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Research Article

Identification of Prognosis-Related Genes and Key Target Genes for Pancreatic Cancer: A Bioinformatics Analysis

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ABSTRACT

Objective: The mortality and morbidity rates associated with Pancreatic Cancer (PaCa) are extremely high. Various studies have demonstrated that pancreatic cancer will be the fourth cancer related death by 2030, raising more concern for scholars to find effective methods to prevent and treat in order to improve the pancreatic cancer outcome. Using bioinformatic analysis, this study aims to pinpoint key genes that could impact PaCa patients' prognosis and could be used as therapeutic targets.

Materials and methods: The TCGA and GEO datasets were integratively analyzed to identify prognosis-related differentially expressed genes. Next, the STRING database was used to develop PPI networks, and the MCODE and CytoNCA Cytoscape in Cytoscape was used to screen for critical genes. Through CytoNCA, three kinds of topology analysis were considered (degree, betweenness, and eigenvector). Essential genes were confirmed as potential target treatment through Go function and pathways enrichment analysis, a developed predictive risk model based on multivariate analysis, and the establishment of nomograms using the clinical information.

Results: Overall, the GSE183795 and TCGA datasets associated 1311 and 2244 genes to pancreatic cancer prognosis, respectively. We identified 132 genes that were present in both datasets. The PPI network analysis using, the centrality analysis approach with the CytoNCA plug-in, showed that, *CDK2*, *PLK1*, *CCNB1*, and *TOP2A* ranked in the top 5% across all three metrics. The independent analysis of a risk model, revealed that the four keys genes had a Hazard Ratio (HR)>1. The monogram showed the predictive risk model and individual patient survival predictions were accurate. The results indicate that the effect of the selected vital genes was significant and that they could be used as biomarkers to predict a patient's outcome and as possible target therapy in patients with pancreatic cancer. GO function and pathway analysis demonstrated that crucial genes might affect the p53 signaling pathway and FoxO signaling pathway, through which meiotic nuclear division and cell cycle may have a significant function in essential genes affecting the outcome of patients who have pancreatic cancer.

Conclusion: This study suggests that *CDK2*, *CCNB1*, *PLK1* and *TOP2A* are four key genes having a significant influence on PaCa migration and proliferation. *CDK2*, *CCNB1*, *PLK1*, and *TOP2A* can be used as potential PaCa prognostic biomarkers and therapeutic targets. However, experimental validation is necessary to confirm these predictions. Ours study comes into contributions to the development of personalized target therapy for pancreatic cancer patients.

Keywords: Pancreatic Cancer (PaCa); Target genes; Protein-protein network; Bioinformatics

INTRODUCTION

Pancreatic Cancer (PaCa) ranks seventh in terms of cancer prevalence globally and the fourth most prominent cause of mortality due to cancer, with more than 30000 deaths annually [1]. Globally, over 400,000 new cases of pancreatic cancer are diagnosed annually, and the number of pancreatic cancer is still predicted to increase exponentially. High recurrence rates and metastasis following surgery are the most prominent causes of poor outcome in pancreatic cancer patients [2]. Many factors contribute to the minimal survival proportion of pancreatic cancer patients, such as those diagnosed at a late stage due to lack of a systemic screening.

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Previous studies have identified responsive and efficient molecular markers that can significantly influence pancreatic cancer's biological initiation and progression. For instance, the Tumor Suppressor Gene (TSG) *KRAS* has been shown in studies to be mutated in more than 90% of pancreatic cancer cases [3]. Given the vital role of TSG *KRAS* in pancreatic cancer, it's now considered a potential therapeutic target of choice. Besides *KRAS*, TSGs such as *TP53* have also been demonstrated by studies that it's a prognostic indicator that significantly influences the outcome of patients with pancreatic cancer [4]. These findings further research on molecular pathology and gene mutation-initiating pancreatic cancer development. Studies on pancreatic cancer biomarkers usually focused on single-gene patterns, whereas cancer typically involves several genes and biological processes. How to scientifically improve the prognosis of pancreatic cancer patients has been the focus for more and more scholars trying to understand and elucidate the molecular mechanisms behind pancreatic cancer initiation and progression to identify significant biomarkers and signaling networks. Bioinformatics has revolutionized biological data analysis and management, enabling research on large amounts of data in a short period. Bioinformatics is widely used to screen essential specific genes for specific cancer patients. These give the possibilities of personalized treatment plans for a cancer patient with specific drugs targeting a particular biomarker [5,6]. Large-scale cancer genomics projects like TCGA and GEO have advanced our understanding of cancer genetics, revealing a comprehensive view of pancreatic cancer-related genomic alterations and facilitating further research [7]. Using bioinformatics tools and techniques, common significant prognosis-related differentially expressed genes (prognosis-related DEG) of pancreatic cancer were identified between the GEO and TCGA databases. In addition, based on module and centrality analysis, we formed a protein-protein network to screen out essential genes in PR-DEGs, developed a predictive risk model, and verified and validated favourable vital genes. The present study establishes a solid platform for investigating the biological processes at the molecular level underlying pancreatic cancer development and identifying biomarker targets for clinical management.

MATERIALS AND METHODS

Data collection

The gene expression profiles of PaCa patients were acquired from a GEO dataset (GSE183795). The sample size was 244 PaCa patients. Moreover, the expression profiles and clinical details of 182 cases of PaCa were also retrieved from the TCGA database. All original data were corrected, and only patients with all information were included in this study.

Identification of prognostic related differentials gene expression

The pancreatic cancer expression profile was collected from the (GEO=189) and (TCGA=178) databases. Subsequently, the data underwent analysis using R software. The gene expression normalization of the pancreatic dataset in this study was generated through the Limma package, and the missing value was handled through the imput package. Using K-M analysis, we categorized the gene expression profile as high-expression and low-expression categories according to each gene's Median Value (MV) within the gene profile. Afterwards, the survival disparity among all the categories was assessed and validated. With a p-value ($p<0.05$) set as the criteria, the multivariate method and survival analysis using the proportional hazards model were conducted to analyze, confirm, screen, and identify genes that exhibited significant connection with the prognosis of pancreatic cancer patients. Finally, the GEO and TCGA datasets were used to verify these survival analysis-filtered genes independently. We used the term prognosis-related-DEGs to stand for the commonly significant prognosis-related differentially expressed genes.

PPI network analysis and module centrality analysis

Protein-protein interaction prediction was made with the help of the online tool STRING, which allows the analysis of genetic interactions, both structural and functional. This network's connections had to have a confidence score of at least>0.15, and the disconnected nodes were left out of this study. The network was used to create a PPI network of prognostic DEGs. Cytoscape was used to map out the prognosis-related DEGs' PPI connections. The MCODE plug-in was used to determine and quantify the PPI network's functional modules and gene associations. If a module had a maximum score, its protein correlation was more substantial, and the top score module was taken as the findings of the MCODE assessment. Three topologies, degree, betweenness and eigenvector from the CytoNCA were used to conduct a centrality analysis. The degree of a node is a measure of its importance in a network since it indicates the number of edges that lead to that node. Finding the betweenness of two nodes is the fastest way to analyze them. However, the eigenvector considers both the node's and its neighbours' significance. The significance of CytoNCA's analysis is inferred from the genes represented by the top 5% of nodes in the three topology configuration. By integrating the MCODE and CytoNCA extension results, the crucial genes were found within the protein-protein network of prognosis-related DEGs.

Prognostic key genes verification

The MV of the critical gene profile was established as the threshold in the profile data analysis of gene expression in patients with PaCa from the TCGA and GEO, and the essential gene expression profile of patients with pancreatic cancer was categorized into high-expression and low-expression key genes categories. Through R software applying the “survival” package, K–M assessment followed by multivariate Cox model testing was used to examine the disparity in total survival status between the crucial genes high- and low-expression categories. The survival proportion and plot were then interpreted and graphed. Independent prognostic identification of individual and multiple gene merging of crucial genes was performed using the "survival" package, and the hazard ratio and graphs were plotted based on univariate and multivariate Cox model testing. Finally, the Risk Scores (RS) of crucial genes and all the available clinical and pathological parameters were associated with precisely predicting the survival outcome of pancreatic cancer patients. We calculated the risk score of the model using the following formula:

$$\text{Risk Score (RS)} = \Sigma\ (\text{Gene expression} \times \text{weight})$$

The prognostic risk score was determined using K-M analysis, which classified PaCa patients into a low-group risk and high-group risk based on the Median Values (MV) of the RS of crucial genes in the expression profile of PaCa patients. The R language's "RMS" tool is then used to construct the nomogram according to the multivariate Cox model testing.

Go and KEGG analysis of prognostic genes

Pancreatic cancer gene expression datasets from the GEO and TCGA repositories were categorized into two categories considering the median expression value of each essential gene, namely high-expression and low-expression categories. The DEG was then identified between the two categories of crucial genes. Subsequently, the Go functional and the pathways enrichment analysis of each DEG were performed using Go and KEKK through R software packages, including limma," "clusterProfiler," "enrichplot," and "ggplot2." With criteria p<0.05 and log (fold-change) >0.5.

Statistics analysis

Data statistical analysis was conducted using R Software (2023 version) and involved K–M method and Cox model testing (univariate and multivariate) to determine the essential genes. The "survival" package in the R software was used to create survival curves and forest plots for analyzing the prognostic significance of individual-gene or multiple-gene merging of crucial genes. With P<0.05 as the criteria.

RESULTS

Identification of prognosis-related genes

Using R software, we mined the TCGA-PAAD (n=178) and GSE-183795 (n=189) databases for gene expression profile data from PaCa patients. The log transformation and normalization were performed using the 'limma' sets, and the K-M method was used to categorize genes into high-expression and low-expression categories in the gene expression matrix using the MV of each gene before comparing the two groups for significant differences. Multivariate and survival analysis were used through the proportional hazard model testing to identify DEGs within the gene expression datasets of GSE183795 (1311 genes) and TCGA (2244 genes) that were strongly associated with the prognosis of PaCa. Then, 132 shared prognostic DEGs were obtained using cross-validation of two datasets: 132 of 1311 genes from GSE183795 and 132 of 2244 genes from TCGA-PAAD data (Figure 1A).

Module-centrality assessment of the prognosis-related genes

To systematically investigate the molecular mechanization that can alter the prognosis of PaCa patients, we constructed a PPI network of prognosis-related DEGs in STRING with a confidence score >0.15 while excluding unconnected nodes. The data shows that the PPI network comprised 131 nodes and 1665 edges. In addition, the modules for investigating even more closely linked genes within the PPI network were analyzed using the MCODE extension in the Cytoscape platform. Module 1, with a score of 48.500; Module 2, with a score of 4.000; and Module 3, with a score of 3.333, were the three modules revealed by the analysis (Figure 1B). Since the first module's score was the highest and it was the section of the PPI network with the most interactions, this was taken as the outcome of the MCODE analysis. By inspecting each gene's degree, betweenness, and eigenvector scores, we could do a centrality analysis of the PPI network using the CytoNCA plug-in. Next, *CDK2*, *PLK1*, *CCNB1*, and *TOP2A*, rated in the top 5% across all three topologies and present in module 1, were chosen as crucial genes, all from module 1 (Figure 1C).

Prognostic value of key genes in PaCa

To figure out what roles essential genes play in the development of PaCa, we used the K-M method to look at the survival of our genes of interest. Survival curves were made for PaCa patients, who were put into two categories: Those with high expression and those with low expression. In the TCGA and GEO databases, the survival assessment for patients with PaCa demonstrated a close relationship between the frequency of specific genes and the length of time they survived. Based on survival analysis, the median overall survival of pancreatic cancer patients with decreased expression of *CDK2*, *PLK1*, *CCNB1*, and *TOP2A* was 1.79, 1.74, 1.90, and 1.92 years. In contrast, those with higher expression of *CDK2*, *PLK1*, *CCNB1*, and *TOP2A* had 1.36, 1.36, 1.45, and 1.33 years, respectively.

Figures 2A and 2B shows that the patients (GEO, n=103; TCGA, n=90) whose essential genes were more active had a much worse prognosis. As shown by univariate and multivariate Cox model testing, crucial genes with hazards ratio >1, that were 1.75, 1.34, 1.43, and 1.50, in corresponding order with a (p<0.05) in the GEO and TCGA repositories, can autonomously influence the prognosis of pancreatic cancer patients. The impact of crucial genes is significant and could be used as biomarkers to predict a patient's prognosis and as therapeutic targets for PaCa patients (Figure 3).

GO and pathways enrichment analyses

To better understand how the essential genes impact the prognosis of pancreatic cancer, we conducted GO functional and pathways enrichment analyses. The GO functional analysis revealed that the majority of the enriched terms were associated with functions such as nuclear division, organelle fission, mitotic nuclear division, meiotic nuclear division and more. Additionally, the findings from the pathways analyses revealed significant enrichment of pathways such as p53 signaling pathways, FoxO signaling pathways, cell cycle, cellular senescence and others (Figures 4 and 5).

Key gene prognostic risk model construction and validation

Using univariate and multivariate Cox model testing, *CDK2*, *PLK1*, *CCNB1*, and TOP1A were combined to create a key gene prognostic risk model (Table 1). The risk score of key genes was determined as follows: HR*CDK2* × expression value of *CDK2*+HR*PLK1* × expression value of *PLK1*+HR*CCNB1* × expression value of *CCNB1*+HR*TOP2A* × expression value of *TOP2A*. As per the prognostic risk model, the medical significance and prognostic importance of the available clinicopathology, namely the age, gender, and TNM classification, were used to construct a nomogram to validate the prognostic importance of the risk factors. The overall scores, the sum of the scores of each component, can be used to calculate the 1-year, 3-year, and 5-year survival probability represented in the nomogram. The monogram showed the prognostic risk model and individual patient survival predictions were accurate (Figure 6). To explore in more detail the validity of crucial genes, PaCa patients were categorized into high- and low-risk categories based on the risk score cutoff value derived using the maximally selected rank statistics approach in each database (TCGA and GEO).

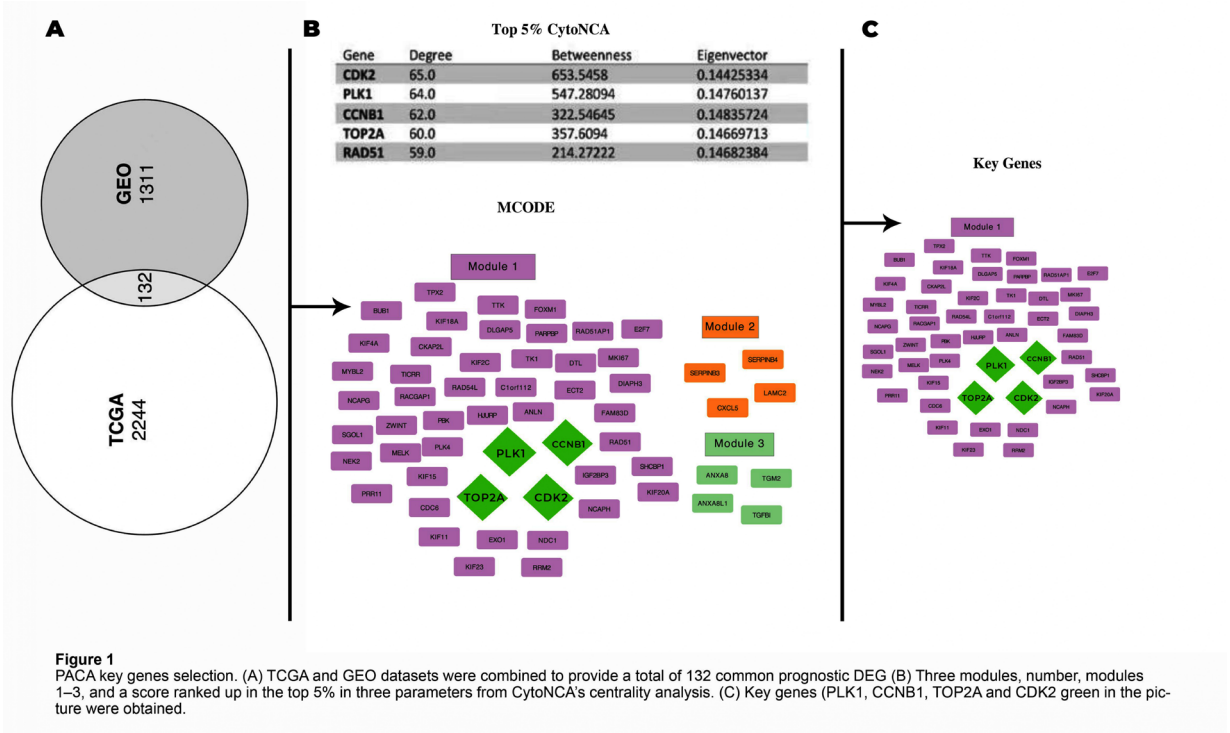

Figure 1
PACA key genes selection. (A) TCGA and GEO datasets were combined to provide a total of 132 common prognostic DEG (B) Three modules, number, modules 1–3, and a score ranked up in the top 5% in three parameters from CytoNCA's centrality analysis. (C) Key genes (PLK1, CCNB1, TOP2A and CDK2 green in the picture were obtained.

Figure 1: Selection of key genes for pancreatic cancer patients, (A) In total, 132 common prognosis-related-DEGs were obtained from the overlapping of TCGA and GEO datasets, (B) Three modules 1-3, and a score ranked up in the top 5% in three topology from CytoNCA's centrality analysis, (C) Key genes (*CDK2*, *CCNB1*, *PLK1*, and *TOP2A*, green in the picture) were obtained.

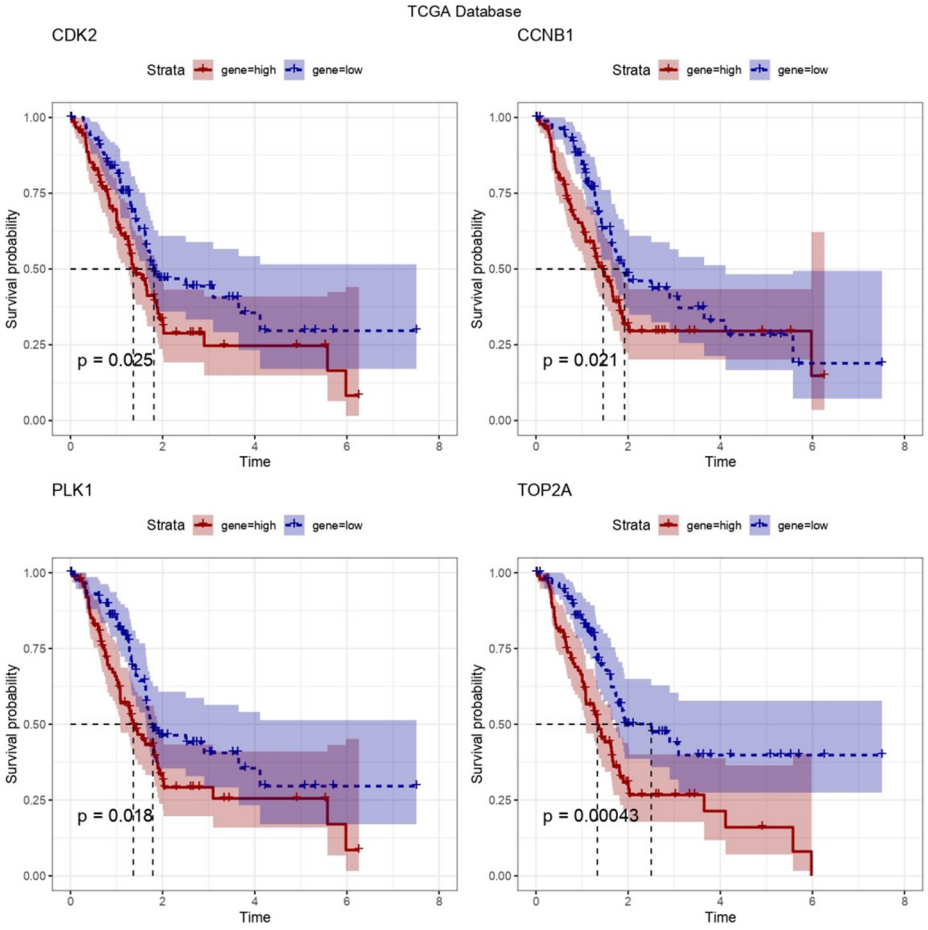

Figure 2 (A): Survival analyses of key genes *CDK2*, *CCNB1*, *PLK1*, and *TOP2A*, patients with high expression of key genes have a poor prognosis in the TCGA database (p<0.05).

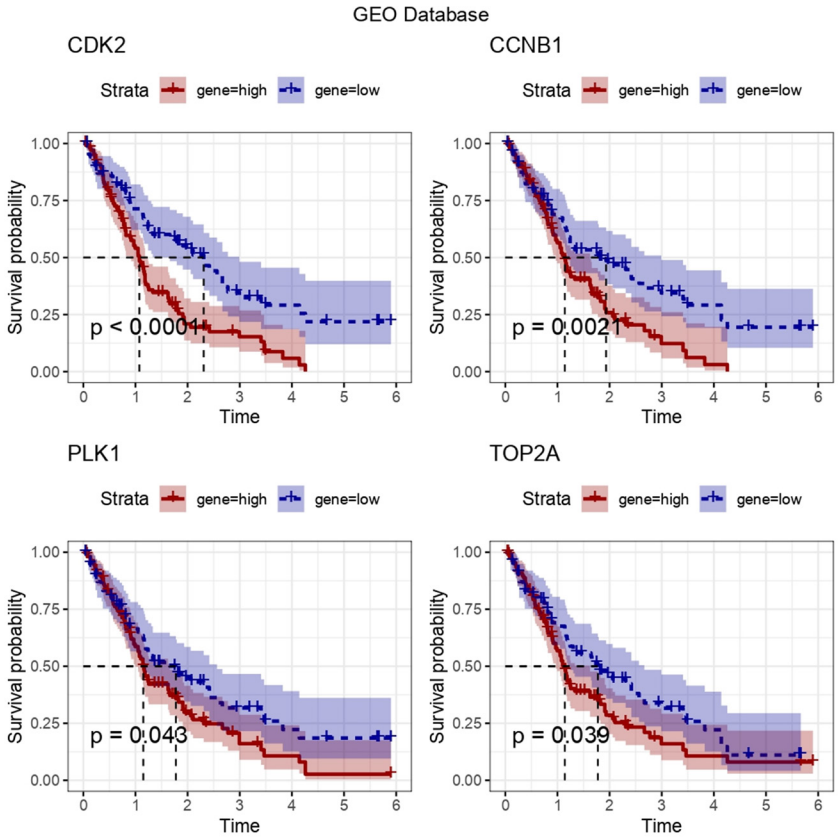

Figure 2 (B): Survival analyses of key genes *CDK2*, *CCNB1*, *PLK1*, and *TOP2A*, patients with high expression of key genes have a poor prognosis in the GEO database (p<0.05).

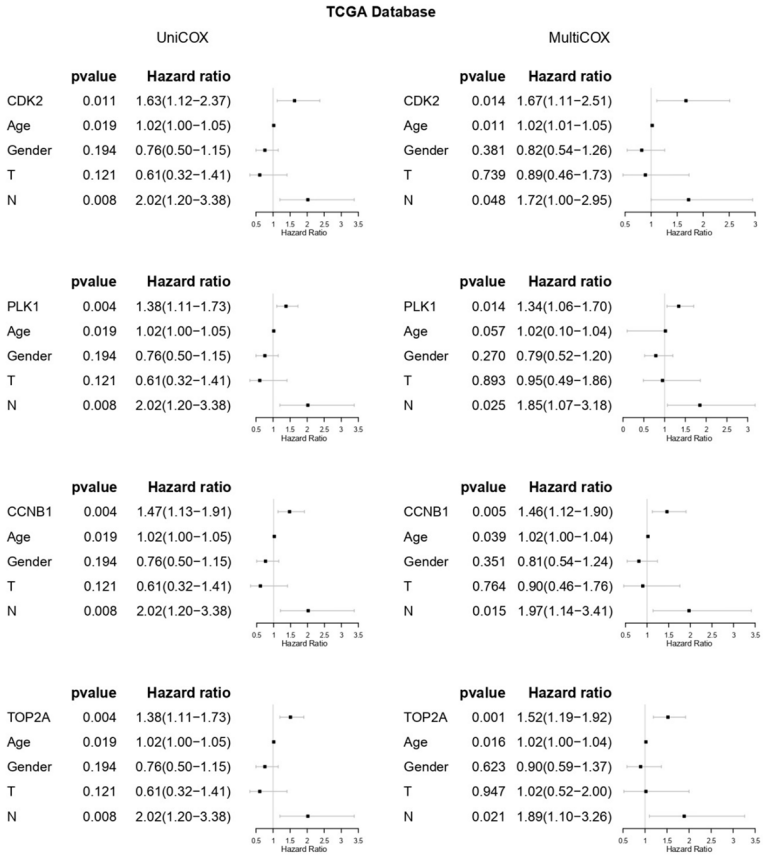

Figure 3: Independent prognostic analyses based on key genes in TCGA database.

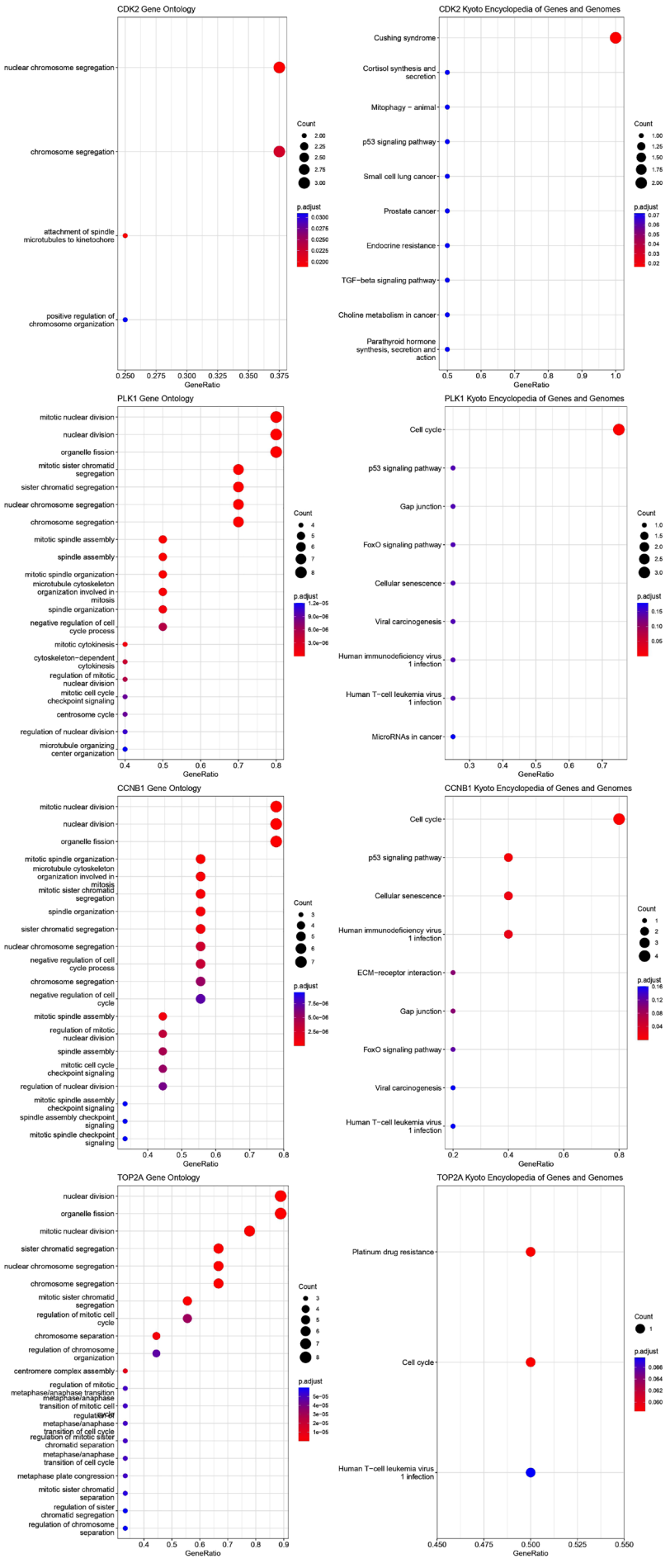

Figure 4: Go function and pathways enrichment analyses from the TCGA database.

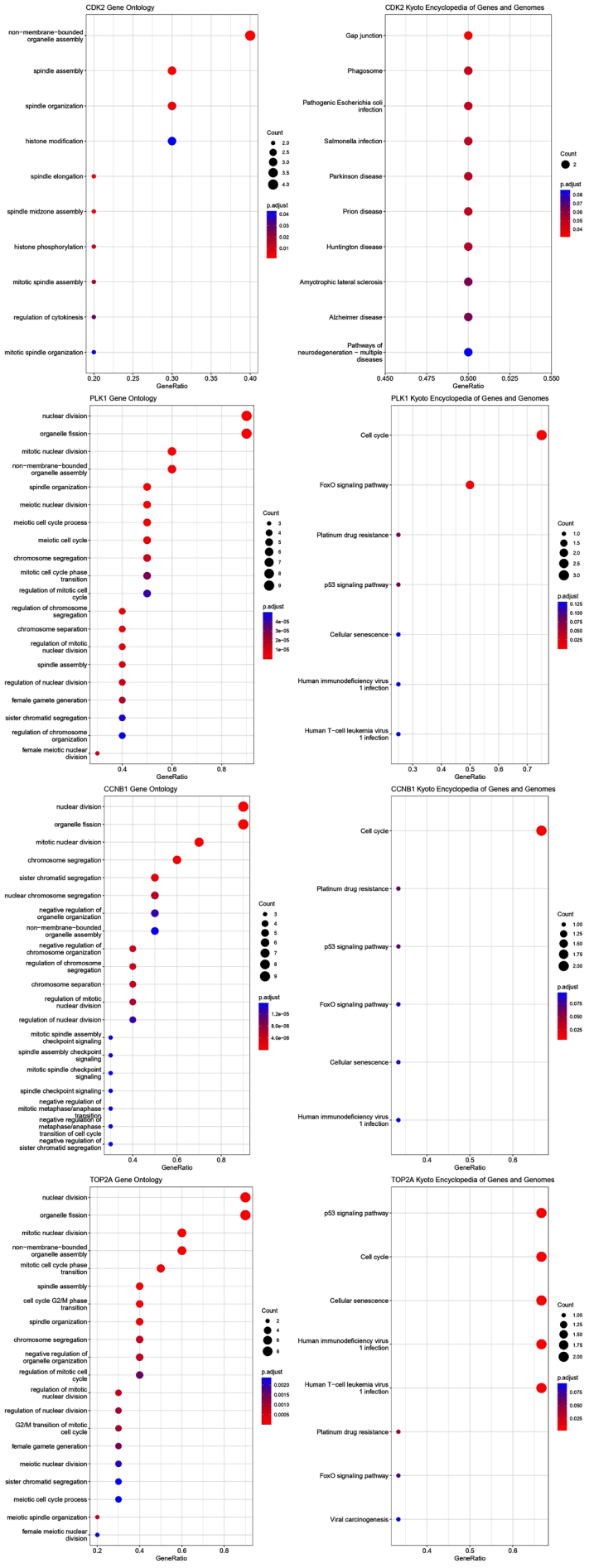

Figure 5: Go function and pathways enrichment analyses from the GEO database.

Table 1: Univariate and multivariate analyses of overall survival in TCGA database.

Variables	Univariate analysis		Multivariate analysis	
	HR	P-value	HR	P-value
Risk score	1.1167	0.0002	1.10163	0.00126
Age	1.02227	0.0346	1.01746	0.00897
Gender-Male	0.8324	0.375	0.90881	0.64695
T lower stage	0.5348	0.052	0.80397	0.51866
NN1	1.8378	0.0144	1.53677	0.09834

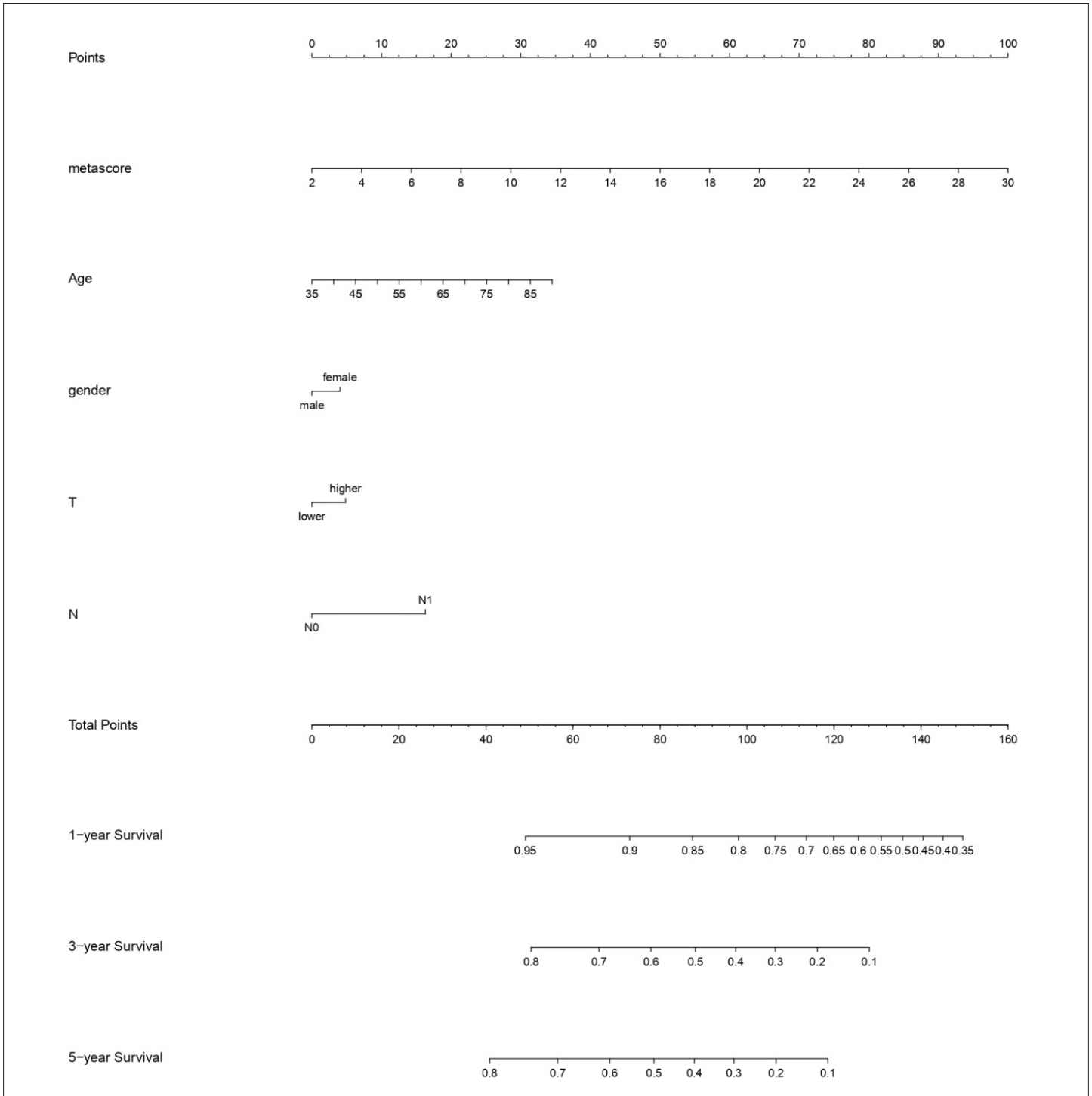

Figure 6: Monogram based on risk model and clinicopathological parameters.

The survival graph (Figures 7A and 7B) demonstrated that the category with higher risk had a poorer outcome than the category with lower risk. Both univariate and multivariate Cox model testing was done according to the gene expression profile data. The findings revealed that the RS for crucial genes were autonomously associated with the total survival proportion of PaCa patients. The findings suggest the key genes could be referenced as PaCa prognostic genes. The key genes (*CDK2*, *TOP2A*, *CCNB1*, and *PLK1*) can be used to plan the next treatment step. These genes could also be used to improve the prognosis of pancreatic cancer.

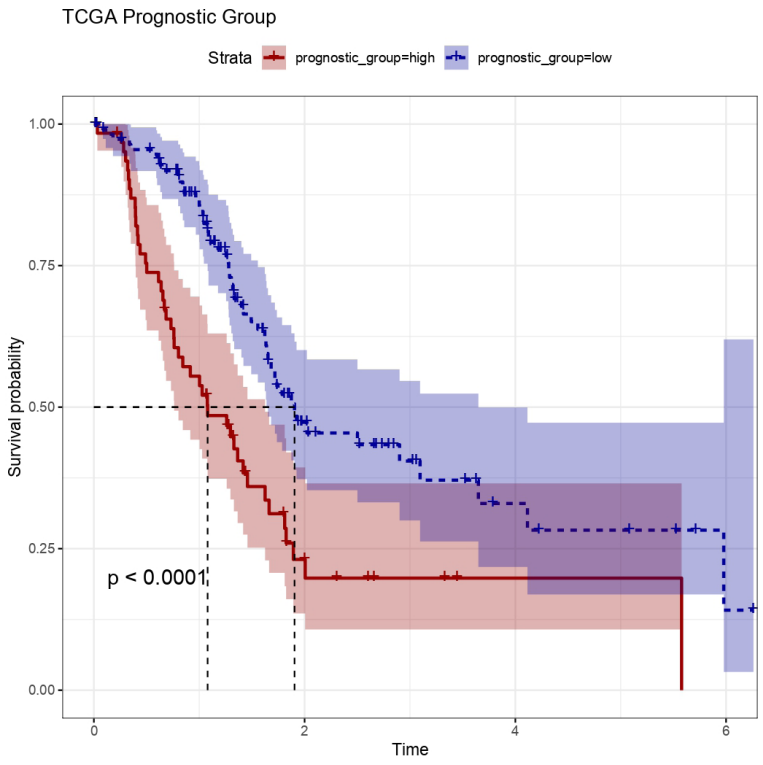

Figure 7 (A): Survival analyses of the risk score of key genes from the prognostic group from the TCGA database.

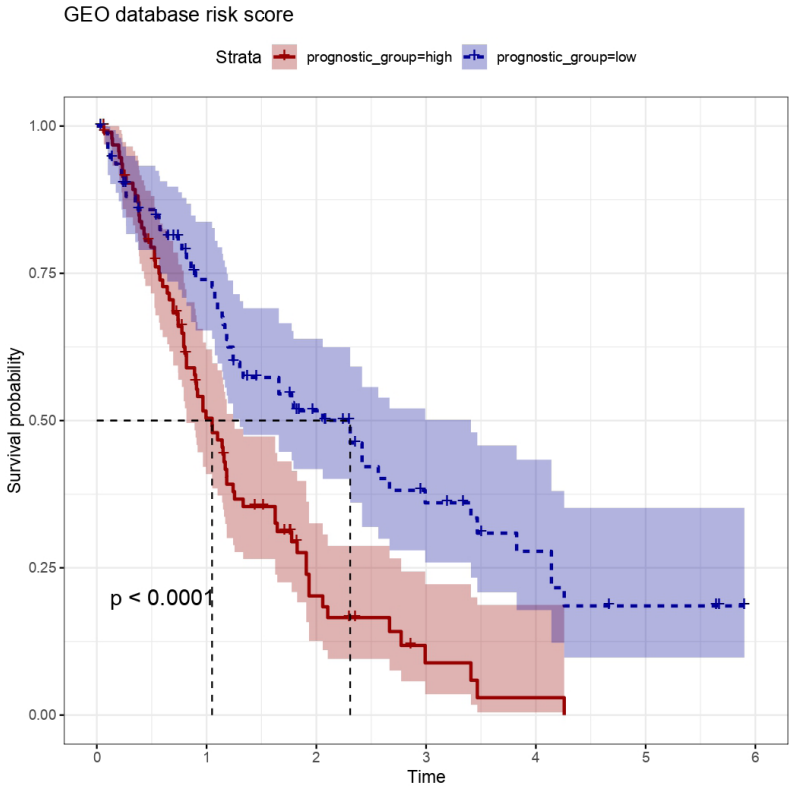

Figure 7 (B): Survival analyses of the risk score of key genes from the GEO database.

DISCUSSION

In industrialized countries, pancreatic cancer will soon be the fourth leading cause of cancer death after lung cancer in the 2030s. With more than 30,000 deaths per year due to pancreatic cancer, this death rate goes hand in hand with the number of cases in these countries exponentially rising. There isn't yet a systematic way to screen for pancreatic cancer like some other types of cancer, such as breast and colon cancer, which can be screened early. Pancreatic cancer has the trait of being able to lie dormant for years. Usually, when symptoms show up, the disease is already at its late stage [8]. The development of pancreatic cancer is a slow molecular process described by a previous report to have more than 60 genetic mutations and abnormal molecular signaling pathways networks that can all play a crucial function in the development of pancreatic cancer [9].

Findings of unique prognostic biomarkers of pancreatic cancer in order to come up with a more specific treatment plan for cancerous pancreatic tissues have become the focus of more and more scholars. These problems show the importance of finding biomarkers with prognosis significance in pancreatic cancer. To date, big data platforms for screening gene expression have been broadly used in others to identify novel targets that can be used as new therapeutic strategies and predictive to create cancer.

Studies have shown that crucial genes that can impact the initiation and proliferation of cancers tend to be in the modules with the top scores and obtain the top ranking in centrality assessment results. Those findings suggest that the MCODE and CytoNCA extensions in the protein–protein interactions network significantly contribute to identifying and selecting molecular biomarkers in many cancers, such as gastric and breast cancer [10]. Researchers have demonstrated that module analysis can improve the accuracy of many cancers' crucial gene screening [11]. CytoNCA, on the other hand, can assess the importance of each gene's connections over the whole PPI network and highlight those genes with the most significant links [12]. With MCODE and CytoNCA analysis methods, we were able to identify four genes (*CDK2*, *CCNB1*, *PLK1*, and *TOP2A*) that play crucial roles throughout the whole protein-protein interaction network.

Previous studies have highlighted the effects of key genes in many cancers. First, *CCNB1*, a crucial protein essential for cell cycle division, particularly at the G2/M phase, significantly impacts tumour development and progression. For instance, multiple studies have shown that *CCNB1* is overexpressed in many cancer, such as gastric and lung cancer, compared to normal tissues [13,14]. In addition, *CCNB1* overexpression has also been reported by studies to be correlated with poor outcomes in some patients with cancer [15,16]. Moreover, overexpression of *CCNB1* was also said to be associated with cancer metastasis and to have a poor outcome [16-19]. Besides overexpression of *CCNB1*, reducing the level of CCB1 can lead to DNA damage [20]. *PLK1* has been reported by studies to be overexpressed in many cancer; it has also been associated with poor prognosis [21,22]. *PLK1* plays a role in cell division, regulating stability in the cell division process and responding to DNA damage [23,24]. Silencing *PLK1* can significantly impact cancer progression by inhibiting its proliferation and stopping tumour cell growth [25,26]. Previous research has shown that the overexpression of *CDK2* deregulates the cell cycle and significantly impacts various cancer development [27,28]. The overexpression of one of The *CDK2*, known as cyclin E1, has been reported in many cancer [29,30]. Besides *CDK2* overexpression, silencing *CDK2* inhibitors was associated with poor outcomes in various tumours compared to normal tissues [31,32]. The overexpression of *TOP2A*-induced genomic deregulation and this mechanism has not yet been elucidated. For instance, previous research has shown that the overexpression of *TOP2A* is associated with poor outcome in various cancer parents [33]. Another study reported that *TOP2A* overexpressions could be independent predictive biomarkers for survival outcomes in patients with resected pancreatic cancer; at the same time, *TOP2A* expression combined with some other biomarkers can have a significant positive impact in various cancer patients [34]. Meiotic nuclear division is a protein involved in the meiosis process; it's known to facilitate the pairing of homologous chromosomes and repair DNA double-strand [35]. In tumor cells, MND interacts with some homologous pairing protein, to facilitate the use of an alternative mechanism for lengthening telomeres when telomerase is not reactivated [36,37] this mechanism drives the development of cancer and boosts cell proliferation, thereby increasing the evolutionary capacity of cancer cells [38,39]. Previous research has demonstrated that the meiotic component can be a biomarker and therapeutic target in cancer patients [40-43]. p53 signaling pathways consist of a complex network such as genes and their components that are activated in response to endogenous and exogenous stress signals. These signals can affect the mechanism that regulates DNA replication and cellular division, which are fundamental for maintaining cellular stability [44]. Previous studies reported that p53 is significantly elevated intracellularly to fixed abnormal intracellular function [45,46]. On the other hand, the activation of the FoxO signaling pathways is known to be initiated by P3IK/AKT pathways [47]; the FoxO signaling pathways play a fundamental role in controlling cellular functions such as cell proliferation and growth [48]. Various studies showed that the FoxO signaling pathways, known to be activated by the PI3K/AKT pathways, play a significant role in the initiation and development of many cancer, such as hepatocellular carcinoma [49,50]. In this research base on bioinformatics tools, we overlap the GEO and TCGA matrix data to extract and analyze high-volume data to perform through the MCODE and CytoNCA the module and centrality assessment of the protein-protein network; based on all those techniques, we identified four essential genes (*CDK2*, *CCNB1*, *PLK1* and *TOP2A*) who have a significant influence on the prognosis of pancreatic cancer patients. They can also be used as potential biological markers and targets for treating pancreatic cancer prognosis. We established a predictive risk model in accordance with the four essential genes to confirm that they play a crucial role in pancreatic cancer development.

CONCLUSION

The overlapping analysis of the GEO and the TCGA genes expression matrix has led us to identify 132 typical prognosis-significant DEGs *CDK2*, *CCNB1*, *PLK1* and *TOP2A* of the CPR-DEGs can be considered prognosis biomarkers and therapeutic targets for pancreatic cancer patients. However, the results of these analyses should be confirmed through verification with laboratory experiments, even though this study supports similar findings in previous research on the development of personalized pancreatic cancer management.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable

CONSENT FOR PUBLICATION

Not applicable

ACKNOWLEDGMENT

Not applicable

CONFLICT OF INTEREST STATEMENT

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

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AUTHOR CONTRIBUTIONS

Woulaidjei Ntomo Nicaise Patient and Zhong-Hua Shang: designed the research. Woulaidjei Ntomo and Achi Ntiak collected, processed the data. Woulaidjei Ntomo Nicaise Patient and Achi Ntiak, Apeku Ernestina Proofread and revised the research paper. All authors contributed to this study and agreed to the publication of this article in the present form. All authors contributed to the article and approved the submitted version.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. These GEO data can be found at: https://www.ncbi.nlm.nih.gov/geo/geo2r/?acc=GSE183795 and the TCGA data can be found at: https://cancergenome.nih.gov

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