Original Article

A gene signature associated with cellular senescence serves as an important prognostic indicator in hepatocellular carcinoma

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Background: Hepatocellular carcinoma (HCC) is a lethal tumor. Predicting the prognosis of HCC remains challenging. Cellular senescence, which is one of the hallmarks of cancer, and its related prognostic-gene signature can provide critical information for clinical decision making. Our objective was to investigate the role of cellular senescence in HCC.

Methods: The RNA sequencing data and clinical information of HCC patients from The Cancer Genome Atlas (TCGA) database were obtained. The HCC subtypes and a senescence score model were established to predict the prognosis of HCC.

Results: In this study, patients from TCGA-HCC dataset were stratified into low- and high-risk groups based on cellular senescence-related genes. The analysis of the various subtypes revealed that the distribution of Cluster 1 (C1) was significantly correlated with numerous factors, including age, sex, pathological T stage, tumor node metastasis (TNM) classification, and grade staging. Further, the Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis indicated that the upregulated genes in the high-risk C1 group were primarily engaged in pathways related to the cell cycle, DNA replication, cellular senescence, extracellular matrix (ECM)-receptor interactions, and the mechanisms of mismatch repair. Conversely, the 90 downregulated genes were mainly associated with metabolic pathways, chemical carcinogenesis involving DNA adducts, complement and coagulation cascades, and the peroxisome proliferator-activated receptor (PPAR) signaling pathway. The resultant boxplots revealed significant differences in the populations of immune cells, such as B cells, endothelial cells, natural killer (NK) cells, macrophages, cluster of differentiation (CD)4+ T cells, and CD8+ T cells, in the C1 HCC samples compared to the C2 HCC samples. Additionally, the prognostic outcomes of the HCC patients were predicted using a cellular senescence-related gene model that included *VDAC2*, *CXCL8*, *MYBL2*, *RAD9A*, *LIN52*, *RHEB*, *GADD45G*, *E2F5*, *MAP2K2*, *CDC25A*, *PPP1CB*, and *HRAS*.

Conclusions: This study established a prognostic model of HCC based on cellular senescence-related gene expression. Our findings may provide insights that can be used to develop novel potential targeted therapies.

Keywords: Hepatocellular carcinoma (HCC); biomarkers; cellular senescence; cellular senescence-related signature

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Introduction

Hepatocellular carcinoma (HCC) is an especially aggressive type of cancer. In 2020, approximately one million new cases were reported worldwide (1,2). The primary risk factors contributing to the onset of HCC are chronic alcohol consumption, diabetes mellitus, metabolic disorders, and infection with the hepatitis B virus (2-4). Each of these risk factors can lead to cirrhotic changes, subsequently elevating the risk of HCC development (3-5). The limitations in treatment options for HCC primarily stem from factors such as tumor size, the presence of metastasis, and underlying liver conditions like cirrhosis. As HCC often presents at an advanced stage, surgical interventions become less viable, and systemic therapies may have limited efficacy due to the tumor's heterogeneity and resistance mechanisms. If HCC is diagnosed at an advanced stage, the range of available treatment options becomes markedly restricted (5).

Extensive research has shown that several factors can significantly compromise the efficacy of targeted therapeutic interventions for HCC. These factors include the disruption of telomere maintenance, alterations in chromatin structure, dysregulation of the cell cycle, oxidative stress in HCC cells, and substantial genetic mutations or atypical gene expression (6,7). Ongoing research into various gene expression profiles continues to refine therapeutic strategies; however, research on prognostic prediction for HCC patients remains limited. While existing prognostic models provide some insights, they often fail to account for the molecular heterogeneity of HCC and do not integrate key factors such as aging-related genetic alterations. Additionally, there is a scarcity of research focusing on the specific impact of these aging-related genes on prognosis, which limits our understanding of their role in HCC progression. Thus, novel biomarkers urgently need to be identified to facilitate clinical decision making and identify individuals with an increased risk of HCC.

Over the past decade, research has revealed a close association between cellular senescence—a crucial hallmark of cancer—and the conventional mechanisms of carcinogenesis, tumor advancement, and the invasiveness of HCC (8-11). Cellular senescence is characterized by an irreversible cessation of cellular proliferation (10,11). Moreover, these genes can induce cellular senescence, a state that halts the proliferation of damaged or stressed cells, thereby preventing the progression of potential tumors. This tumor-suppressive effect is crucial in maintaining tissue homeostasis and preventing the accumulation of mutations that could lead to cancer. Various therapeutic modalities can induce senescence in malignant cells via mechanisms such as genotoxic stress, enhanced mitogenic signaling, and oxidative stress, leading to the permanent arrest of the cell cycle (12). Therapy-induced senescence is an initial anti-tumor strategy aimed at curtailing cellular proliferation and alleviating genomic instability. In the tumor microenvironment, senescent cells can secrete pro-inflammatory cytokines, growth factors, and proteases, collectively known as the senescence-associated secretory phenotype (SASP).

Despite extensive research, the exact role of cellular senescence in HCC remains unclear. An in-depth evaluation of prognostic signatures associated with cellular senescence in HCC patients could extend our understanding of the underlying mechanisms of HCC, and yield innovative approaches for accurate diagnosis and treatment. Gene signatures derived from machine-learning methodologies could enhance cancer prognosis assessment and inform immunotherapeutic strategies (13). This study conducted a comprehensive analysis of gene expression data relevant to prognosis, integrating relevant clinical information from HCC patients. Consequently, a model was developed based on the genes associated with cellular senescence scores, which could serve as a novel prognostic tool for individuals diagnosed with HCC. We present this article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-2025-335/rc).

Highlight box

Key findings

- Cellular senescence is one of the hallmarks of cancer, and its related prognostic-gene signatures can provide critical information for clinical decision making. Cellular senescence-related genes may serve as good prognostic indicators of hepatocellular carcinoma (HCC).

What is known, and what is new?

- HCC can be evaluated based on cellular senescence-related genes.
- This study identified HCC subtypes and biomarkers related to cellular senescence.

What is the implication, and what should change now?

- We established a prognostic model of HCC based on cellular senescence-related gene expression. Our findings may provide insights into novel potential targeted therapies.

Methods

Data acquisition and preparation

Gene expression datasets along with clinical follow-up information pertaining to patients with HCC were sourced from The Cancer Genome Atlas (TCGA) repository. To ensure the integrity of the prognostic evaluations, samples lacking overall survival (OS) data were excluded from the analysis, and only those with relevant prognostic indicators were retained. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Subtype identification using cellular senescence-related genes

HCC was categorized into subtypes based on significant expression differences in the cellular senescence-related genes. Unsupervised hierarchical clustering was performed using R (version 3.6.1) of the ConsensusClusterPlus package. A range of 2 to 6 was used to determine the ideal number of clusters (k value). To examine the correlation between various HCC subtypes and survival outcomes, Kaplan-Meier (KM) survival curves were generated using the R survival package (version 2.41-1).

Clinical characteristics associated with HCC subtypes

The clinical characteristics, including age, tumor grade, pathological stage, tumor node metastasis (TNM) classification, and prior exposure to radiation, of the HCC patients was assessed. The relationships between these clinical characteristics and the identified HCC subtypes were examined using the chi-square test, with the significance threshold set at $P<0.05$.

DEG identification across HCC subtypes

To examine the molecular mechanisms that differentiate the HCC subtypes, linear regression and empirical Bayesian techniques were employed to screen the differentially expressed genes (DEGs) using the limma package (version 3.10.3). In our study, the gene expression values were normalized using the transcripts per million (TPM) method. This normalization approach was chosen to account for both sequencing depth and gene length, allowing for a more accurate comparison of gene expression levels across samples. Differences were considered statistically significant if the following criteria were met: a P value threshold of <0.05, and a $|\log_2 \text{fold change}| >1$. A heatmap illustrating the DEGs was generated using the R package "pheatmap" (version 1.0.12). Additionally, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed using the "clusterProfiler" package in R.

Comparative analysis of the immune microenvironment among the subtypes

The "immunoeconomics" framework was employed to evaluate the immune functionality of the cellular senescence-related genes. A comparative analysis of immune activity between the two clusters related to cellular senescence was conducted by examining the expression levels of 10 immune checkpoint genes (i.e., *CD274*, *PDCD1*, *PDCD1LG2*, *CTLA4*, *LAG3*, *HAVCR2*, *IGSF8*, *ITPRIPL1*, *TIGIT*, and *SIGLEC1*). Heatmaps and box plots were generated using the R packages "pheatmap" and "ggplot2", respectively. The Wilcoxon test was used to assess the infiltration of the immune cells and the activation of immune pathways across the two clusters. P values <0.05 were considered statistically significant.

Development of a risk score-based prognostic model

Using the DEGs identified in our study, a univariate Cox regression analysis was conducted to identify the gene expression levels that were significantly associated with survival based on a significance threshold of $P<0.05$. The least absolute shrinkage and selection operator (LASSO) algorithm in the R survminer package (version 0.4.9) was also used to analyze the prognostic-gene signatures and to develop a prognostic model based on the risk scores. For each sample in TCGA dataset, individual risk scores were computed, and the patients were subsequently categorized into high- and low-risk groups based on the median score. To evaluate variances in the actual survival outcomes, a KM curve was subsequently plotted.

Statistical analysis

Differences were considered statistically significant if the following criteria were met: a P value threshold of <0.05, and a $|\log_2 \text{fold change}| >1$. The relationships between these clinical characteristics and the identified HCC subtypes were examined using the chi-square test, with the significance threshold set at $P<0.05$. A univariate Cox

regression analysis was conducted to identify the gene expression levels that were significantly associated with survival based on a significance threshold of P<0.05.

Results

Two HCC subtypes were identified based on the cellular senescence-related genes

The critical genes associated with cellular senescence were integrated into the unsupervised clustering analysis, resulting in the identification of the optimal number of subtypes (designated as k=2). To assess the reliability of the clustering outcomes, the degree of ambiguous clustering was evaluated, which reaffirmed k=2 as the optimal choice (*Figure 1A*). The HCC samples were categorized into two distinct subtypes, referred to as Cluster 1 (C1) and Cluster 2 (C2) (*Figure 1B,1C*). The survival analysis revealed that the patients in C1 had a significantly worse prognosis than those in C2 (*Figure 1D*). These findings emphasize that the low expression of cellular senescence-related genes, as observed in C2, may serve as a favorable prognostic indicator.

Differences in the clinical characteristics of the two HCC subtypes

The expression levels of the critical cellular senescence-related genes in relation to various clinical characteristics were examined. The analysis across the different subtypes showed that the distribution of C1 was significantly correlated with factors such as age, gender, pathological T stage, TNM classification, and grade staging (*Figure 2*). These findings suggest that C1 may serve as a prognostic indicator of risk, potentially reflecting the progression of clinical symptoms.

The molecular regulatory mechanisms based on the DEGs between the two HCC subtypes

To extend our understanding of the distinct molecular regulatory mechanisms present among the subtypes, a differential analysis of the gene expression levels between C1 and C2 was conducted. The distribution of the DEGs across these two clusters is illustrated in *Figure 3A*. Our analysis revealed that 947 genes were upregulated while 90 genes we downregulated (*Figure 3A*). The accompanying heatmap, in which red represents upregulation, and blue indicates downregulation (*Figure 3B*), further shows the expression levels of the DEGs across the various subgroups.

Subsequent KEGG and GO enrichment analyses were performed to examine the biological functions associated with the 1,137 DEGs identified. The results of the GO analysis pertaining to biological processes indicated that the majority of the upregulated genes were associated with mitotic nuclear division, nuclear division, chromosome segregation, DNA replication, and cell-cycle checkpoint activities (*Figure 3C*). Conversely, the downregulated genes were linked to processes such as metabolic functions, organic acid biosynthesis, isoprenoid metabolism, and alcohol metabolism (*Figure 3D*). The KEGG analysis further revealed that the 947 upregulated genes were predominantly involved in pathways associated with the cell cycle, DNA replication, cellular senescence, extracellular matrix (ECM)-receptor interactions, and mismatch repair mechanisms (*Figure 3E*). Conversely, the 90 downregulated genes were mainly implicated in metabolic pathways, chemical carcinogenesis-DNA adducts, complement and coagulation cascades, and the peroxisome proliferator-activated receptor (PPAR) signaling pathway (*Figure 3F*).

Previous research has indicated that cell cycle, DNA replication, cellular senescence, and ECM-receptor interactions can serve as tumor markers (6-10). Based on the aforementioned finding, it appears that the C1 HCC subtypes had a greater propensity for migration and proliferation than their C2 HCC counterparts.

Immune activity between the two cellular senescence-related groups in HCC

Numerous studies have reported a relationship between cellular senescence and immune response across various cancer types (6-8). Using a significance threshold of P<0.05, a significant difference in the infiltration of 10 distinct immune cell types was detected between C1 and C2 (*Figure 3A*). The resulting boxplots illustrated a pronounced variation in the immune cell populations, including B cells, endothelial cells, natural killer (NK) cells, macrophages, cluster of differentiation (CD)4$^+$ T cells, and CD8$^+$ T cells, in the C1 HCC samples compared to the C2 HCC samples (*Figure 4A*).

Further, the boxplots revealed that the expression levels of the 10 immune checkpoint inhibitor (ICI)-related genes (i.e., *CD274*, *PDCD1*, *PDCD1LG2*, *CTLA4*, *LAG3*, *HAVCR2*, *IGSF8*, *ITPRIPL1*, *TIGIT*, and *SIGLEC15*) were significantly higher in C1 than C2 (*Figure 4B*). These results

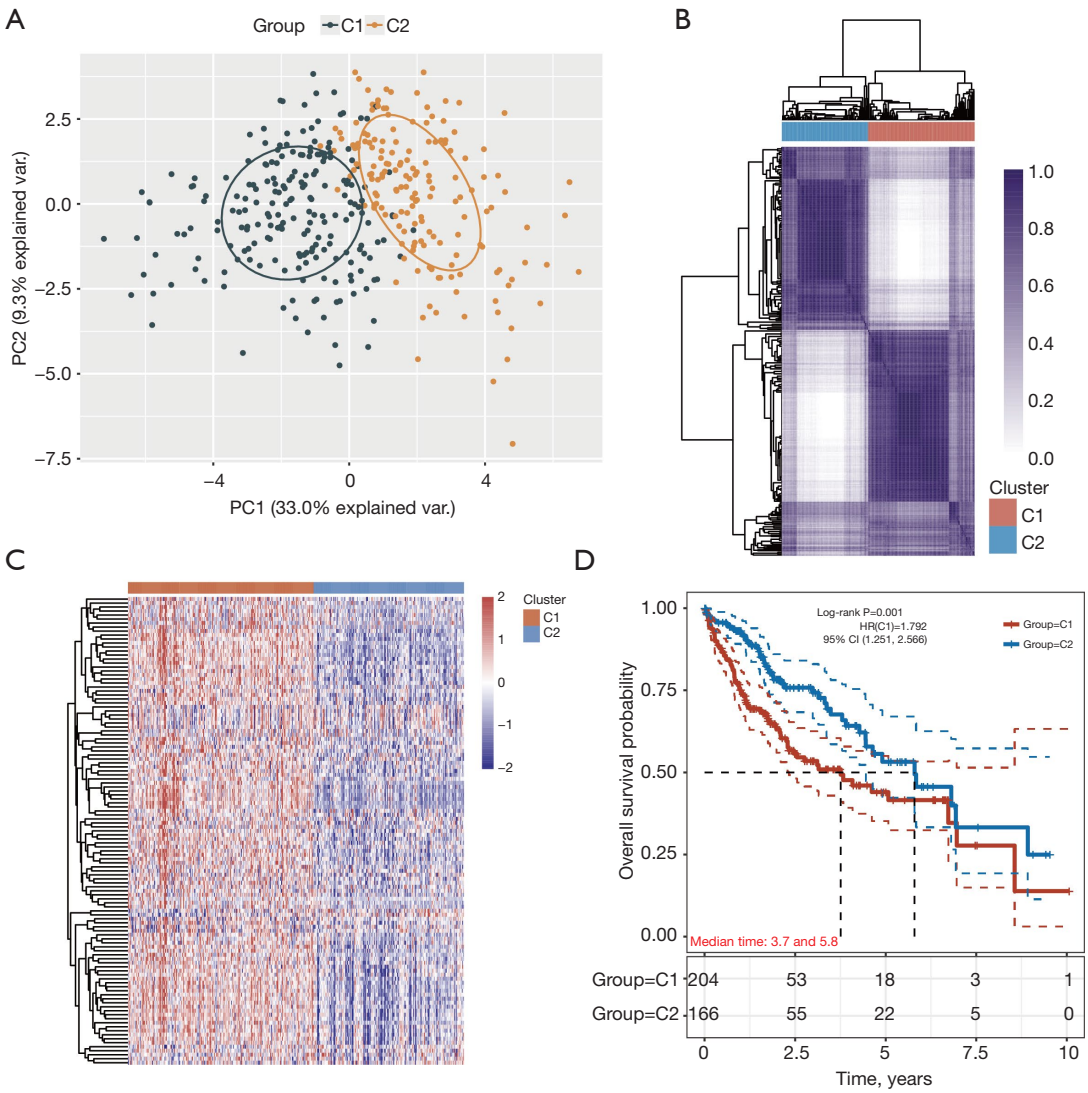

Figure 1 Two HCC subtypes associated with prognosis were identified based on cellular senescence-related genes. (A) The principal component analysis plot revealed two separate subtypes among the HCC samples. (B) Heatmap showing the consensus clustering solution with k=2 for the cellular senescence-related genes in the HCC samples. Red represented C1 and blue represented C2. (C) Heatmap detailing the expression levels of the cellular senescence-related genes across various subgroups; red indicates elevated expression; blue signifies reduced expression. (D) KM survival curve illustrating the survival differences between patients with high and low expression levels of cellular senescence-related genes. C1, Cluster 1; C2, Cluster 2; CI, confidence interval; HCC, hepatocellular carcinoma; HR, hazard ratio; KM, Kaplan-Meier; PC, principal component.

revealed a notable connection between cellular senescence and immune activity.

Prognostic signature development of the two cellular senescence-related groups in HCC

A univariate Cox analysis was performed on the patients from TCGA-HCC cohort to identify the prognostic genes and their respective functions. A total of 4,352 prognostic genes were identified, and a Venn diagram was used to isolate those associated with cellular senescence. Ultimately, 41 genes relevant to this biological phenomenon were identified (*Figure 5A*,*5B*). Further, the LASSO regression analysis suggested a significant correlation

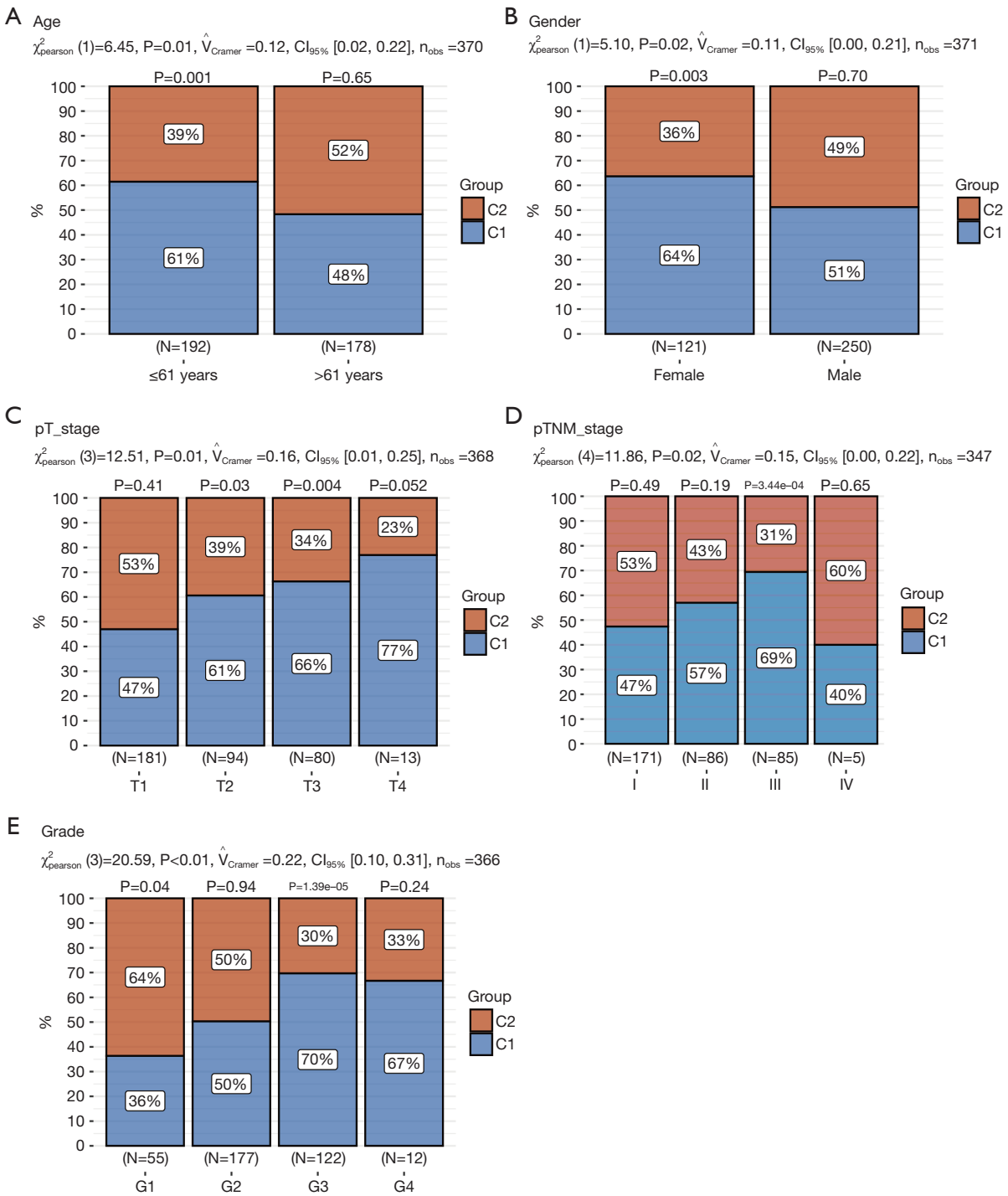

Figure 2 Variations in the distribution of the clinical characteristics between C1 and C2 were evident. (A) The proportions of individuals in C1 and C2 exhibited a significant difference in terms of age. (B) A notable difference was observed in the distribution proportions of C1 and C2 in terms of gender. (C) The distribution proportions of C1 and C2 demonstrated significant differences in terms of T stage. (D) There were significant differences in the distribution proportions of C1 and C2 in terms of TNM classification. (E) The distribution proportions of C1 and C2 varied significantly in terms of grade staging. n_{obs} means the number of patients. C1, Cluster 1; C2, Cluster 2; CI, confidence interval.

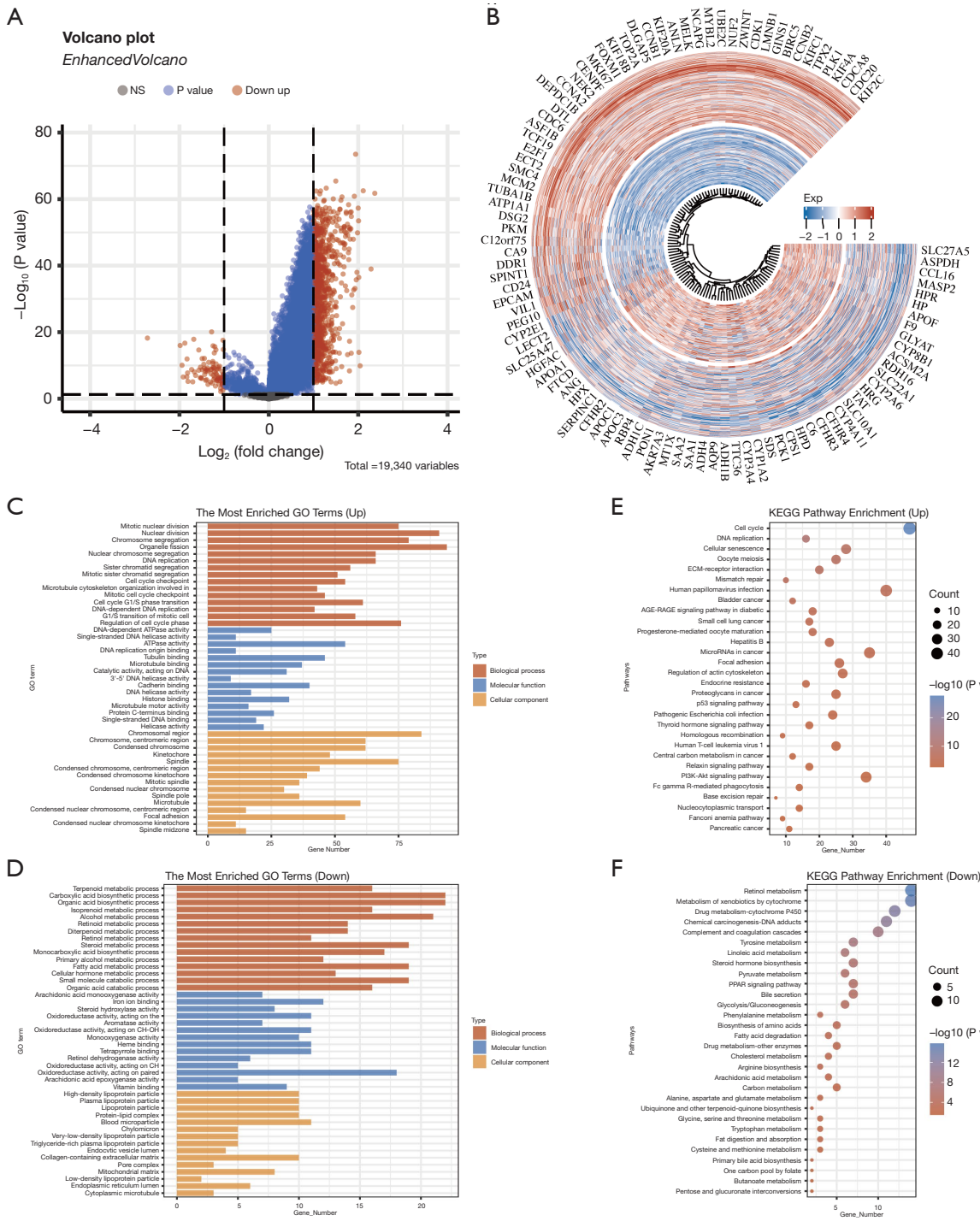

Figure 3 The molecular regulatory mechanisms based on the DEGs between the two HCC subtypes. (A) Volcano plot showing that 947 DEGs were upregulated, while 90 DEGs were downregulated, established via criteria of an adjusted P value <0.05, and a $|\log_2$ fold change$|$ >1. (B) Heatmap showing the expression profiles of the 678 DEGs observed between C1 and C2. Further, the enriched biological processes corresponding to the upregulated DEGs are shown in panel (C), while the downregulated DEGs are shown in panel (D). The KEGG pathways enriched for the upregulated DEGs are presented in panel (E), while those enriched for the downregulated DEGs are presented in panel (F). Akt, serine/threonine kinase B; DEGs, differentially expressed genes; ECM, extracellular matrix; GO, Gene Ontology; HCC, hepatocellular carcinoma; KEGG, Kyoto Encyclopedia of Genes and Genomes; PI3K, phosphatidylinositol 3-kinase.

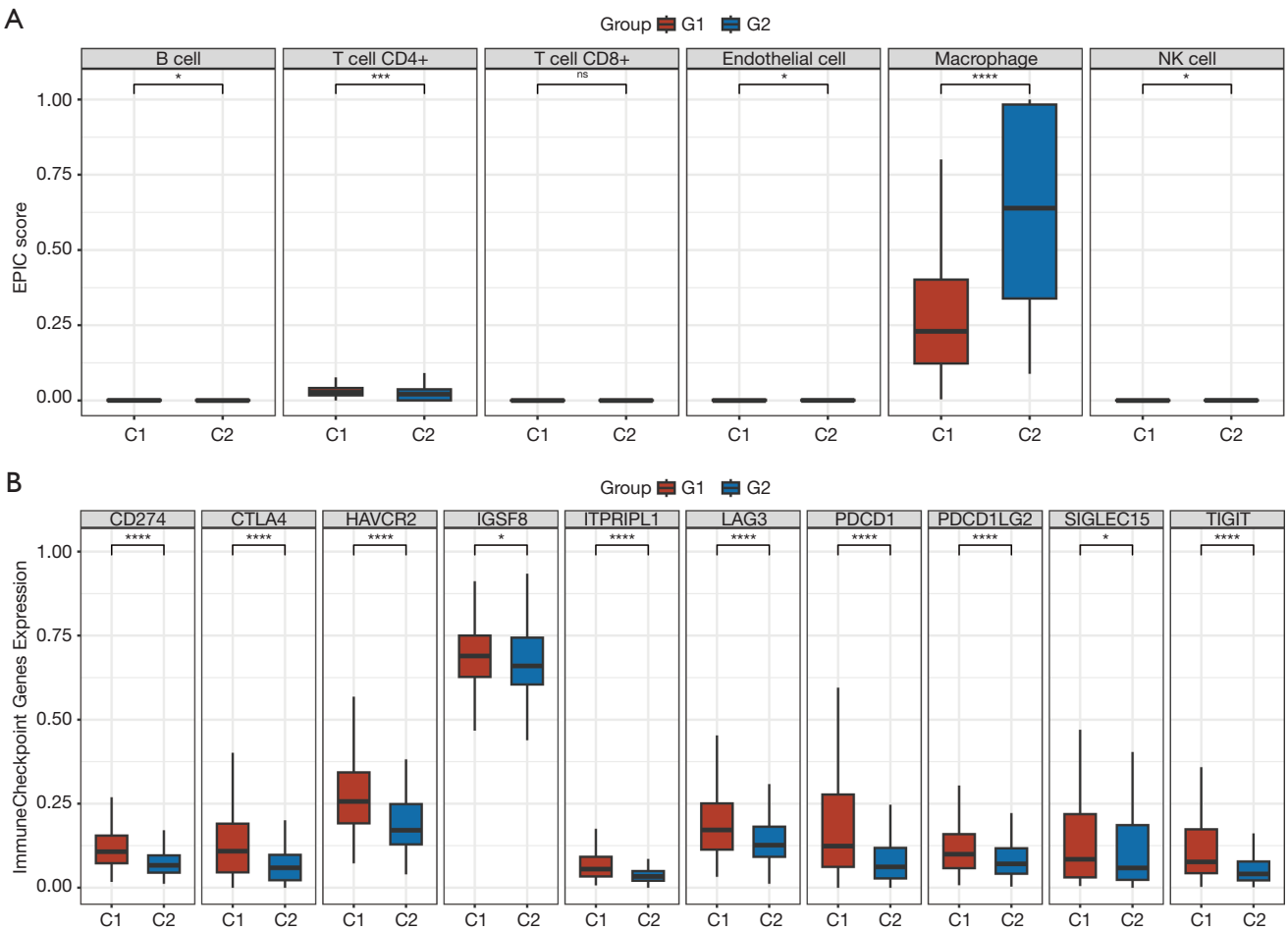

Figure 4 Immune activity between the two cellular senescence-related groups in HCC. (A) The enrichment scores of six distinct types of immune cells were compared across the two cellular senescence-related clusters in HCC. (B) The expression levels of the genes encoding immune checkpoint inhibitors were evaluated between the two clusters in HCC. Statistical significance was determined using the following P value thresholds: *, P<0.05; ***, P<0.001; ****, P<0.0001; ns, non-significant. C1, Cluster 1; C2, Cluster 2; EPIC, estimating the proportion of immune and cancer cells; HCC, hepatocellular carcinoma.

between the genes related to cellular senescence and OS (*Figure 5A*,*5B*). Through this thorough analysis, 12 prognostic genes were identified: *VDAC2*, *CXCL8*, *MYBL2*, *RAD9A*, *LIN52*, *RHEB*, *GADD45G*, *E2F5*, *MAP2K2*, *CDC25A*, *PPP1CB*, and *HRAS* (*Figure 5A*,*5B*). The KM survival analysis revealed that individuals in the high-risk group had significantly worse clinical outcomes in terms of OS than those in the low-risk group (*Figure 5C*). Additionally, an evaluation of the area under the curve (AUC) values for the prognostic markers of the three aforementioned genes in comparison to each gene individually indicated that the composite marker formed by these three genes produced a higher AUC value. This suggests that the risk-score model, which incorporates these genes, showed improved stability in predicting survival outcomes at 1 year (AUC: 0.764), 3 years (AUC: 0.701), and 5 years (AUC: 0.706) (*Figure 5D*).

Discussion

In this study, cellular senescence-related genes were employed to stratify patients from TCGA-HCC dataset into low- and high-risk groups. The subtype analysis revealed that the distribution of C1 was significantly correlated with numerous factors, including age, sex, pathological T stage, TNM classification, and grade staging. Further, the KEGG

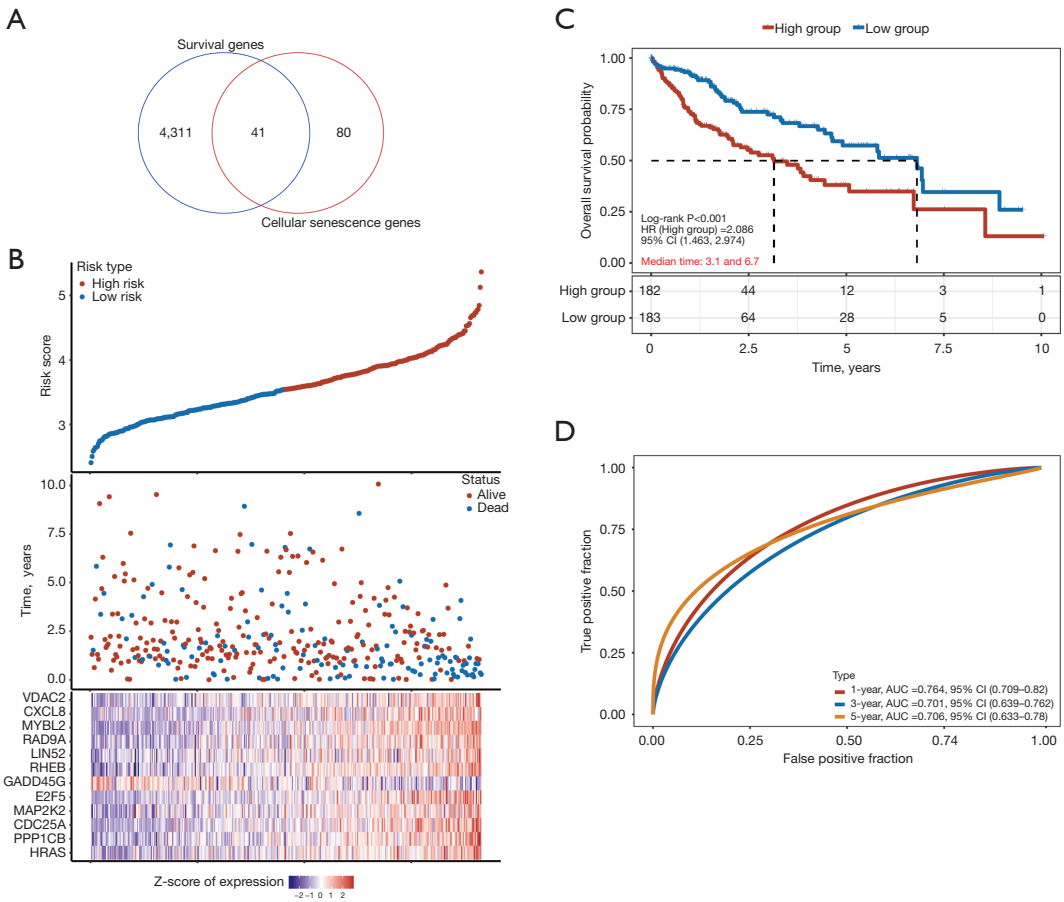

Figure 5 Development of prognostic signatures derived from genes linked to cellular senescence. (A) Venn diagram showing the prognostic genes associated with cellular senescence. The univariate Cox regression analysis identified a total of 4,352 prognostic genes, of which 121 genes were specifically relevant to cellular senescence. (B) An assessment of the prognostic-gene signature was carried out in TCGA cohort. The heatmap shows the expression profiles of the prognostic genes, which were classified as low risk and high risk. (C) A KM survival analysis was conducted to examine the prognostic signature. (D) A time-dependent receiver operating characteristic analysis of the gene signature was performed. AUC, area under the curve; CI, confidence interval; HR, hazard ratio; KM, Kaplan-Meier; TCGA, The Cancer Genome Atlas.

analysis indicated that the genes that were upregulated in the high-risk C1 group were primarily engaged in pathways related to the cell cycle, DNA replication, cellular senescence, ECM-receptor interactions, and mechanisms of mismatch repair. Conversely, the 90 genes that were downregulated were mainly associated with metabolic pathways, chemical carcinogenesis involving DNA adducts, complement and coagulation cascades, and the PPAR signaling pathway. The resultant boxplots revealed significant differences in the populations of immune cells, such as B cells, endothelial cells, NK cells, macrophages, $CD4^+$ T cells, and $CD8^+$ T cells, in C1 compared to C2. Additionally, the prognostic outcomes of the HCC patients were predicted using a cellular senescence-related gene model that included *VDAC2*, *CXCL8*, *MYBL2*, *RAD9A*, *LIN52*, *RHEB*, *GADD45G*, *E2F5*, *MAP2K2*, *CDC25A*, *PPP1CB*, and *HRAS*.

Recent research has revealed a significant correlation between cellular senescence, and the established pathways of carcinogenesis, tumor progression, and the invasive behavior of HCC. Cellular senescence is defined as a permanent halt in cellular division (11). Numerous therapeutic approaches can induce senescence in cancerous cells via mechanisms, such as genotoxic stress, augmented mitogenic signaling, and oxidative stress, which results in a definitive interruption of the cell cycle (10-12). Our research indicates that senescence-related genes may indeed contribute to tumor progression through the SASP. The

SASP is characterized by the secretion of various pro-inflammatory cytokines, growth factors, and proteases that can modify the tumor microenvironment (10-12). This secretory phenotype has the potential to promote tumor growth, invasion, and metastasis by enhancing cellular proliferation and survival of adjacent tumor cells. Furthermore, components of the SASP can recruit immune cells to the tumor site, which might initially have a tumor-suppressive effect but can also lead to immune evasion strategies employed by the cancer cells over time (10-12). Despite substantial research, the precise function of cellular senescence in HCC remains inadequately understood. The prognostic outcomes of HCC patients were predicted using a model comprising 12 cellular senescence-related genes (i.e., *VDAC2*, *CXCL8*, *MYBL2*, *RAD9A*, *LIN52*, *RHEB*, *GADD45G*, *E2F5*, *MAP2K2*, *CDC25A*, *PPP1CB*, and *HRAS*). Additionally, this model can serve as a complementary tool to traditional staging systems, helping to refine prognosis and enabling better risk stratification. We envision that with further validation in larger cohort studies, our 12-gene model could be incorporated into clinical guidelines, assisting healthcare providers in making informed decisions that improve patient outcomes.

Celastrol liposomes promote ferroptosis and apoptosis via the direct modulation of the voltage-dependent anion channel 2 (VDAC2) in HCC (14). C-X-C motif ligand 8 (CXCL8) serves as a chemokine that functions as a crucial multifunctional cytokine involved in regulating tumor growth, invasion, and migration (15). The transcription factor MYB proto-oncogene like 2 (MYBL2) facilitates the enhancement of both proliferation and metastasis in bladder cancer via the transactivation of CDCA3 (16). The silencing of cell-cycle checkpoint control protein RAD9A augments the DNA damage elicited by trichostatin A in esophageal cancer cell lines (17). MicroRNA-146a affects advanced gastric cancer patients' sensitivity to chemotherapy and prognosis by modulating the expression of LIN52 (18). RHEB enhances the viability of cancer cells via the p27Kip1-mediated stimulation of autophagy (19). 4-methoxydalbergione induces anti-cancer activity via the upregulation of GADD45G in human HCC cells (20). E2F5 enhances the proliferation and invasion of gastric cancer by directly increasing the transcription of UBE2T (21). CDC25A plays a role in obstructing autophagy-driven ferroptosis by enhancing the expression of ErbB2 via the dephosphorylation of PKM2 in cervical cancer cells (22). Histone methyltransferase NSD3 plays a critical role in inhibiting the glycolytic process in lung adenocarcinoma by engaging with PPP1CB (23). Notably, our senescence-related gene signature (SRGS) holds particular promise for optimizing patient stratification in systemic therapy. Recent clinical studies highlight capecitabine—an oral fluoropyrimidine prodrug—as an emerging option for advanced HCC patients refractory to first-line therapies (24-26). Mechanistically, capecitabine induces tumor cell senescence through thymidylate synthase inhibition and DNA damage response activation (26), mirroring key pathways enriched in our SRGS-high subgroup (e.g., p16INK4a/CDKN2A upregulation and SASP factor overexpression). Further functional validation and screening will be necessary to determine the efficacy and specificity of targeting these genes. Our findings lay a foundation for future studies aimed at exploring these therapeutic avenues in the context of HCC treatment.

It is essential to acknowledge the limitations of this study. Further *in vitro* and *in vivo* analyses of the 12 cellular senescence-related genes are required to validate our findings. It is essential to validate the model using independent datasets to enhance its generalizability. Future research plan to conduct a comprehensive analysis of existing patient databases to evaluate the correlation between identified molecular subtypes and clinical outcomes. By stratifying patients based on these subtypes, we can assess overall survival, disease-free survival, and response to treatment, which will help to reinforce the prognostic value of our molecular classifications. Additionally, future research should take into account the underlying molecular mechanisms pertinent to this study.

Conclusions

In summary, this study found a significant correlation between cellular senescence-related genes, and tumor classification and the immune response in patients with HCC. The cellular senescence-related signature established could serve as promising prognostic tools for HCC. Our findings may lead to developments in diagnostic and therapeutic approaches for HCC.

Acknowledgments

None.

Footnote

Reporting Checklist: The authors have completed the

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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