RESEARCH ARTICLE

ANKRD19P is an ideal prognostic factor for pancreatic cancer

Jun Li[1], Hongye He[2], Yongxiang Wang[1,2*]

[1]Department of Nursing, Zigong First People's Hospital, Zigong, Sichuan Province, China

[2]Department of General Surgery, Second Xiangya Hospital, Central South University, Changsha, Hunan Province, China

ABSTRACT

Pancreatic cancer is a highly aggressive malignant tumor that significantly impacts patients' quality of life and imposes a considerable socioeconomic burden. Despite progressive advancements in treatment modalities, early diagnosis and prognostic assessment remain essential for improving patient outcomes. This study aims to investigate the expression of the ANKRD19P gene in pancreatic cancer and its correlation with patient prognosis. The findings demonstrate that elevated levels of ANKRD19P expression in pancreatic cancer patients are associated with improved overall survival ($p = 4.4e-6$, HR = 0.38), disease-specific survival ($p = 1.7e-5$, HR = 0.36), and progression-free interval ($p = 5.7e-5$, HR = 0.45). Immunoinfiltration analysis reveals that high expression of ANKRD19P is positively correlated with CD8 T cell infiltration ($p < 0.05$) and negatively correlated with the number of tumor-infiltrating macrophages ($p < 0.05$), thereby impacting the immune microenvironment. Additionally, functional enrichment analyses indicate that ANKRD19P influences pathways associated with MAPK, Ras, and cAMP, consequently affecting the proliferation and metastasis of pancreatic cancer.

Keywords: Pancreatic cancer; Prognostic; Biological; Patients; Research; Microenvironment; Infiltration; Prognosis

BACKGROUND

Pancreatic cancer is an exceedingly aggressive malignant tumor with a high mortality rate, frequently diagnosed at an advanced stage, which results in a significantly limited survival period for patients. The five-year survival rate for pancreatic cancer is less than 5%, rendering early diagnosis and effective treatment critical clinical challenges [1].Despite some progress in genomics and biomarker research in recent years, systematic studies on the molecular mechanisms, subtype characteristics, and prognostic biomarkers related to pancreatic cancer are still insufficient [2].Current treatments for pancreatic cancer primarily rely on traditional methods such as surgery, chemotherapy, and radiation therapy. However, due to the subtlety of early symptoms, many patients miss the opportunity for surgery by the time of diagnosis, and the efficacy of existing treatments is also limited. Therefore, developing new biomarkers to evaluate the prognosis of pancreatic cancer patients has become key to improving patient survival and treatment outcomes [3].

Research at the genetic level will elucidate the potential associations between survival time and molecular changes in pancreatic cancer patients, thereby providing new prognostic assessment tools and personalized treatment options for clinical practice [4].Additionally, the study will analyze the tumor microenvironment and its impact on immune responses to enhance our understanding of the biological characteristics and clinical manifestations of pancreatic cancer [5].Researchers have identified several gene mutations closely linked to the prognosis of pancreatic cancer, including KRAS and TP53 [6]. In addition to these protein-coding functional genes, pseudogenes important components of the genome have garnered increasing attention from researchers. Pseudogenes are sequences similar to functional genes but devoid of expression potential. Studies indicate that they may play significant roles in tumorigenesis and development, participating in the regulation of processes such as tumor cell proliferation, migration, and invasion. This growing recognition has intensified the focus on the relationship between pseudogenes and pancreatic cancer [7].ANKRD19P (Ankyrin Repeat Domain 19, Pseudogene) is a pseudogene. Currently, there is a lack of research on ANKRD19P in the context of pancreatic cancer, and studies regarding its specific role and biological mechanisms remain relatively scarce, lacking systematic analysis and in-depth exploration. Through a comprehensive analysis of omics data, we hope to clarify the pathogenesis of pancreatic cancer and lay a solid foundation for personalized medicine [8].In summary, this study aims to

Received 21-Mar-2025 Manuscript No. IPP-25-22666 **Editor assigned** 24-Mar-2025 PreQC No. IPP-25-22666 (PQ) **Reviewed** 07-Apr-2025 QC No. IPP-25-22666 **Revised** 14-Apr-2025 Manuscript No. IPP-25-22666 (R) **Published** 21-Apr-2025 DOI: 10.51268/1590-8577-25. S11.4-10

Correspondence Yongxiang Wang

Department of Nursing, Zigong First People's Hospital, Zigong, Sichuan Province, China; Department of General Surgery, Second Xiangya Hospital, Central South University, Changsha, Hunan Province, China

E-mail 228202102@csu.edu.cn

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bridge the gap in pancreatic cancer biomarker research to enhance understanding and management of the disease, ultimately improving patient survival rates and quality of life.

This study aims to explore the expression pattern of ANKRD19P in pancreatic cancer and its relationship with patient prognosis by integrating clinical sample analysis with bioinformatics methods. We will measure the expression levels of ANKRD19P in samples from pancreatic cancer patients and conduct systematic association analyses with clinical data to evaluate whether ANKRD19P can serve as a prognostic target for pancreatic cancer. This research not only focuses on the expression of ANKRD19P in pancreatic cancer and its association with prognosis but also seeks to fill gaps in existing research through systematic analysis and exploration, providing new insights and evidence for clinical practice. By delving into the biological functions and clinical application potential of ANKRD19P, we hope to offer new perspectives and approaches for the management and treatment strategies of pancreatic cancer patients, ultimately improving their survival rates and quality of life.

METHODS

Data Acquisition and Preprocessing: RNA-Seq (mRNA expression data) and clinical information files were obtained from the GDC data portal for the Pancreatic Adenocarcinoma (PAAD) project. The clinical information encompasses variables such as gender, age, stage, and survival time. Clinical data from multiple sources were integrated, and missing values were addressed by removing samples with a missing rate exceeding 50%. Key fields, including Overall Survival (OS) and Progression-Free Survival (PFS), were extracted for subsequent survival curve analysis.

Analysis of Differential Genes: Differential gene analysis was performed using the DESeq2 package. Initially, PAAD samples were classified into high-expression and low-expression groups based on the expression levels of ANKRD19P. The dataset included a gene expression count matrix, where rows corresponded to genes and columns to samples, along with sample grouping information. Subsequently, a DESeqDataSet object was created by integrating the data with the experimental design (e.g., design = ~condition) using the function DESeqDataSetFromMatrix (ss), establishing a foundational structure for normalization and analysis. Next, normalization and model fitting were conducted by invoking the DESeq() function, which performed data normalization (estimating size factors and dispersion), fitted a negative binomial distribution model, and conducted hypothesis testing (e.g., Wald test or LRT). Finally, differential genes were extracted and identified using the results() function to obtain statistical outcomes (such as log2FC, p-values, and FDR-corrected values) and significant differential genes were filtered based on specified thresholds ($|log2FC| > 0.58$ and $padj < 0.05$).

Statistical Method: Data presentation methods are tailored according to the types of variables. For normally distributed quantitative data, the mean ± standard deviation is utilized, whereas non-normally distributed data is represented by the median (interquartile range). In hypothesis testing, comparisons between two groups of normal data employ independent samples t-tests or paired t-tests, while multiple group comparisons utilize one-way ANOVA. For non-parametric data, the Mann-Whitney U test or Kruskal-Wallis H test is applied. Categorical variable analysis employs the χ^2 test or Fisher's exact probability method, whereas ordinal data is analyzed using the rank-sum test. Correlation analysis selects either the Pearson or Spearman method depending on the characteristics of the data. Survival analysis is performed using the survival package, and the GSVA score is computed through the R package GSVA. Furthermore, the clusterProfiler package is employed for various functional enrichment analyses, including Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis.

RESULTS

ANKRD19P affects the prognostic prediction indicators of pancreatic cancer

The association between the prognosis of pancreatic cancer patients and gene expression information shows that pancreatic cancer patients with high ANKRD19P expression have longer overall survival (p = 4.4e-6). Compared to patients with low ANKRD19P expression, those with high ANKRD19P expression have a hazard ratio (HR) of 0.38 (Fig 1A). In terms of disease-specific survival, patients with high ANKRD19P expression also exhibit a longer disease-specific survival period (p = 1.7e-5). Compared to patients with low ANKRD19P expression, those with high ANKRD19P expression have a HR of 0.36 (Fig 1B). Similarly, high ANKRD19P expression in pancreatic cancer patients correlates with a longer progression-free interval (p = 5.7e-5), with a HR of 0.45 compared to patients with low ANKRD19P expression (Fig 1C).

Subsequently, ROC curves were used to evaluate the accuracy and stability of ANKRD19P in predicting the prognosis of pancreatic cancer patients. The results showed that, concerning overall survival, the AUC values for one-year, three-year, and five-year survival rates were 0.66, 0.7, and 0.82, respectively (Fig 1D). In terms of disease-specific survival, the AUC values for one-year, three-year, and five-year survival rates were 0.69, 0.7, and 0.82, respectively (Fig 1E). Regarding the progression-free interval, the AUC values for one-year, three-year, and five-year survival rates were 0.64, 0.7, and 0.85, respectively (Fig 1F). These results indicate that ANKRD19P predicts the long-term survival rate of pancreatic cancer patients

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better than the short-term survival rate, demonstrating an overall good predictive performance with consistent results across different survival prediction levels.

ANKRD19P is involved in many biological processes related to pancreatic cancer

Based on the median expression level of ANKRD19P, the samples were divided into high-expression and low-expression groups. Subsequently, a set of differential genes related to ANKRD19P was obtained, followed by functional enrichment analysis of these differentially expressed genes to identify the biological processes affected by ANKRD19P in pancreatic cancer. The GO results indicated that ANKRD19P is associated with the cell cycle, cell migration and differentiation, immune cell migration, and T cell activation in pancreatic cancer (Fig 2A). Meanwhile, the KEGG results showed that ANKRD19P is not only related to the cell cycle, T cell function, and cell migration in pancreatic cancer, but also impacts the signaling pathways of MAPK, Ras, and cAMP, thereby affecting the prognosis of pancreatic cancer patients (Fig 2B). These results suggest that ANKRD19P influences not only the proliferation and migration of pancreatic cancer cells but is also closely related to the tumor's immune microenvironment.

Analyzing the prognostic impact of the ANKRD19P-related differential gene set identified 1,581 differential genes affecting pancreatic cancer prognosis. Subsequently, a protein-protein interaction network associated with ANKRD19P was constructed using these 1,581 genes (Fig 3). The MCODE program was utilized to analyze the core network of the protein interaction network, ultimately yielding the top three ranked core networks (Fig 4A-C). The GSVA scores were calculated for the genes in these three core networks and correlated with clinical information. The results showed that the gene set of cluster 1 did not exhibit statistically significant differences regarding pancreatic cancer prognosis (Fig 5A); among pancreatic cancer patients, a lower GSVA score for the cluster 1 gene set corresponded to a higher tumor stage (Fig 5B). The GSVA score of the cluster 1 gene set was positively correlated with the PI3K/AKT and TSC/mTOR pathways but negatively correlated with the Apoptosis pathway (Fig 5C). The cluster 2 gene set was associated with overall survival (OS), progression-free survival (PFS), disease-specific survival (DSS), and disease-free interval (DFI) in pancreatic cancer; higher GSVA scores for the cluster 2 gene set indicated better prognosis for OS, PFS, DSS, and DFI (Fig 5D). Correspondingly, lower GSVA scores for the cluster 2 gene set corresponded to higher tumor stages (Fig 5E). The GSVA score of the cluster 2 gene set was positively correlated with the PI3K/AKT and TSC/mTOR pathways while negatively correlated with the Apoptosis pathway (Fig 5F). The cluster 3 gene set was associated with OS, PFS, and DSS in pancreatic cancer; higher GSVA scores for the cluster 3 gene set corresponded to better prognosis for OS, PFS, and DSS (Fig 5G). Similarly, lower GSVA scores for the cluster 3 gene set corresponded to higher tumor stages (Fig 5H). The GSVA score of the cluster 3 gene set was also positively correlated with the PI3K/AKT and TSC/mTOR pathways but negatively correlated with the Apoptosis pathway (Fig 5I).

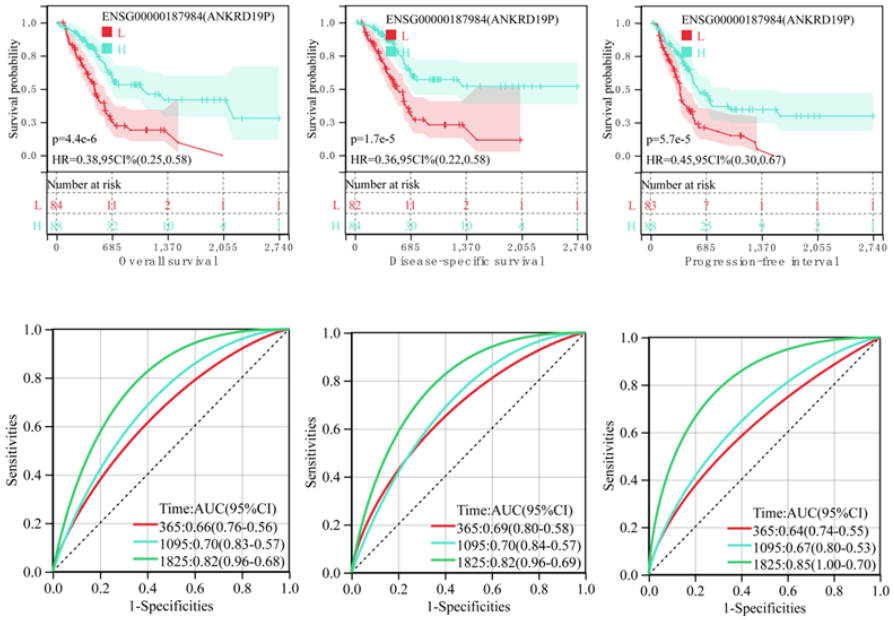

Figure 1. The relationship between ANKRD19P and the prognosis of pancreatic cancer. (A) The effect of ANKRD19P on the overall survival of pancreatic cancer. (B) The effect of ANKRD19P on disease-specific survival in pancreatic cancer. (C)The effect of ANKRD19P on the progression-free interval in pancreatic cancer. (D) ROC curve for overall survival associated with ANKRD19P. (E) ROC curve for disease-specific survival associated with ANKRD19P. (F) ROC curve for the progression-free interval associated with ANKRD19P.

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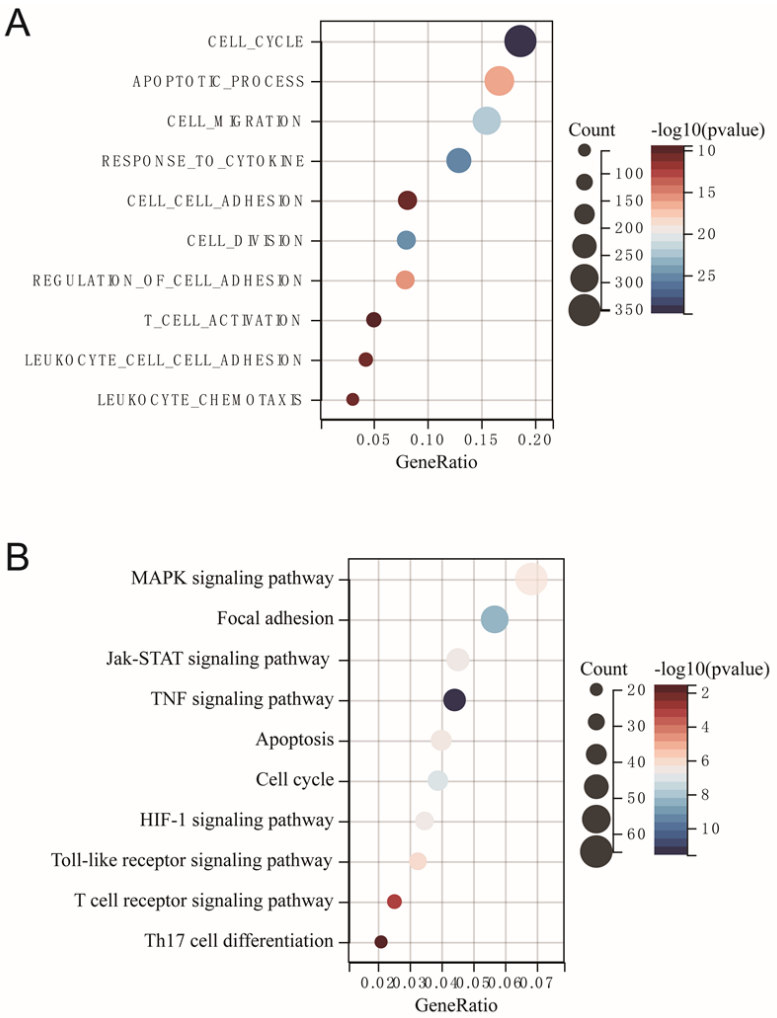

Figure 2. Functional enrichment associated with ANKRD19P. (A) GO analysis of differential genes related to ANKRD19P. (B) KEGG analysis of differential genes related to ANKRD19P.

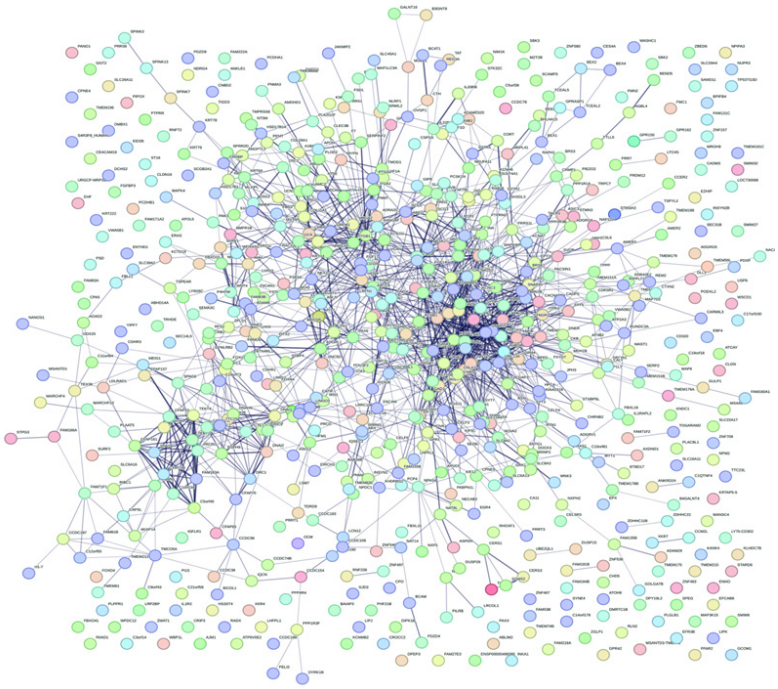

Figure 3. Protein-protein interaction network of differential genes related to ANKRD19P that affect prognosis.

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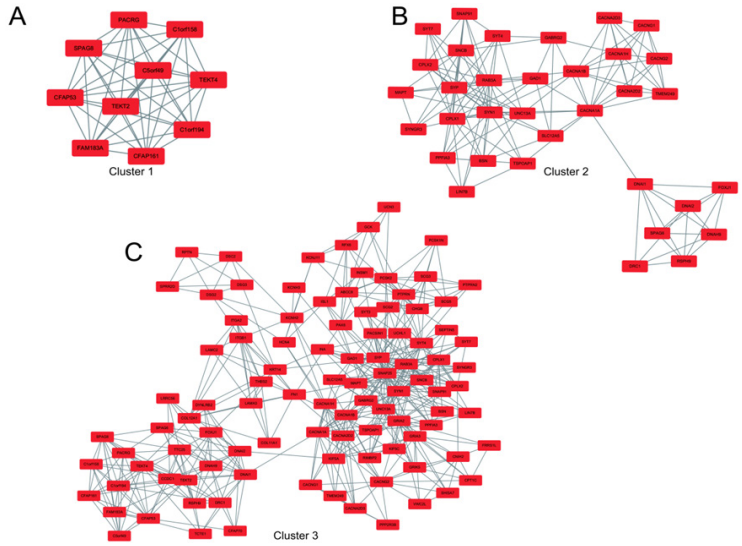

Figure 4. The top three core networks in the protein-protein interaction network. (A) Core network cluster 1 for TOP 1. (B) Core network cluster 2 for TOP 2. (C) Core network cluster 3 for TOP 3.

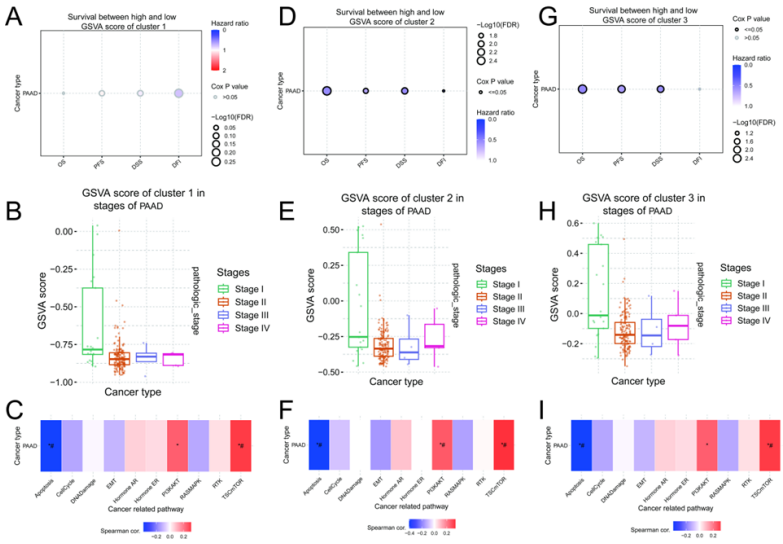

Figure 5. Clinical analysis and pathway analysis related to the core networks. (A) The relationship between core network cluster 1 and the prognosis of pancreatic cancer. (B) The relationship between core network cluster 1 and the clinical staging of pancreatic cancer. (C)The relationship between core network cluster 1 and relevant pathways in pancreatic cancer. (D) The relationship between core network cluster 3 and the prognosis of pancreatic cancer. (E) The relationship between core network cluster 2 and the clinical staging of pancreatic cancer. (F) The relationship between core network cluster 2 and relevant pathways in pancreatic cancer. (G) The relationship between core network cluster 3 and the prognosis of pancreatic cancer. (H) The relationship between core network cluster 3 and the clinical staging of pancreatic cancer. (I) The relationship between core network cluster 3 and relevant pathways in pancreatic cancer.

DISCUSSION

This study aims to explore molecular prognostic biomarkers in pancreatic cancer patients through omics analysis, with a particular focus on biomarkers associated with the tumor microenvironment and genetic mutations. Changes in the expression of specific genes are significantly correlated with patient survival rates, providing new prognostic assessment tools for clinical practice [9]. Previous research has indicated that these genes are not only involved in tumorigenesis and progression but may also represent new targets for personalized treatment. This study reveals, for the first time, the correlation between the pseudogene ANKRD19P and pancreatic cancer prognosis, as well as the biological processes influenced by this gene in pancreatic cancer.

Previous studies have demonstrated that the pseudogenes GAS5 and LINC00174 interact with known tumor suppressor genes, such as p53 and PTEN, and that their low expression levels may be closely associated with patient prognosis [10, 11]. The findings of this study indicate that high expression of the pseudogene ANKRD19P is similarly associated with

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improved prognosis. Pathway analyses further revealed significant activation of the Wnt and PI3K/Akt signaling pathways in pancreatic cancer, which are linked to tumor aggressiveness. Activation of these pathways may present new targets for therapeutic intervention. Additionally, existing research has shown that inhibiting relevant targets within these pathways can effectively reduce the proliferation and metastatic potential of tumor cells [12].

Functional enrichment analysis of the ANKRD19P-related gene set revealed its influence on the PI3K/AKT and TSC/mTOR pathways, suggesting that ANKRD19P may modulate PI3K/AKT signaling. Previous studies also indicate a significant correlation between pseudogenes and the Wnt signaling pathway, with activation of this pathway potentially affecting cell proliferation and migration [13]. Furthermore, pseudogenes may contribute to tumorigenesis and progression by influencing the stability of the tumor genome and epigenetic regulation [14]. This study further demonstrates that ANKRD19P influences the proliferation and migration of pancreatic cancer cells while also impacting the MAPK, Ras, and cAMP signaling pathways. The effects of ANKRD19P on these pancreatic cancer pathways correspond with its prognostic implications.

Previous studies have also found that the pseudogene TUG1 influences the tumor microenvironment by regulating the functions of various immune cells, which may further affect patient responses to immunotherapy and chemotherapy [15]. In terms of immune response, the infiltration of CD8+ T cells in pancreatic cancer tissue is positively correlated with patient survival, while the infiltration of tumor-associated macrophages is negatively correlated.

This study shows that the pseudogene ANKRD19P is positively correlated with CD8+ T cell infiltration and negatively correlated with macrophage infiltration. These results suggest that variations in the pattern of immune cell infiltration may serve as a new indicator for predicting patient prognosis. Existing literature indicates that enhancing the immune response may increase the response rate of pancreatic cancer patients to immunotherapy, particularly when there is a high level of anti-tumor immune cell infiltration in the tumor microenvironment [16].

The limitations of this study primarily lie in the relatively small sample size and the lack of clinical validation analysis. Although we identified key biomarkers through omics methods, the small sample size may affect the statistical significance and generalizability of the results. Additionally, the diversity of the datasets may lead to batch effects, potentially impacting the reliability of the findings. Therefore, future research should aim to increase the sample size and conduct multi-center clinical validation to further confirm the association between the identified biomarkers and pancreatic cancer prognosis.

DATA AVAILABILITY

Data is provided within the manuscript or supplementary information.Data is provided within the manuscript or supplementary information files. The data supporting this research result has been stored in the TCGA database (https://www.cancer.gov/ccg/research/genome-sequencing/tcga)

FUNDING

None.

AUTHOR CONTRIBUTIONS

LJ and HHY contributed equally to this work. LJ and HHY: Writing - original draft. HHY: Project administration. YXW: Supervision, Writing - review & editing. All authors read and approved the final manuscript.

DECLARATIONS

Ethics approval and consent to participate

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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