

Increased Co-Expression of PD-L1 and CTLA-4 Predicts Poor Overall Survival in Patients with Acute Myeloid Leukemia Following Allogeneic Hematopoietic Stem Cell Transplantation

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Purpose: Our previous study has demonstrated that high expression of immune checkpoints (ICs) was significantly associated with adverse clinical outcomes in patients with acute myeloid leukemia (AML). This study aims to investigate the significance of the alteration of IC co-expression for evaluating the prognosis of AML patients following allogeneic hematopoietic stem cell transplantation (allo-HSCT).

Patients and Methods: Quantitative real-time PCR (qRT-PCR) data of bone marrow (BM) samples from 62 de novo AML patients, including 37 patients who received allo-HSCT and 25 patients who received chemotherapy only, were used for prognostic analysis.

Results: High expression of PD-1, PD-L1, PD-L2, CTLA-4, and LAG-3 was associated with poor overall survival (OS) in AML patients receiving allo-HSCT, while the expression levels of PD-1, PD-L2, CTLA-4, and LAG-3, other than PD-L1, were not significantly correlated with OS in AML patients receiving chemotherapy. Importantly, PD-L1/CTLA-4 was the best combination model for predicting poor OS in AML patients following allo-HSCT, especially combined with minimal residual disease (MRD).

Conclusion: High expression of ICs in BM of AML patients following allo-HSCT was related to poor outcomes, and increasing co-expression of PD-L1 and CTLA-4 might be one of the best immune biomarkers to predict outcomes in patients with AML.

Keywords: acute myeloid leukemia, allo-HSCT, immune checkpoint, biomarker, prognosis

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the most effective consolidation therapy for patients with intermediate and high-risk acute myeloid leukemia (AML).¹ Although allo-HSCT significantly improves the long-term survival of AML patients, the strong heterogeneity of AML leads to recurrence in approximately 40% of patients and is the main cause of mortality after allo-HSCT.^{2,3} The main reason is not only related to the clinical and genomic diversity of AML but also closely related to the patients' T cell dysfunction which is induced by AML immune suppression microenvironment.^{4,5}

T cell dysfunction is mainly manifested by T cell senescence and exhaustion, the latter is thought to be induced by high expression of immune checkpoints (ICs), such as programmed cell death 1 (PD-1), cytotoxic T-lymphocyte

associated protein 4 (CTLA-4), T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), and lymphocyte activation gene-3 (LAG-3) etc.^{6–10} High expression of PD-1 in T cells and PD-L1 in AML cells has been observed, contributing to the inability of the immune system to effectively eliminate leukemic cells, which allows AML cells to persist and potentially relapse post-transplantation.¹¹ Recently, several studies have investigated the safety and efficacy of IC inhibitors (ICIs) in relapsed AML patients after allo-HSCT.^{12,13} However, the overall response rate (complete remission and partial remission) was 25%, and another 25% of the patients achieved stable disease.¹¹ Therefore, it is necessary to explore the important role of combining two ICIs under allo-HSCT, as well as the prognostic value of the co-expression pattern of the two ICs in AML. Our previous findings demonstrated that high expression of ICs predicts poor overall survival (OS) in AML patients.^{4,14,15} However, the prognostic significance of the co-expression patterns of ICs in AML patients following allo-HSCT is still unclear. In this study, the prognostic value of ICs in de novo AML patients following allo-HSCT from our clinical center was investigated.

Materials and Methods

AML Patients

During the period ranging from January 1, 2013, to December 31, 2018, a total of 62 BM samples were obtained from patients newly diagnosed with AML at our clinical center, including 37 patients who received allo-HSCT and 25 patients who received chemotherapy only, and the clinical characteristics were listed in [Table S1](#). The median follow-up time for the 62 surviving patients was 45.6 months (range: 22.7–80.5 months). Positive minimal residual disease (MRD) was defined as $\geq 0.1\%$ following the European Leukemia Net (ELN) recommendations.^{16,17} In addition, BM samples from 12 healthy individuals were used as controls.

Extraction of RNA and Quantitative Real-Time PCR (qRT-PCR)

Total RNA was extracted based on the manufacturer's protocol for the TRIzol reagent (Invitrogen). RNA was reverse transcribed into cDNA using a reverse transcription kit (Promega, USA). The expression levels of PD-1, PD 1 ligand 1 (PD-L1), PD 1 ligand 2 (PD-L2), CTLA-4, and LAG-3 were quantified with a qRT-PCR kit (TIANGEN, China), and 18S rRNA was used as an internal control using the Real-Time System (Bio-Rad, USA).⁴ The list of primers for qRT-PCR is shown in [Table S2](#). The expression levels of PD-1, PD-L1, PD-L2, CTLA-4, and LAG-3 are presented as $2^{-\Delta\Delta CT}$ values.

Statistical Analysis

All statistics were performed on SPSS (version 22.0, IBM, Armonk, NY, USA) and R (version 4.3.2, <https://www.r-project.org/>), as appropriate. Differences between the two or multiple groups of categorical variables were determined by chi-square or Fisher tests, as appropriate. Differences in Kaplan–Meier curves were analyzed using the Log rank test.^{18–20} The nomogram model was constructed using the R packages “foreign” and “rms”.²¹ The area under curve (AUC) in the receiver operating characteristic (ROC) curve was determined by the R package “pROC”. The best model was obtained by the package “glmulti”.²² The “survRM2” package was used to confirm the restricted mean survival time (RMST). The optimal cut-points of quantitative variables were determined by X-tile software (version 3.6.1, Yale University, New Haven, CT, USA). A two-tailed *P* value < 0.05 was considered statistically significant.

Results

Higher Expression of ICs Was Associated with Poor OS in AML Patients Receiving allo-HSCT

Based on our previous findings that higher expression of PD-1, PD-L1, PD-L2, CTLA-4, and LAG-3 predicted poor OS in AML patients;⁴ thus, these five ICs were used for prognostic analysis in AML patients treated with allo-HSCT ([Figure 1](#)). Interestingly, a clear trend suggesting that high expression of PD-1 was associated with poor OS in AML patients, although there is no significant difference at that point [hazard ratio (HR) = 2.70, 95% confidence interval (CI): 0.83–8.80, *P* = 0.086; [Figure 2A](#)]. Moreover, the high expression of PD-L1 was associated with poor OS in AML patients (HR = 5.91, 95% CI: 1.90–18.33, *P* < 0.001), as well as PD-L2 (HR = 5.34, 95% CI: 1.18–24.22, *P* = 0.015)

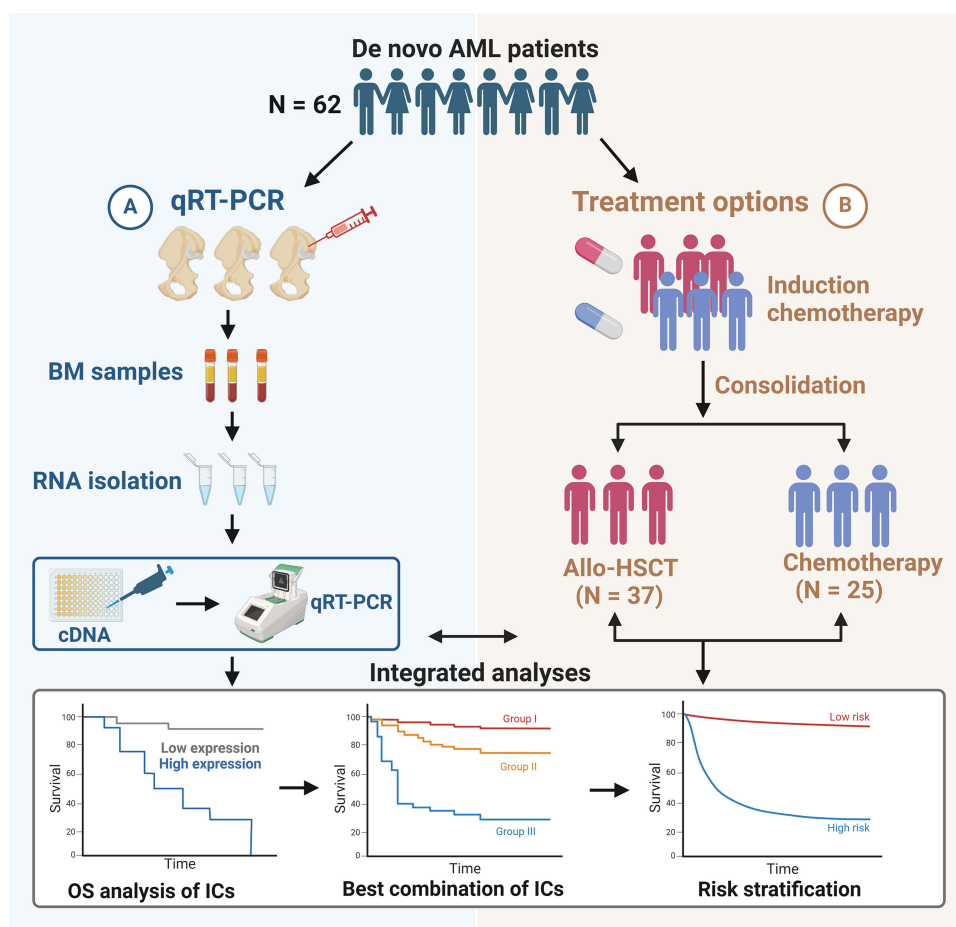


Figure 1 Study schematics. A total of 62 bone marrow (BM) samples from de novo AML patients were first collected for quantitative real-time PCR (qRT-PCR) detection of immune checkpoints (IC) mRNA expression levels, of which 37 patients received allogeneic hematopoietic stem cell transplantation (allo-HSCT) and 25 patients received chemotherapy. Then, overall survival (OS) analysis of ICs and identifies the optimal combination to predict the prognosis of AML patients and construct new risk stratification.

(Figure 2B and C). Additionally, the high expression of CTLA-4 and LAG-3 significantly predicts poor OS in AML patients (CTLA-4: HR = 6.72, 95% CI: 1.84–24.57, $P < 0.001$; LAG-3: HR = 6.56, 95% CI: 1.79–24.00, $P < 0.001$) (Figure 2D and E). However, the expression levels of PD-1, PD-L2, CTLA-4, and LAG-3, other than PD-L1, were not significantly correlated with OS in AML patients who underwent chemotherapy ($P > 0.05$, Figure S1A–E).

PD-L1/CTLA-4 Was the Best Combination Model for Predicting Poor OS in AML Patients Following allo-HSCT

Our previous publications indicated that increased co-expression of ICs was better than a single one in predicting adverse clinical outcomes for patients with hematological malignancies.^{4,23} In this study, we analyzed co-expression patterns of ICs and also found that PD-L1/CTLA-4 was the best combination model for predicting poor OS in AML patients following allo-HSCT (Figure 2F). AML with PD-L1^{high}CTLA-4^{high} (group I) has worse OS and 3-year RMST than PD-L1^{high}/CTLA-4^{low} and PD-L1^{low}/CTLA-4^{high} (group II) and PD-L1^{low}/CTLA-4^{low} (group III) (3-year OS: 30% vs 50% vs 90%; $P < 0.001$) (Figure 2G and H). Importantly, age, gender, and European Leukemia Network (ELN) risk stratification were included in univariate and multivariate Cox regression analyses to balance confounding factors, and the results suggested that age and increased co-expression of PD-L1 and CTLA-4 are independent OS predictors for AML patients (group III vs I: HR = 26.89, 95% CI: 2.84–254.18, $P = 0.004$; Table 1). Because MRD assessment helps refining prognosis and can support the adoption of post-transplant therapeutic modalities, MRD and PD-L1/CTLA-4 were combined for survival analysis. A total of 34 AML patients who received allo-HSCT had MRD data were collected,

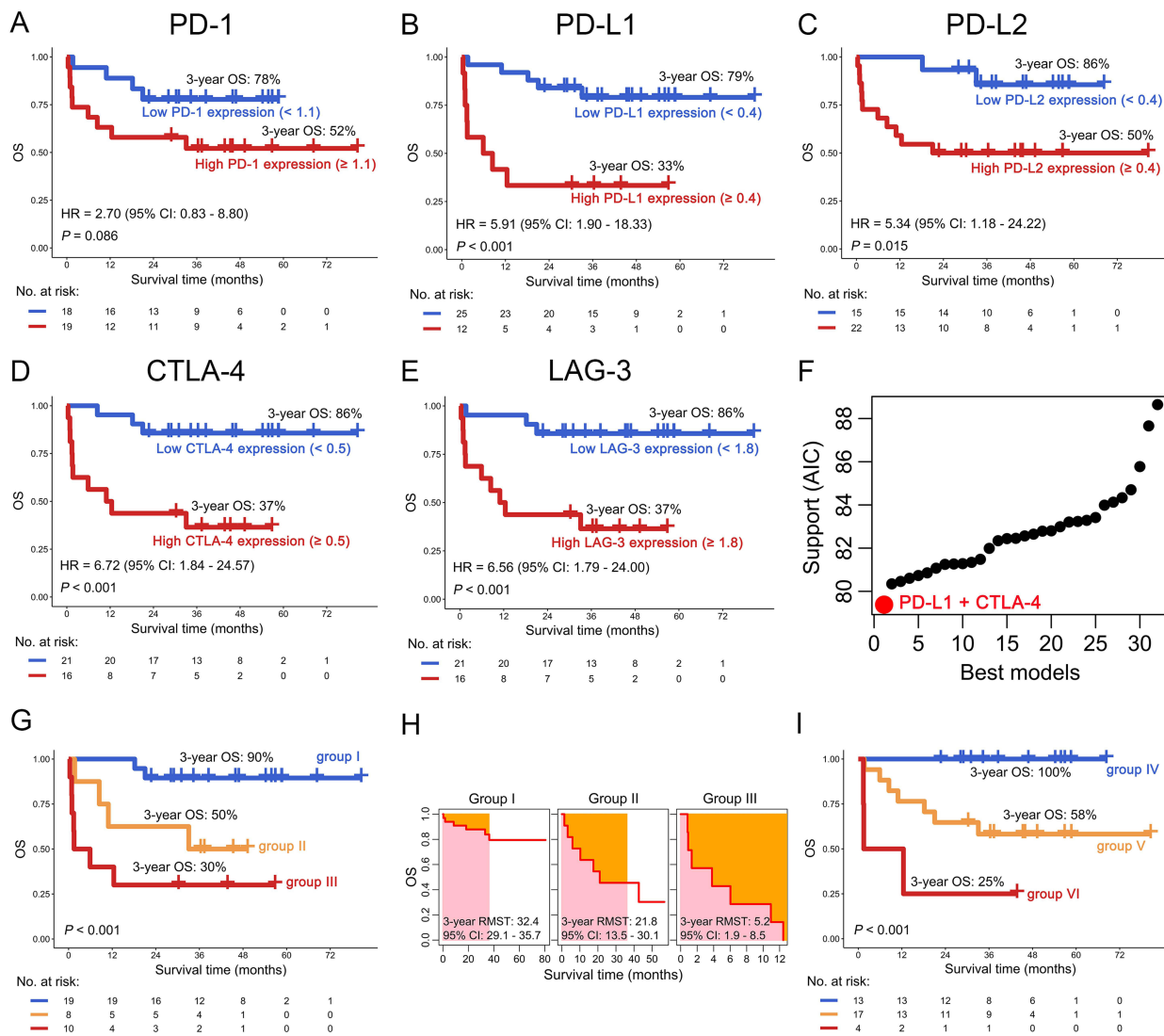


Figure 2 Overall survival (OS) analysis of immune checkpoints (ICs) in AML patients receiving allo-HSCT. (A–E) OS differences between AML patients with high and low expression of PD-1 (A), PD-L1 (B), PD-L2 (C), CTLA-4 (D), and LAG-3 (E). (F) Akaike information criterion (AIC) support profile from the best to the worst models of IC combinations. The red dots represent the best IC combination. (G and H) The differences of OS and 3-year restricted mean survival time (RMST) in groups I, II, and III based on the expression of PD-L1 and CTLA-4. Group I: PD-L1^{low} and CTLA-4^{low}; group II: PD-L1^{high}/CTLA-4^{low} and PD-L1^{low}/CTLA-4^{high}; group III: PD-L1^{high} and CTLA-4^{high}. (I) The differences of OS in groups IV, V, and VI based on the status of minimal residual disease (MRD) and expression of PD-L1/CTLA-4. Group IV: PD-L1^{low}, CTLA-4^{low} and negative MRD; group V: PD-L1^{high} or CTLA-4^{high} or positive MRD; group VI: PD-L1^{high}, CTLA-4^{high} and positive MRD.

and the results indicated that positive MRD or high PD-L1/CTLA4 expression predicted poor OS in patients, especially when they occurred simultaneously ($P < 0.001$, Figure 2I).

Construction of Risk Stratification for AML Patients Following allo-HSCT

As shown in Table 1, age and PD-L1/CTLA-4 are independent OS predictors for AML patients following allo-HSCT; thus, PD-L1, CTLA-4 and age were used to construct a nomogram model to visualize 5-year OS rates for AML patients (Figure 3A). Then, AML patients were divided into two subgroups according to the total risk score derived from the nomogram model, and the high-risk score was significantly associated with poor OS in AML patients (HR = 17.17, 95% CI: 2.22–132.60, $P < 0.001$; Figure 3B, left panel and Figure S2). However, ELN risk stratification cannot predict the OS of AML patients following allo-HSCT ($P = 0.566$; Figure 3B, right panel). The receiver operating characteristic curve (ROC) was used to further evaluate the performance of two different risk stratification in predicting prognosis, and we

Table 1 Univariate and Multivariate Cox Regression Analysis in AML Patients Following allo-HSCT

Variables*	Univariate Cox		Multivariate Cox	
	HR (95% CI)	P	HR (95% CI)	P
PD-L1/CTLA-4 (ref: group I)				
Group II	5.67 (1.03–31.02)	0.046	6.19 (0.96–39.83)	0.055
Group III	13.51 (2.77–65.99)	0.001	26.89 (2.84–254.18)	0.004
Gender (ref: Female)				
Male	1.31 (0.44–3.90)	0.628	4.29 (0.82–22.39)	0.084
Age, y (ref: <60)				
≥60	9.36 (2.91–30.04)	<0.001	4.31 (1.13–16.50)	0.033
Risk stratification (ref: Intermediate)				
Poor	0.81 (0.18–3.70)	0.785	1.02 (0.18–5.72)	0.986
Unknown	0.49 (0.06–3.81)	0.493	1.14 (0.12–11.13)	0.911

Note: *Analysis of AML patients with complete clinical information.

Abbreviations: CI, Confidence interval; group I, PD-L1^{low} and CTLA-4^{low}; group II, PD-L1^{high}/CTLA-4^{low} and PD-L1^{low}/CTLA-4^{high}; group III, PD-L1^{high} and CTLA-4^{high}; HR, Hazard ratio.

found that the risk stratification based on the nomogram model was better than ELN in predicting poor OS in patients following allo-HSCT [nomogram: area under the curve (AUC) = 0.82, 95% CI: 0.70–0.94, $P = 0.002$; ELN: AUC = 0.55, 95% CI: 0.36–0.75, $P = 0.602$] (Figure 3C).

Discussion

The intricate interplay between ICs, which are critical regulators of immune responses, underscores the importance of considering their combined expression patterns in the context of cancer and other immune-mediated diseases.^{23–25} Our previous studies have revealed that the simultaneous expression of multiple ICs, such as PD-1, PD-L1, PD-L2, CTLA-4, and LAG-3, was significantly associated with adverse clinical outcomes of AML patients.^{4,14,15,23} By analyzing the co-expression patterns of ICs, researchers have discovered that certain combinations of these molecules are more predictive of patient prognosis than individual markers.²³ This finding suggests that the interplay between these immune regulators is complex and that a holistic approach, considering their collective influence, is necessary for accurate prognostication.^{24,25} In this study, high expression of PD-1, PD-L1, PD-L2, CTLA-4, and LAG-3, which play the role in the key immune suppression, was associated with poor OS in AML patients receiving allo-HSCT. Importantly, PD-L1/CTLA-4 was the best combination model for predicting poor OS in AML patients following allo-HSCT. This result is similar to our previous findings that increased co-expression of PD-1/CTLA-4 and PD-L2/CTLA-4 correlated with poor AML prognosis.⁴ Meanwhile, the different combination may indicate the special marker in subgroup of AML patients with allo-HSCT. Notably, previous reports have shown that AML patients with positive MRD have a higher recurrence rate and also predict poor OS,^{26–28} which might provide evidence that MRD assessment could help refining prognosis and support the adoption of post-transplant therapeutic modalities. Positive MRD after receiving allo-HSCT may lead to T cell exhaustion, and they might need other treatment options for consolidation, such as chemotherapy, ICIs or secondary transplantation.

In the context of AML transplantation, ICIs may offer several potential benefits.^{11–13} First, they may improve the graft-versus-leukemia (GVL) effect, where donor T cells attack residual AML cells, thereby reducing the risk of relapse. Second, ICIs may modulate the immune microenvironment, creating a more favorable landscape for the engraftment and function of donor immune cells. Lastly, ICIs may help restore immune homeostasis, reducing the risk of graft-versus-host disease (GVHD).^{11–13} However, the overall response rate of AML patients who relapse after allo-HSCT using ICI alone

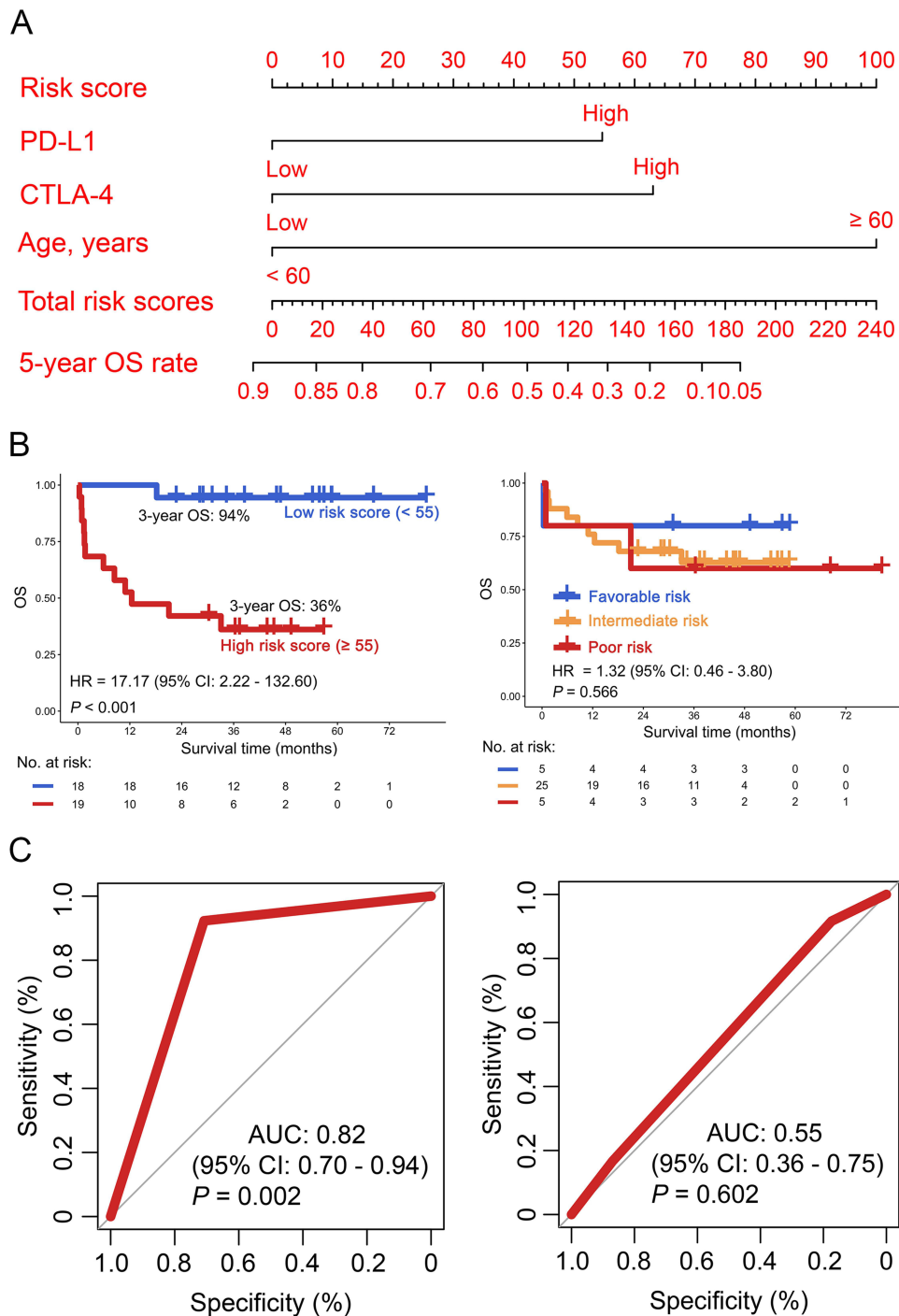


Figure 3 Risk stratification for AML receiving allo-HSCT. **(A)** The nomogram model was constructed by PD-L1, CTLA-4, and age. **(B)** Kaplan–Meier curves of new risk stratification based on risk score (left panel) and European Leukemia Net (ELN) risk stratification (right panel) were plotted. **(C)** The Receiver Operating Characteristic (ROC) curve was used for assessing the performance of new (left panel) and ELN risk stratification (right panel).

is limited.¹¹ Therefore, combining two ICIs under allo-HSCT may improve the prognosis of AML patients, and further exploration with clinical trials is needed. This study may provide a reference that the co-expression pattern of PD-L1 /CTLA-4 may be a potential immune biomarker for designing ICIs combined allo-HSCT for AML.

It is well known that AML is a complex and heterogeneous hematological malignancy and necessitates a tailored therapeutic approach tailored to individual patient characteristics. ELN risk stratification, achieved through a meticulous evaluation of cytogenetic profiles, molecular mutations, and clinical factors, allows for the categorization of patients into

distinct risk groups.^{29,30} This stratification is crucial for guiding treatment regimens, prognostic assessment, and clinical trial design.^{30,31} However, the ELN-2022 and ELN-2017 systems have limited prognostic utility for AML patients following allo-HSCT,³² which was consistent with this study that ELN risk stratification cannot predict the OS of AML patients following allo-HSCT. It is thought that allo-HSCT can overcome adverse genetic alterations or chromosomal abnormalities.³³ Notably, various studies have demonstrated the efficacy and utility of nomogram models in risk stratification across various medical specialties. For example, in oncology, nomograms have been developed to predict survival outcomes and guide treatment decisions for various cancer types, including T-cell lymphoma, esophageal cancer, and AML.^{21,34,35} Altogether, risk stratification based on nomogram models represents a significant advancement in medical practice. By providing accurate and personalized risk assessments, these models enable clinicians to make more informed decisions, optimize patient management, and ultimately improve patient outcomes.³⁶ In this study, the nomogram model based on age and PD-L1/CTLA-4 was used to divide AML patients receiving allo-HSCT into high- and low-risk subgroups, which better evaluated the prognosis of AML patients than ELN risk stratification. However, the nomogram model and risk stratification lack validation from a large cohort and dataset from another clinical center.

Conclusion

High expression of PD-1, PD-L1, PD-L2, CTLA-4, and LAG-3 was associated with poor OS in AML patients receiving allo-HSCT, with PD-L1/CTLA-4 being the optimal combination to predict the clinical outcomes of patients, especially combined with MRD. Moreover, PD-L1/CTLA-4 might be potential immune biomarkers to supplement the risk stratification for AML patients treated with allo-HSCT.

Abbreviations

allo-HSCT, allogeneic hematopoietic stem cell transplantation; AML, Acute myeloid leukemia; BM, Bone marrow; CI, Confidence interval; CTLA-4, Cytotoxic T-lymphocyte associated protein 4; ELN, European Leukemia Network; HR, Hazard ratio; IC, Immune checkpoint; LAG-3, Lymphocyte activation gene-3; OS, Overall survival; PD-1, Programmed cell death 1; PD-L1, Programmed cell death 1 ligand 1; PD-L2, Programmed cell death 1 ligand 2; qRT-PCR, Quantitative real-time PCR; RMST, Restricted mean survival time.

Data Sharing Statement

All supporting data are included in the manuscript and supplemental files. Additional data are available upon reasonable request to the corresponding author.

Ethics Approval and Informed Consent

This study complies with the Declaration of Helsinki and was approved by the Ethics Committee of Guangzhou First People's Hospital (No. K-2021-202-01). All participants provided written informed consent.

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Disclosure

The authors report no conflicts of interest in this work.

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