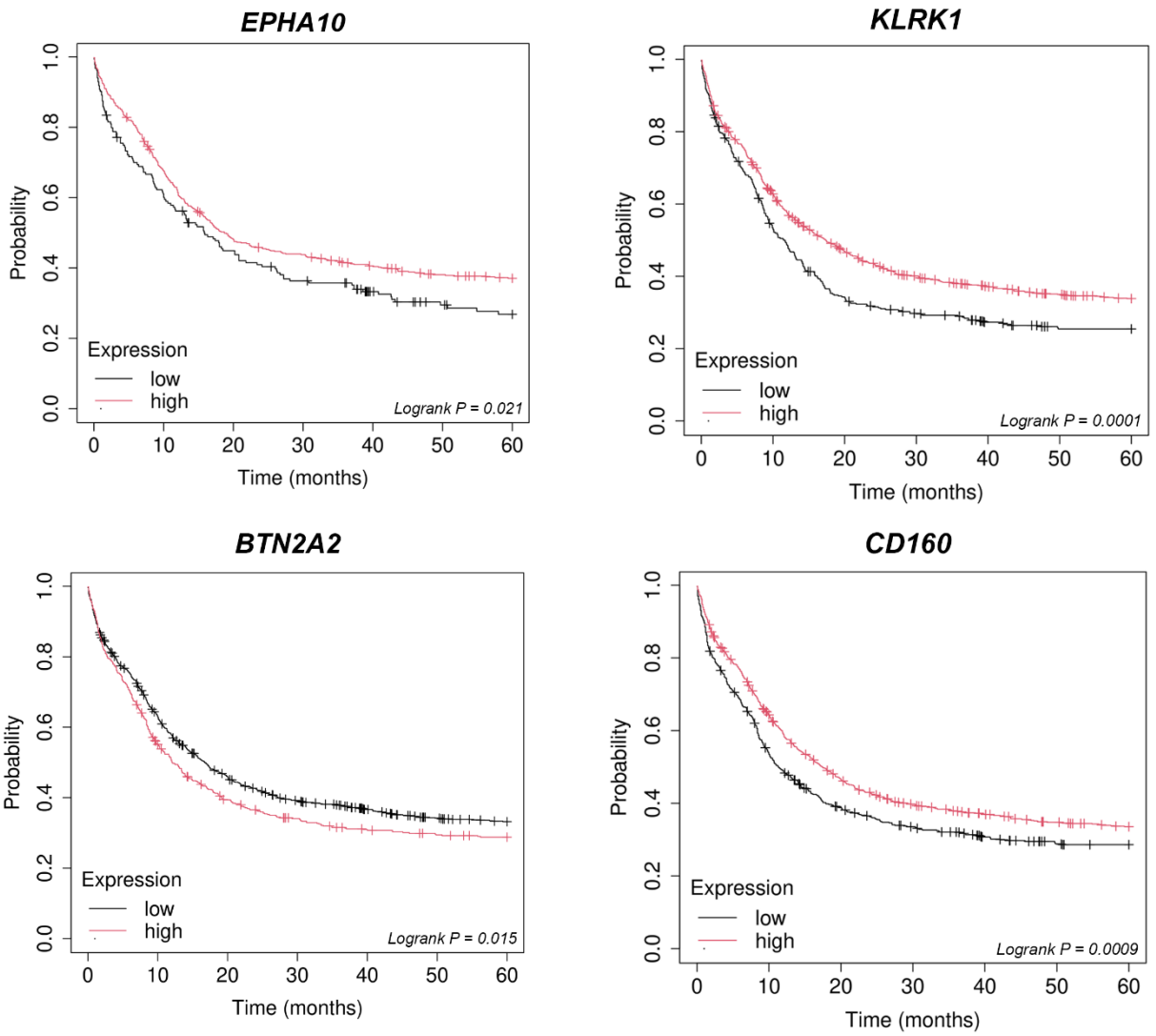

Figure 2. Kaplan-Meier survival analysis of the four candidate genes. Kaplan-Meier curves comparing overall survival between high- and low-expression groups for EPHA10, KLRK1, BTN2A2, and CD160 over a 60-month follow-up period. High and low expression groups are shown in red and black, respectively. Log-rank P values indicate significant survival associations for all four genes.

and REACTOME highlighted immune-related cellular components (CC) and extracellular biological processes (BP), yielding 29 immune-associated and 9 extracellular genes, with 5 overlapping candidates. Kaplan-Meier analysis confirmed 4 genes; *EPHA10*, *CD160*, *BTN2A2*, and *KLRK1* as significant prognostic markers ($p<0.05$), all associated with favorable outcomes (*HR* <*1*). External validation in GEPIA2 demonstrated their differential expression across cancers, supporting generalizability. These findings emphasize the role of immune-extracellular crosstalk in AML prognosis, potentially guiding targeted immunotherapies.

The enrichment in immune signaling and extracellular matrix pathways aligns with emerging evidence that AML exploits immunosuppressive microenvironments for evasion [9]. REACTOME analysis (Figure 1C) revealed pathways like adaptive immune response and cell surface interactions, consistent with prior studies showing AML blasts remodel the bone marrow niche to suppress T-cell and NK-cell activity [10]. For instance, a multidimensional single-cell analysis identified immune aggregates in pediatric AML, with hotspots of CD8+ T cells and M1 macrophages correlating with better survival, mirroring our immune-biological process enrichments [11], [12]. Similarly, GO bar charts (Figure 1A) underscore

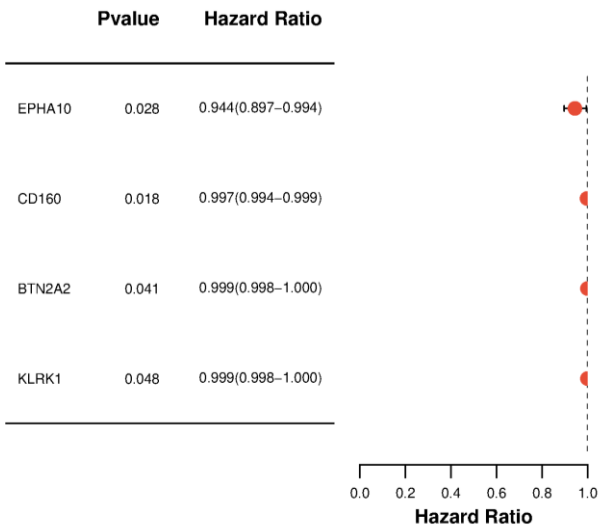

Figure 3. Forest plot of prognostic hazard ratios for the four candidate genes. Forest plot showing univariate Cox regression hazard ratios, 95% confidence intervals, and P values for EPHA10, CD160, BTN2A2, and KLRK1. The dashed vertical line indicates HR = 1. All four genes showed HR values below 1, suggesting that higher expression was associated with reduced mortality risk in AML.

extracellular CC terms, vital for liquid biopsy, as secreted immune modulators facilitate non-invasive monitoring. Venn overlap (Figure 1B) pinpointed dual-function genes, validating the logic of intersecting immune and extracellular profiles for biomarker discovery.

EPHA10, an Eph receptor tyrosine kinase, emerged as a protective prognostic factor (Figure 2), with high expression linked to improved OS. Eph receptors mediate cell-cell communication, influencing migration and adhesion in the hematopoietic niche [13], [14]. In AML, *EPHA10*'s extracellular domain suggests potential as a soluble biomarker, with GEPIA2 validation showing upregulation in AML versus normal tissues (Figure 4). Although direct AML studies are limited, Eph family members like *EPHA3* are overexpressed in leukemic blasts, promoting survival via PI3K/AKT signaling; *EPHA10* may counter this by stabilizing immune synapses [15], [16]. A pan-cancer analysis reported *EPHA10*'s association with immune infiltration in non-small cell lung cancer (NSCLC), where high expression predicted better immunotherapy response via enhanced T-cell recruitment, paralleling our findings [17], [18]. In breast cancer, *EPHA10* isoforms regulate E-cadherin/β-catenin complexes to suppress metastasis, suggesting a tumor-suppressive role in AML's invasive microenvironment. Our forest plot (Figure 3) confirms *EPHA10*'s *HR<1*, aligning with EphA10's negative correlation to progression in solid tumors, positioning it as a favorable immune modulator in AML [19].

CD160, an immunoglobulin superfamily immune checkpoint, exhibited significant prognostic value ($p<0.05$), with high expression favoring OS, as visualized in Kaplan-Meier plots (Figure 2) [20]. Expressed on NK and T cells, *CD160* inhibits activation via HVEM binding, but in AML, its dual role suppressing exhausted effectors while enhancing anti-leukemic signaling may explain protective effects. GEPIA2 (Figure 4) revealed CD160 upregulation in AML blasts, potentially amplifying NK-mediated cytotoxicity in the microenvironment [21]. In AML, high *CD160* correlates with poor NK function and exhaustion markers like TIGIT, yet our analysis indicates a favorable HR, possibly due to its extracellular shedding enabling liquid biopsy detection of immune competence [22]. A TCGA-based study identified *CD160* in a prognostic score, where elevated levels inversely associated with adverse outcomes via interferon-γ pathway activation [23]. In chronic lymphocytic leukemia (CLL), *CD160* aids minimal residual disease detection and correlates with event-free survival post-therapy, supporting its biomarker utility in myeloid malignancies [24]. Single-cell omics further showed *CD160*+ NK cells in AML niches, with high expression linked to reduced relapse, validating our univariate selection and REACTOME immune enrichments [25].

BTN2A2, a butyrophilin family member, was selected for its immune-extracellular overlap, showing *HR<1* and validation in GEPIA2 across cancers (Figure 4). *BTN2A2* modulates T-cell responses by coregulating MHC class II, acting as a co-inhibitory ligand to fine-tune activation and prevent autoimmunity [26], [27]. In our gene ontology biological process analysis, *BTN2A2*'s enrichment in immune compartments highlights its role in AML's suppressive niche, where high expression may restore T-cell vigor. Though AML-specific data are sparse, *BTN2A2* knockout mice exhibit hyperactive *CD4+/CD8+* responses and exacerbated autoimmunity, implying its restraint on excessive inflammation benefits AML control [28]. A glioma study reported *BTN2A2* upregulation correlating with poor prognosis but enhanced immune infiltration (CIBERSORT), contrasting our favorable HR; this discrepancy may reflect tissue-specificity, with AML's myeloid context favoring anti-tumor immunity [29]. Recent anti-*BTN2A2* antibodies normalized tumor microenvironments in pancreatic models by boosting *CD8+* TILs and reducing MDSCs, suggesting therapeutic potential. Our bar chart enrichments (Figure 1A) align with *BTN2A2*'s regulation of ILC2-T cell crosstalk,

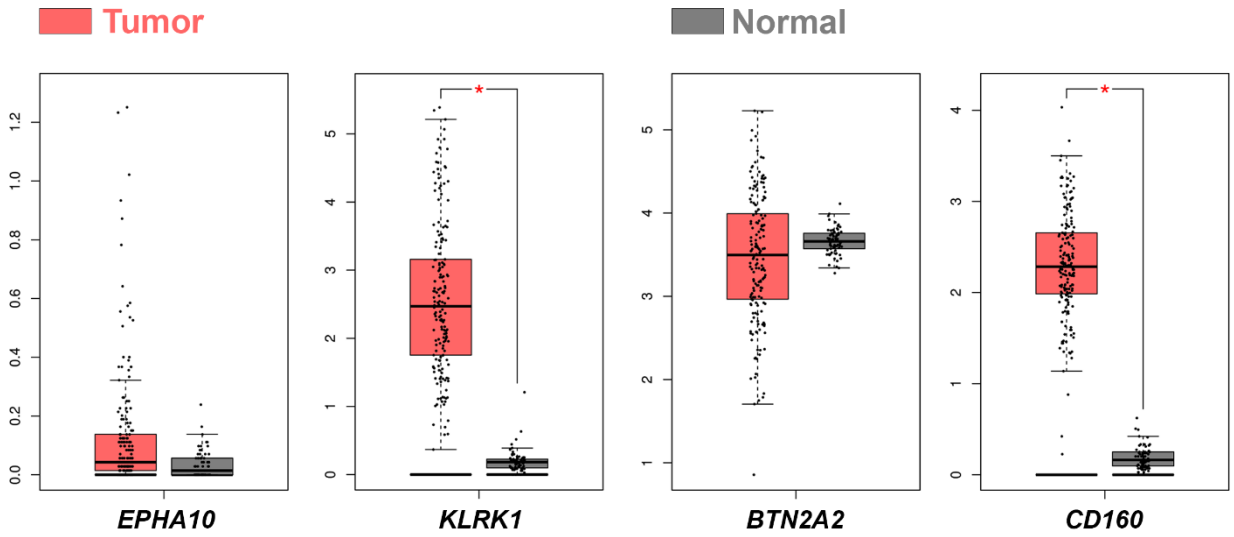

Figure 4. Tumor-normal expression validation of the four prognostic genes in AML. Boxplots showing expression levels of EPHA10, KLRK1, BTN2A2, and CD160 in AML tumor samples and normal reference samples. Tumor and normal groups are shown in red and gray, respectively. Individual points represent sample-level expression values, and red asterisks indicate statistically significant tumor–normal differences.

positioning it as a target to reprogram AML's immunosuppressive landscape [30]. *KLRK1* (encoding NKG2D), an activating NK/T-cell receptor, demonstrated strong prognostic significance ($p<0.05$), with high expression predicting better survival (Figure 2). NKG2D recognizes stress ligands on blasts, triggering cytotoxicity crucial for immune surveillance. In AML, *KLRK1* expression on effectors inversely correlates with relapse, as our forest plot illustrates (Figure 3) [31]. External validation confirmed *KLRK1*'s differential patterns (Figure 4), with upregulation in AML versus normals. A prospective AML cohort showed high NKG2D+ NK cells associated with relapse-free survival (>35 months vs. 24 months), mediated by calreticulin exposure on blasts enhancing phagocytosis [32], [33]. Gene variants in *KLRK1* influence immunotherapy outcomes, with activating alleles improving OS in AML trials. In lung adenocarcinoma, high *KLRK1* inhibited proliferation/migration and predicted superior survival, mirroring our findings. REACTOME pathways (Figure 1C) link *KLRK1* to natural killer-mediated cytotoxicity, supporting its selection from immune-CC terms. However, NKG2D ligand shedding in AML can dampen responses, suggesting our favorable HR reflects intact receptor signaling in responsive subsets [34].

Collectively, these biomarkers validate an immune-centric prognostic model, with nomograms potentially integrating HRs for personalized risk stratification. Unlike prior signatures focusing on autophagy or ferroptosis, ours emphasizes extracellular immune genes, addressing AML's evasion via checkpoints like PD-1/TIGIT. Limitations include reliance on bulk RNA-seq, potentially masking heterogeneity; single-cell validation could refine this [22]. Future studies should explore functional assays, like CRISPR knockdown in AML models, to confirm causality and test combinatory immunotherapies targeting these genes.

5. CONCLUSION

In conclusion, our comprehensive analysis of TCGA data identified novel biomarkers in AML patients. Gene ontology and pathway enrichment analyses underscored the involvement of key genes in primary bile acid biosynthesis and steroid hormone biosynthesis, suggesting a vital role for metabolic dysregulation in AML underlying pathogenesis processes. Kaplan–Meier survival analysis further emphasized the prognostic value of specific genes, including *EPHA10*, *CD160*, *BTN2A2*, and *KLRK1*, which are associated with overall survival in AML patients. These findings help us to further understand the molecular mechanisms underlying AML pathogenesis and open new avenues for targeted therapeutic interventions. Moreover, the identification of bile acid and bile salt metabolism

pathways as crucial items in AML pathogenesis suggests promising potential for the development of new treatment strategies aimed at modulating these metabolic processes to improve patient outcomes.

6. LIMITATIONS AND PERSPECTIVES

Although our study identified extracellular immune genes with prognostic value, several limitations must be acknowledged. First, we used unadjusted p-value thresholds for gene selection; multiple-testing correction and independent cohorts should validate these candidates. Second, gene expression from bulk RNA-seq does not distinguish between malignant and immune cells, complicating interpretation of BTN2A2 and EPHA10 expression. Single-cell sequencing and flow cytometry could clarify the cellular sources of these transcripts. Finally, while our literature review suggests plausible mechanisms linking each gene to immunity and prognosis, functional studies are necessary to determine whether these genes are drivers of improved survival or merely biomarkers of an active immune microenvironment.

Acknowledgment

Not applicable.

Conflict of interest

The author declares that there are no competing financial interests or personal relationships that could have influenced the research reported in this study.

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Ethical statement

Not applicable.

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