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ORIGINAL RESEARCH

The Predictive Significance of Interleukin-2 Receptor in Patients with Hepatocellular Carcinoma

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Background: The tumor immune microenvironment (TME) plays a key role in the development of hepatocellular carcinoma (HCC). As the important components of TME, interleukin-2 (IL-2) mediates immune responses by specifically binding to the interleukin-2 receptor (IL-2R). This study aimed to explore the role of IL-2R in HCC development and provided possible clinical implications in HCC prognosis and treatment.

Methods: The IL-2R genetic data were acquired from publicly available TCGA and CCLE databases. Data processing and analysis, including construction of the prognostic model and evaluation of immune status in HCC, were performed on Xiantao platform by using statistical methods including the Wilcoxon test, Cox regression analysis, correlation analysis. GEPIA2 was used to explore the relationship between IL-2R genes expression and clinical stages, while genetic variations in IL-2R subunits in HCC were determined using cBioPortal. The IL-2Rα co-expression gene analysis was conducted on the LinkedOmics database. Enzyme-linked immunosorbent assay (ELISA), colorimetric method, and flow cytometric method were used to analyze peripheral blood samples from patients with HCC.

Results: A prognostic risk model was established by incorporating IL-2Rα, IL-2Rβ, and IL-2Rγ expression. The infiltration levels of B cell memory, T cell regulatory cells (Tregs), and immune checkpoints (PDCD1, CTLA4, CD274 and TIGIT) were significantly elevated in high-risk group of the risk model. Additionally, sIL-2Rα levels were positively correlated with tumor-specific growth factor (TSGF) and Tregs in the peripheral blood of HCC patients.

Conclusion: The prognostic risk model based on IL-2R subunits may play a role in the regulation of immune function within the HCC tumor microenvironment. Besides, IL-2Rα may act as a more important role in HCC development among the three IL-2R subunits. Further research will be needed to verify these initial findings. Overall, these results may provide important insights in clinical prognosis and therapeutic strategies for HCC.

Keywords: HCC, hepatocellular carcinoma, IL-2R, tumor microenvironment, prognosis, bioinformatics

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Introduction

Primary liver cancer is the sixth most commonly diagnosed cancer worldwide. According to the latest global cancer statistics, primary liver cancer accounts for over 750,000 deaths in 2022, ranking as the third leading cause of cancer-related mortality.[1] In China, an estimated 368,000 new cases of liver cancer occurred in 2022, accounting for 42.4% of the global incidence, while liver cancer-related deaths reached 317,000, accounting for 41.7% of the total cancer deaths. Histopathologically, primary liver cancer is mainly composed of hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC), and combined hepatocellular carcinoma and cholangiocarcinoma (cHCC-CCA), with HCC accounting for approximately 75–85% of cases.[2] Although the precise etiology of HCC remains incompletely understood, accumulating evidence suggests it is associated with viral hepatitis, aflatoxin, metabolic and genetic factors, and life style-related risks, including long-term cigarette smoking and alcohol consumption.[3] Due to its occult onset and atypical early clinical manifestation, HCC is frequently diagnosed at intermediate to advanced stages. Despite the rapid development in clinical diagnostic and treatment

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techniques, the prognosis of HCC remains poor owing to its substantial molecular heterogeneity, high recurrence and metastasis.[4,5] Consequently, elucidating the underlying molecular mechanisms and searching for novel biomarkers is necessary for improving early detection and developing therapeutic interventions for HCC.

As early as the 19th century, the "seed and soil" theory was proposed to describe the importance of tumor microenvironment (TME) in cancer development.[6] Apart from tumor cells, TME also includes immune cells, resident stromal cells, extracellular matrix and cytokines secreted by these cells. Interleukin-2 (IL-2) is a glycoprotein-like cytokine primarily produced by activated T lymphocytes. It plays a crucial role in mediating immune regulation by specifically binding to the interleukin-2 receptor (IL-2R), a complex comprising α, β and γ subunits.[7,8] Effective binding of IL-2 and IL-2R could promote the interaction of IL-2Rβ and IL-2Rγ with JAKA kinases, thus triggering downstream intracellular signaling through transphosphorylation. Activated JAK kinases subsequently initiate the PI3K, STAT5, and MAPK signaling pathways, facilitating signal conversion and regulating immune cellular metabolism and function. However, the role of IL-2R in the tumor microenvironment of HCC was still unclear.

IL-2R exists in two forms: membrane interleukin-receptor (mIL-2R) and soluble interleukin-receptor (sIL-2R). Additionally, sIL-2R, also called sIL-2Rα, is generated by shedding the α-subunit of IL-2R at the plasma membrane. As an immunosuppressive factor, sIL-2Rα inhibits lymphocyte proliferation and activation by competitively blocking IL-2 binding to mIL-2R, eventually leading to immune dysfunction immune responses.[9] Previous studies have reported the elevated concentrations of sIL-2Rα correlated with therapeutic effects and prognosis of malignant tumors.[10]

IL-2 was the first cytokine to be successfully used clinically in cancer therapy.[11] Since receiving approval for application in renal carcinoma and melanoma, IL-2 and engineered IL-2 products have been used in the treatment of advanced solid tumors, especially IL-2 biologics, which have proven to be effective in preclinical studies in the modern era of cancer immunotherapy.[12,13] Given the effect of IL-2/IL-2R signaling on cancer progression, this study attempted to evaluate the function of IL-2R in HCC by bioinformatic analysis, which may provide important insights into the prognosis and treatment of HCC.

Methods

Data Collection and Processing

The procedures used in our study are illustrated in the flow chart shown in Figure 1. The gene expression profiles of patients with HCC were downloaded from the TCGA database (https://portal.gdc.cancer.gov/), including 407 tumor samples and 32 paracancerous samples (Supplementary Material 1). The gene expression of each HCC cell line was acquired from the CCLE database (https://portals.broadinstitute.org/ccle/). Further visualized data processing and analysis were operated on the Xiantao online platform (https://www.xiantaozi.com/). The relationship between the expression of IL-2R subunits and clinical stage in HCC was assessed using GEPIA2 (http://gepia2.cancer-pku.cn/#index). Genetic variation features of IL-2R subunits in HCC were determined using the cBioPortal (http://cbioportal.org).

Construction of Prognostic Risk Model

The prognostic risk model was conducted using the R language package on the Xiantao online platform (LASSO regression analysis). Patients were categorized into either high- or low-risk group, with the median risk score serving as the threshold (Supplementary Material 2). The survival outcomes in these two groups were drawn by Kaplan-Meier survival curve. The predictive power of the prognostic model was evaluated through the receiver operating characteristic (ROC) curve.

Analysis of Immune Infiltration in HCC

Based on the CIBERSORT algorithm,[14,15] the immune cell infiltration in different risk groups of HCC was quantified using the markers of immune cells, and the analysis results were conducted on the Xiantao online platform. Additionally, an analysis of the expression levels of immune checkpoints in TME was conducted to quantify the differences between these two risk groups.

Gene Function Enrichment Analysis

The Xiantao online tool was applied to the functional enrichment analysis involving three IL-2R subunits genes. Gene Ontology and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis of IL-2Rα co-expression genes was performed using the LinkedOmics database (http://www.linkedomics.org).

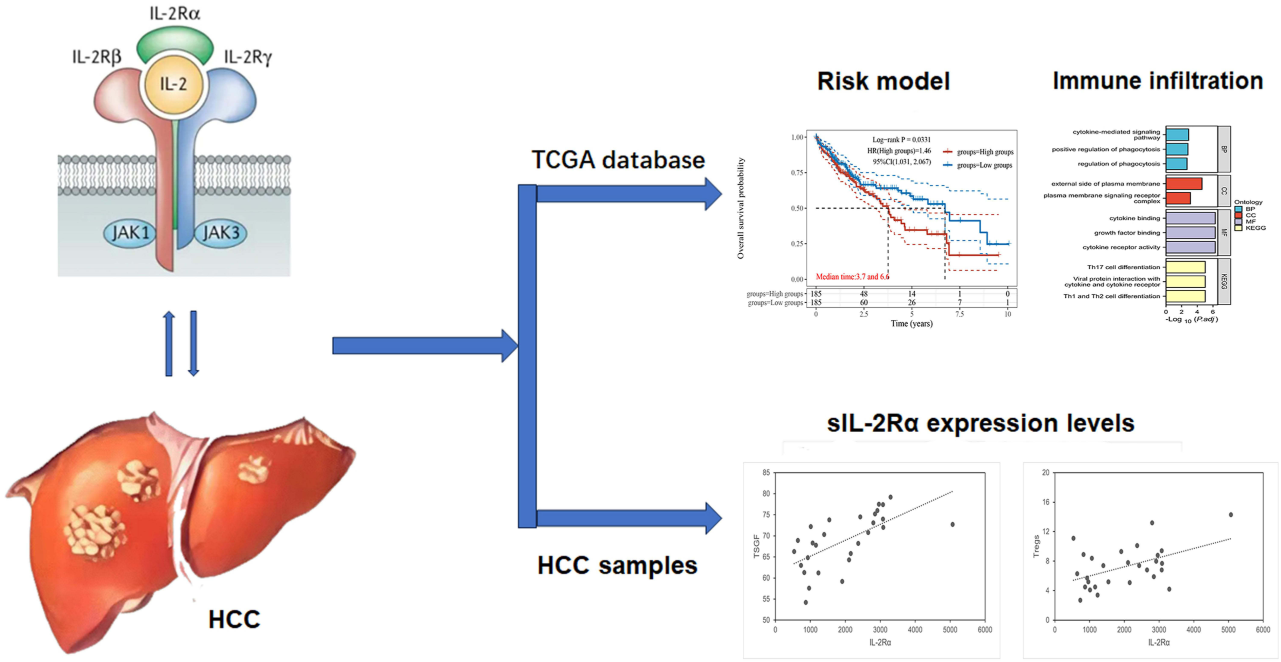

Figure 1 Flowchart of the study procedures.

The Immunologic Detection in Peripheral Blood of Patients with HCC

The clinical data were retrospectively collected from the electronic medical records of 28 treatment-naive patients with advanced HCC. These patients were admitted to the Department of Gastroenterology at the Shanxi Province Cancer Hospital between January 2021 and December 2022. None of the patients had undergone previous chemotherapy, radiotherapy, interventional therapy, or any other treatment. There were 22 males and 6 females aged 41–86 years with an average age of 61.3± 10.2 years old, of which 22 (78.6%) were chronic hepatitis B patients. The main inclusion criteria were complete clinical information, age $\geq$ 18 years, unresectable metastatic hepatocellular carcinoma, confirmed by histopathological examination, who had received no previous systemic therapy for metastatic disease, baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and adequate hematological and organ function. Key exclusion criteria were combined with other systemic tumors, secondary liver malignancy, hematological and immunological diseases, and severe dysfunction of the heart, lungs, and other functional organs. The serum levels of sIL-2Rα were detected by ELISA, and the serum levels of TSGF were measured using a colorimetric method. The kits were purchased from MULTI SCIENCES(LIANKE) BIOTECH Co., Ltd. Flow cytometry was used for lymphocyte subpopulation determination (BD FACSCalibur Cell Sorting System). Written informed consent was obtained from all patients.

Statistical Analysis

For parametric data, the Wilcoxon test was used to compare differences between HCC tissues and corresponding non-cancerous tissues. Kaplan-Meier and log-rank analysis were used to assess differences in survival outcomes between the different groups. Univariate and multivariate Cox regression analysis were used to evaluate the prognostic significance of the genes in HCC. Peripheral blood data were presented as mean ± standard deviation, and one-sample t-tests were used to conduct statistical comparisons. Correlation analysis was used to determine the Pearson correlation coefficient. Statistical significance was set at $P < 0.05$.

Results

IL-2R Subunits mRNA Expression Was Different in HCC Tissues from TCGA Database

The IL-2Rα and IL2-Rγ mRNA expression levels were significantly upregulated in the HCC tissues. However, the mRNA expression levels of IL-2Rβ were significantly downregulated in the HCC tissues (Figure 2A). No significant

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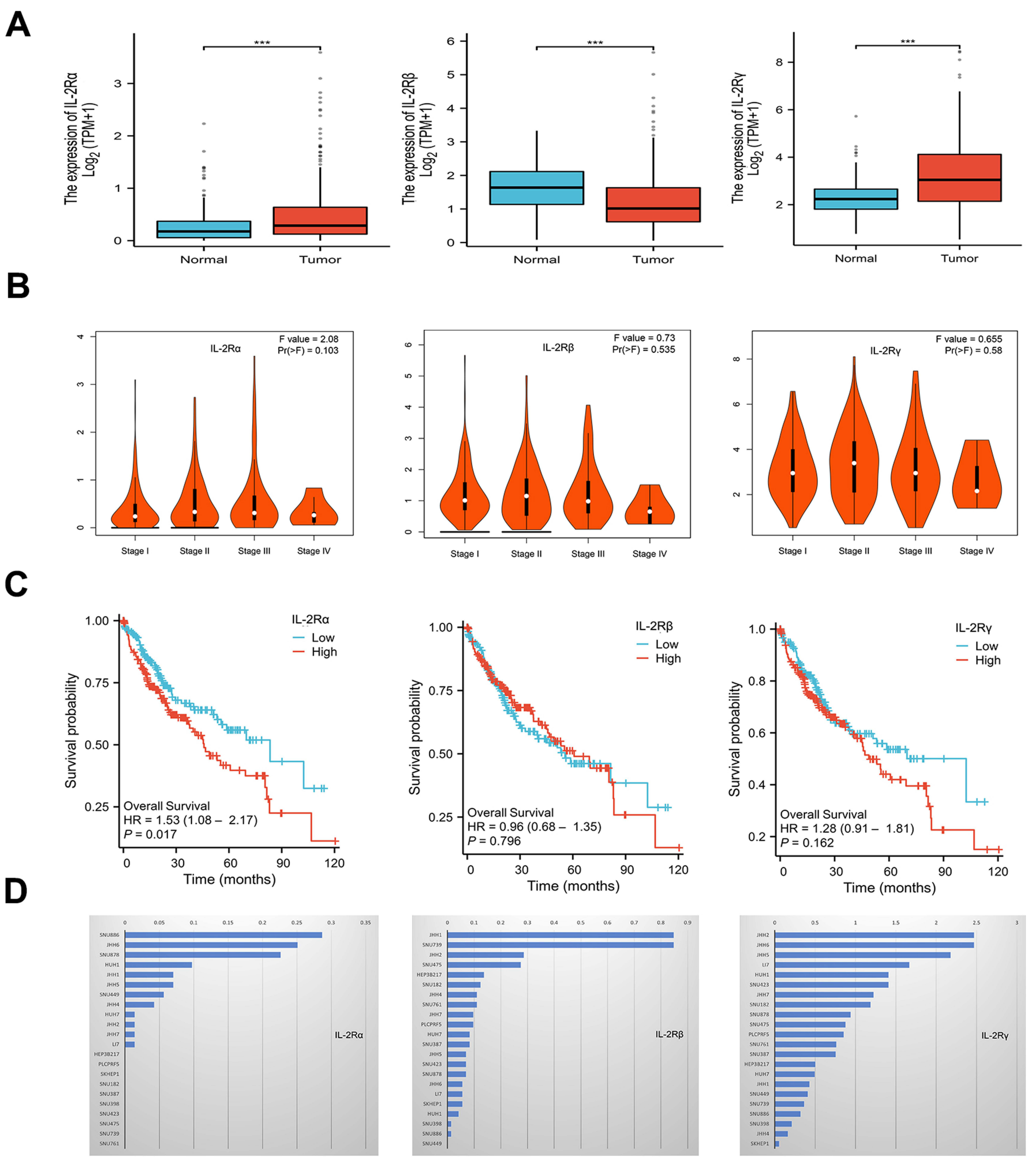

Figure 2 The mRNA expression of three IL-2R subunits genes in HCC tissues from TCGA database. (**A**) The mRNA expression of IL-2Rα, IL-2Rβand IL2-Rγ in HCC and normal tissues in TCGA database (***p<0.001). (**B**) IL-2Rα, IL-2Rβand IL2-Rγ expression at various clinical stages of HCC. (**C**) The effect of IL-2Rα, IL-2Rβand IL2-Rγ expression on OS in HCC. Higher IL-2Rα expression was associated with worse OS. IL-2Rβand IL2-Rγ were not significantly associated with OS (p<0.05). (**D**) The mRNA expression profiles of the three IL-2R subunits across 22 HCC cell lines from cell dataset.

association was observed between the expression of IL-2R subunits and the clinical stage of HCC (Figure 2B). Kaplan-Meier survival curves demonstrated high expression levels of IL-2Rα, signifying a correlation with poor overall survival (OS). In contrast, IL-2Rβ and IL-2Rγ expression levels were not significantly associated with patient survival

(Figure 2C). The cell dataset comprised the mRNA expression profiles of the three IL-2R subunits across 22 HCC cell lines, suggesting HCC cell heterogeneity in the expression of IL-2R subunits mRNA (Figure 2D).

Genetic Variation Features of IL-2R Subunits Were Present in HCC

The cBioportal database was used to obtain genetic alteration information for IL-2R subunits in HCC (TCGA, PanCancer Atlas). The analysis results revealed that genetic alterations in the IL-2R subunits were present in 39 (10%) patients with HCC. These alterations included elevated mRNA expression (58.97%), gene amplification (20.51%), gene mutations (15.39%), and deep gene deletion (5.12%) (Figure 3A). Additionally, the frequency of genetic variation in IL-2R subunits was 5% for IL-2Rα, 3% for IL-2Rβ, and 5% for IL-2Rγ (Figure 3B). Notably, genetic alterations in IL-2R subunits were significantly associated with OS but not with progression-free survival (PFS) (Figure 3C).

The High-Risk Scores of Prognostic Model Correlated with Poor Survival in Patients with HCC

To assess the prognostic significance of three IL-2R subunits genes in HCC, we used the LASSO regression analysis to construct a prognostic risk model, yielding the following formula: Risk score=(0.3271)*IL-2Rα+(−0.2443)*IL-2Rβ +(0.1001)*IL-2Rγ (Figure 4A and B). Based on the median value of the risk scores, patients were categorized into high- and low-risk groups The results revealed that the mortality rates of patients with HCC increased with higher risk scores (Figure 4C and D). The expression of three IL-2R subunits genes was visualized on a heat map (Figure 4E). The Kaplan-Meier survival curve showed that high-risk scores correlated with poor survival in patients with HCC (Figure 4F). ROC curve analysis demonstrated that the predictive performance of the model for OS yielded AUC values of 0.531 for 1-year OS, 0.605 for 3-year OS, and 0.658 for 5-year OS, suggesting the relatively weak precision of this risk model prognostic signature in HCC development (Figure 4G).

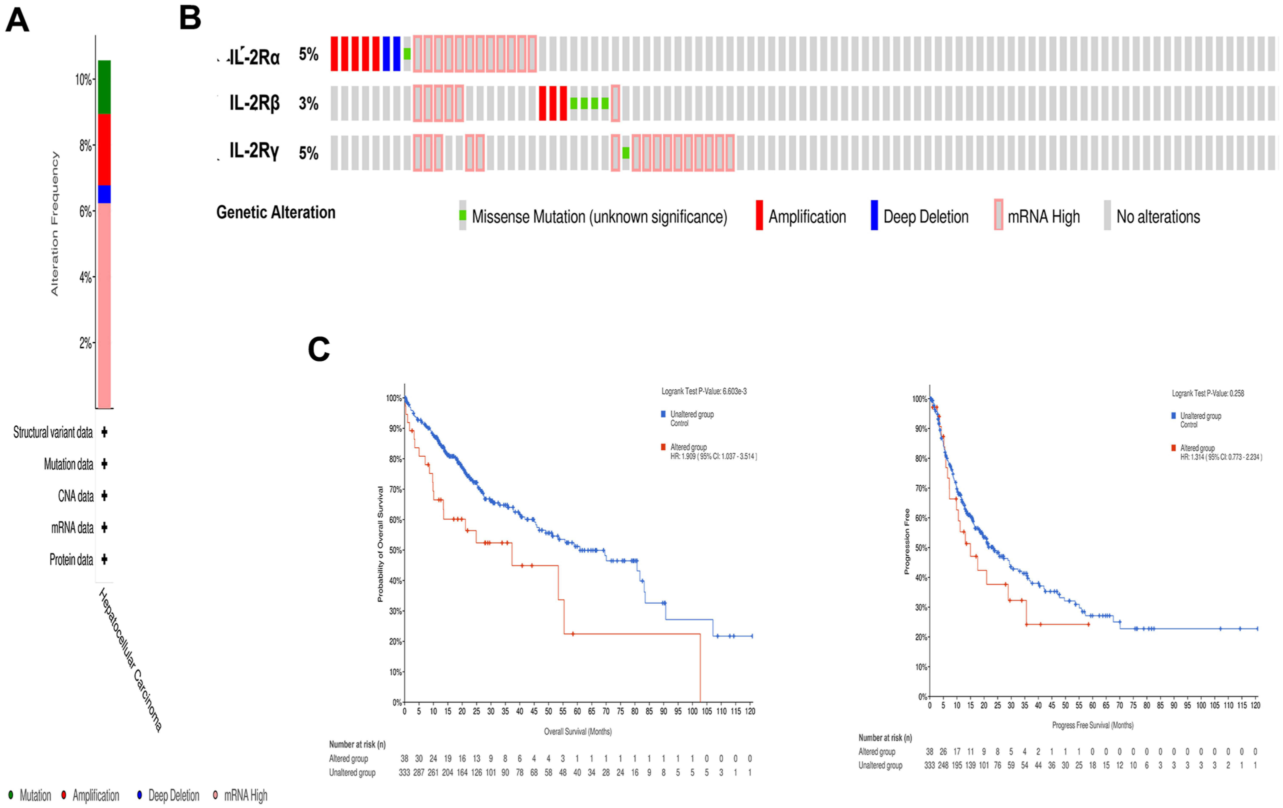

Figure 3 Genetic variation of IL-2R subunits in HCC. (**A**) and (**B**) The genetic alteration frequency of IL-2R subunits in HCC. (**C**) Kaplan-Meier curve showing genetic alterations in IL-2R subunits were associated with OS, but not with PFS.

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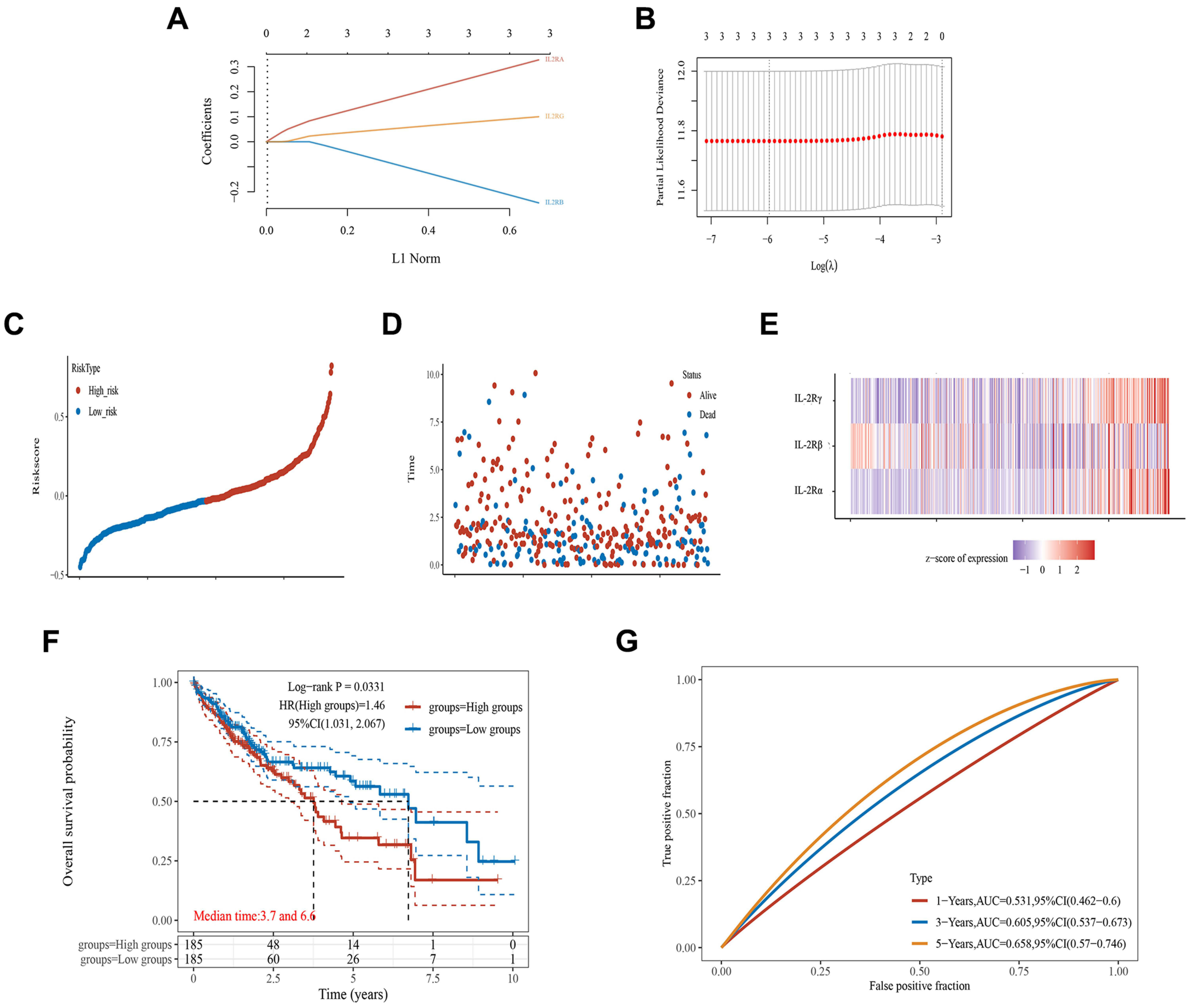

Figure 4 The prognostic role of IL-2R subunits genes in HCC. (**A**) LASSO regression coefficient distribution. (**B**) Optimal parameters determined using cross-validated LASSO regression. (**C**) Risk scores of HCC patients in the high- and low-risk groups. (**D**) Survival status of each HCC patient in the high- and low-risk groups. (**E**) Expression of IL-2Rα, IL-2Rβand IL2-Rγ in the heatmap. (**F**) Kaplan-Meier survival curve showing that patients in the high-risk group had worse prognosis than those in the low-risk group. (**G**) AUC values were 0.531 (1-year OS), 0.605 (3-years OS), and 0.658 (5-years OS).

The Immune Status Was Different in High and Low Risk Groups of HCC

GO and KEGG enrichment analysis revealed that IL-2R subunits played a key role in immune regulation and cytokine-mediated signaling pathways (Figure 5A). Subsequently, we evaluated immune infiltration in HCC in different risk groups using the CIBERSORT algorithm. The results indicated that the infiltration levels of B cell memory and T cell regulatory (Tregs) were significantly higher in the high-risk group than in the low-risk group, while the infiltration levels of naïve B cells, resting NK cells, and monocytes were significantly higher in the low-risk group than in the high-risk group (Figure 5B). Additionally, the expression levels of immune checkpoints (PDCD1, CTLA4, CD274, and TIGIT) were significantly higher in the high-risk group than in the low-risk group (Figure 5C).

IL-2Rα Regulated the Immune Function of HCC

Univariate and multivariate Cox regression analysis demonstrated that pathological T stage and IL-2Rα were independent prognostic predictors of HCC (Figure 6A). Subsequently, the LinkedOmics database was used to identify IL-2Rα co-

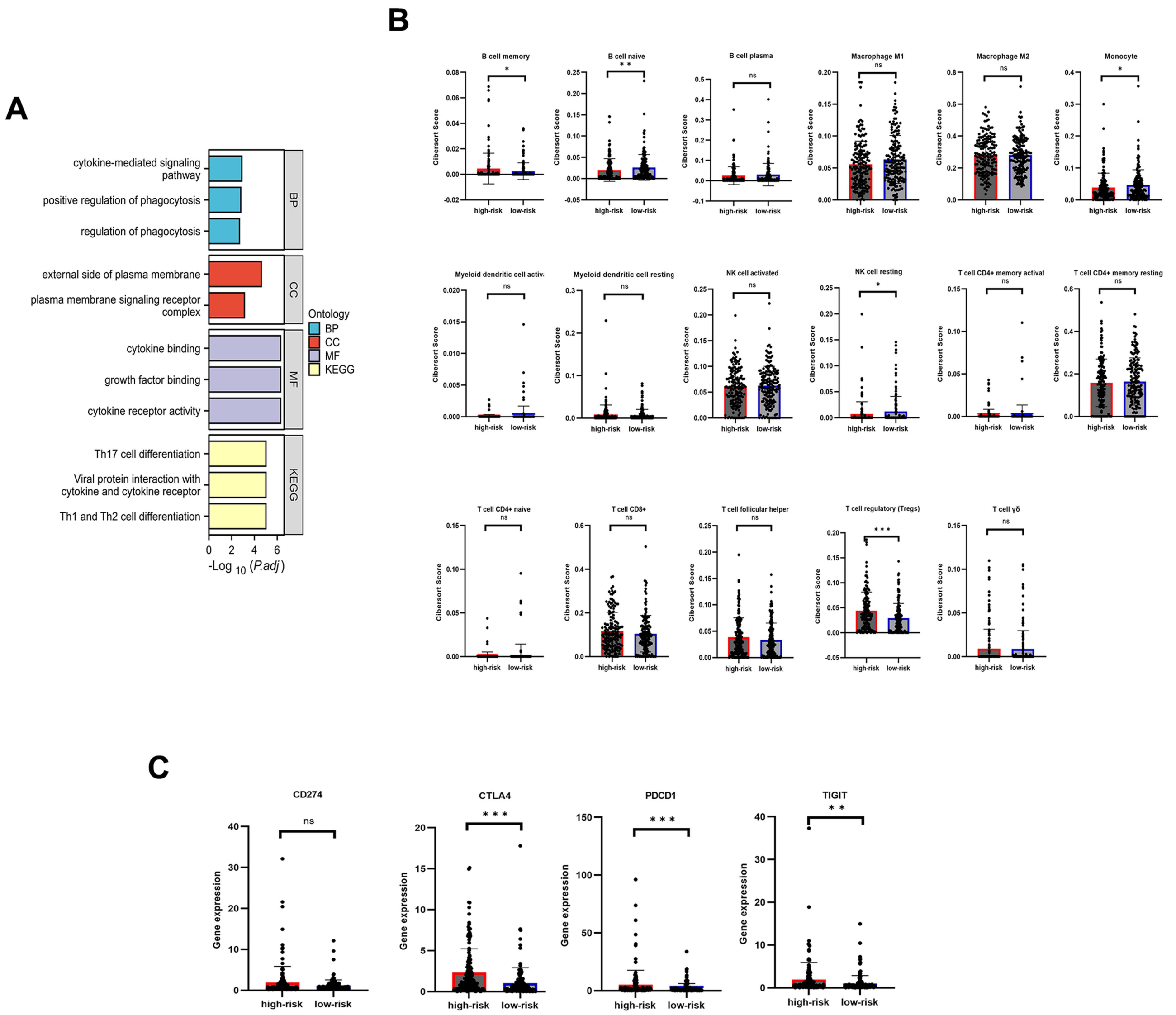

Figure 5 Immune infiltration in high and low risk groups of HCC. (**A**) GO and KEGG enrichment analyses of IL-2R subunits. (**B**) Immune cell infiltration in the high- and low-risk HCC groups. (**C**) Expression of immune checkpoint genes in the high- and low-risk HCC groups. *p<0.05, **p<0.01, ***p<0.001, ns: no significance.

expression patterns in HCC. The top 50 genes that were positively and negatively related to IL-2Rα were visualized in a heat map (Figure 6B). IL-2Rα related genes might play a role in cellular immunity, cell metabolism, and other biological processes (Figure 6C). Additionally, IL-2Rα expression positively correlated with the infiltration levels of T cell CD4+ T cells (Figure 6D). The expression levels of the immune checkpoints (PDCD1, CTLA4, CD274 and TIGIT) were significantly upregulated in the high IL-2Rα expression group (Figure 6E). The expression levels of sIL-2Rα and TSGF in the peripheral blood of patients with HCC were significantly elevated above the reference value limits (Table 1). Correlation analysis revealed that sIL-2Rα positively correlated with TSGF ($r = 0.6445$, $p < 0.01$) and Tregs ($r = 0.4875$, $p < 0.01$) (Figure 6F; Supplementary Material 3).

Discussion

Hepatocellular carcinoma is one of the most aggressive cancers and is associated with high mortality and poor prognosis. It is estimated that 70% of HCC patients remain undiagnosed until the disease has progressed to an advanced stage, with a 5-year survival rate of less than 10%.[2] Therefore, systematic therapies play a crucial role in the treatment of patients with advanced HCC. HCC is inherently resistant to chemotherapy and often exhibits poor responsiveness to the currently

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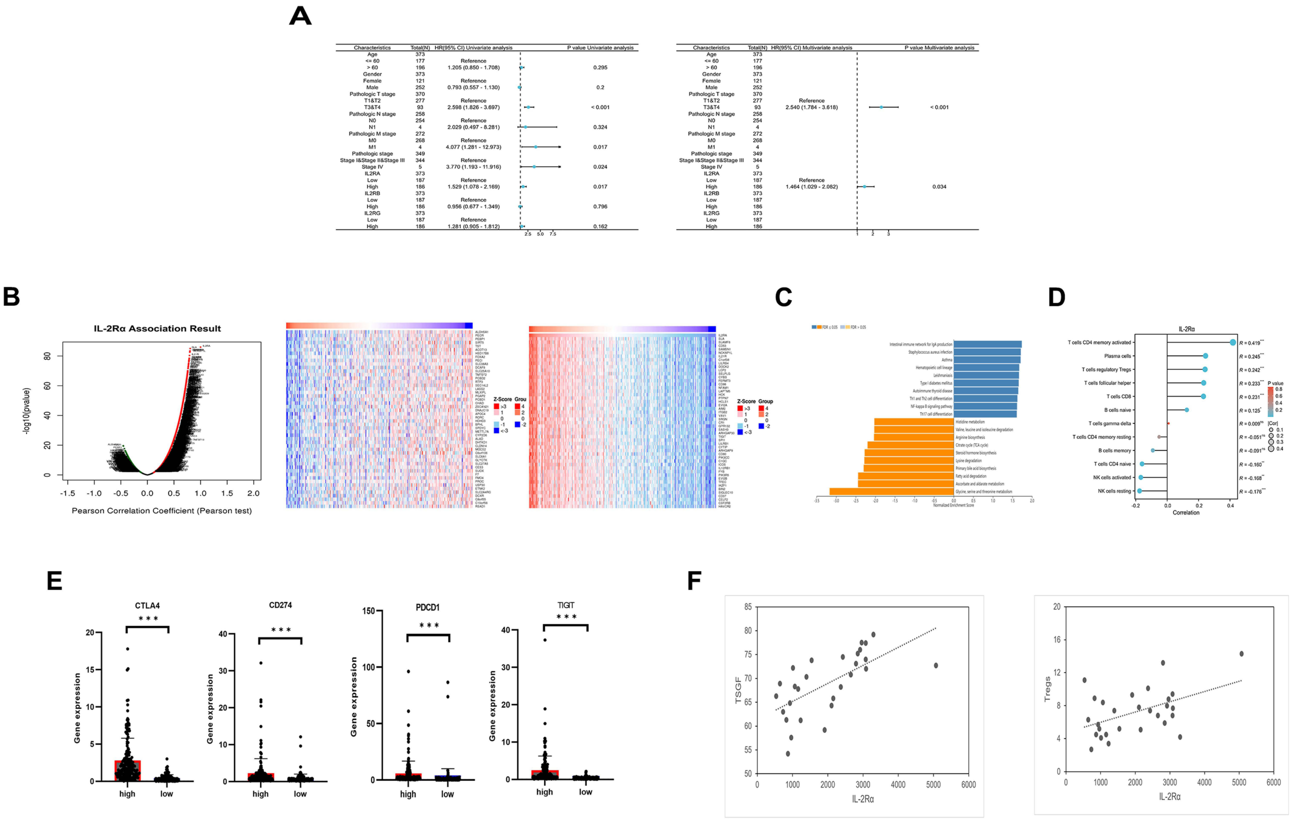

Figure 6 The potential role of IL-2Rα in HCC. (**A**) Univariate and multivariate Cox regression analysis for IL-2Rα genes and clinical data (Forest plot). (**B**) LinkedOmics database shows the correlation between IL-2Rα and genes differentially expressed in HCC. The top 50 genes that were positively and negatively associated with IL-2Rα in HCC were listed in heat maps. (**C**) KEGG enrichment analysis of IL-2Rα co-expression genes in HCC. (**D**) Correlation between IL-2Rα and the infiltration of immune cells in HCC. (**E**) The expression of immune checkpoint genes in high and low IL-2Rα expression groups of HCC. (**F**) Correlation between IL-2Rα and Tregs in HCC; Correlation between IL-2Rα and TSGF in HCC. *p<0.05, **p<0.01, ***p<0.001, ns: no significance.

available chemotherapeutic agents. In recent years, the clinical development and application of molecularly targeted therapies and immunotherapeutic agents have significantly improved the prognosis of HCC.[16–21] As a typical inflammation-related cancer, the tumor immune microenvironment is considered to play a key role in the occurrence, development, and anti-tumor therapeutic interventions of HCC.[22–26] Thus, future therapeutic approaches targeting the immune TME have a significant potential for HCC treatment.

Interleukin-2 is an important cytokine that activates multiple cellular signaling pathways by binding to IL-2R on the cell surface. This interaction facilitates the regulation of various cellular processes, including cell proliferation, apoptosis, and immune response.[27–31] Subsequently, IL-2 has been used to treat certain types of cancers,[13] autoimmune diseases,[32] immunodeficiency diseases,[33] infectious diseases[34] and so on. IL-2R complexes are commonly expressed in human cells, including immune cells, tumors, and various non-immune cells. In this study, we evaluated the expression levels of the three IL-2R subunits in HCC using TCGA and GTEx databases. We observed that IL-2Rα and IL-2Rγ mRNA expression was upregulated, but IL-2Rβ mRNA expression was downregulated in the HCC tissues. Compared to IL-2Rα and IL-2Rγ, IL-2Rβ was predominantly expressed in NK and CD8+ T cells, which play a significant role in suppressing cancer. Thus, we observed L-2Rβ was downregulated and negatively weighted in the risk model. Additionally, IL-2Rα overexpression correlated with poor prognosis in HCC patients. These preliminary observations suggest that IL-2R subunits play distinct roles within the TME and are associated with the development of HCC. Moreover, genetic alterations in IL-2R subunits were correlated with the OS of patients with HCC. Subsequently, we constructed a risk model to evaluate the prognostic significance of the three IL-2R subunits in HCC. Although the AUC derived from the model does not fully reflect the precision of the prognostic signature, our study tentatively found that the risk score based on these three IL-2R subunits genes may serve as a potential prognostic indicator for HCC.

Table 1 The Immunologic Detection in Peripheral Blood of Patients with HCC

Variables (N=28)	$\bar{x} \pm s$	Reference Values
sIL-2Rα (pg/mL)	1987.04 ± 1081.20***	<850
TSGF (U/mL)	68.91 ± 6.35*	<66
B cells (%)	9.21 ± 5.28	
T cells (%)	67.81 ± 10.14	
CD4+ T cells (%)	38.66 ± 10.93	
CD8+ T cells (%)	27.19 ± 12.44	
NK cells (%)	18.35 ± 10.27	
Tregs (%)	7.22 ± 2.76	

Notes: *p<0.05 and ***p<0.001.

As the main metabolic organ of the body, the liver constantly filters microorganisms, metabolites and pathogens from the gut to protect itself against immune-mediated damage, ultimately establishing a tolerant and immunosuppressive microenvironment.[35,36] Thus, the liver is also referred to as an immune-exempt organ dominated by immunosuppressive cells and is involved in various signaling pathways.[22] The pathophysiology of HCC is a complex multifactorial process characterized by a significantly heterogeneous tumor immune microenvironment.[37] In recent years, the advent of immunotherapy-based combination regimens has significantly improved HCC prognosis. This approach has become the standard treatment for patients with advanced HCC. However, research has shown that approximately 10–30% of patients with advanced HCC who undergo immunotherapy achieve complete or partial remission.[16,19,20,38,39] Therefore, further understanding the role of tumor immune microenvironment is vital to facilitate the development of more targeted therapeutic strategies with improved outcomes in patients with HCC. CD8+ T cells are the main actors in the anti-tumor immune response, exerting their ability to eliminate tumor cells through effector molecules, such as perforin, granase, and Fas ligand.[40] Dysregulation of CD8+ T cells is affected by multiple factors, and new research has also identified some co-inhibitory molecules (CTLA-4, PDCD1, CD274, TIGIT, etc.) and their corresponding ligands that play an important role in CD8+T inactivation and depletion in HCC.[41] In this study, we observed no significant difference in CD8+ T cell infiltration between the two groups, however, these four molecules were overexpressed in the high-risk group. This observation suggests the possible dysfunction of CD8+ T cell in HCC development. Unlike CD8+ T cells, CD4+ T cells consist of different subtypes with distinct biological functions and phenotypes, including T helper 1 (Th1), T helper 2 (Th2), T helper 17 (Th17), regulatory T cells (Tregs), and follicular helper T cells (Tfh).[42] Our results indicate that Treg infiltration was significantly greater in the high-risk group among CD4+ T cell subtypes. Tregs exert immunosuppressive effects in the tumor microenvironment, and promote tumor evasion from immune surveillance by weakening the anti-tumor specific immune response. Studies have shown that high infiltration of Tregs is related with shorter OS and worse prognosis in patients with HCC.[43] B cells are mainly distributed in the invasion front area of HCC. While these tumor-infiltrating B cells did not exhibit immunoprotective properties, their infiltration levels were positively related with the early postoperative recurrence of HCC. Research has shown that mature B cells secrete antibodies that may induce polarization of M2 macrophages, ultimately promoting liver cancer progression by reducing the therapeutic effect of epigenetic reprogramming.[44,45] Additionally, we observed that the infiltration levels of B cell memory were significantly elevated in the high-risk group, while the infiltration levels of naïve B cell infiltration were significantly elevated in the low-risk group. NK cells are generally considered the first line of defense against tumors. However, a hypoxic tumor microenvironment may lead to impairment of NK cell activation and promote immune escape.[46,47] Although no significant difference was observed between the two groups in terms of activated NK cell infiltration, the low-risk group exhibited higher levels of resting NK cell infiltration. This finding suggests that the low-risk group may have a more favorable prognosis if the NK cells are activated. Monocytes play an indispensable role in local immune regulation within the tumor microenvironment. Through their direct interaction with CD8+ T cells, monocytes may enhance the expression of CD8+ T cells, thus effectively inhibiting tumor growth.[48] Here we observed that monocyte infiltration was significantly higher in the low-risk group than in the high-risk group of patients with HCC. Moreover, our

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analysis showed that low-risk HCC patients exhibited better prognostic outcomes and may benefit from immune checkpoint inhibitors, which could help develop therapeutic regimens for patients to improve HCC outcomes. Previous research has found that sIL-2Rα are highly expressed in a variety of cancers, including papillary thyroid, breast, and lung cancers, which often predict poor prognosis.[49–51] Besides, the aberrant expression of IL-2Rα was associated with the occurrence of autoimmune diseases. Given that sIL-2Rα is an independent predictor of HCC prognosis, we evaluated the relationship between IL-2Rα expression and the immune status in HCC. Our findings indicate that the group with high IL-2Rα expression exhibited a greater degree of activated CD4+ memory T cell infiltration. TSGF is a special "signal molecule" released by malignant tumor cells and is composed of small molecules, such as sugars, amino acids, and metabolites. This molecule promotes the supply of oxygen and nutrition for tumor growth by inducing tumor angiogenesis, thereby contributing to tumor progression.[52] Serum TSGF has been used for the clinical identification and assessment of treatment effects in various malignancies, including hepatocellular carcinoma.[53–57] Subsequently, we retrospectively collected clinical data to evaluate immune function in the peripheral blood of HCC patients. The results showed that the expression levels of sIL-2Rα and TSGF were above the reference value limits in HCC. Correlation analysis revealed that sIL-2Rα positively correlated with TSGF and Tregs. These data suggest that sIL-2Rα may influence TSGF secretion and immune function in HCC patients. Although this study represents the first attempt to construct a prognostic model for HCC based on IL-2R subunits using a publicly available database, real-world clinical data are essential to further evaluate the feasibility of this model. In addition, we aimed to investigate the role of IL-2R in HCC development from a histopathological perspective. However, due to the diverse clinical classifications of HCC, these factors may have influenced the conclusions drawn from this study. Therefore, future research should explore the role of IL-2R in the different clinical subtypes of HCC. Additionally, a comprehensive series of experimental studies, including functional cell experiments, animal models, and expanded clinical data collection, is essential to validate the role of IL-2R in HCC progression.

Conclusion

In short, this study attempts to construct a prognostic risk model based on IL-2R subunits, which may play a role in the regulation of immune function within the HCC tumor microenvironment. Besides, IL-2Rα may act as a more important role in HCC development among the three IL-2R subunits. Further research will be needed to verify these initial findings. Overall, these results may provide important insights in clinical prognosis and therapeutic strategies for HCC.

Data Sharing Statement

These datasets can be acquired from TCGA database (https://portal.gdc.cancer.gov/) and are included in the Supplementary Information Files.

Ethics Approval and Consent to Participate

This study was performed in accordance with the principles of the Declaration of Helsinki and approved by the Ethics Review Committee of the Shanxi Province Cancer Hospital (IIT-2025-023).

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Disclosure

All authors declare that they have no conflicts of interest in this work.

References

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74(3):229–263. doi:10.3322/caac.21834
2. Llovet JM, Kelley RK, Villanueva A, et al. Hepatocellular carcinoma. *Nat Rev Dis Primers*. 2021;7(1):6. doi:10.1038/s41572-020-00240-3
3. McGlynn KA, Petrick JL, El-Serag HB. Epidemiology of Hepatocellular Carcinoma. *Hepatology*. 2021;73(Suppl 1):4–13. doi:10.1002/hep.31288
4. Craig AJ, von Felden J, Garcia-Lezana T, Sarcognato S, Villanueva A. Tumour evolution in hepatocellular carcinoma. *Nat Rev Gastroenterol Hepatol*. 2020;17(3):139–152. doi:10.1038/s41575-019-0229-4
5. Wu Y, Liu Z, Xu X. Molecular subtyping of hepatocellular carcinoma: a step toward precision medicine. *Cancer Commun*. 2020;40(12):681–693. doi:10.1002/cac2.12115
6. Paget S. The distribution of secondary growths in cancer of the breast. 1889. *Cancer Metastasis Rev*. 1989;8(2):98–101.
7. Boyman O, Sprent J. The role of interleukin-2 during homeostasis and activation of the immune system. *Nat Rev Immunol*. 2012;12(3):180–190. doi:10.1038/nri3156
8. Malek TR. The biology of interleukin-2. *Annu Rev Immunol*. 2008;26(1):453–479. doi:10.1146/annurev.immunol.26.021607.090357
9. Lissoni P, Barni S, Rovelli F, et al. The biological significance of soluble interleukin-2 receptors in solid tumors. *Eur J Cancer*. 1990;26(1):33–36. doi:10.1016/0277-5379(90)90253-p
10. Kuhn DJ, Dou QP. The role of interleukin-2 receptor alpha in cancer. *Front Biosci*. 2005;10(1–3):1462–1474. doi:10.2741/1631
11. Rosenberg SA. IL-2: the first effective immunotherapy for human cancer. *J Immunol*. 2014;192(12):5451–5458. doi:10.4049/jimmunol.1490019
12. Hernandez R, Poder J, LaPorte KM, Malek TR. Engineering IL-2 for immunotherapy of autoimmunity and cancer. *Nat Rev Immunol*. 2022;22(10):614–628. doi:10.1038/s41577-022-00680-w
13. Wrangle JM, Patterson A, Johnson CB, et al. IL-2 and Beyond in Cancer Immunotherapy. *J Interferon Cytokine Res*. 2018;38(2):45–68. doi:10.1089/jir.2017.0101
14. Chen B, Khodadoust MS, Liu CL, Newman AM, Alizadeh AA. Profiling Tumor Infiltrating Immune Cells with CIBERSORT. *Methods Mol Biol*. 2018;1711:243–259. doi:10.1007/978-1-4939-7493-1_12
15. Newman AM, Liu CL, Green MR, et al. Robust enumeration of cell subsets from tissue expression profiles. *Nat Methods*. 2015;12(5):453–457. doi:10.1038/nmeth.3337
16. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *N Engl J Med*. 2020;382(20):1894–1905. doi:10.1056/NEJMoa1915745
17. Llovet JM, Kudo M, Merle P, et al. Lenvatinib plus pembrolizumab versus lenvatinib plus placebo for advanced hepatocellular carcinoma (LEAP-002): a randomised, double-blind, Phase 3 trial. *Lancet Oncol*. 2023;24(12):1399–1410. doi:10.1016/S1470-2045(23)00469-2
18. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet*. 2018;391(10126):1163–1173. doi:10.1016/S0140-6736(18)30207-1
19. Yau T, Park JW, Finn RS, et al. Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): a randomised, multicentre, open-label, phase 3 trial. *Lancet Oncol*. 2022;23(1):77–90. doi:10.1016/S1470-2045(21)00604-5
20. Ren Z, Xu J, Bai Y, et al. Sintilimab plus a bevacizumab biosimilar (IBI305) versus sorafenib in unresectable hepatocellular carcinoma (ORIENT-32): a randomised, open-label, Phase 2-3 study. *Lancet Oncol*. 2021;22(7):977–990. doi:10.1016/S1470-2045(21)00252-7
21. Liu X, Song Y, Cheng P, Liang B, Xing D. Targeting HER2 in solid tumors: unveiling the structure and novel epitopes. *Cancer Treat Rev*. 2024;130:102826. doi:10.1016/j.ctrv.2024.102826
22. Li X, Ramadori P, Pfister D, Seehawer M, Zender L, Heikenwalder M. The immunological and metabolic landscape in primary and metastatic liver cancer. *Nat Rev Cancer*. 2021;21(9):541–557. doi:10.1038/s41568-021-00383-9
23. Yang X, Yang C, Zhang S, et al. Precision treatment in advanced hepatocellular carcinoma. *Cancer Cell*. 2024;42(2):180–197. doi:10.1016/j.ccell.2024.01.007
24. Ma Q, Jiang H, Ma L, et al. The moonlighting function of glycolytic enzyme enolase-1 promotes choline phospholipid metabolism and tumor cell proliferation. *Proc Natl Acad Sci U S A*. 2023;120(15):e2209435120. doi:10.1073/pnas.2209435120
25. Wang XH, Fu YL, Xu YN, et al. Ginsenoside Rh1 regulates the immune microenvironment of hepatocellular carcinoma via the glucocorticoid receptor. *J Integr Med*. 2024;22(6):709–718. doi:10.1016/j.joim.2024.09.004
26. Wu J, Liu W, Qiu X, et al. A Noninvasive Approach to Evaluate Tumor Immune Microenvironment and Predict Outcomes in Hepatocellular Carcinoma. *Phenomics*. 2023;3(6):549–564. doi:10.1007/s43657-023-00136-8
27. Spolski R, Li P, Leonard WJ. Biology and regulation of IL-2: from molecular mechanisms to human therapy. *Nat Rev Immunol*. 2018;18(10):648–659. doi:10.1038/s41577-018-0046-y
28. Taniguchi T. Cytokine signaling through nonreceptor protein tyrosine kinases. *Science*. 1995;268(5208):251–255. doi:10.1126/science.7716517
29. Marabondo S, Kaufman HL. High-dose interleukin-2 (IL-2) for the treatment of melanoma: safety considerations and future directions. *Expert Opin Drug Saf*. 2017;16(12):1347–1357. doi:10.1080/14740338.2017.1382472
30. Kagoya Y, Tanaka S, Guo T, et al. A novel chimeric antigen receptor containing a JAK-STAT signaling domain mediates superior antitumor effects. *Nat Med*. 2018;24(3):352–359. doi:10.1038/nm.4478
31. Lin JX, Leonard WJ. Signaling from the IL-2 receptor to the nucleus. *Cytokine Growth Factor Rev*. 1997;8(4):313–332. doi:10.1016/s1359-6101(97)00021-x
32. Yuan Y, Kolios AGA, Liu Y, et al. Therapeutic potential of interleukin-2 in autoimmune diseases. *Trends Mol Med*. 2022;28(7):596–612. doi:10.1016/j.molmed.2022.04.010
33. Davey Jr RT, Murphy RL, Graziano FM, et al. Immunologic and virologic effects of subcutaneous interleukin 2 in combination with antiretroviral therapy: a randomized controlled trial. *JAMA*. 2000;284(2):183–189. doi:10.1001/jama.284.2.183
34. Hamilton SE, Schenkel JM, Akue AD, Jameson SC. IL-2 complex treatment can protect naive mice from bacterial and viral infection. *J Immunol*. 2010;185(11):6584–6590. doi:10.4049/jimmunol.1001215
35. Jenne CN, Kubes P. Immune surveillance by the liver. *Nat Immunol*. 2013;14(10):996–1006. doi:10.1038/ni.2691
36. Gao B, Jeong WI, Tian Z. Liver: an organ with predominant innate immunity. *Hepatology*. 2008;47(2):729–736. doi:10.1002/hep.22034

37. Llovet JM, Castet F, Heikenwalder M, et al. Immunotherapies for hepatocellular carcinoma. *Nat Rev Clin Oncol*. 2022;19(3):151–172. doi:10.1038/s41571-021-00573-2
38. Kudo M. Durvalumab plus tremelimumab in unresectable hepatocellular carcinoma. *Hepatobiliary Surg Nutr*. 2022;11(4):592–596. doi:10.21037/hbsn-22-143
39. Finn RS, Ryoo BY, Merle P, et al. Pembrolizumab As Second-Line Therapy in Patients With Advanced Hepatocellular Carcinoma in KEYNOTE-240: a Randomized, Double-Blind, Phase III Trial. *J Clin Oncol*. 2020;38(3):193–202. doi:10.1200/JCO.19.01307
40. van der Leun AM, Thommen DS, Schumacher TN. CD8(+) T cell states in human cancer: insights from single-cell analysis. *Nat Rev Cancer*. 2020;20(4):218–232. doi:10.1038/s41568-019-0235-4
41. Lu C, Rong D, Zhang B, et al. Current perspectives on the immunosuppressive tumor microenvironment in hepatocellular carcinoma: challenges and opportunities. *Mol Cancer*. 2019;18(1):130. doi:10.1186/s12943-019-1047-6
42. Speiser DE, Chijioke O, Schaeuble K, Munz C. CD4(+) T cells in cancer. *Nat Cancer*. 2023;4(3):317–329. doi:10.1038/s43018-023-00521-2
43. Gao Q, Qiu SJ, Fan J, et al. Intratumoral balance of regulatory and cytotoxic T cells is associated with prognosis of hepatocellular carcinoma after resection. *J Clin Oncol*. 2007;25(18):2586–2593. doi:10.1200/JCO.2006.09.4565
44. Liu RX, Wei Y, Zeng QH, et al. Chemokine (C-X-C motif) receptor 3-positive B cells link interleukin-17 inflammation to protumorigenic macrophage polarization in human hepatocellular carcinoma. *Hepatology*. 2015;62(6):1779–1790. doi:10.1002/hep.28020
45. Wei Y, Lao XM, Xiao X, et al. Plasma Cell Polarization to the Immunoglobulin G Phenotype in Hepatocellular Carcinomas Involves Epigenetic Alterations and Promotes Hepatoma Progression in Mice. *Gastroenterology*. 2019;156(6):1890–1904e16. doi:10.1053/j.gastro.2019.01.250
46. Hasmim M, Messai Y, Ziani L, et al. Critical Role of Tumor Microenvironment in Shaping NK Cell Functions: implication of Hypoxic Stress. *Front Immunol*. 2015;6:482. doi:10.3389/fimmu.2015.00482
47. Wu SY, Fu T, Jiang YZ, Shao ZM. Natural killer cells in cancer biology and therapy. *Mol Cancer*. 2020;19(1):120. doi:10.1186/s12943-020-01238-x
48. Elewaut A, Estivill G, Bayerl F, et al. Cancer cells impair monocyte-mediated T cell stimulation to evade immunity. *Nature*. 2024;637(8046):716–725. doi:10.1038/s41586-024-08257-4
49. Gonda K, Horita S, Maejima Y, Takenoshita S, Shimomura K. Soluble interleukin-2 receptor as a predictive and prognostic marker for patients with familial breast cancer. *Sci Prog*. 2021;104(3):368504211039590. doi:10.1177/00368504211039590
50. Siemiatkowska A, Bryl M, Kosicka-Noworzyn K, et al. Serum sCD25 Protein as a Predictor of Lack of Long-Term Benefits from Immunotherapy in Non-Small Cell Lung Cancer: a Pilot Study. *Cancers (Basel)*. 2021;13(15):3702. doi:10.3390/cancers13153702
51. Xu X, Wang W, Sun T, Tian B, Du L, Jing J. The Predicting Role of Serum TSGF and sIL-2R for the Lymph Node Metastasis of Papillary Thyroid Carcinoma. *Dis Markers*. 2022;2022:3730679. doi:10.1155/2022/3730679
52. Nair B, Kuriakose A, Baby B, Nath LR. Tumor-Specific Growth Factor (TSGF): a Futuristic Tumor Biomarker in Early Diagnosis of Cancer. *Adv Pharm Bull*. 2023;13(3):483–488. doi:10.34172/apb.2023.051
53. Song X, Liang B, Wang C, Shi S. Clinical value of color Doppler ultrasound combined with serum CA153, CEA and TSGF detection in the diagnosis of breast cancer. *Exp Ther Med*. 2020;20(2):1822–1828. doi:10.3892/etm.2020.8868
54. Yu C, Sun C. Diagnostic Value of Multislice Spiral Computed Tomography Combined with Serum AFP, TSGF, and GP73 Assay in the Diagnosis of Primary Liver Cancer. *Evid Based Complement Alternat Med*. 2022;2022:6581127. doi:10.1155/2022/6581127
55. Hu Y, Wang JL, Tao HT, et al. Expression and significance of TSGF, CEA and AFP in patients before and after radical surgery for colon cancer. *Asian Pac J Cancer Prev*. 2013;14(6):3877–3880. doi:10.7314/apjcp.2013.14.6.3877
56. Xu X, Wang W, Tian B, Zhang X, Ji Y, Jing J. The predicting role of serum tumor-specific growth factor for prognosis of esophageal squamous cell carcinoma. *BMC Cancer*. 2023;23(1):1067. doi:10.1186/s12885-023-11602-x
57. Jiang JT, Wu CP, Deng HF, et al. Serum level of TSGF, CA242 and CA19-9 in pancreatic cancer. *World J Gastroenterol*. 2004;10(11):1675–1677. doi:10.3748/wjg.v10.i11.1675