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ORIGINAL RESEARCH

# Neutrophil-Related Genes Predict Prognosis and Contribute to Immunosuppression in Acute Myeloid Leukemia

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**Introduction:** Acute myeloid leukemia (AML) prognosis remains challenging due to limited biomarkers integrating tumor microenvironment (TME) dynamics. Neutrophils, key mediators of immune regulation, exhibit dual roles in cancer progression, yet their prognostic significance in AML is poorly defined. This study aimed to construct a neutrophil-related gene signature for AML risk stratification and explore its clinical and immunological implications.

**Methods:** Utilizing transcriptomic and clinical data from TCGA (The Cancer Genome Atlas), GEO (Gene Expression Omnibus), and OHSU cohorts (n=1537), we identified 148 neutrophil-related genes through literature mining. Prognostic genes were selected via univariate Cox regression and LASSO regression (R packages: survival, glmnet). A 5-gene model (CSF3R, BRAF, FFAR2, CD300A, CD37) was validated across internal (TCGA) and external cohorts (GSE10358, GSE14468, OHSU). Immune profiling, drug sensitivity analysis (GDSC database), and TIDE scoring were performed to assess immunotherapy relevance.

**Results:** The neutrophil-based model stratified AML patients into high- and low-risk groups with distinct overall survival (OS, $p<0.0001$ in TCGA). Multivariate Cox analysis confirmed its independence from age, FLT3, and TP53 mutations (HR=2.14, $p=0.015$). CD37 emerged as the strongest prognostic marker (AUC 5-year=0.680, $p=0.0026$), correlating with immunosuppressive TME features: elevated myeloid-derived suppressor cells (MDSCs, $p<0.01$), Treg infiltration ($p<0.05$), and upregulated immune checkpoints (PD1, CTLA4, LAG3; $p<0.001$). High CD37 expression predicted immunotherapy responsiveness (TIDE score, $p=0.004$) and interacted with 146 potential therapeutic agents (eg, BCL2 inhibitors).

**Discussion:** This study advances a novel 5-gene prognostic model integrating neutrophil biology into AML risk stratification. CD37, a key regulator of immune evasion, serves as a dual biomarker for prognosis and immunotherapy prediction. While validated across multiple cohorts, experimental studies are warranted to unravel CD37's mechanistic role. Our findings highlight the potential of neutrophil-centric biomarkers in guiding personalized AML therapy.

**Keywords:** neutrophil, CD37, AML, immunotherapy, tumor microenvironment

## Introduction

Acute myeloid leukemia (AML) is a highly aggressive cancer characterized by a block in myeloid differentiation that leads to the uncontrolled proliferation of myeloblasts.[1] It stands as the most prevalent leukemia in adults, with an age-adjusted incidence rate of 4.3 cases per 100,000 individuals annually.[2] AML can affect any age group but is most prevalent among adults, with its incidence increasing with age.[3] Chemotherapy serves as a main treatment strategy for AML, a neoplastic cancer characterized by the accumulation of aberrant immature cells in the bone marrow (BM).[4] Despite recent advances in targeted therapies, AML remains a formidable disease with a dismal prognosis.[5] Therefore, there is an urgent need for novel therapeutic targets, and one of the promising approaches is cancer immunotherapy. Indeed, targeting an immune checkpoint regulator in combination with chemotherapeutics has been proven to be more effective than the chemotherapeutic regimen alone.[6,7] With immense success in the treatment of various solid tumors and lymphomas, immune checkpoint inhibitors (ICIs) are now considered as a potential immunotherapeutic option for AML

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patients.[8] Encouraging results from clinical trials using ICIs have demonstrated improved response rates and OS in patients with relapsed or refractory AML.[9] Thus, effective indicators and prognostic biomarkers must be explored to identify AML patients who will benefit from ICIs therapies, ultimately facilitating risk stratification and personalized treatment approaches.

Neutrophils are key mediators of chronic inflammation and innate inflammatory response, as well as important regulators of cancer development.[10] Neutrophils are abundant and heterogeneous leukocytes in human peripheral blood functioning as the early responder to infection or injury.[11] Unlike terminally differentiated cell populations, tumor-associated neutrophils are susceptible to environmental factors and exhibit great plasticity and diversity, thereby promoting or interfering with tumor growth.[12] While neutrophils can potentially inhibit tumor progression by generating anti-tumor factors, prevailing evidence suggests they more commonly act as facilitators of cancer progression and metastasis, by orchestrating various processes such as tumor survival, migration, immune evasion, and angiogenesis.[13–17] Notably, neutrophils have been implicated in influencing cancer prognosis and responses to diverse anticancer treatments, from chemotherapy to immunotherapy. In numerous malignancies, tumor-associated neutrophil infiltration, peripheral blood neutrophil to lymphocyte ratios (NLR), and neutrophil-based transcriptional profiles are correlated with unfavorable clinical outcomes and reduced drug sensitivity.[18–20] However, the prognostic role of neutrophils in AML remains elusive, nor is the predictive value of neutrophils in specific therapeutic regimens.

In this study, we conducted a comprehensive analysis of gene expression profiles within the TCGA, GEO, and OHSU databases to assess the influence of neutrophils on AML prognosis. A prognostic model based on neutrophil-associated genes was developed and validated. The relationship between neutrophil-related genes and immune dysregulation, as well as drug sensitivity was further investigated to uncover potential indicators of immunotherapy response and identify novel therapeutic targets for AML treatment.

# Materials and Methods

## Data Source and Processing

The Cancer Genome Atlas (TCGA) is a comprehensive database sponsored by the government of the United States, collecting more than 11,000 cases across 33 tumor types. The Gene Expression Omnibus (GEO) is the largest public resource for gene expression data, storing chips, second-generation sequencing, and other high-throughput sequencing data. Beat AML 1.0 was developed from an agreement 6 years ago between Oregon Health & Science University (OHSU) and the Leukemia and Lymphoma Society to develop a consortium of 11 academic medical center partners. OHSU data comes from the Beat AML 1.0 program. We downloaded clinical information and transcriptome data of 151 AML patients from TCGA for our analysis. Overall, 151 patients were randomly divided into two data sets in a 7:3 ratio by the R package "Caret": training set (n = 107) and internal validation set (n = 44). AML patients from GEO datasets, including GSE10358 (n = 178), GSE14468 (n = 262), GSE37642-GPL570 (n = 136), GSE71014 (n = 104, CN-AML), and OHSU (n = 576) was downloaded as an external validation set. To ensure analytical robustness, raw transcriptomic data underwent rigorous preprocessing: (1) genes with missing expression values were excluded; (2) technical variability across datasets was harmonized via the ComBat algorithm implemented in the R package; and (3) RNA-seq data were normalized to Fragments Per Kilobase Million (FPKM) to account for gene length and sequencing depth.

## Source of Neutrophil-Related Gene

Neutrophil-related genes were retrieved from published studies, which can be classified into three gene sets: genes involved in neutrophil function, specificity, and infiltration, respectively. For genes involved in neutrophil function, 55 genes were extracted from the observation by Rincón et al.[21] They were vital for the function of cell surface receptors, reactive oxygen species, guanine nucleotide exchange factors, and adhesion receptors in neutrophils. For genes involved in neutrophil specificity, 31 genes specifically expressed in neutrophils were obtained from research defining the immune landscape of human colon cancer.[22] Finally, 84 genes associated with neutrophil infiltration were obtained from the LM22, a leukocyte gene signature matrix applied in the CIBERSORT algorithm, which was widely used for the

estimation of immune cell abundance from tissue expression profiles.[23] After removing the duplicated genes in the three gene sets, a total of 148 genes were identified as neutrophil-related genes for subsequent analyses.

## Construction and Validation of the Risk Model

To select prognostic genes associated with neutrophils, univariate COX regression was performed on AML patients using the R package "survival", and these genes could be used as candidates for the construction of prognostic models. The forest map of prognostic neutrophil-related genes was constructed using the R package "forestplot". The prognostic genes were then identified by Least Absolute Shrinkage and Selection Operator (LASSO) regression analysis via the R packages "glmnet" and a 5-gene risk model was established. The function "predict" in the R package "glmnet" was used to calculate the risk score of individual patients. Patients were divided into high-risk and low-risk groups based on median risk scores. The prognostic value of the 5-gene risk models was verified by the R packages "survival" and "survminer" using Kaplan-Meier curves and the log-ranking method, and the sensitivity of the model was assessed by receiver operating characteristic (ROC) curve analysis of the R packages "ROCR" and "rms".

## Nomogram Construction

To determine the survival probabilities predicted by the risk model and to facilitate its clinical application, a nomogram was drawn using the R package "rms".

## Survival Analysis

Kaplan-Meier plots were drawn to elucidate the effect of each prognostic gene on the OS of AML patients. The Log rank test was used to evaluate their relationships.

## Analysis of Differentially Expressed Genes

The R package "limma" was used to select differentially expressed genes (DEGs). DEGs meeting the following criteria were considered significant: adjusted p-values $<0.05$ and $|\log2 \text{ fold change (FC)}| \geq 1$.

## Pathway Enrichment Analysis

Gene Ontology (GO) and Kyoto Gene Genome Encyclopedia (KEGG) pathway analyses were performed via the R package "clusterprofiler", with a cutoff value of FDR $< 0.05$. To study the differences in biological processes between the high and low expression groups of CD37, we applied gene set variation analysis (GSVA) with the R package "GSVA".

## Immune Cell Infiltration

To assess the composition of immune cells in the tumor microenvironment, we used the ESTIMATE algorithm to evaluate the immune score, tumor purity, and stromal score of tumor samples. CIBERSORT is an analytical tool from the Alizadeh Lab and Newman Lab to impute gene expression profiles and provide an estimation of the abundances of member cell types in a mixed cell population, using gene expression data. xCell is a recently published method based on ssGSEA that estimates the abundance scores of 64 immune cell types, including adaptive and innate immune cells, hematopoietic progenitors, epithelial cells, and extracellular matrix cells. CIBERSORT and xCell algorithm was applied to assess the proportion of immune cell infiltration. The relative abundance of 24 tumor-infiltrating immune cells was obtained by single sample gene set enrichment analysis (ssGSEA) using the R package "GSVA". We then obtained gene sets of CD4+ T cells, naive CD8+T cells, and naive CD4+T cells from the Molecular Signatures Database (MSigDB) and calculated their enrichment using the GSEA algorithm.

## Statistical Analysis

The *T* test was used to determine the difference between two groups. The "survminer" package divided patients into the high- and low-risk score groups or high- and low-CD37 groups based on median. The Log rank test was used to determine the *P* values between the groups in the Kaplan–Meier survival analysis. The univariate and multivariate Cox regression analyses were used to identify the prognostic factors. A ROC curve analysis was used to determine the

specificity and sensitivity of the related metrics. R version 4.2.3 software was used for statistical processing. Visualization of data was performed with R software and GraphPad Prism V.9.4.1. $p<0.05$ was considered significant.

# Results

## Establishment of the Neutrophil-Based Prognostic Model

To evaluate the impact of neutrophils on the clinical outcome of AML patients, we performed a univariate Cox regression analysis using the TCGA dataset. The results revealed eight neutrophil-related genes associated with prognosis, including six genes detrimental to OS (LST1, ITGAX, FFAR2, CD300A, ITGAL, CD37), and two genes beneficial to OS (CSF3R, BRAF) (Figure 1A). Subsequently, we employed LASSO regression analysis on these prognostic genes to construct a neutrophil-based prognostic model. By determining the active coefficients, the model achieved optimal performance with a specified λ value of 0.0313 and five key prognostic genes (CSF3R, BRAF, FFAR2, CD300A, and CD37) were incorporated (Figures 1B–D). The individual-level risk score determined by this prognostic model was utilized for risk stratification and prediction of prognosis.

## Validation of the Neutrophil-Based Prognostic Model

The neutrophil-based prognostic model was used to calculate the risk score for each patient in the training cohort form TCGA dataset. According to the median risk scores of 0.97 in the training dataset, AML patients were divided into high-risk and low-risk groups. Survival analysis showed that patients in the high-risk group exhibited significantly shorter OS than patients in the low-risk group ($p < 0.0001$, Figure 2A). Then a ROC curve was drawn to assess the predictive performance of the prognostic model. As shown in Figure 2B, the area under the curve (AUC) of 1, 3, and 5 years was 0.750, 0.726, and 0.821, respectively. A similar trend was displayed in the internal validation dataset that patients with high-risk scores demonstrated inferior clinical outcomes ($p = 0.044$, Figure 2C), with the AUC values of 0.733, 0.739, and 0.637 at 1, 3, and 5 years (Figures 2D).

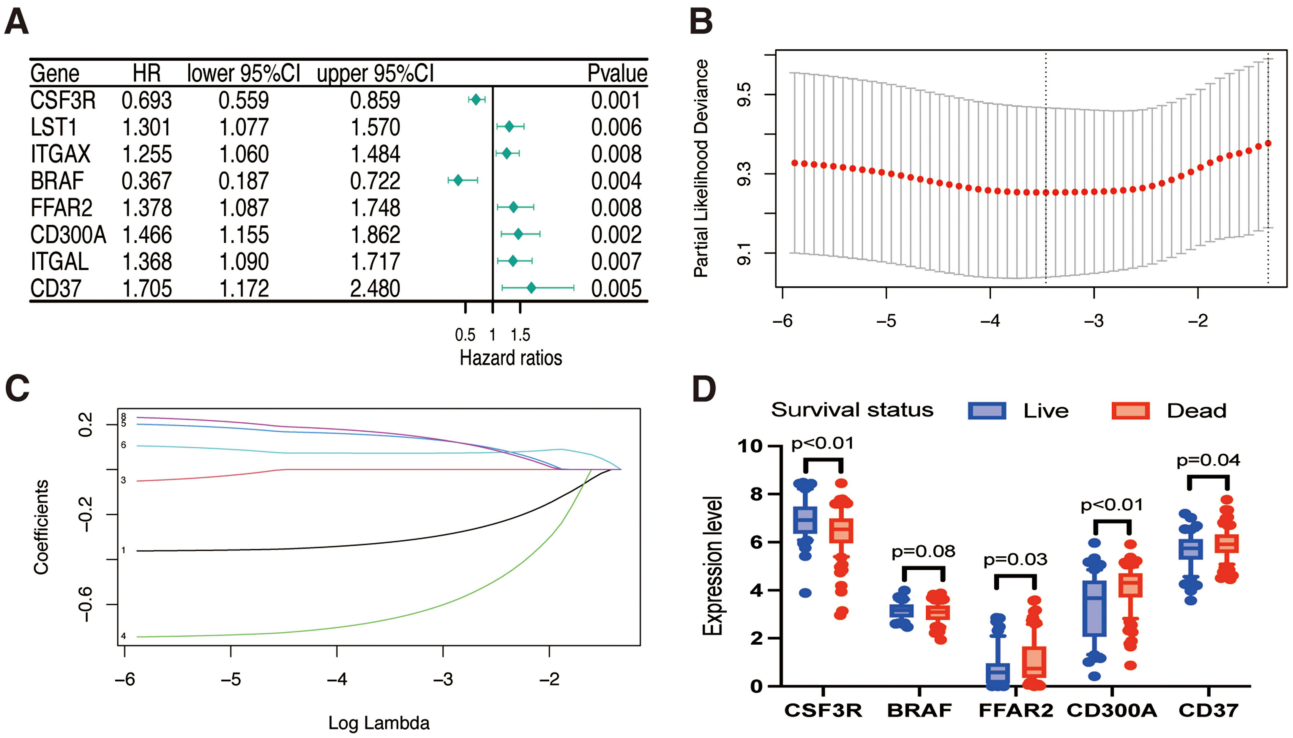


**Figure 1** Establishment of the neutrophil-based prognostic model (**A**) Forest plot of eight neutrophil-related genes associated with survival. (**B**) Cross-validation for parameter selection (**C**) LASSO coefficient profile plot against the log lambda sequence. (**D**) Expression of the five prognostic genes in patients with different outcomes. **Abbreviation**: LASSO, least absolute shrinkage and selection operator.

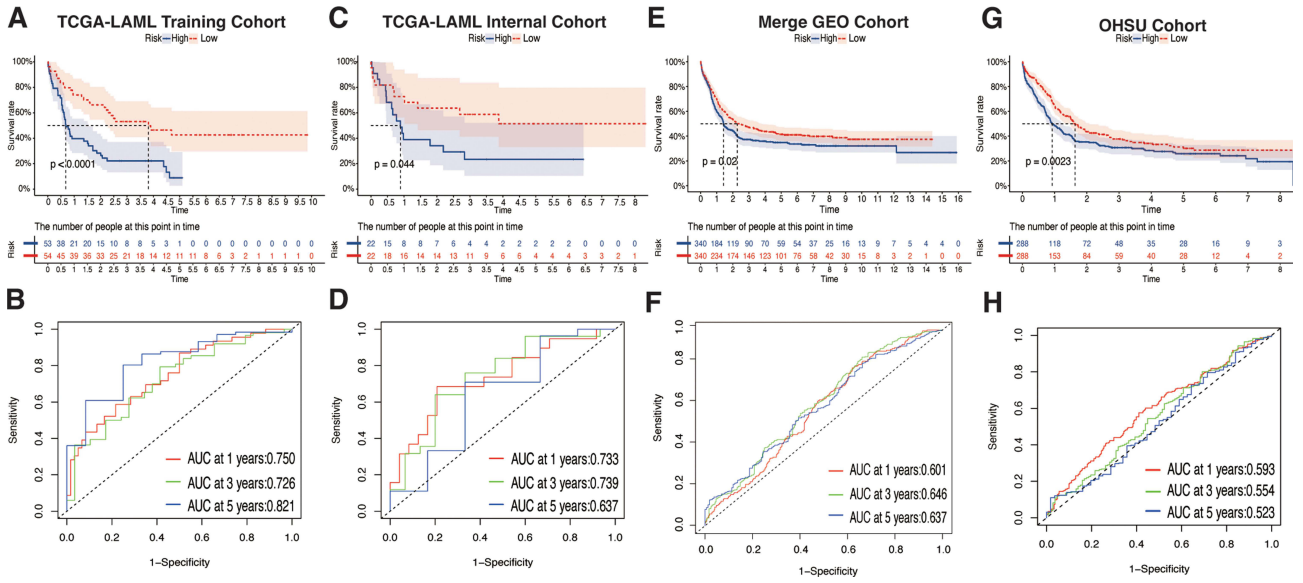


**Figure 2** Validation of the neutrophil-based prognostic model (**A, C, E** and **G**) Kaplan-Meier survival curves of AML patients from the high-risk group and the low-risk group. (**A**) training dataset ($p$<0.0001). (**C**) internal validation dataset ($p$=0.044). (**E**) external validation dataset ($p$=0.02). (**G**) OHSU dataset ($p$=0.0023). (**B, D, F** and **H**) ROC curves evaluating the sensitivity and specificity of the neutrophil-based prognostic model. (**B**) training dataset. (**D**) internal validation dataset. (**F**) external validation dataset. (**H**) OHSU dataset.

**Abbreviation**: ROC, receiver operating characteristic.

Furthermore, the analysis of external validation datasets from the GSE10358 cohort (n=178, Figure S1A-B), the GSE14468 cohort (n=262, Figure S1C-D), the GSE71014 cohort (n=104, Figure S1E-F), the GSE37642-GPL570 (n=136, Figure S1G-H), corroborated these results, implying an adverse prognostic impact of the neutrophil-based model. In the merged GEO datasets (n=680), OS of the high-risk group was significantly shorter than that of the low-risk group ($p$ =0.02) and the AUC of 1, 3, and 5 years was 0.601, 0.646 and 0.637 (Figure 2E and F). Additionally, we confirmed our findings using the OHSU dataset (n=576), where the high-risk group illustrated significantly lower OS compared to the low-risk group ($p$ = 0.0023) and the AUC of 1, 3, and 5 years was 0.593, 0.554 and 0.523 (Figure 2G and H). Together, through rigorous validation in both internal and external cohorts, our developed risk-score model demonstrated reliable and stable prognostic predictive value.

## Construction of Predictive Nomogram

To assess whether the neutrophil-based prognostic model impacted OS independent of recognized prognostic indicators for AML, we carried out univariate and multivariate Cox regression analyses. In multivariate models for the TCGA cohort, including the variables with $P$ value less than 0.05 under univariate analysis (Figure 3A), the risk score remained an independent prognostic indicator for OS ($p$ = 0.015), along with age ($p$ < 0.001), WBC ($p$ = 0.040), cytogenetics risk ($p$ = 0.023), FLT3 mutation ($p$ = 0.003), RUNX1 mutation ($p$ = 0.006) and TP53 mutation ($p$ < 0.001) (Figure 3B). Subsequently, we developed a nomogram to predict 1-, 3- and 5-year OS in AML patients for the convenience in clinical utility. Based on the results of the multivariate Cox analysis, the risk score, age, WBC, cytogenetics risk, FLT3 mutation, RUNX1 and TP53 mutation were included in the nomogram. The cytogenetic risk stratification in this analysis refers to the genetic risk categories (favorable, intermediate, adverse) defined by the European Leukemia Net (ELN) 2022[24] recommendations, which classify patients based on integrated cytogenetic and molecular profiles. The total point scores for all parameters were matched with the corresponding survival time scales (Figure 3C). For details, see Supplementary Table 1. Collectively, we validated the remarkable predictive capability of our prognostic signatures and underscored its substantial potential for clinical applicability from multiple perspectives.


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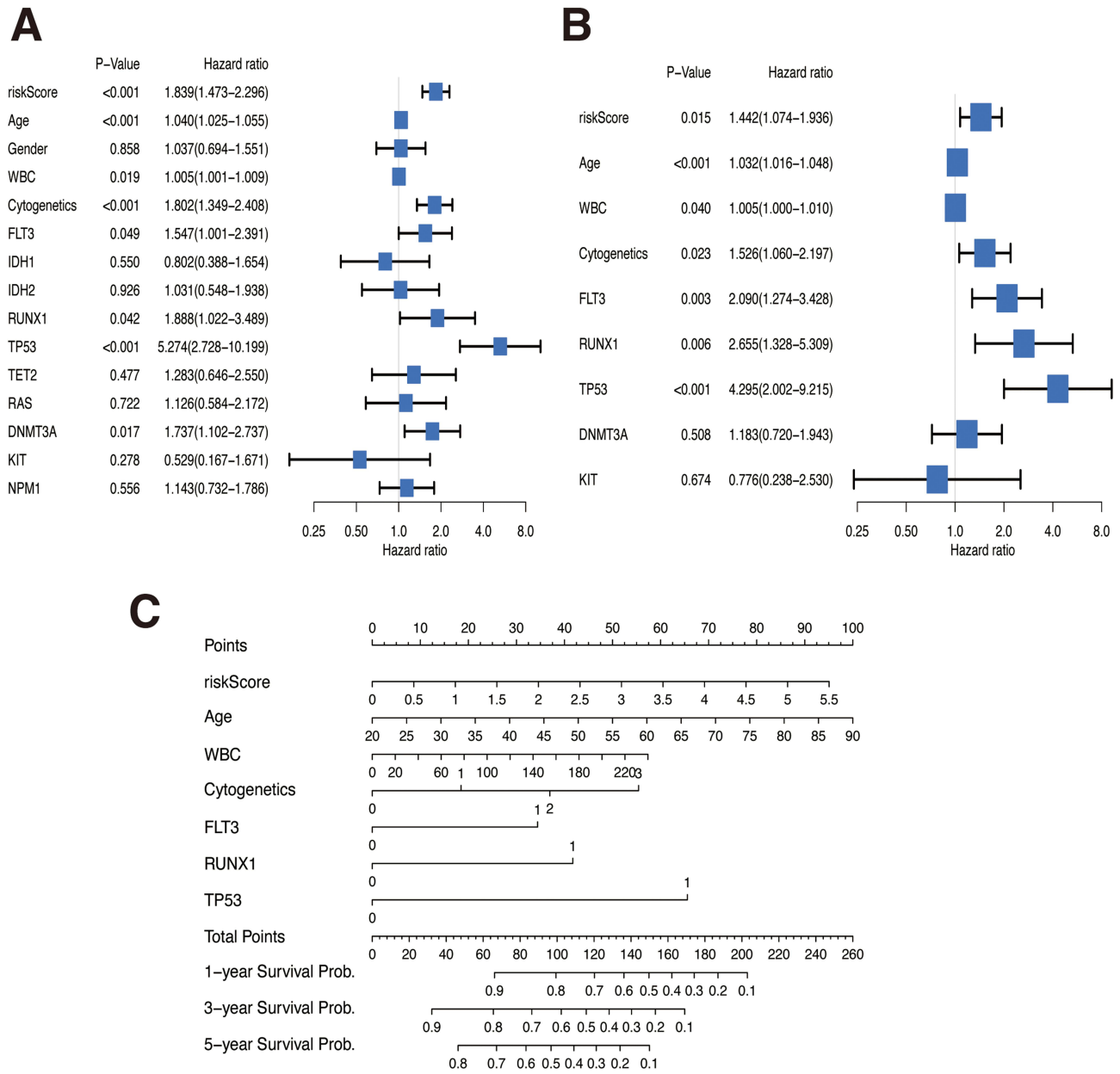


**Figure 3** The nomogram to predict 1-, 3- and 5- year overall survival of AML patients (**A**) Univariate Cox regression analysis revealing clinical characteristic related to prognosis. (**B**) Multivariate Cox regression analysis revealing clinical characteristics related to prognosis. (**C**) The nomogram predicting overall survival of AML patients.

## Correlation of Neutrophil-Related Genes with Prognosis in AML

With the aim of exploring the function of neutrophil-related genes incorporated into the prognostic model, survival analysis and ROC curve were performed (Figure 4A, B and Figure S2). The Kaplan-Meier curves indicated that four of these genes (CSF3R, BRAF, CD300A, CD37) were involved in the prognosis of AML, while FFAR2 was not significant. Among these genes, CD37 emerged as the strongest predictor of survival ($p$=0.0026), with the AUC values of 0.698, 0.626, and 0.680 at 1, 3, and 5 years (Figure 4A). The prognostic value of CD37 was further validated using GEO datasets from the GSE10358 cohort ($p$=0.00094, Figure 4B), the GSE14468 cohort ($p$=0.041, Figure 4C) and the GSE71014 cohort ($p$=0.0087, Figure 4D), suggesting that CD37 is the critical neutrophil-related signatures linked to an adverse prognosis of AML.

Several gene expression-based prognostic models for AML have been recently emerged, with the LI24 and LSC17 models showing superior prognostic capabilities and the ability to improve risk stratification.[25,26] Therefore, it is

interesting to explore the predictive power of CD37 expression within the context of these novel schemes. We implemented both models in TCGA database and patients were stratified into high- and low-risk groups as shown in Figures 4E and F. When applied to each risk group stratified by LI24, CD37 expression remained a significant predictor for OS in the high-risk group (Figure 4E). Similarly, within the high-risk categories defined by the LSC17 model, CD37 status was able to distinguish survival outcomes (Figure 4F). In summary, these results indicate that CD37 could serve as a valuable candidate for refining existing classification schemes, potentially improving patient management and treatment stratification in AML.

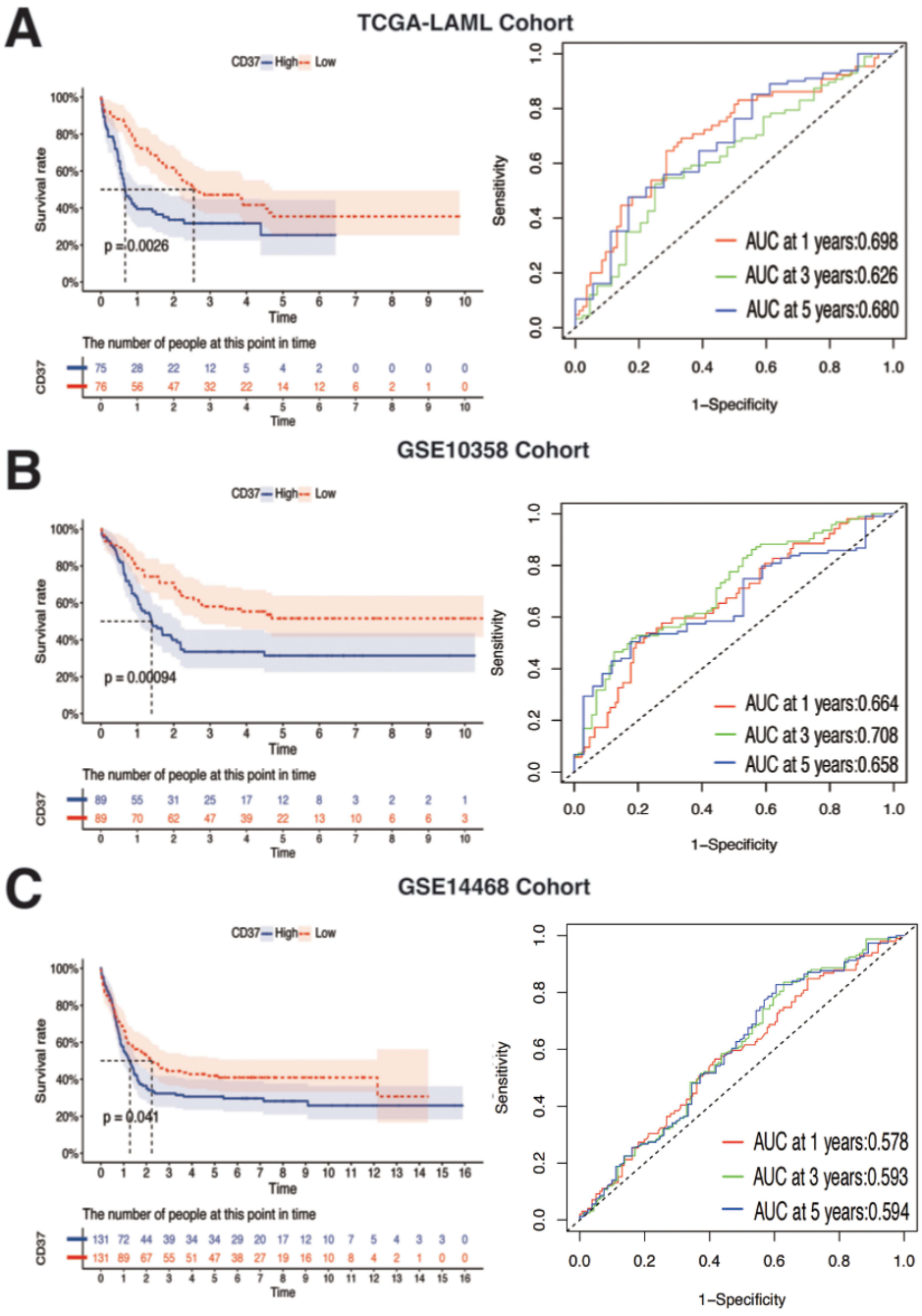


**Figure 4** Continued.


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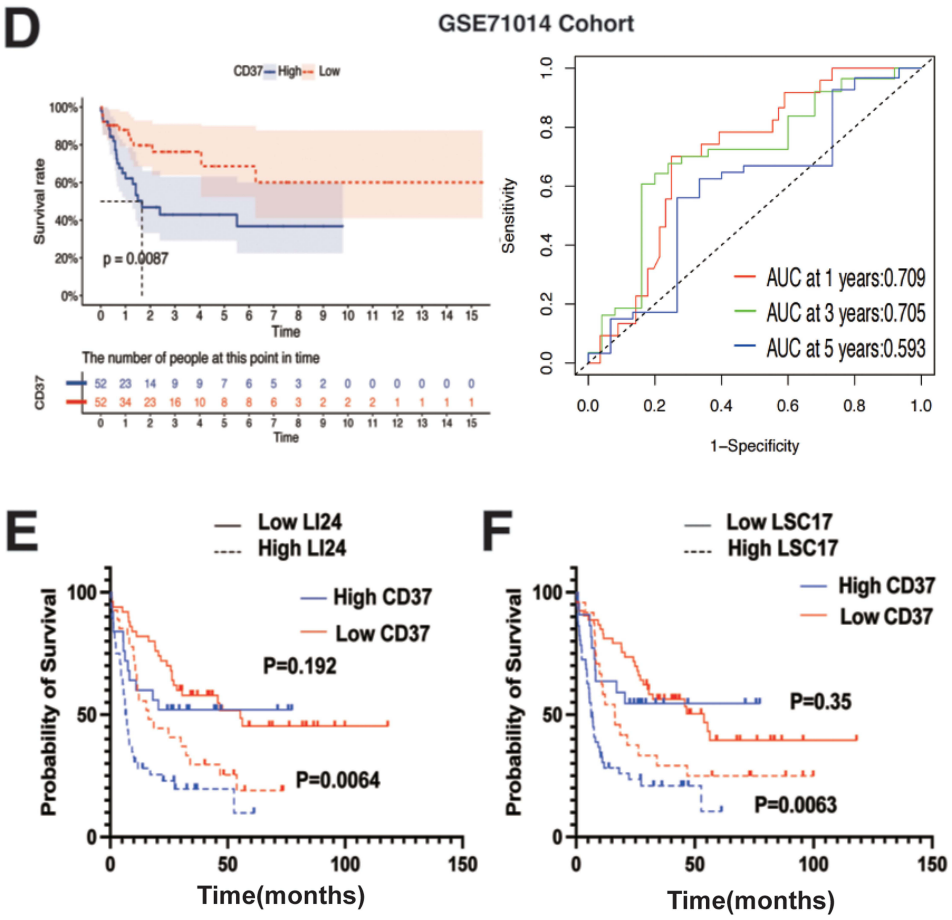


**Figure 4** Prognostic value of CD37 expression in the context of established risk stratification schemes. ROC curves evaluating the sensitivity and specificity of CD37. (**A**) TCGA-LAML Cohort ($p$=0.0026). (**B**) GSE10358 Cohort ($p$=0.00094). (**C**) GSE14468 Cohort ($p$=0.041). (**D**) GSE71014 Cohort ($p$=0.0087). OS of patients from TCGA as stratified by the LI24 (**E**) and the LSC17 (**F**) signature.

## Association of CD37 Expression with Immunity and Cellular Structure

To gain insight into the involvement of CD37 in AML development, patients in the TCGA dataset were dichotomized at the median expression of CD37. The principal component analysis showed that the gene expression profiles were significantly different between the CD37 high and CD37 low groups (Figure 5A). The "limma" package was then used in the R environment to identify DEGs between the two groups. A total of 902 DEGs, including 584 up-regulated genes and 318 down-regulated genes, were selected with a cutoff $P$-value of 0.05 and |fold- change| > 1 (Figure 5B).

Functional enrichment analysis was performed using the GO and KEGG databases to elucidate the biological functions of DEGs. GO enrichment analysis revealed that upregulated DEGs were primarily associated with immune reaction, including leukocyte mediated immunity, regulation of immune effector process, negative regulation of immune system process, negative regulation of T cell proliferation and regulation of leukocyte mediated immunity (Figure 5C). Meanwhile, downregulated DEGs were enriched in cellular structure, such as synapse assembly, extracellular matrix organization, extracellular structure organization, and cell junction assembly (Figure 5D). KEGG enrichment analysis demonstrated that upregulated DEGs were predominantly enriched in antigen processing and presentation, as well as the B cell receptor signaling pathway (Figure 5E), while downregulated DEGs were mainly associated with the cAMP signaling pathway and GABAergic synapse (Figure 5F). Furthermore, GSEA analysis yielded similar conclusions to the GO and KEGG analysis. High CD37 expression was closely correlated with immune reaction, including adaptive immune response, leukocyte mediated immunity, lymphocyte mediated immunity, T cell activation, immune receptor activity and antigen processing and presentation (Figure 5G, I and J). Additionally, high CD37 expression was associated

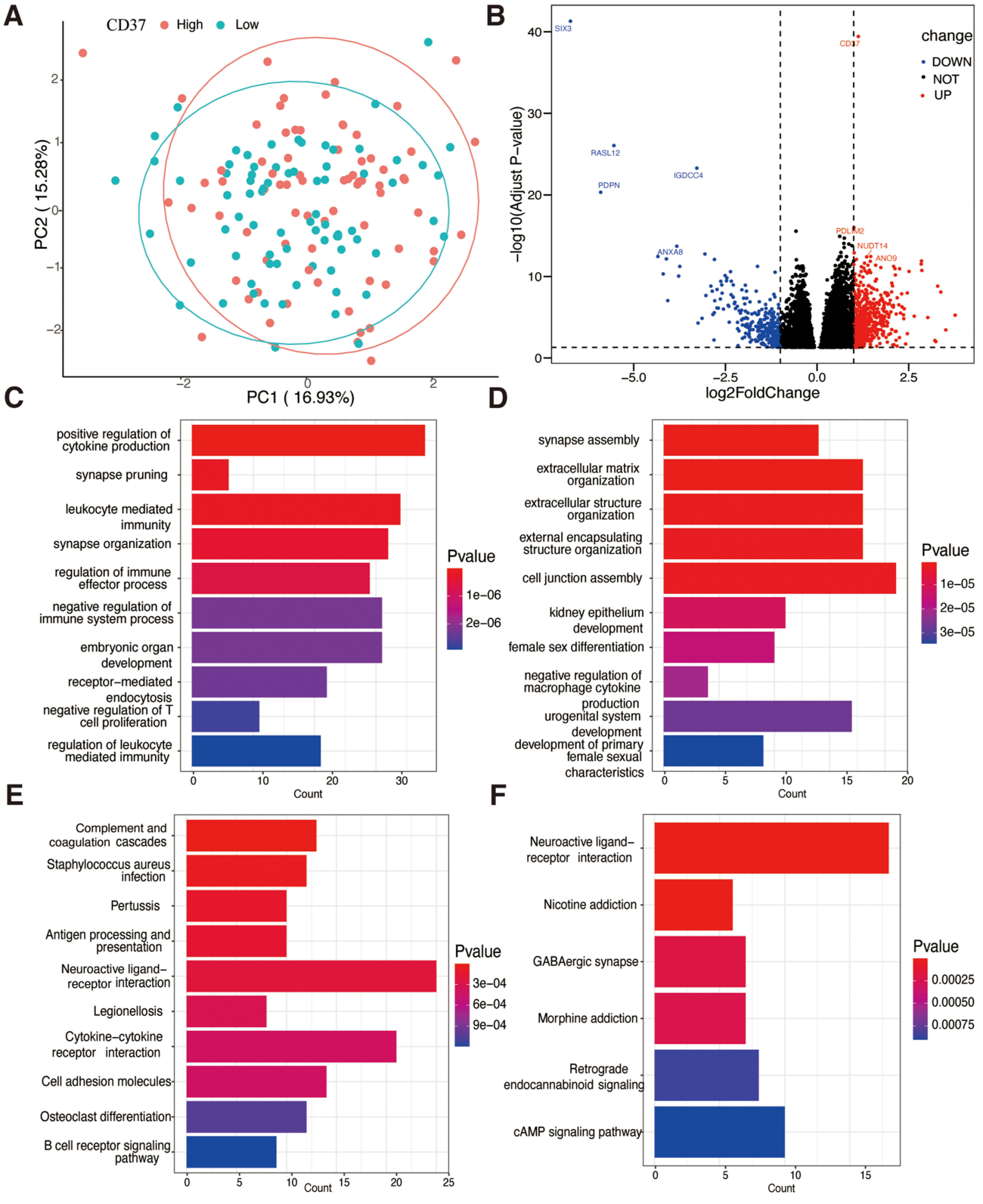


**Figure 5** Continued.


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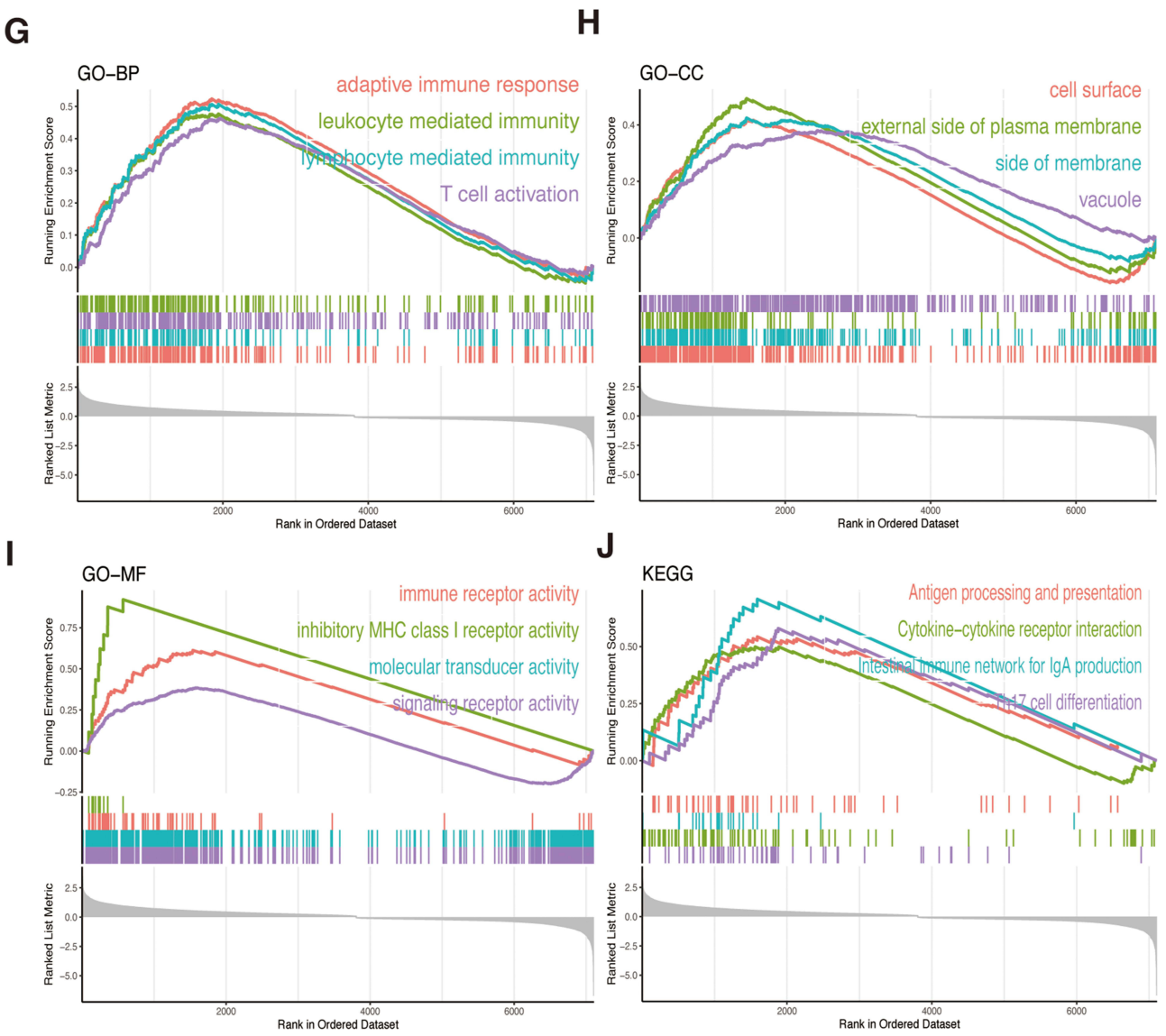


**Figure 5** (**A**) Comparison of gene expression profiles of the CD37 high and CD37 low group. (**B**) The Volcano plot of DEGs. DEGs, differentially expressed genes. Enrichment analysis of DEGs. (**C**) The most enriched GO terms of up-regulated DEGs. (**D**) The most enriched GO terms of down-regulated DEGs. (**E**) The most enriched KEGG pathways of up-regulated DEGs. (**F**) The most enriched KEGG pathways of down-regulated DEGs. (**G, I** and **J**) Immunity related pathways in GSEA enrichment analysis. (**H**) cellular structure pathways in GSEA enrichment analysis.
**Abbreviations**: GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; GSEA, gene set enrichment analysis.

with gene signatures related to cellular structures, such as cell surface, external side of the plasma membrane, membrane side, and vacuole (Figure 5H). These results allow us to reasonably infer that CD37 is involved in immune regulation of AML.

## CD37-Shaped Immune Disorders Context

To further elucidate the role of CD37 in the immune microenvironment of AML, we performed ESTIMATE analysis to assess the level of immune infiltration. The results showed that the CD37 high group had higher immune scores and overall ESTIMATE scores compared to the CD37 low group (Figure 6A). Consistently, xCell analysis demonstrated that the higher CD37 expression levels, the more immunescore fractions (Figure 6B). Similar results were observed when the immune fractions were calculated by ESTIMATE and xCell analysis in another two distinct cohorts (GSE10358 and

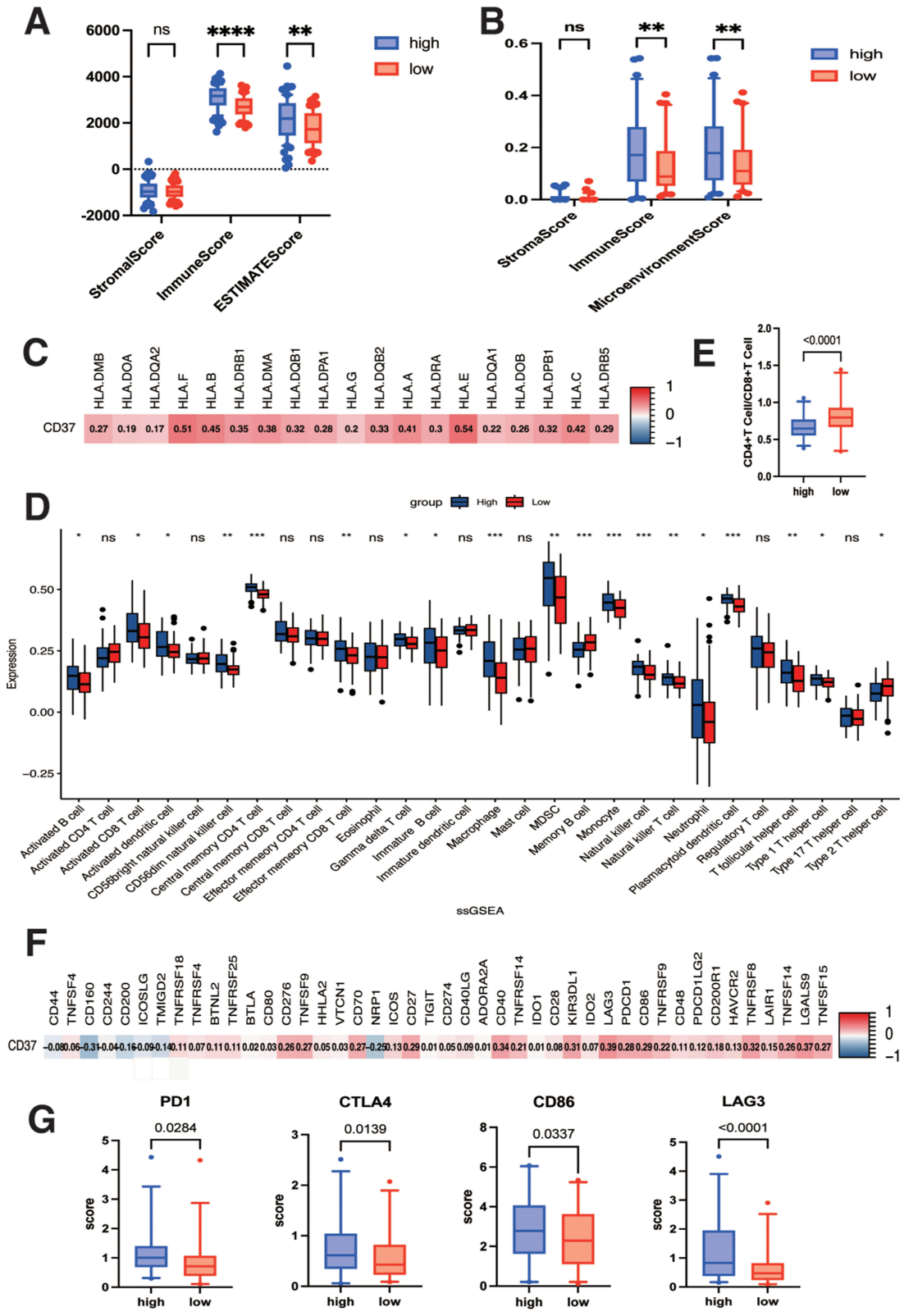


**Figure 6** Comparison of immune profiles in two groups with different CD37 expression. Immune scores in the two groups, in ESTIMATE (**A**) and xCell (**B**). (**D**) Boxplot of the ESTIMATE score. (**E**) $CD4^+/CD8^+$ T cells were elevated in the CD37 high group. Heatmap showing correlation between the expression of CD37 with HLA genes (**C**) and immune checkpoint genes (**F**) in the TCGA dataset. (**G**) In CD37 high group, PD1, CTLA4, CD86 and LAG3 were all increased. (*: $p<0.05$; **: $p<0.01$; ***: $p<0.001$; ****: $p<0.0001$; ns: not significant; The bold text indicates correlation.).


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GSE14468, Figure S3A-D). Since cancers with higher human leukocyte antigen (HLA) gene expression were often more immunologically active,[27] we thereafter investigated the correlation of CD37 and the HLA markers. Indeed, CD37 expression was positively associated with the majority of these HLA genes (Figure 6C). These findings provided insight into the increased immune cell infiltration of high CD37 expressers, which warrants further exploration.

ssGSEA analysis was then applied to calculate the proportion of each type of immune cell within the tumor microenvironment (TME). As shown in Figure 6D, neutrophils were significantly enriched in AML patients with a CD37 high score compared to those with a CD37 low score. Furthermore, the preferential enrichment of neutrophils in the CD37 high group was also found in GSE10358 and GSE14468 datasets (Figure S4A and B). In the CD37 high group, myeloid-derived suppressor cells (MDSCs), NK cells, NKT cells and Th1 cells were increased (Figure 6D), whereas Th2 cells and the ratio of $CD4^+$ T /$CD8^+$ T cells were decreased (Figure 6E), indicating the presence of an immunosuppressive environment. This was also true for the higher fractions of immunosuppressive components like MDSC, NK cells and NKT cells in the CD37 high group within two independent AML cohorts (Figure S4C and D). By CIBERSORT analysis, we also observed a significant enrichment of Treg cells and activated NK cells as well as a concomitant reduction in the ratio of $CD4^+$ T /$CD8^+$ T cells in the CD37 high group, as compared to the CD37 low group (Figure S5A and B). These data suggest that CD37 plays a significant role in shaping the highly disturbed immune microenvironment of AML.

Considering the crucial roles of immune checkpoints in the TME, it is therefore of great interest to evaluate the relationship between CD37 and these immune signatures. Our findings revealed robust positive correlations between CD37 expression and immune checkpoint molecules such as LAG3, LGALS9, CD40, and TNFRPSF8 (Figure 6F). Moreover, high CD37 expressers exhibited significant increases in those key targets relevant to AML, including PD1, CTLA4, CD86, and LAG3 (Figure 6G).

## Predictive Value of CD37 in Responsiveness to Immunotherapies

Given the immunophenotypic discrepancy between the CD37 high and CD37 low group, it is reasonable to speculate that CD37 holds promise in predicting the immunotherapy response. Subsequent unsupervised group analysis revealed significant distinctions in the immune profiles of these two groups (Figure 7A). Further correlation analysis indicated strong associations of CD37 expression with immune cell infiltration, particularly highlighting central memory $CD4^+$ T cell, NK cell and MDSCs (Figure 7B). Additionally, we explored the relationship between CD37 expression and the functional status of immune cells. GSEA analysis showed that $CD4^+$ T cells, naïve T cells, naïve $CD8^+$ T cells, naïve B cells, naïve $CD4^+$ T cells, monocytes and neutrophils gene sets were significantly enriched in the CD37 high group (Figure 7C). This suggests that CD37 may play a role in coordinating the aberrant function of immune cells.

Recently, a gene expression-based coring system called Tumor Immune Dysfunction and Exclusion (TIDE) has demonstrated outstanding performance in predicting clinical responses to immunotherapy.[28] We therefore assessed the relationship between CD37 and the expression signatures associated with T-cell dysfunction and T-cell exclusion. Surprisingly, we discovered a negative correlation of CD37 with T cell exclusion signatures, including MDSCs, M2 subtype of tumor-associated macrophages (TAMs), Exclusion and the TIDE score, whereas a positive correlation with the T-cell dysfunction score, IFNG, and Merck18 signatures (Figure 7D). This indicates that CD37 molecules might contribute to immune evasion through the induction of T-cell dysfunction. Based on these results, we further explored whether CD37 could serve as a predictive marker for immunotherapy response in AML. In the TCGA AML cohort, we observed significantly higher expression levels of CD37 in predicted responders (Figure 7E), suggesting CD37 expression could indeed be a valuable predictor for immunotherapy in AML.

Additionally, drug sensitivity was predicted utilizing mRNA expression profiles and anti-tumor drug activity data of CD37 in the GDSC database through the oncoPredict algorithm. As illustrated in Figure 7F, a total of 146 drugs were found to interact with CD37, indicating its potential as a druggable target. While CD37 is closely associated with immune regulation, small molecular inhibitors such as BCL2 inhibitors could potentially target CD37. These findings implied that treatment targeting a crucial neutrophil-related gene CD37 might improve the TME of AML patients.

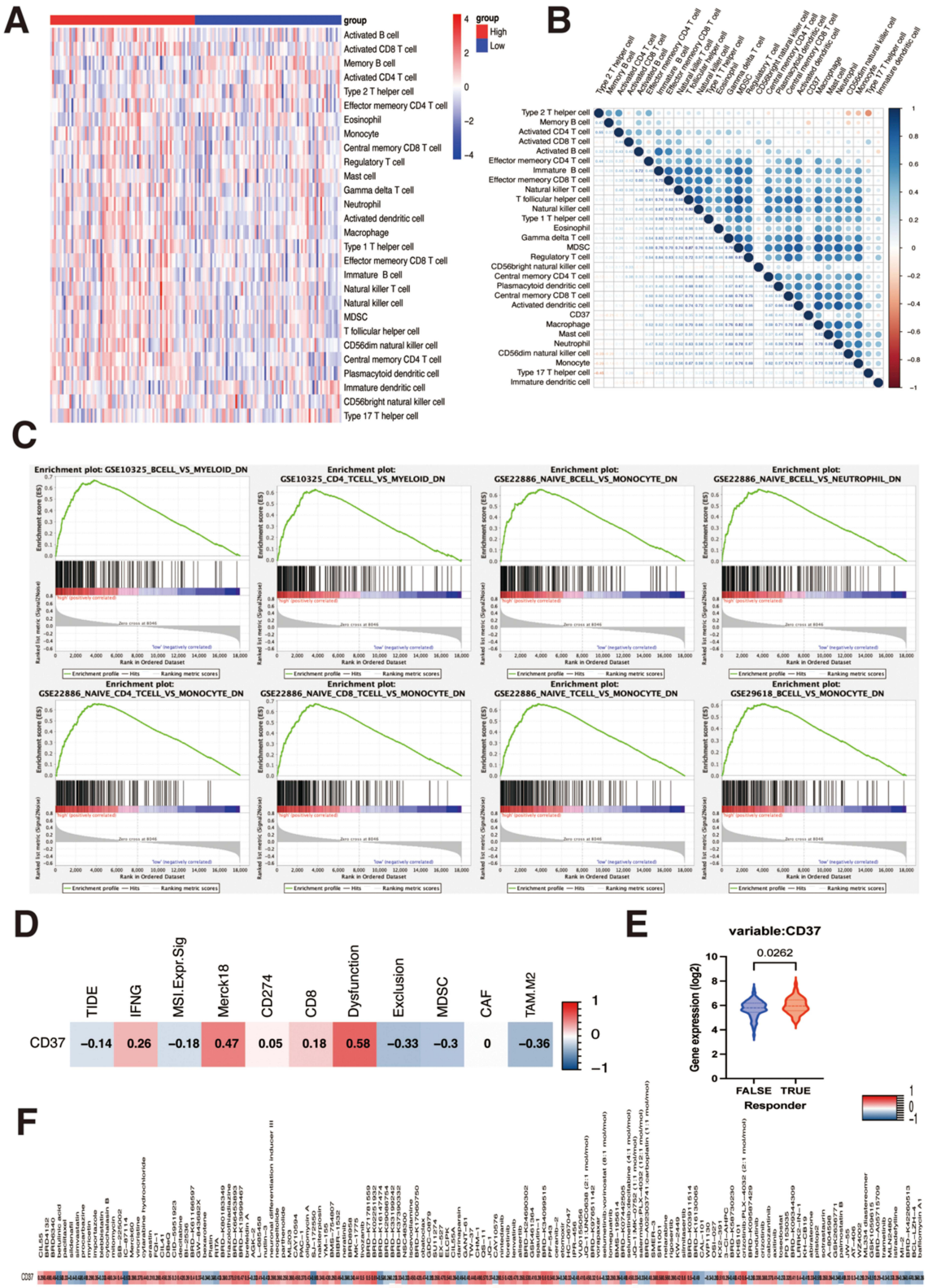


**Figure 7** CD37-shaped immune disorder context (**A**) Heatmap of the infiltration of 28 immune cells in the two groups. (**B**) correlation between CD37 expression and immune cell infiltration. The P-value of the correlation is indicated in box. (**C**) The enriched genes set in the CD37 high group. (**D**) Correlation matrix showing the association between CD37 expression with T-cell dysfunction and T-cell exclusion signatures in TCGA AML cohort, as determined using the tumor immune dysfunction and evasion (TIDE) method. (**E**) Violin plots comparing the expression of CD37 between patients who benefitted or did not benefit from immunotherapy in AML, as predicted by the TIDE algorithm. (**F**) Drug sensitivity analysis results of CD37 in the GDSC database. (The bold text indicates correlation.).


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## Discussion

The current risk stratification of AML patients relies on chromosomal variants and genetic mutations, categorizing them into high risk, intermediate risk, and low risk. However, these conventional prediction tools have mainly focused on the intrinsic characteristics of cancer, ignoring the contribution of TME to cancer development.[29] Recently, the involvement of tumor-associated neutrophils, a key component of the TME, has become increasingly prominent in cancer progression. Tumor-infiltrating neutrophils exhibit pro-carcinogenic effects and predict poor prognosis in bladder urothelial cancer.[30] Furthermore, peripheral NLR has emerged as a potential prognostic factor in various solid tumors[31,32–34] as well as in certain hematological malignancies such as non-Hodgkin lymphoma and multiple myeloma.[35,36] Additionally, neutrophils have been implicated in influencing the efficacy of immunotherapy and mediating resistance to radiation therapy.[37] In this study, we investigated the effect of neutrophil-related genes on AML prognosis and explored a potential prediction system. Importantly, CD37 was identified as a critical neutrophil-related gene associated with adverse AML prognosis. It is important to note that our study did not incorporate certain fusion genes, such as KMT2A, which may play a critical role in specific AML subtypes. This limitation has been explicitly addressed in the Discussion section, underscoring the need for future research to integrate these genetic markers for a more comprehensive prognostic model.

Advancements in next-generation sequencing (NGS) technology have revolutionized our ability to access the genomic profiles of cancer, aiding in precise cancer classification and prognosis prediction. In this study, we focused on investigating the prognostic role of neutrophil-related genes in AML. Our analysis revealed that eight neutrophil-related genes—CSF3R, LST1, ITGAX, BRAF, FFAR2, CD300A, ITGAL, and CD37—exhibited strong correlations with the prognosis of AML. By integrating five of these genes, we constructed an effective prognostic model. The model demonstrated robust prognostic accuracy across multiple cohorts, offering a complementary tool to existing genetic risk frameworks, particularly for AML patients lacking canonical cytogenetic abnormalities. Notably, a significant prevalence of acquired CSF3R mutations has been observed in patients with severe congenital neutropenia during the pre-leukemia stage, progressing to overt AML or myelodysplastic syndrome (MDS).[38] Intriguingly, there is a high incidence of transformation to MDS or AML in patients who harbor acquired CSF3R mutations, suggesting the importance of CSF3R in the pathogenesis and prognosis of AML.[39] BRAF gene, belonging to the RAF kinase family, plays pivotal roles in transmitting growth signals in physiological pathways.[40,41] As a critical constituent of the MAPK pathway, BRAF has been detected as driver mutation in several tumor types, including melanoma, non-small cell lung cancer (NSCLC), and anaplastic thyroid cancer (ATC). Consequently, BRAF has emerged as an appealing target for therapeutic inhibition.[42]

Activation of FFAR2 by microbiota-derived metabolites has been shown to decrease the proliferation of leukemic cells in vitro.[43] Moreover, FFAR2 itself impacts leukemia cell growth in vivo.[44] Deletion of FFAR2 compromises the immunosuppressive capabilities of MDSCs on T cells within the tumor microenvironment.[45] CD300A, also recognized as CMRF-35 or IRp60, belongs to the CD300 cell surface molecule superfamily,[46] which plays a critical role in modulating immune function and contributes to the host response against various diseases, including infectious diseases,[47,48] cancer,[49] and allergy.[50,51] The expression levels of CD300A were associated with risk stratification and the clinical relevance of AML. Elevated CD300A expression may serve as an independent adverse prognostic indicator for OS and relapse-free survival (RFS) in AML.[52] Furthermore, CD300A is involved in regulating neutrophil recruitment, IL-1β production, and participates in the processes of neutrophil apoptosis and efferocytosis.[53]

CD37, belonging to the transmembrane 4 superfamily (TM4SF), is a tetraubiquitin protein prominently expressed on B cell surfaces. CD37 promotes neutrophil adhesion and recruitment by enhancing cytoskeletal function downstream of integrin-mediated adhesion processes.[54] This characteristic makes CD37 an attractive molecular target for immunotherapy against B-cell lymphomas and leukemias.[55] AML patients with high CD37 expression were shown to have shorter OS and disease-free survival (DFS).[56] While previous studies primarily analyzed CD37 survival data from TCGA datasets, our study extended this analysis by incorporating three additional independent AML datasets and two AML prognostic models. Our investigation provided a comprehensive evaluation of the prognostic relevance of CD37 in AML, confirming its association with poorer outcomes. The consistent findings across multiple datasets and prognostic models underscore CD37's potential as a promising biomarker for assessing cancer risk in AML patients. However, the precise mechanism of CD37 in AML remains to be fully elucidated.

CD37 plays a pivotal role in cancer immunity. Our study unveiled a significant correlation between CD37 expression and gene signatures associated with immune regulation in AML. These signatures encompassed various aspects such as leukocyte-mediated immunity, regulation of immune effector processes, negative regulation of the immune system and inhibition of T cell proliferation. Furthermore, the multifaceted involvement of CD37 protein in diverse biological processes including cell adhesion, motility, differentiation, proliferation, metastasis, growth, survival, trafficking, intercellular communication via exosomes, and immune responses is widely acknowledged.[57] Additionally, CD37 interacts with key proteins such as integrins, immune receptors, and signaling molecules, which serve as regulators for leukocyte activation, motility, and antigen presentation.[58]

Emerging studies suggest the pivotal role of CD37 in regulating B-cell survival and shaping immune evasion. Specifically, tumors with high expression of CD37 demonstrate increased infiltration by various immune cell subsets, compared to those with lower CD37 expression levels. It has been known that AML patients commonly present with dysfunctional T cells and NK cells at diagnosis.[59,60] In our investigation, we observed an augmented presence of immunosuppressive cells such as MDSC, Treg cells and NK cells in the high CD37 expression group. Moreover, the elevated ratio of $CD4^+$ T cells to $CD8^+$ T cells suggests an immunosuppressive leukemic microenvironment. This milieu facilitates AML blast evasion from immune surveillance and collaborates to promote disease progression, which might explain the poorer outcomes observed in individuals with high CD37 expression. Furthermore, CD37 may play a role in orchestrating the dysfunction of antitumor immune cells. Our analysis also reveals enrichment of gene sets associated with $CD4^+$ T cells, naive T cells, naive $CD8^+$ T cells, naive B cells and naive $CD4^+$ T cells in the high CD37 expression group. However, further investigations are warranted to elucidate the precise mechanisms by which CD37 influences the development and activation of immune cells.

Although ICIs remain investigational and are not yet standard therapeutics for AML, their potential to enhance antileukemic immunity has prompted extensive clinical exploration, particularly in combination regimens. ICIs therapies, which rejuvenate the effective antitumor immune response mediated by T cells, have revolutionized cancer treatment. Our research indicates a positive association of CD37 expression with T-cell dysfunction scores in AML. High CD37 expression predicts a more favorable response to immunotherapy. Additionally, CD37 correlates positively with inhibitory immune checkpoints like PD1, CTLA4, CD86, and LAG3, which are often overexpressed in AML cells, presenting promising therapeutic targets. Furthermore, our study reveals a positive correlation between CD37 and MHC class II molecules. The complexes of tetraspanins MHC class II molecules exhibit enrichment with the CD86 co-stimulatory molecule and the HLA-DM peptide editor.[61] We propose that CD37 regulates peptide presentation on MHC molecules, potentially influencing T-cell activation. Collectively, these findings suggest CD37 as a potential biomarker for AML immunotherapy.

In summary, we developed a prognostic model for AML incorporating five neutrophil-related genes, demonstrating its potential independent prognostic significance. This model transcends conventional genetic risk stratification frameworks and is the first to systematically link neutrophil biology to AML prognosis. Moreover, we identified a robust link between CD37 expression and immune response in AML. However, the validation of our findings is constrained by insufficient data. Increased clinical samples and prospective studies are necessary to confirm the predictive efficacy of the neutrophil-based model in real-world clinical scenarios. The underlying mechanism of neutrophil-related genes within tumor microenvironment remains ambiguous and requires further exploration in future studies. While our findings are validated across multiple cohorts, experimental confirmation of CD37's mechanistic role in AML immunosuppression is warranted. Future studies should integrate in vitro models and clinical trials to assess CD37-targeted therapies.

## Conclusion

This study establishes a novel 5-gene prognostic model (CSF3R, BRAF, FFAR2, CD300A, CD37) by systematically integrating neutrophil biology into AML risk stratification. Breaking away from conventional genetic frameworks, our model highlights CD37 as a dual-functional biomarker—predicting adverse prognosis and orchestrating an immunosuppressive microenvironment via T-cell dysfunction and immune checkpoint upregulation (PD1, CTLA4). Clinically, the model offers a rapid risk stratification tool compatible with RT-PCR/NGS platforms, while CD37's correlation with immunotherapy sensitivity (TIDE score, $p = 0.004$) and drug interactions (146 agents) positions it as a therapeutic target.

Future work will prioritize experimental validation of CD37's mechanistic role and multicenter trials to translate computational insights into personalized AML therapy.

## Data Sharing Statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors. This paper has been uploaded to Research Square as a preprint: https://www.researchsquare.com/article/rs-4853209/v1.

## Ethical Statement

This study utilized publicly available de-identified data from TCGA, GEO, and OHSU databases. According to Article 32, Paragraphs 1 and 2 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects (China, February 18, 2023), research involving publicly available anonymized data is exempt from IRB approval.

## Statement of Informed Consent

After fully understanding the research content, all participants voluntarily signed the written informed consent form, indicating their agreement to participate in this study.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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