SVOA Medical Research
ISSN: 2977-3644

ScienceVolks Open Access

Research Article

A Transcriptomics Analysis for Potential Biomarker in Pancreatic Cancer

S M Jahid Mostofa*

School of Health and Life Sciences, Teesside University, Middlesbrough, England.

***Corresponding Author:** S M Jahid Mostofa, School of Health and Life Sciences, Teesside University, Middlesbrough, England.

https://doi.org/10.58624/SVOAMR.2025.03.004

Received: October 11, 2024 **Published:** April 01, 2025

Citation: Mostofa SMJ. A Transcriptomics Analysis for Potential Biomarker in Pancreatic Cancer. *SVOA Medical Research* 2024, 3:1, 21-50. doi: 10.58624 SVOAMR.2025.03.004

Abstract

Background: Pancreatic cancer, also known as Pancreatic ductal adenocarcinoma (PDAC), is the deadliest cancer. CA19 -9 (carbohydrate antigen 19-9) is the only FDA-approved biomarker used in the diagnosis of PDAC. The majority of PDAC death is due to late screening and invasiveness. As a result, it is still essential to discover novel biomarkers for the early detection of PDAC.

Method: Two datasets (GSE16515, GSE211398) were chosen for the bioinformatics analysis. The limma and limma voom packages were used to analyze the data for DEGs. The DAVID (Database for Annotation, Visualization, and Integrated Discovery) database was used to undertake pathway analysis of the DEGs utilizing the Gene Ontology (GO) and Kyoto Encyclopaedia of Genes and Genomes (KEGG) databases. The STRING database was used to identify the protein-protein interaction (PPI) network. The Gene Expression Profiling Interactive Analysis (GEPIA) method was applied to assess the differential expression of hub genes in PDAC patients.

Result: 871 DEGs were found to be present in total and DEGs enriched in cell adhesion, extracellular matrix organization, cell migration, extracellular exosome, space, region, focal adhesion, integrin binding, pathways in cancer, and PI3K-Akt signaling pathway. Among the DEGs, 17 hub genes were identified. MKI67, AURKA, CDK1, ANLN, KIF20A, RRM2, BUB1B, CCNA2, CCNB1, SDC1, LGALS3, and ITGB1 were found to be associated with carcinogenesis and could be used as a diagnostic and therapeutic target in PDAC.

Conclusion: The findings imply that DEGs and hub genes are important in the pathogenesis of the disease, and they are crucial in both the detection and treatment of PDAC.

Keywords: *Pancreatic Cancer, Bioinformatics, Biomarker, DEG, Hub gene*

Introduction

A mass of uncontrolled cell growth and division develops in the pancreas called pancreatic cancer, which is a glandular organ located beneath the stomach. Cancer of the pancreas signs can be difficult to detect and is aggressive also called a silent killer (Ryan, Hong, and Bardeesy, 2014). Pancreatic cancer is among the most common cancer-related diseases with the poorest prognosis and the world's third cause of death (Rahib et al., 2014). The two main subtypes of pancreatic cancer are exocrine pancreatic cancer, which includes adenocarcinoma, and neuroendocrine pancreatic cancer (Melief, 2022). Pancreatic ductal adenocarcinoma (PDAC) accounts for 90% of all pancreatic malignancies (Kleeff et al., 2016). The symptoms and prognosis of the various cancer forms under each category can differ.

As per American cancer statistics, 64,050 new cases of pancreatic cancer would be diagnosed in 2023, with 50,550 mortalities in the USA (American Cancer Society, 2020). All major malignancies except pancreatic cancer have the greatest fatality rate. The 5-year relative survival rate for all phases is 12%. The 5-year survival rate is only 44% for the small fraction (15%) of patients with local illness (American Cancer Society, 2020). Also, in the UK new pancreatic cancer patients were 10,452, and deaths from pancreatic cancer were 9,558 with a 5% survival according to the data of Cancer Research UK (Cancer Research UK, 2019).

Indeed, one of the most difficult aspects of recognizing pancreatic cancer is its late appearance in clinical terms (Yang et al., 2021). Pancreatic cancer is frequently advanced by the time it is diagnosed. According to one study, just 7% of cancers of the pancreas are considered localized at the time of diagnosis (Kim and Ahuja, 2015) comparing this to other cancers such as breast (61%), colon (40%), lung (16%), ovarian (19%), and prostate (91%) shows that it is remarkably low (Jemal et al., 2009). The majority of aggressive cancers can be proficiently treated if discovered in their precancerous stage, but late detection is more likely to result in considerable morbidity and even death. (Yadav et al., 2017). There are now several potential biomarkers for pancreatic cancer collected from serum, tissue, bile, pancreatic juice, saliva, or feces, but the majority have not been widely validated. As a result, there is an immediate need to investigate novel biomarkers with the potential to have a clinically substantial impact on the screening of individuals with extremely dangerous pancreatic cancer (Shibata et al., 2022).

Pancreatic cancer is characterized by genetic and epigenetic alterations (Hung et al., 2019). Using next generation sequencing and computational biology we can trace the prognosis of pancreatic cancer and found that genetic mutation, activation, or inactivation of genes, oncogenes, and suppression of tumor genes might involve in developing pancreatic cancer. The most frequently altered genes known to impact the development and spread of pancreatic cancer are KRAS (90%), TP53 (50-74%), CDKN2A (46-60%), and SMAD4 (31-38%) (Christenson, Jaffee and Azad, 2020; Wang et al., 2021b). Activating oncogenic Kirsten rat sarcoma viral oncogene homolog (KRAS) alterations are found in nearly 90% of pancreatic tumors of all classes (Shi et al., 2022). GAT (aspartic acid; G12D), GTT (valine; G12V), and TGT (cysteine; G12C) mutations are the most frequently detected oncogenic KRAS mutations related to pancreatic cancer in humans, whereas CGT (arginine; G12R) and GCT (alanine; G12A) mutations, along with additional modifications at codons 11, 13, 61, or 146 are shown to be considerably more uncommon (Buscail, Bournet and Cordelier, 2020; Singh et al., 2021).

Histone modification is regulated by epigenetic regulatory genes such as MLL2/3, KDM6A, and numerous HDAC-encoding genes (Wang et al., 2021b; Zahra Sahafnejad, Shahin Ramazi and Abdollah Allahverdi, 2023). ARID2 and SMARCA2/4 regulate chromatin remodeling (Bailey et al., 2016; Wang et al., 2021b). Also, epigenetic factors like smoking, alcohol consumption, inadequate fluid, and fruit intake are risk factors for pancreatic cancer development (Jimeno, 2006; Mimeault et al., 2005; Blackadar, 2016). Furthermore, the dysregulation of molecules in various cell signaling pathways, including EGFR, Akt, NF-B, and others, as well as their molecular interaction, play essential roles in pancreatic cancer molecular pathogenesis (Jimeno, 2006; Mimeault et al., 2005). The ancestral history of pancreatic cancer has long been recognized as an elevated risk factor and a key indicator of disease threat. According to research, roughly 5-10% of pancreatic cancer cases have a close relative who has pancreatic cancer (Hruban et al., 1998; Klein, 2012).

Tissue biopsy is regarded as the golden standard approach for the diagnosis of cancer, but it is invasive, painful, and done at a late stage (Kendall et al., 2003). Biomarkers are most effective, non-invasive, and can be used for early diagnosis (Messadi, 2013; Ott, Ullrich, and Miller, 2009). Biomarkers are biological markers found in tissues, serum, blood, etc. Biomarker testing is an easy, accurate, and non-invasive technique used for diagnosis. It is popular for cancer diagnosis, and it is an essential component of precision medicine. The U.S. Food and Drug Administration (FDA) only granted approval to the carbohydrate antigen 19-9 (CA19-9) as a serum biomarker (Yang et al., 2021); however, because of its poor sensitivity as well as poor specificity, it cannot be used in clinical practice to make a diagnosis (Xing et al., 2018). As a result, some investigations are currently concentrating on the detection of CA19-9 in conjunction with other tumor markers (Gu et al., 2015). At present, no biomarkers, or components of markers with appropriate diagnostic precision for the early detection of pancreatic cancer have been granted approval (Yang et al., 2021).

Treatment for pancreatic cancer has various limitations, including chemotherapeutic and resistance to drugs, changes in the metabolism of drugs, and decreased apoptosis (Binenbaum, Na'ara, and Gil, 2015). As a result, numerous researchers are now working on novel approaches for pancreatic cancer treatment, such as the use of nanotechnologies (Von Hoff et al., 2013), approaches targeting tumor metabolism (Blum and Kloog, 2014), immunotherapy (Riquelme, Maitra and McAllister, 2018), therapy with stem cells, stroma strategies (Eltawil, Renfrew and Molinari, 2012), signaling pathway tactics, and microorganism-derived chemotherapy.

In that work, the main focus is on the importance of potential biomarkers as a therapeutic target in pancreatic cancer. To further our understanding of the molecular underpinnings of pancreatic cancer and development, 871 DEGs and 17 hub genes were discovered using bioinformatics analysis such as differentially expressed genes, Gene Ontology (GO), KEGG pathways, Gene Set Enrichment Analysis (GSEA), hub-gene analysis and statistical analysis. According to the bioinformatics and hub gene analysis, MKI67, AURKA, CDK1, ANLN, KIF20A, RRM2, BUB1B, CCNA2, CCNB1, SDC1, LGALS3, and ITGB1 are possible biomarkers and therapeutic targets for pancreatic cancer.

Methods

Collecting and preprocessing data:

The pancreatic cancer datasets were found in the National Center of Biotechnology Information (NCBI) Gene Expression Omnibus (GEO) database. The NCBI website address is ncbi.nlm.nih.gov. It has a large number of databases pertaining to biotechnology, bioscience, and biomedicine, as well as numerous bioinformatics tools. The NCBI manages the GEO database, which is used for gene expression profiling and RNA methylation profiling, and these data were obtained using experimental microarray or RNA-Seq data.

GSE16515, expression profiling by array, and GSE211398, expression profiling by high throughput sequencing gene expression datasets were found (Table 1) and retrieved from the GEO database using R Bioconductor package geoquery (Davis and Meltzer, 2007) and utilized to detect differentially expressed genes between pancreatic cancer and comparable normal pancreas tissue.

Table 1. The details of gene expression profiles datasets.

GEO Dataset	Country	Platform	Gene Chip	Case	Control	Gender
GSE16515	USA	GPL570	Affymetrix Human Genome U133 Plus 2.0 Array	36	16	Male: 34 Female: 18
GSE211398	USA	GPL18573	Illumina nextseq 500 (Homo sapiens)	16	12	Male: 14 Female: 14

Preparing R for analysis:

In Rstudio (v 4.1.2) Bioconductor and CRAN packages (https://cran.rproject.org/web/packages/available_packages_by_name.htm) such as limma, tidyverse, readxl, edger, dplyr, Biobase, arrayqualitymetrics, pheatmap, ggplot2, ggrepel, readr, rcolorbrewer, maptools and to execute the analysis, various more useful tools for plotting, data processing, and viewing was used (Wu et al., 2021b; Ritchie et al., 2015). Voom outperforms existing RNA-seq techniques in terms of performance (Law et al., 2014)

Identification of DEGs:

GSE16515: The R program was used to process, check platforms, annotation, and then analyze the files obtained from GEO. The data in the files were also inspected for normalization the make standardized and transformed to a log2 scale. A box plot was created to validate the normalization of the data. Clinical variables were examined, and techniques were employed for assessing sample information. The sample information's row names were printed and compared to the correlation matrix. A Principal component analysis (PCA) was built, then samples were assigned to groups and a design matrix was created. The data was then analyzed for DEGs using statistical techniques. DEGs were screened with the adjusted P-value of < 0.05 and log fold change of ≥ 1 and log fold change of ≤ 1 from the top table of significant over expression genes.

GSE211398: The R limma voom was used to process the downloaded file from the NCBI GEO database. Limma is a valuable library for analyzing microarray data, and voom is a limma package function that transforms RNA-Seq data for usage with limma (Ritchie et al., 2015).

After setup, the file was preprocessed, normalized, filtered low expressed gene, then voom transformation and fit the linear model to make a voom plot. Finally, find out DEGs with the adjusted P-value of < 0.05 and log fold change of ≥ 1 and log fold change of ≤ 1 from the top table of significant overexpression gene.

Statistical analyses were performed on each dataset. Common DEGs were identified using the same statistical approach and excluded downregulation DE from the top table. DEGs were then visualized using Venn diagrams and were constructed using a web tool (https://bioinformatics.psb.ugent.be/webtools/Venn/).

Functional analysis of DEGs:

DAVID (http://david.ncifc rf.gov, version 2021) is an online biological information database that integrates biological data and analysis tools and provides a comprehensive set of functional annotation information of genes and proteins for users to extract biological information (Plenary Presentations, 2021). DAVID was used to evaluate GO and KEGG pathways for the DEGs. The Laboratory of Human Retrovirology and Immunoinformatic (LHRI) created DAVID, a free public bioinformatics tool.

The DAVID Bioinformatics tools are all designed to offer a meaningful interpretation of enormous lists of genes acquired from genomic research, such as microarray and proteomics studies (Sherman et al., 2022). The DAVID Bioinformatics Resources is made up of the DAVID Knowledgebase, the DAVID Functional Annotation Tool, the DAVID Gene ID Conversion Tool, the DAVID Gene Name Viewer, and the DAVID NIAID Pathogen Genome Browser. These five incorporated internet-based functional annotation tool suites are also included.

DEGs biological roles were determined using GO and KEGG pathway enrichment studies from DAVID (Kanehisa and Goto, 2000). The GO is a popular tool for functional annotation and enrichment analysis. GO is a large bioinformatics endeavor that aims to standardize the way genes are represented by gene and gene product properties across every species of organism. The three basic components of gene function are biological process (BP), molecular function (MF), and cellular component (CC). KEGG is a database that collects a significant quantity of data on molecular-level information, biological processes, and chemical compounds generated by high-throughput experimental technology. The statistical significance level was chosen at $p < 0.05$.

PPI network construction and hub gene identification:

STRING (http://strin g-db.org, version 11.5) was used to build the protein-protein interactions (PPI) network (Szklarczyk et al., 2015), which incorporates both known and anticipated PPIs. A biological database and online resource for protein-protein interactions, known as STRING. The STRING database incorporates information derived from a variety of sources like data from experiments, computational prediction approaches, and publicly available text libraries (Szklarczyk et al., 2019). When STRING is given a list of proteins as input, it can look for their neighbor interactors, proteins that interact directly with the list of inputted proteins, and subsequently create a PPI network that includes all of those proteins along with all of their connections. STRING also includes many analytic tools and files for additional investigation that are integrated with Cytoscape.

PPI connections with combined scores greater than 0.4 were taken out and the PPI network was visualized in Cytoscape version 3.9.1. Cytoscape is a platform that is open with numerous plugins that improve both visualization and network evaluation capabilities (Shannon, 2003). Through Cytoscape, it is simple to get to a network's visual representation, and many layers of information, such as extensive genome-wide experiments and function-based protein annotations, can be made available for the interactome. MCODE found significant components of the PPI network. An MCODE score of 4 was selected as the cutoff. The enrichment analysis plot was constructed using bioinformatics tools SRplot (http:// www.bioinformatics.com.cn/srplot)

Selection and analysis of hub genes:

Differential expression of hub genes in pancreatic cancer patients was assessed using Gene Expression Profiling Interactive Analysis (GEPIA) (http://gepia.cancer-pku.cn/), a newly developed interactive web server for analyzing the RNA sequencing expression data of 9736 tumors and 8587 normal samples from the TCGA and gtex projects using a standard processing pipeline (Tang et al., 2017; Shi et al., 2022). Functions including patient survival analysis, similar gene recognition, correlation analysis, and dimensionality reduction analysis are among the user-configurable features offered by GEPIA.

Other features include tumor vs normal variation in expression research, characterization according to cancer forms or clinical stages, and patient survival analysis. The Kaplan-Meier method was used to assess the relationship between hub genes and overall survival.

Cytohubba, a cytoscape plug-in, was used to choose the hub genes based on the number of interactions with other genes in the PPI network (Chin et al., 2014). The evaluation and selection of hub genes involved the application of seven widely used algorithms that are MCC, MNC, Degree, Closeness, Radiality, Stress, and EPC (Albert and Barabási, 2002). The accuracy of essential protein predictions from the yeast PPI network performs better with MCC (Chin et al., 2014).

Statistical analysis

The relevant data in this study were analyzed utilizing GEPIA online tools and the rstudio (https:// www.R- project. Org) programming language. In GEPIA, the box diagram was used to analyze the expression of associated genes, and Kaplan-Meier survival analysis with a log-rank test was used to analyze overall survival and depict survival curves (Shi et al., 2022). A one-way analysis of variance was used to make comparisons between several groups. R uses various thresholds and cutoffs to normalize, validate the expression levels, and filter low-expressed data to make the data suitable for analysis. The statistical significance level was chosen at p-value < 0.05.

Result

Data analysis of the Datasets:

Data were normalized, checked, and filtered to remove low-expression data for both datasets. In GSE16515 data showed a higher value needs to be log2 transformation. A summary function was used to view the distribution of the samples values and it was above the range 0 to 16. So, log2 transformation was performed and then it goes beyond the value of 16. To understand the expression of the data box plot (Figure 1,2) was drawn. The correlations between the samples can be visualized using hierarchical clustering. The correlation is calculated on a scale of 0 to 1 and visualized using a heatmap (Figure 3). For analysis, the quality of the result MD plot, Q-Q plot (Figure 6), and histogram (Figure 7) was created for each gene to aid in visualizing and quality-controlling the results. To display the DE analysis, a volcano plot (Figure 4A) was built.

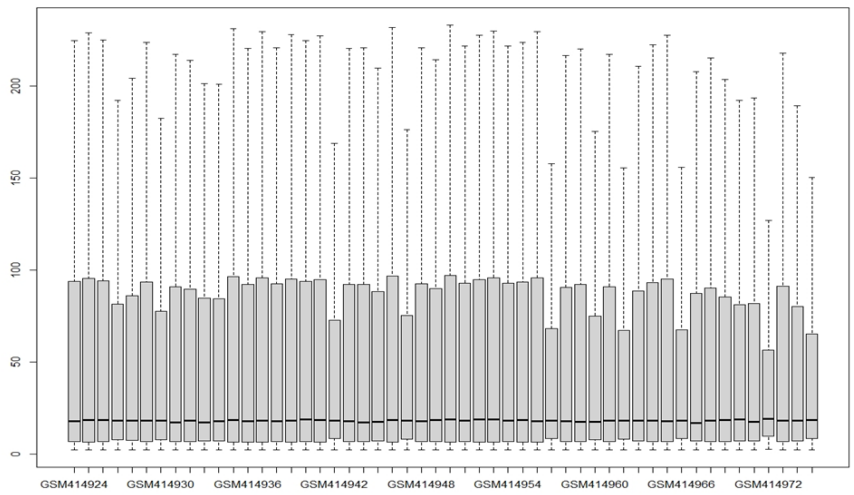


Figure 1. *Boxplot of GSE16515 before Normalized. Data shows skewness and need to be normalized.*

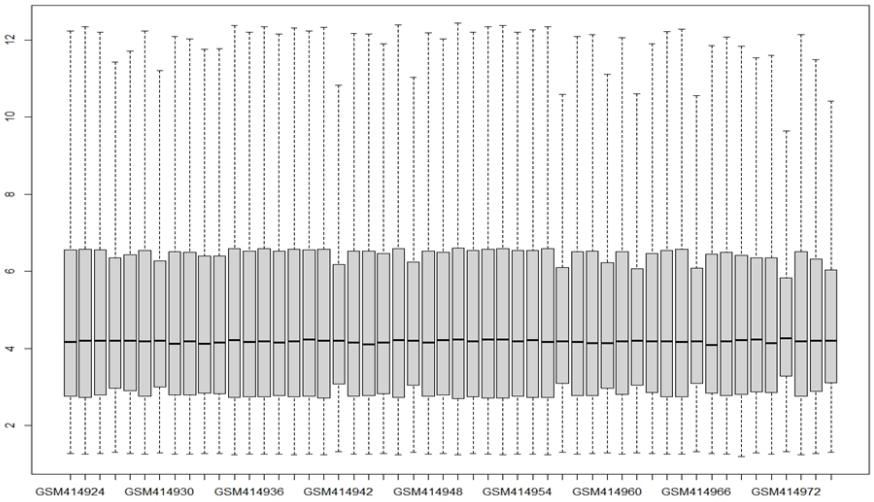


Figure 2. *Boxplot of GSE16515 after Normalized.*

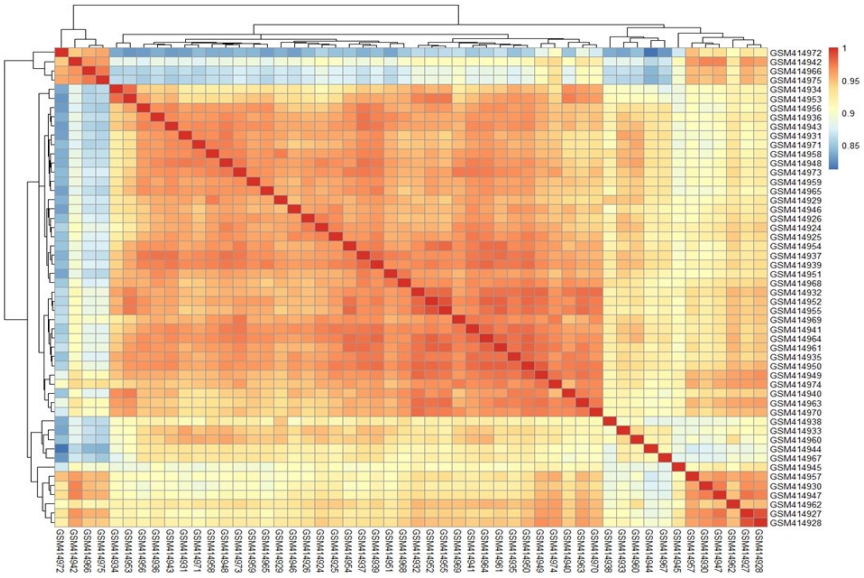


Figure 3. *Heatmap of GSE16515 on a scale of 0 to 1.*

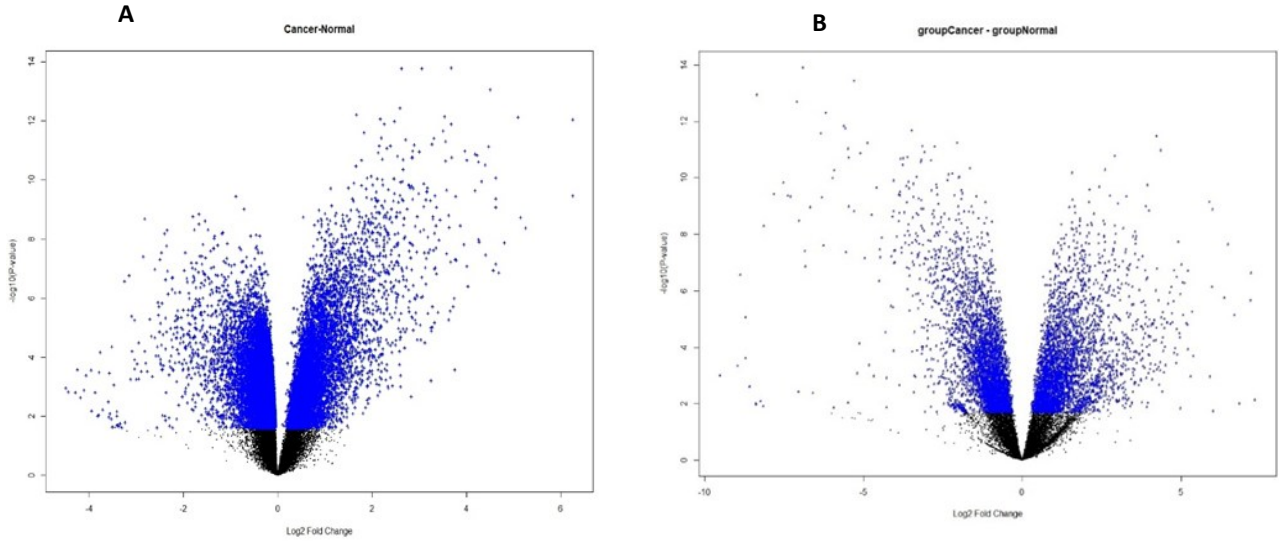


Figure 4. *Overexpression genes of A) GSE16515 B) GSE211398. In that Volcano plot blue points denote genes that are overexpressed whereas black points are not overexpressed.*

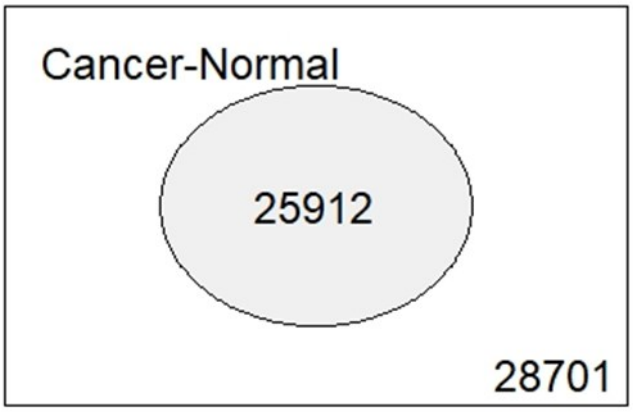


Figure 5. *Venn diagram showed significant genes of GSE16515*

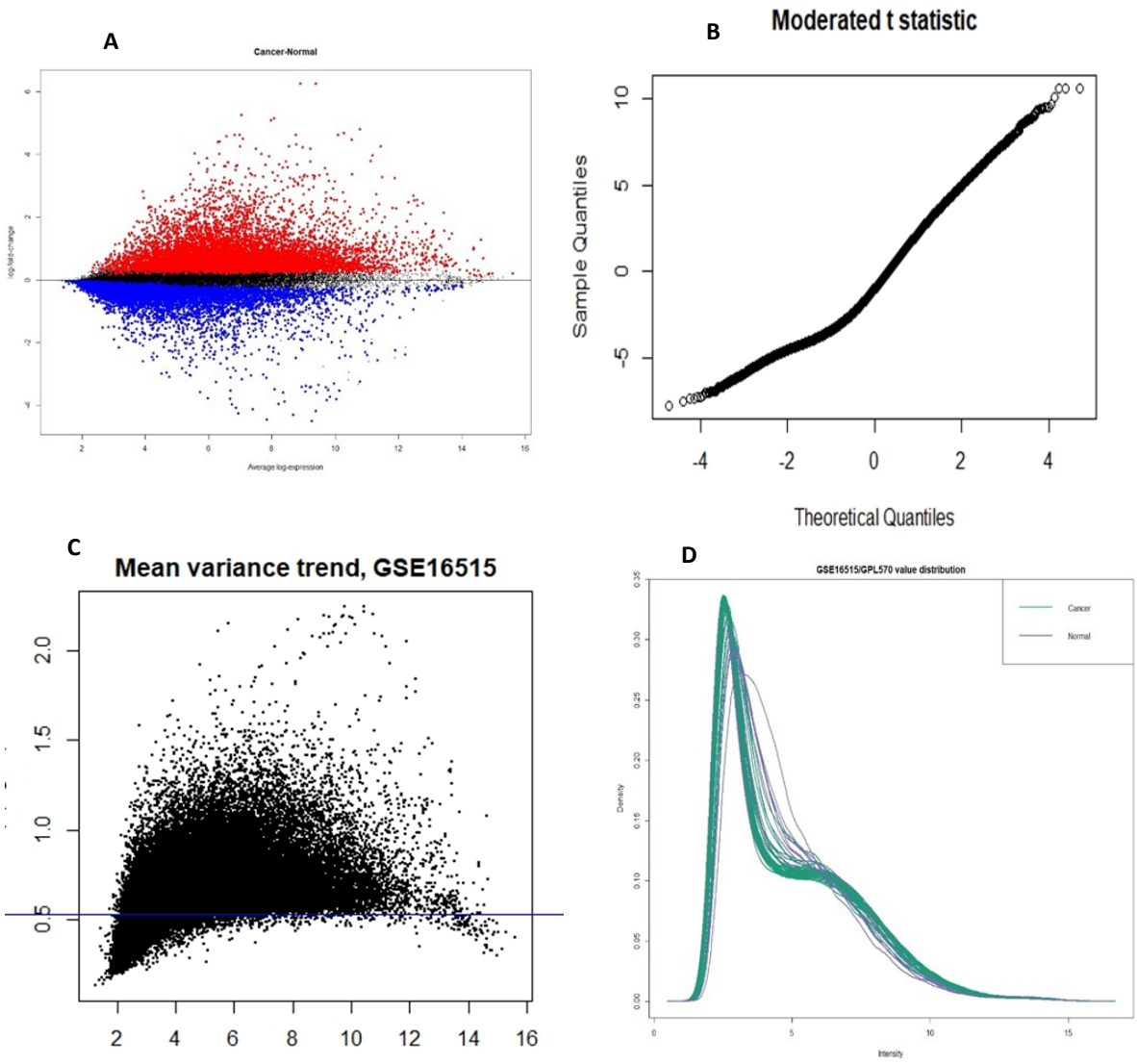


Figure 6. *For GSE16515, A) A mean difference (MD) plot, which is useful for DEGs analysis, represents log2 fold change vs average log2 expression values. B) The moderated t-statistic quantile-quantile (Q-Q) plot demonstrated the quality of the limma result, with points falling along a straight line. C) After fitting a linear model, the following diagram is used to examine the mean-variance relationship of the expression data. Each point represents a gene. D) After normalization, expression density is used to see the difference between samples.*

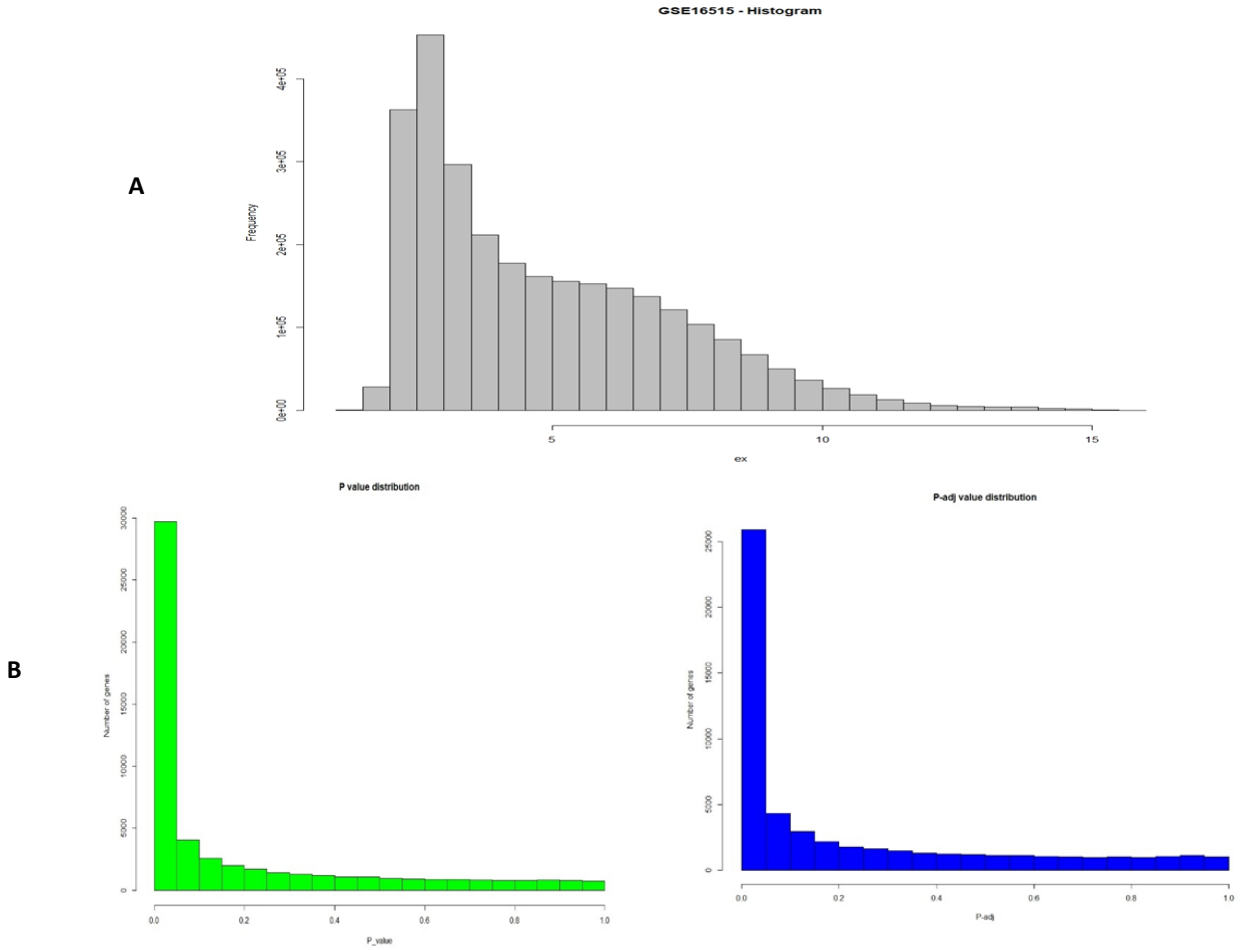


Figure 7. *A) Histogram of the GSE16515 gene to aid in visualizing and quality-controlling. B) P value and P adjusted value distribution of GSE16515 samples.*

In order to better understand the GSE213198 data, an MDS plot (Figure 8) was created to evaluate which samples were most closely connected with every element. Multidimensional scaling (MDS) is a graphical depiction of distances or differences between groups of items. MDS can be used to reduce the dimensions of high-dimensional data in addition to representing differences as graph distances (Buja et al., 2008). Simply said, the basic goal of MDS is to maintain these discrepancies in the decreased dimensionality. Voom was applied to log-CPM to obtain a mean-variance trend that demonstrates considerable biological variance (Figure 9). A volcano plot (Figure 4B) was created to represent the differential expression analysis.

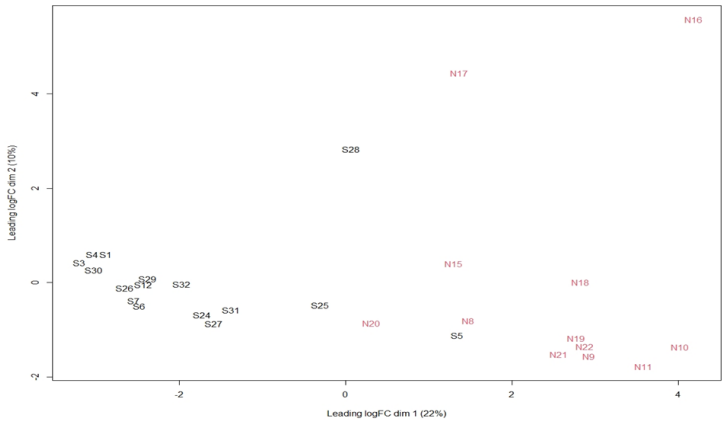
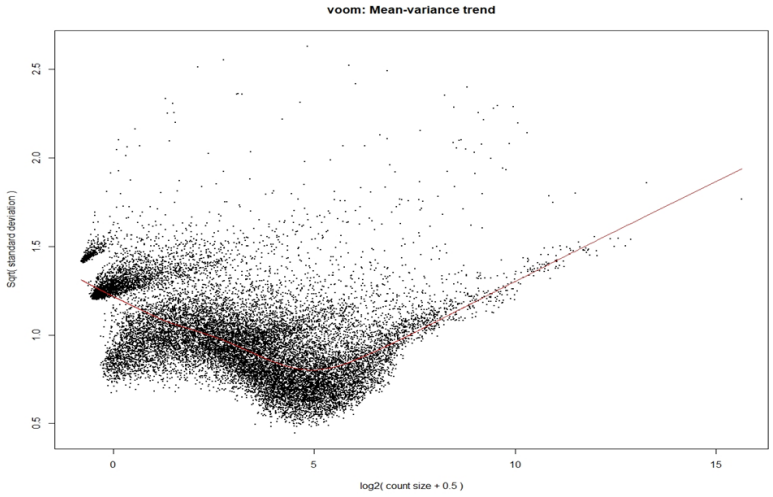


Figure 8. *MDS plot was used to interpret each sample dissimilarity. Sample with letter S denotes tumor and N denotes normal.*



Identification of DEGs

Two gene expression datasets GSE16515 and GSE211398 were chosen for this study. GSE 16515 had 36 tumors and 16 normal pancreatic samples, and GSE211398 had 16 tumors and 12 normal pancreatic samples, as stated in Table 1.

Using the rstudio, 2682 and 4329 overexpression genes were identified from the dataset GSE16515 and GSE211398. Among them, upregulation expression was 1971 and 2203 on the other hand downregulation expression was 711 and 2126 based on the significance level of adjusted p value less than 0.05 and log fold change 1 for upregulation and -1 for downregulation. For further analysis upregulated genes were considered from the overexpression gene to determine the most common differential gene expression (DEGs). In 1971 and 2203 DEGs there was some repeated gene in the expression list and from there 871 common DEGs (Figure 10) were identified to do the analysis.

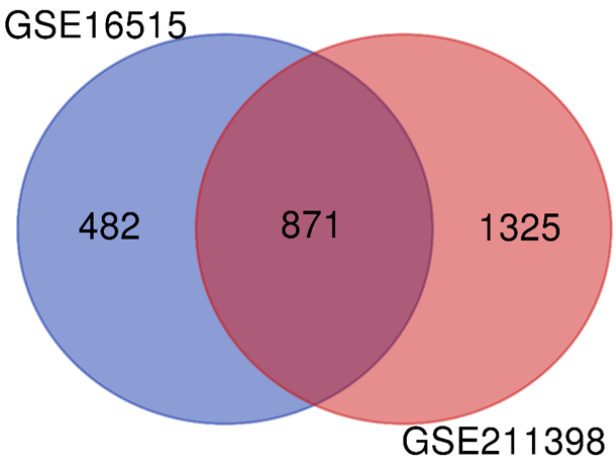


Figure 10. *Venn Diagram of common DEGs of datasets.*

KEGG and GO enrichment analyses of DEGs

DAVID was then utilized to undertake the GO and KEGG pathway analyses. DEGs were shown to be concentrated in cell adhesion, extracellular matrix organization, cell migration, cell-cell adhesion, innate immune response, integrin-mediated signaling pathway, collagen fibril organization, response to the virus, positive regulation of cell migration, apoptotic process, glycolytic process, endodermal cell differentiation, cell adhesion mediated by integrin, defense response to the virus, cell division, mitotic spindle organization, collagen catabolic process, cell-matrix adhesion, skeletal system development, cell-cell signaling, canonical glycolysis for BP (Figure 11). CC (Figure 12) was mainly enriched in extracellular exosome, space, region, cell surface, focal adhesion, extracellular matrix, basement membrane, endoplasmic reticulum lumen, cornified envelope, apical plasma membrane vesicle, membrane raft, an anchored component of the membrane, adherens junction, cell junction, collagen trimer, cell-cell junction, cytoskeleton, stress fiber, lateral plasma membrane, integrin complex.

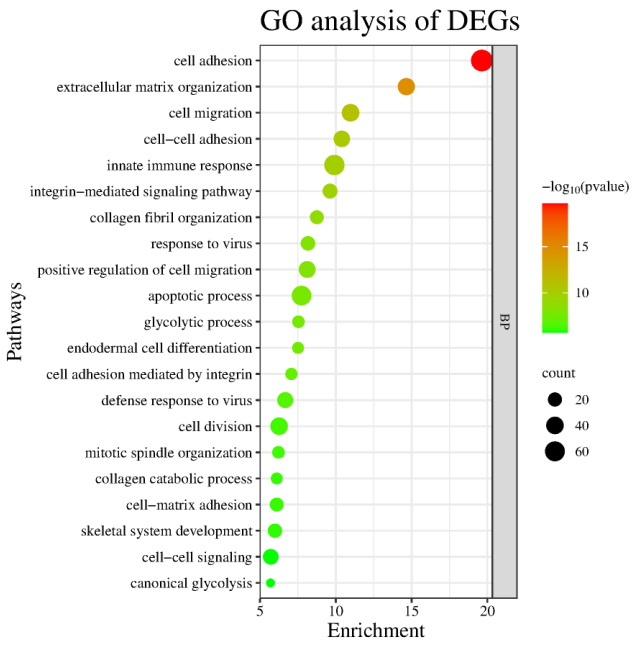


Figure 11. *Functional enrichment analysis of DEGs for biological processes (BP).*

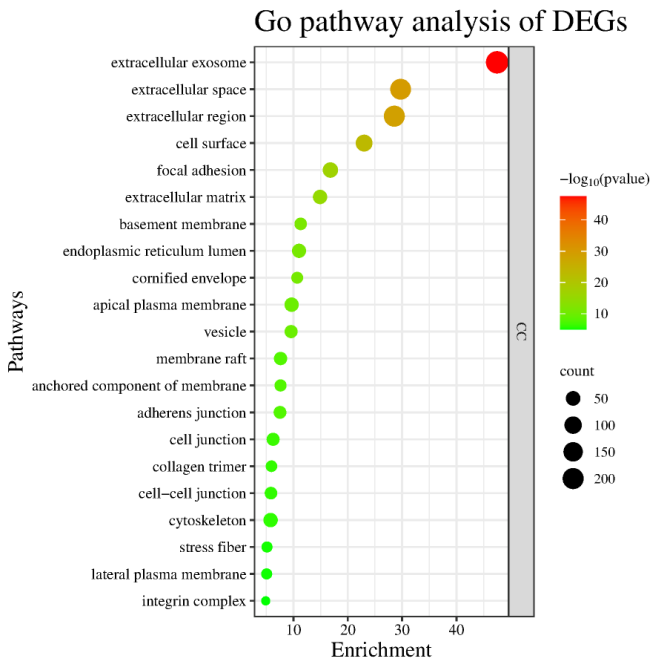


Figure 12. *Functional enrichment analysis of DEGs for Cellular component (CC)*

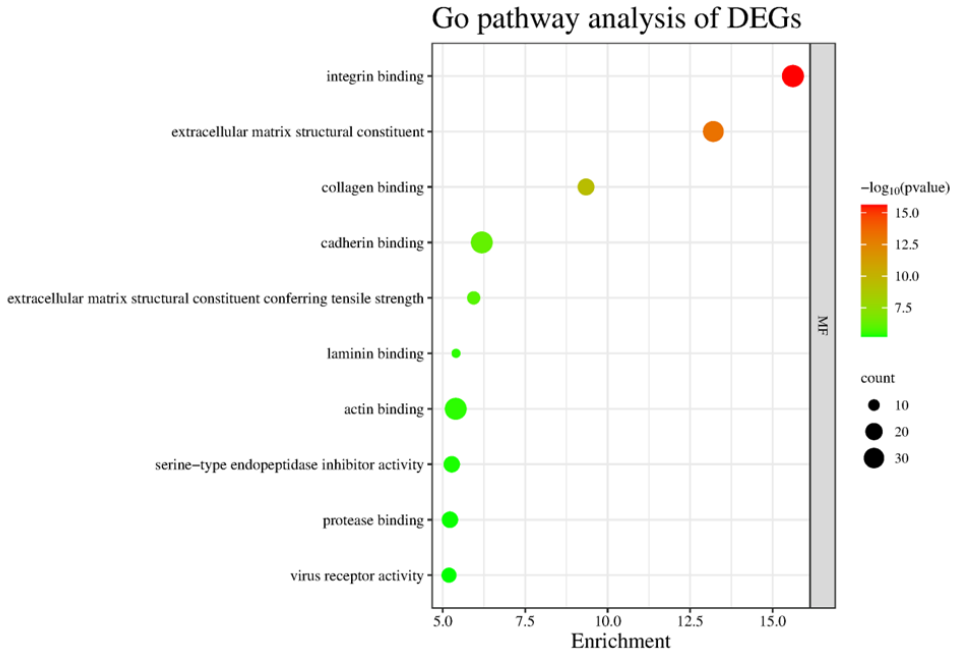


Figure 13. *Functional enrichment analysis of DEGs for Molecular function (MF).*

For MF (Figure 13), DEGs were shown to be enriched in integrin binding, extracellular matrix structural constituent, collagen binding, cadherin binding, extracellular matrix structural constituent conferring tensile strength, laminin-binding, actin binding, serine-type endopeptidase inhibitor activity, protease binding, virus receptor activity.

According to the KEGG pathway (Figure 14) analysis, the DEGs were connected with Pathways in cancer, Leukocyte transendothelial migration, PI3K-Akt signaling pathway ECM-receptor interaction, Focal adhesion, PI3K-Akt signaling pathway, Phagosome, p53 signaling pathway, Salmonella infection.

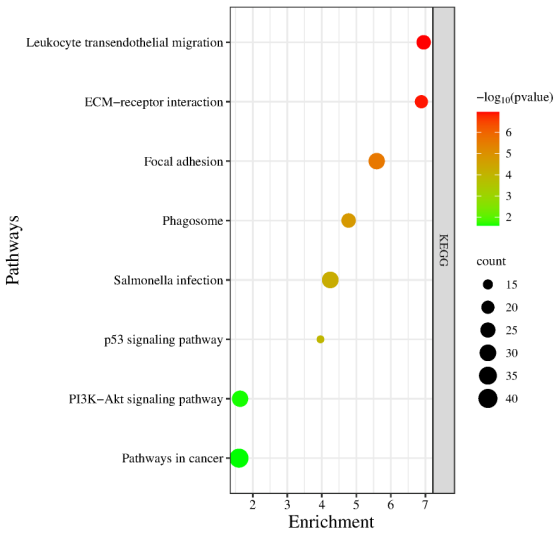


Figure 14. *KEGG pathways of DEGs.*

PPI network construction and Hub gene selection

STRING was used to assess the relationship and evaluation of interactions between pathways, and for better understanding, the PPI network was built. The PPI network of DEGs had 868 nodes and 8068 interactions were constructed to find gene interactions, as shown in (Figure 15). The network exhibited substantially more interaction than expected, given the expected Edges were 3392. This denotes those genes have potential links for the progression of the pathogenesis. PPI enrichment P value was 1.0e-16. A low p-value for PPI enrichment indicates that the nodes are not random and that the number of edges detected is significant. The top 20 hub genes were determined using the seven algorithms (MCC, MNC, Degree, Closeness, Radiality, Stress, and EPC) of the cytohubba plug-in (Figure 16). Cytoscape was used to establish the most critical module from the PPI network. After determining the intersection of the top hub genes from the seven analyses, 17 hub genes were discovered (Figure 17) and survival analysis was performed. Those genes functional roles are shown in Table 2.

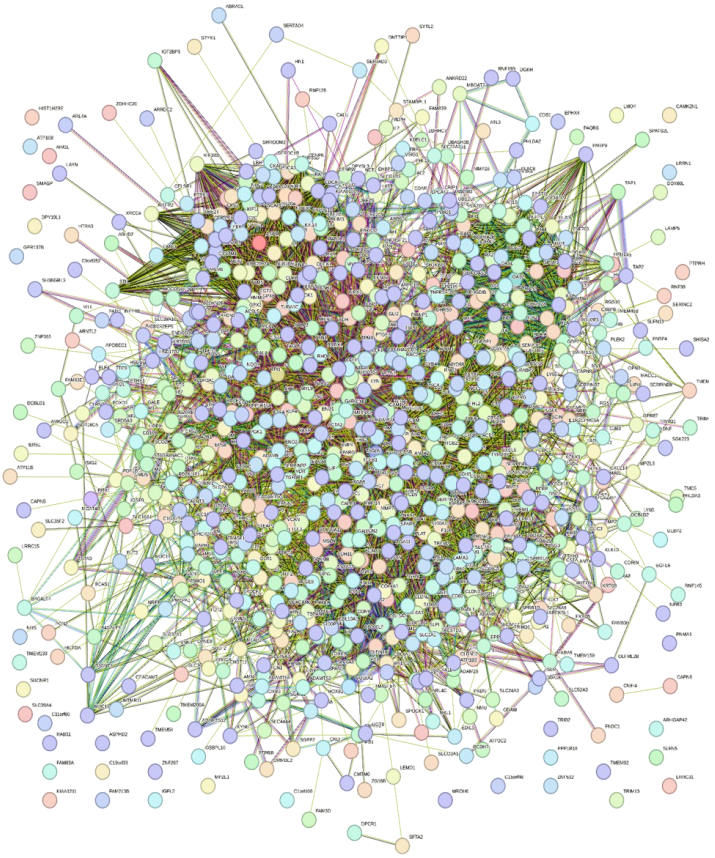


Figure 15. *The PPI network of DEGs constructed using the STRING database.*

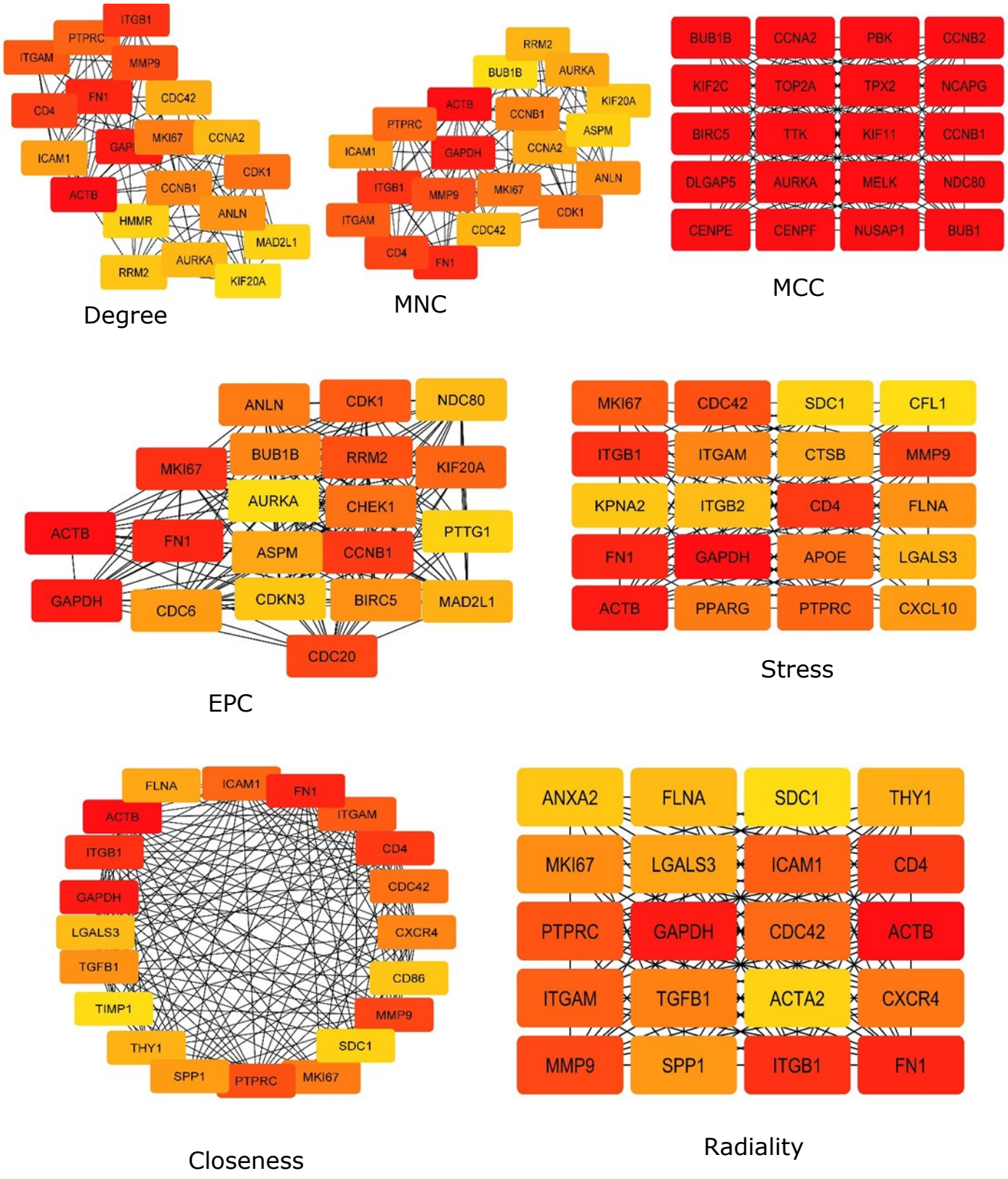


Figure 16. *Hub gene identified by seven different algorithms.*

According to GO analysis, the genes were primarily involved in the G2/M transition of the mitotic cell cycle, cell division, cyclin B1-CDK1 complex, midbody, cyclin-dependent protein kinase holoenzyme complex, protein kinase binding, Cellular senescence, and ATP binding. The KEGG pathway analysis found that Progesterone-mediated oocyte maturation, Cell cycle, p53 signaling pathway, and Cellular senescence.

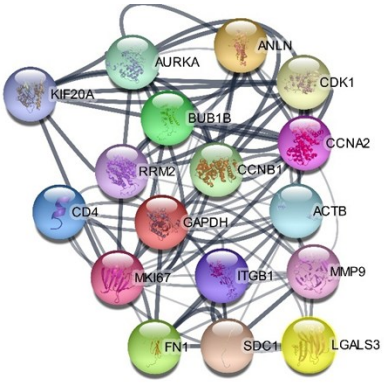


Figure 17. *Hub genes identified using the co-expression analysis.*

Table 2. Functional roles of 17 hub genes.

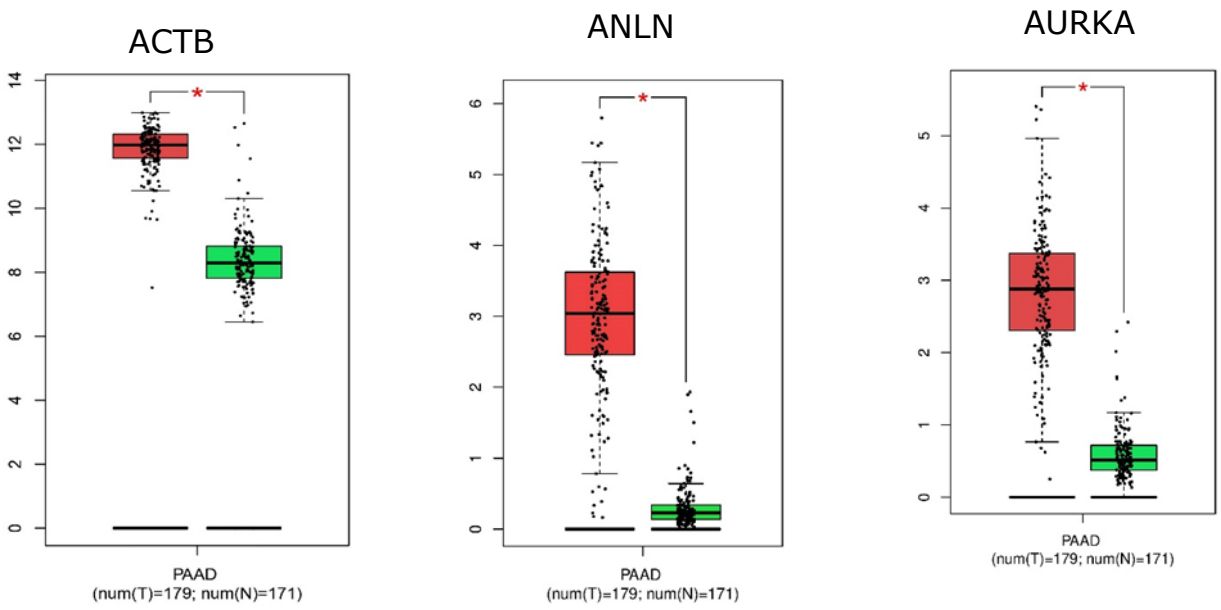
Gene Symbol	Full Name	Function
ACTB	Actin beta	Six distinct actin proteins are encoded by this gene. Actins comprise highly stable proteins which are essential for cell motility, structure, integrity, and intercellu-
GAPDH	Glyceraldehyde-3-phosphate dehydrogenase	GAPDH is essential for glycolysis and nuclear functions, organization and assembly of the cytoskeleton, RNA transport, DNA replication, and apoptosis.
FN1	Fibronectin 1	FN1 plays a role in cell adhesion, motility, opsonization,
MKI67	Marker of proliferation Ki-67	MKI67 is required for the formation of a steric and electrostatic charge barrier, which inhibits chromosomes from collapsing into a single chromatin mass.
ITGB1	Integrin subunit beta 1	ITGB1 is essential for Cell adhesion, Host-virus interac-
MMP9	Matrix metallopeptidase 9	MMP9 is essential for bone osteoclastic resorption, Extracellular matrix proteolysis, leukocyte migration, and Collagen degradation.
CD4	CD4 molecule	CD4 plays an important role in the immune system,
SDC1	**Syndecan** 1	The cytoskeletal structure, cell signaling, cell binding, cell migration, and cell proliferation are all mediated by the SDC1.
LGALS3	Galectin 3	LGALS3 is involved in differentiation, immunity, innate immunity, mRNA processing, and mRNA splicing. The results from The Human Protein Atlas show that gene

Table 2 continued on the next page...

CCNB1	**Cyclin B1**	CCNB1 is required for cell cycle regulation, mitosis, and
AURKA	Aurora kinase A	AURKA is important in microtubule formation, regulation of the p53/TP53 pathway, mitosis regulation, and tumor development and progression.
CDK1	**Cyclin dependent kinase 1**	CDK1 is required for early embryonic development, phosphorylation, and cytokinesis.
ANLN	**Anillin, actin binding protein**	ANLN is crucial for cell growth and migration and in cytokinesis.
KIF20A	**Kinesin family member 20A**	KIF20A is involved in the molecular function of the motor protein.
RRM2	**Ribonucleotide reductase regulatory subunit M2**	RRM2 plays an important role in DNA synthesis, Inhibits Wnt signaling.
BUB1B	**BUB1 mitotic checkpoint serine/threonine kinase B**	BUB1B is an essential component of the mitotic checkpoint, controlling apoptosis, cell cycle, and spindle checkpoint function. Many types of cancer have been discovered to have impaired spindle checkpoint function.
CCNA2	**Cyclin A2**	CCNA2 promotes and binds with cyclin-dependent kinase 2 and regulates both the G1/S and G2/M transition phases of the cell cycle.

Validation of hub genes expression

GEPIA analysis of the expression of these hub genes in PDAC and noncancerous samples demonstrated that the activity of 12 hub genes was significantly greater in PDAC samples compared with noncancerous samples (Figure 18). The overexpression of MKI67, AURKA, CDK1, ANLN, KIF20A, RRM2, BUB1B, CCNA2, CCNB1, SDC1, LGALS3, and ITGB1 was associated with a poor prognosis for PDAC, according to our subsequent analysis using GEPIA (Figure 19). Despite this, no statistically significant relationship was seen between ACTB, GAPDH, FN1, MMP9, and CD4 expression and prognosis where the P value was less than 0.05. The results of this study emphasize the therapeutic and diagnostic potential of these hub genes.



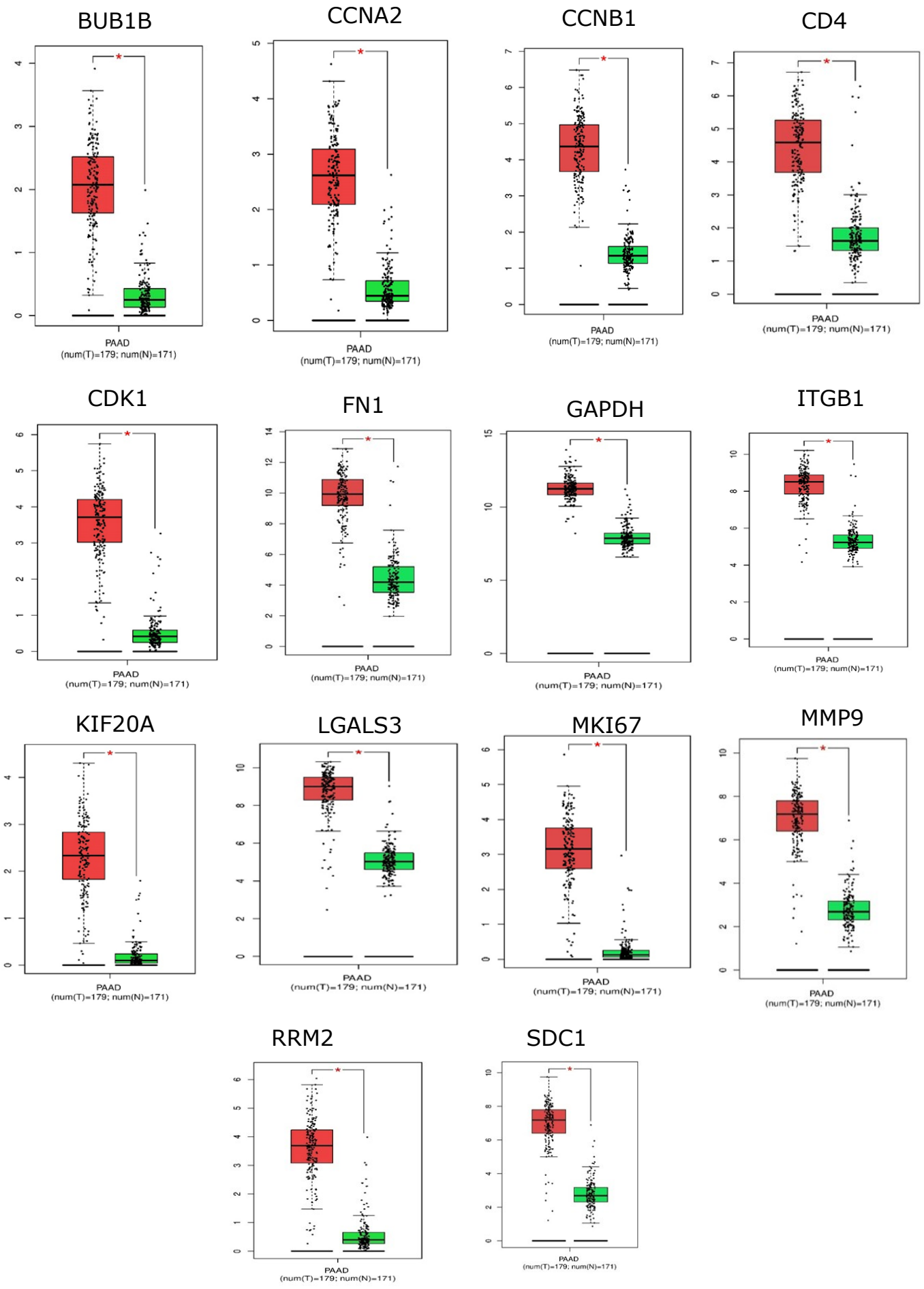
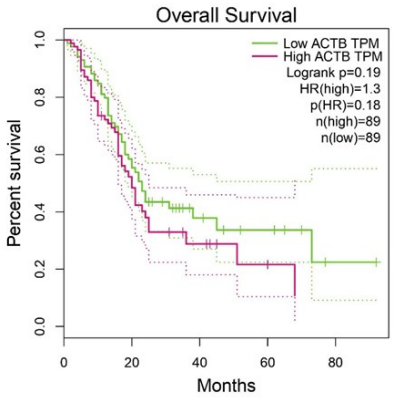
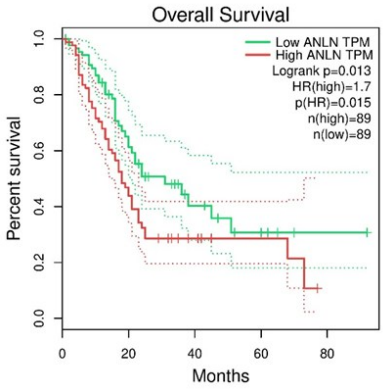
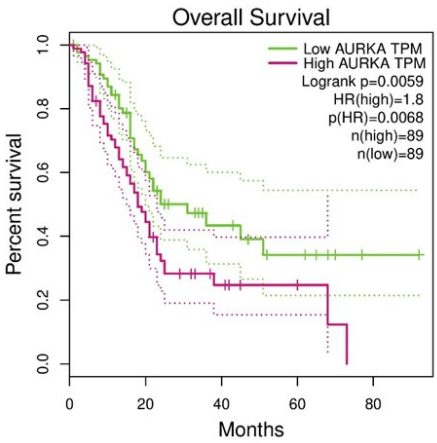
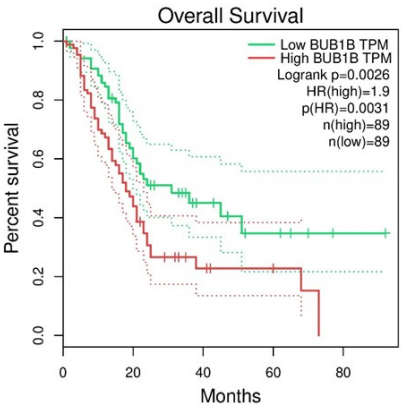


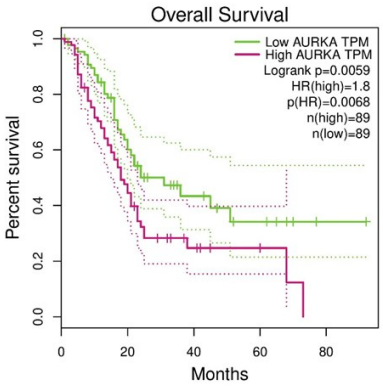
Figure 18. *The expression of 17 hub genes in PDAC and normal samples was studied using the GAPIA database. In tumor patients, all hub genes were increased. Red signifies tumor tissue, and green indicates normal tissue.*

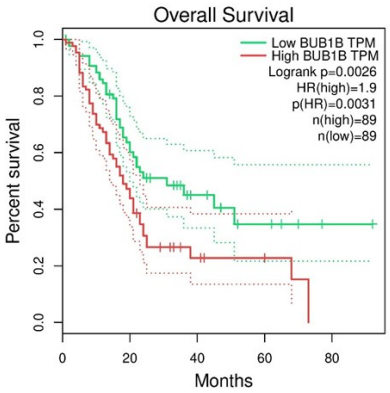

Overall Survival
Low ACTB TPM
High ACTB TPM
Logrank p=0.19
HR(high)=1.3
p(HR)=0.18
n(high)=89
n(low)=89
Percent survival
Months

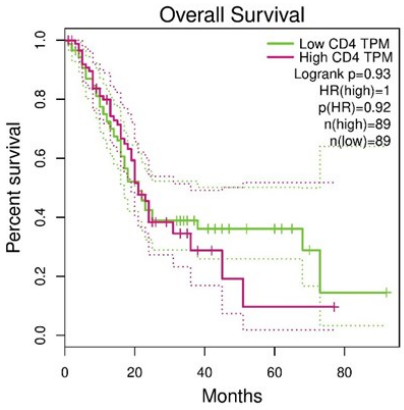

Overall Survival
Low ANLN TPM
High ANLN TPM
Logrank p=0.013
HR(high)=1.7
p(HR)=0.015
n(high)=89
n(low)=89
Percent survival
Months

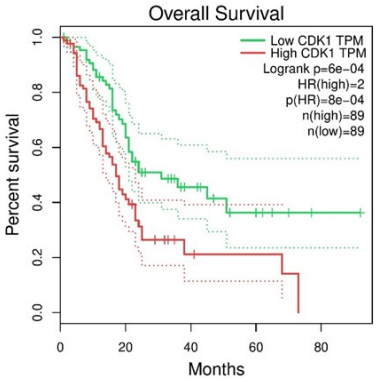

Overall Survival
Low AURKA TPM
High AURKA TPM
Logrank p=0.0059
HR(high)=1.8
p(HR)=0.0068
n(high)=89
n(low)=89
Percent survival
Months

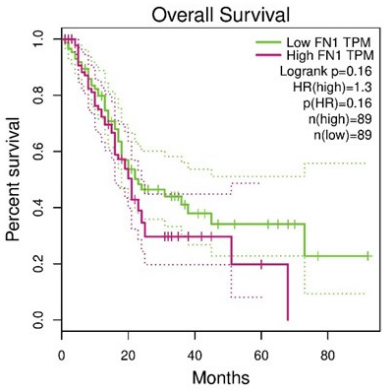

Overall Survival
Low BUB1B TPM
High BUB1B TPM
Logrank p=0.0026
HR(high)=1.9
p(HR)=0.0031
n(high)=89
n(low)=89
Percent survival
Months

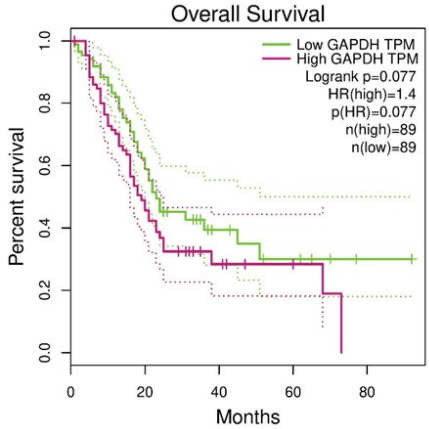

Overall Survival
Low AURKA TPM
High AURKA TPM
Logrank p=0.0059
HR(high)=1.8
p(HR)=0.0068
n(high)=89
n(low)=89
Percent survival
Months

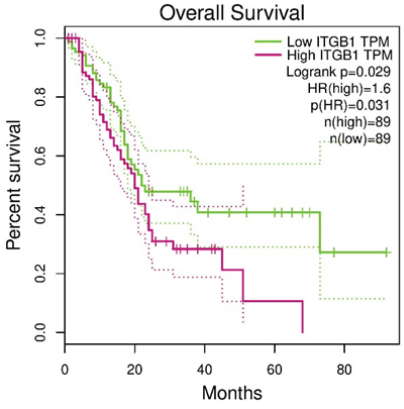

Overall Survival
Low BUB1B TPM
High BUB1B TPM
Logrank p=0.0026
HR(high)=1.9
p(HR)=0.0031
n(high)=89
n(low)=89
Percent survival
Months

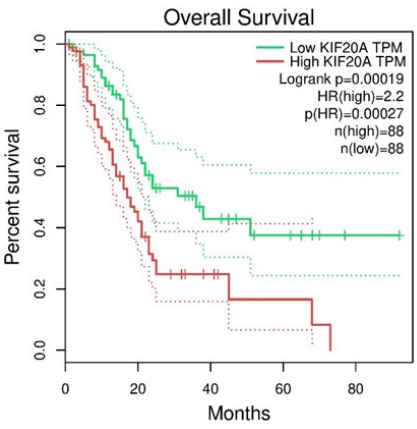

Overall Survival
Low CD4 TPM
High CD4 TPM
Logrank p=0.93
HR(high)=1
p(HR)=0.92
n(high)=89
n(low)=89
Percent survival
Months


Overall Survival
Low CDK1 TPM
High CDK1 TPM
Logrank p=6e-04
HR(high)=2
p(HR)=8e-04
n(high)=89
n(low)=89
Percent survival
Months


Overall Survival
Low FN1 TPM
High FN1 TPM
Logrank p=0.16
HR(high)=1.3
p(HR)=0.16
n(high)=89
n(low)=89
Percent survival
Months


Overall Survival
Low GAPDH TPM
High GAPDH TPM
Logrank p=0.077
HR(high)=1.4
p(HR)=0.077
n(high)=89
n(low)=89
Percent survival
Months


Overall Survival
Low ITGB1 TPM
High ITGB1 TPM
Logrank p=0.029
HR(high)=1.6
p(HR)=0.031
n(high)=89
n(low)=89
Percent survival
Months


Overall Survival
Low KIF20A TPM
High KIF20A TPM
Logrank p=0.00019
HR(high)=2.2
p(HR)=0.00027
n(high)=88
n(low)=88
Percent survival
Months

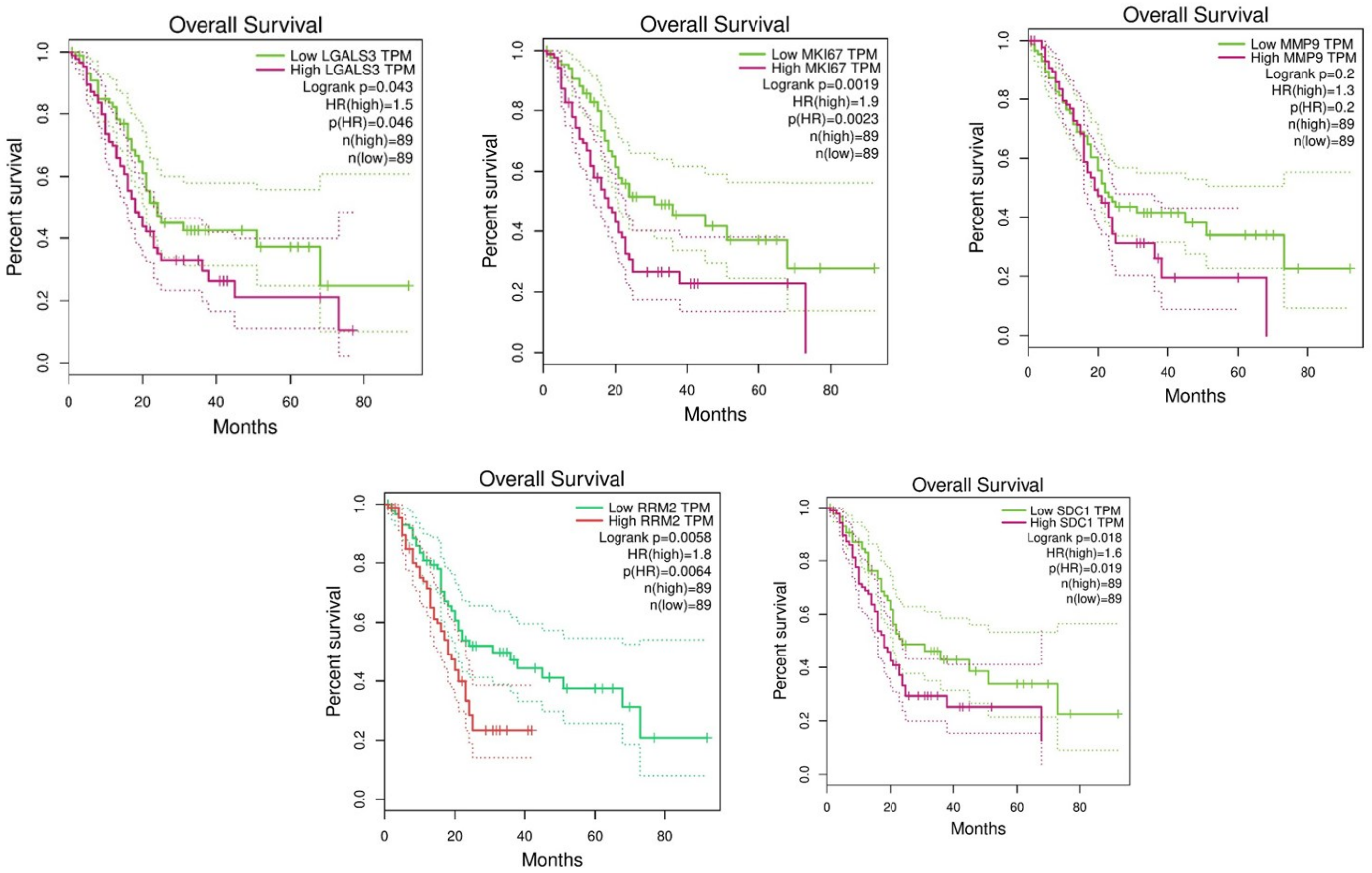


Figure 19. *Analysis of the Kaplan-Meier survival curve. GEPIA was used to assess the overall survival of seventeen hub genes expression in PDAC. The purple line represents genes with greater expression levels. Genes with higher expression are related to poor overall survival (P < 0.05), while genes with lower expression (Green) are associated with good survival.*

Discussion

Two datasets were examined with the use of a programming language and other bioinformatics tools. To conduct the investigation, data was imported from the NCBI GEO database and carefully manipulated. For the completion of the investigation, various R packages and statistical approaches were applied. The study's main goal was to identify DEGs from the dataset and establish potential biomarkers for pancreatic cancer. This analysis identified 871 DEGs with 17 hub genes. These hub genes are the insect outcome of the results obtained using cytohubba. To assess the link between DEGs, a PPI network was built, and several functional and pathway analyses were performed. A web-based platform that offers association analysis, and survival analysis, and is supplemented with various cancer data was utilized to validate hub genes.

All eukaryotic cells contain beta-actin (ACTB), a structural protein and a housekeeping gene with a large number of functions including cell growth, cell division, embryonic development, wound healing, immunological response, and gene expression. ACTB is upregulated in liver cancer tissues, correlated with melanoma, and renal cancer development, unregulated in colorectal cancer, and over-expression is associated with gastric cancer (Guo et al., 2013). The actin microfilament system and the cytoskeleton structure are known to influence tumor cell adhesion and movement, which are critical in tumor growth and metastasis (Ben-Ze'ev, 1985). ACTB is upregulated in pancreatic carcinomas at both RNA and protein levels but is not a reference gene.

Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) plays a significant role in converting glucose into energy. GAPDH is a housekeeping gene that, in addition to glycolysis, is involved in a variety of cellular activities such as DNA repair and apoptosis. According to certain research, GAPDH is unstable in some disease stages, including aging and cancer. High GAPDH expression is associated with poor overall survival, especially brain lower-grade glioma and pancreatic cancer (Shen, Li, and Wang, 2023).

FN1 located 2q35 with 47 exons and participates in the processes of cell adhesion and migration during the process of embryogenesis wound repair, coagulation of blood, defense in the host, and metastasis, in addition to cell proliferation (Pankov, 2002; Zhang, Luo and Wu, 2022). Fibronectin (FN1) is also a significant element of the extracellular matrix of the TME that is produced by both fibroblasts and tumor cells (Topalovski and Brekken, 2016). FN1 normally promotes cell-ECM interactions and is required for the healing of wounds, growth, and tissue homeostasis (Cao et al., 2005). FN1 is primarily expressed in the stroma of PDAC, according to immunohistochemical investigations, while it can also be seen in neoplastic epithelial cells (Shimoyama et al., 1995; Iacobuzio-Donahue et al., 2003) and thyroid cancer (Geng et al., 2022). The main source of FN1 is cancer-associated fibroblasts, which drive tumor migration and invasion through FN1 synthesis (Attieh et al., 2017).

MKI67 is located on 10q26.2 with 15 exons and is involved in chromosomal segregation, cell cycle, cell proliferation, and mitotic nuclear division control, molecular function involved in DNA, RNA, protein, and ATP binding. In general, MKI67 expression is seen only in growing cells ((Scholzen and Gerdes, 2000). Under typical circumstances, MKI67 exhibits cortical nucleolar distribution during interphase and gets recruited into compacted chromosomes throughout mitosis (Wu et al., 2021). A growing number of research studies have shown that MKI67 is an indicator of tumor deterioration as well as its level of expression is associated with poor prognosis and malignancy clinical features in a variety of cancers, including breast cancer (Inari et al., 2017), bladder cancer (Tian et al., 2016), gastric cancer (Xiong et al., 2019), hepatocellular carcinoma (Luo et al., 2015), cervical cancer (NAKANO et al., 2010), and glioma (Chen et al., 2015).

ITGB1 is a member of the integrin family that had a significant role in carcinogenesis and progression (Guo et al., 2019; Shi et al., 2021). The integrin family consists of at least 18 α subunits and 8 β subunits that can combine to generate 24 integrins with diverse distributions in tissues and overlapping ligand sensitivity. The beta-1 subfamily consists of 12 distinct integrin proteins that bind various extracellular matrix components, regulate external integrin binding, cell cycle, phagocytosis, and influence cell adhesion or migration. ITGB1 has also been implicated in a range of processes, including embryonic development (Kaitetzidou et al., 2019), and blood vessel development (Henning et al., 2021), as well as tumor metastasis (32, 33) in pancreatic cancer (Ganguly et al., 2022), breast cancer (Das et al., 2023), lung cancer (Li et al., 2021), and angiogenesis (Lu et al., 2018).

MMP9 plays a role in the destruction of extracellular matrix in normal physiological activities such as embryonic development, reproduction, and tissue remodeling (Visse and Nagase, 2003), as well as in the maintenance of Mitochondrial homeostasis (Wang et al., 2023) and the development of diseases such as arthritis and metastasis (Waltera et al., 2023). MMP9 is found in high concentrations in breast cancer, colorectal cancer, and other malignant tumors.

CD4 is a gene that codes for proteins. This gene appears not only in T lymphocytes but also in B cells, macrophages, granulocytes, and several areas of the brain. CD4 acts as an indicator of systemic inflammation and may be used to predict the prognosis of gastric cancer (You et al., 2021). According to new research, the CD4 T cells work as a Swiss army knife against tumors. They can disrupt the tumor vasculature by releasing cytokines, stimulate tumoricidal macrophages, cause cellular senescence of cancer cells, and kill cancer cells if they express MHC II (Poncette, Bluhm, and Blankenstein, 2022). They can also aid CD8 T cells in the regulatory phase.

SDC1 is a transmembrane heparan sulfate proteoglycan (HSPG) characterized by heparan sulfate (HS) covalent linkages (Szatmári et al., 2017). Syndecan-1 operates as a co-receptor for growth factors, chemokines, and cytokines, regulating a wide range of processes within cells such as cell growth, odontogenesis, cell proliferation, calcium ion binding, cell adhesion, and migration (Sherif Abdelaziz Ibrahim et al., 2017; Chen et al., 2019). Syndecan-1 is known as a cell-surface proteoglycan; however, it is also found in the stroma. Serum levels of SDC1 rise dramatically during infection, inflammation, and tissue injury, contributing to a variety of pathophysiological processes. It has been linked to cancers such as breast cancer (D'Arcy et al., 2022), colorectal cancer (Li et al., 2022), and pancreatic cancer (Yablecovitch et al., 2022) after being found in the nuclear compartment of several tumor types.

Galectins are a group of galactoside-binding proteins found in mammals that share extensively conserved carbohydrate recognition domains (Barondes et al., 1994). LGALS3 (Galectin-3) is a well-studied galectin belonging to the galectin family. Galectin-3 is the sole component of the chimera-type galectin subgroup, with one carbohydrate recognition domains attached to a prolonged non-lectin N-terminal domain (Yang, Rabinovich and Liu, 2008).

In addition to interacting with the calcium-dependent and phospholipid-binding protein synexin, LGALS3 also functions as a critical component of cell survival, cell-matrix interaction, mrna splicing, and apoptosis regulation (Lima et al., 2023; Newlaczyl and Yu, 2011). There is strong evidence that LGALS3 overexpression enhances neoplastic transformation (Elad-Sfadia et al., 2004). Many types of tumor cells, including neuroendocrine tumor pheochromocytoma, ovarian, melanoma, thyroid, and colorectal cancer cells, as well as follicular adenoma and papillary carcinoma, have increased invasiveness and metastasis when galectin-3 is overexpressed (Liu and Rabinovich, 2005; Li, Pritchard and Yu, 2023).

CCNB1 (Cyclin B1) is a cyclin family member that functions as a crucial initiator and control agent in cellular division (Shin et al., 2012). CCNB1 regulates and complexes with CDK1 to enhance the transition from the G2 to the mitotic phase of the cell cycle (Morgan, 1995). CCNB1 has been identified in a number of human cancers, including colorectal, breast, and prostate cancer, according to growing data (Fang et al., 2014; Niméus-Malmström et al., 2010). By changing the expression of G2/M cell cycle regulators, blocking CCNB1 causes cell cycle arrest in a variety of cell types. CCNB1 also plays a role in cancer growth, migration, apoptosis, mitosis, chemoresistance, and metastasis (Song et al., 2007; Zhou et al., 2014; Aljohani et al., 2022; Fu et al., 2022).

CCNB1 facilitates hepatocellular carcinoma development by regulating DNA replication during the cell cycle (Rong et al., 2021). CCNB1 may also be a predictive biomarker according to studies (Zeng and Fan, 2022).

AURKA (Aurora kinase A) is found on 20q13.2 and contains 12 exons. This gene encodes a cell cycle-regulated kinase that appears to be involved in the production and stabilization of microtubules at the spindle pole during chromosomal segregation and is essential for proper pole formation. It is a cyclin whose activation is needed for the process of cell division via mitotic regulation, as well as the regulation of signal transduction by p53 class mediators, and liver regeneration (Janczyk et al., 2023). AURKA influences diabetes-related impairment of ischemia-mediated angiogenesis and has been proposed as a potential therapeutic target for diabetic ischemic disorders (Bai et al., 2023). One of the studies discovered that aurora kinase A is a key gene and might be targeted for liver adenocarcinoma diagnosis and treatment (Dong et al., 2020; Xu et al., 2023). AURKA is a novel proto-oncogenic mitotic kinase that participates in the genomic pathways behind the two most common phenotypic abnormalities in human cancer cells: aneuploidy and centrosome aberrations (Zhang et al., 2010). Several studies have found that AURKA expression is higher in tumor cells than in normal cells and has been associated with a poor prognosis in metastasis (Gritsko et al., 2003; Liao et al., 2018).

CDK1 interacts with numerous cyclins to govern the cell cycle by regulating the centrosome cycle, mitotic initiation, G2-M transition, G1 advancement, and G1-S transition (Mori et al., 2015), it phosphorylates the protein p53 (Nantajit et al., 2010). By controlling the epithelial-mesenchymal transition, G2/M phase transition, and apoptosis, CDK1 acts as a therapeutic target for adrenocortical cancer (Ren et al., 2022). Upregulation of CDK1 contributes to increased Cancer-associated fibroblasts cell proliferation and resistance to medroxyprogesterone acetate, which promotes the progression of benign tumors to malignancy (Omar et al., 2022), and esophageal squamous cell carcinoma (Zhang et al., 2021). It also increases the development of melanoma by interacting with Sox2 (Ravindran Menon et al., 2018). CDK1 inhibition has been linked to effective breast cancer treatment outcomes, whether administered alone or in conjunction with other medicines (Izadi et al., 2020).

ANLN is located in chromosome 7p14.2 and is a highly conserved protein involved in a range of cellular activities, including fitting cleavage furrows together during division, particularly cytokinesis (Hickson and O'Farrell, 2008). ANLN regulates the cell cycle's anaphase and telophase by interacting with myosin, rhoa, actin, and septins to aid in the formation of cleavage furrows and influence cell polarity and motor capacity. ANLN acts as an oncogene in bladder urothelial carcinoma by activating the JNK signaling pathway (Chen et al., 2022), and it also regulates the PI3K/mTOR signaling pathway in oral cancer (Wang et al., 2021). ANLN is thought to be an early predictor of cancer diagnosis in diseases such as bladder urothelial carcinoma (Zeng et al., 2017), colorectal cancer (Wang et al., 2016), pancreatic ductal adenocarcinoma (Idichi et al., 2017), head and neck squamous cell carcinoma (Guo et al., 2021), and breast cancer (Magnusson et al., 2016). ANLN knockdown inhibits hepatocellular carcinoma cell proliferation, migration, and invasion (Lian et al., 2018), and it is a predictive indicator of cancer immunity (Zhang et al., 2022).

KIF20A belongs to the kinesin family of molecular motor proteins and is involved in cell mitosis, migration, and intracellular transport (Sharp, Rogers, and Scholey, 2000; Verhey and Hammond, 2009). KIF20A controls microtubule bundle growth, midbody separation, protein transport, and cytokinesis (Liang et al., 2022). Cell cycle, mitosis, and responses to cytosolic calcium ion boost are all related to KIF20A (Ren et al., 2020). KIF20A is overexpressed in a wide range of solid tumors. The KIF20A gene may play a role in renal cancer, and colorectal cancer as well as poor prognosis, and survival rate (Liu et al., 2023). It enhanced drug resistance in a variety of malignancies (Duan, Huang, and Shi, 2016). It also promotes the growth of fibrosarcoma via the PI3K-Akt signaling pathway (Jin et al., 2022) and castration-resistant prostate cancer by autocrine activation of the androgen receptor (Copello and Burnstein, 2022).

RNR (Ribonucleotide reductase) is responsible for the de novo production of deoxyribonucleotide triphosphate (dNTP), and so plays a crucial role in DNA synthesis and repair (Wu et al., 2022). Defective DNA replication is caused by aberrant dNTP levels, resulting in instability in the genome (Kumar et al., 2010). RRM2 modulates the rate-limiting enzyme RNR's cell cycle-dependent activity. RNR component expression levels have been examined in several types of malignancies, leading to the discovery of RRM2 overexpression in cancer cells (Jin et al., 2020; Wang et al., 2020). RRM2 overexpression has also been linked to a lower chance of survival in cancer patients (Yang et al., 2019). RNR inhibitors, in conjunction with chemotherapy, have been widely used in cancer treatment. RRM2 expression is significantly higher in NF1-associated Malignant peripheral nerve sheath tumors (Chung et al., 2023).

BUB1B is a conserved multifunctional protein required for mitotic spindle checkpoint activity, validating mitosis completion, and rectifying kinetochore-microtubule attachments (Williams, Roberts, and Gjoerup, 2007). BUB1B inactivation has been shown to result in both the loss of the spindle checkpoint and severe chromosomal segregation abnormalities (Klebig, Korinth and Meraldi, 2009). BUB1B has an oncogenic role and could be a promising prognostic biomarker for renal cell carcinoma survival (Sekino et al., 2021). BUB1B accelerated the advancement of extrahepatic cholangiocarcinoma via the JNK/c-Jun pathways, (Jiao et al., 2021) which also play a leading role to the development of psoriasis (Ding et al., 2022).

CCNA2 which has a full length of 7489 bp and is expressed in practically all organs in the human body, is found on human chromosome 4q27 and had 8 exons (Li, Qian and Sun, 2019). CCNA2 is involved in the biological processes of DNA replication regulation, cyclin-dependent protein serine/threonine kinase activity regulation, G2/M transition of mitotic cell cycle DNA-templated, Ras protein signal transmission, and histone phosphorylation, according to GO analysis. KEGG pathway study revealed the AMPK signaling pathway, Cellular senescence, Pathways in cancer, and Transcriptional misregulation in cancer. Several investigations have recently found that CCNA2 may increase cancer-aggressive behavior, recurrence, metastasis, and chemoresistance (Jiang et al., 2022; Mishra et al., 2023). Overexpression of CCNA2 was found to be substantially related to poor outcomes in people with pancreatic cancer (Jiang et al., 2020).

MKI67, AURKA, CDK1, ANLN, KIF20A, RRM2, BUB1B, CCNA2, CCNB1, SDC1, LGALS3, and ITGB1 were found promising biomarkers for early diagnosis and therapy of pancreatic cancer in this study. The identified gene was validated using GEPIA's gene expression level and survival analysis but without qRT-PCR or immunohistochemistry study. That is a notable drawback to this study. Further research and other statistical approaches can be utilized to detect and heal aggressive PDAC.

Conclusion

The findings point to some possible biomarkers and treatment options for pancreatic cancer. Several bioinformatics and statistical methods were used to accomplish this research. The hub gene was discovered and validated in silico. MKI67, AURKA, CDK1, ANLN, KIF20A, RRM2, BUB1B, CCNA2, CCNB1, SDC1, LGALS3, and ITGB1 may be promising predictive biomarkers and therapeutic targets in PDAC treatment and diagnosis.

Conflicts of Interest

None declared.

Acknowledgements

None

References

Albert, R. and Barabási, A.-L. (2002). Statistical mechanics of complex networks. *Reviews of Modern Physics*, 74(1), pp.47–97. doi:https://doi.org/10.1103/revmodphys.74.47.

Aljohani, A.I., Toss, M.S., Green, A.R. and Rakha, E.A. (2022). The clinical significance of cyclin B1 (CCNB1) in invasive breast cancer with emphasis on its contribution to lymphovascular invasion development. *Breast Cancer Research and Treatment*, 198(3), pp.423–435. doi:https://doi.org/10.1007/s10549-022-06801-2.

American Cancer Society (2020). *American Cancer Society | Cancer Facts & Statistics*. [online] American Cancer Society | Cancer Facts & Statistics. Available at: https://cancerstatisticscenter.cancer.org/#.

Attieh, Y., Clark, A.G., Grass, C., Richon, S., Pocard, M., Mariani, P., Elkhatib, N., Betz, T., Gurchenkov, B. and Vignjevic, D.M. (2017). Cancer-associated fibroblasts lead tumor invasion through integrin-β3–dependent fibronectin assembly. *The Journal of Cell Biology*, [online] 216(11), pp.3509–3520. doi:https://doi.org/10.1083/jcb.201702033.

Bai, T., Li, M., Liu, Y., Qiao, Z., Zhang, X., Wang, Y. and Wang, Z. (2023). The promotion action of AURKA on post-ischemic angiogenesis in diabetes-related limb ischemia. *Molecular Medicine*, 29(1). doi:https://doi.org/10.1186/s10020-023-00635-4.

Bailey, P., Chang, D.K., Nones, K., Johns, A.L., Patch, A.-M., Gingras, M.-C., Miller, D.K., Christ, A.N., Bruxner, T.J.C., Quinn, M.C., Nourse, C., Murtaugh, L.C., Harliwong, I., Idrisoglu, S., Manning, S., Nourbakhsh, E., Wani, S., Fink, L., Holmes, O. and Chin, V. (2016). Genomic analyses identify molecular subtypes of pancreatic cancer. *Nature*, 531(7592), pp.47–52. doi:https://doi.org/10.1038/nature16965.

Barondes, S.H., Cooper, D.N., Gitt, M.A. and Leffler, H. (1994). Galectins. Structure and function of a large family of animal lectins. *Journal of Biological Chemistry*, 269(33), pp.20807–20810. doi:https://doi.org/10.1016/s0021-9258(17)31891-4.

Ben-Ze'ev, A. (1985). The cytoskeleton in cancer cells. *Biochimica et Biophysica Acta (BBA) - Reviews on Cancer*, 780(3), pp.197–212. doi:https://doi.org/10.1016/0304-419x(85)90003-4.

Binenbaum, Y., Na'ara, S. and Gil, Z. (2015). Gemcitabine resistance in pancreatic ductal adenocarcinoma. *Drug Resistance Updates*, 23, pp.55–68. doi:https://doi.org/10.1016/j.drup.2015.10.002.

Blackadar, C.B. (2016). Historical review of the causes of cancer. *World Journal of Clinical Oncology*, [online] 7(1), p.54. doi:https://doi.org/10.5306/wjco.v7.i1.54.

Blum, R. and Kloog, Y. (2014). Metabolism addiction in pancreatic cancer. *Cell Death & Disease*, 5(2), pp.e1065–e1065. doi:https://doi.org/10.1038/cddis.2014.38.

Buja, A., Swayne, D.F., Littman, M.L., Dean, N., Hofmann, H. and Chen, L. (2008). Data Visualization With Multidimensional Scaling. *Journal of Computational and Graphical Statistics*, 17(2), pp.444–472. doi:https://doi.org/10.1198/106186008x318440.

Buscail, L., Bournet, B. and Cordelier, P. (2020). Role of oncogenic KRAS in the diagnosis, prognosis and treatment of pancreatic cancer. *Nature Reviews Gastroenterology & Hepatology*, 17(3), pp.153–168. doi:https://doi.org/10.1038/s41575-019-0245-4.

Cancer Research UK (2019a). *Pancreatic cancer statistics*. [online] Cancer Research UK. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/pancreatic-cancer.

Cancer Research UK (2019b). *Pancreatic cancer statistics*. [online] Cancer Research UK. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/pancreatic-cancer.

Cao, D., Maitra, A., Saavedra, J.-A., Klimstra, D.S., Adsay, N.V. and Hruban, R.H. (2005). Expression of novel markers of pancreatic ductal adenocarcinoma in pancreatic nonductal neoplasms: additional evidence of different genetic pathways. *Modern Pathology*, 18(6), pp.752–761. doi:https://doi.org/10.1038/modpathol.3800363.

Chen, S., Gao, Y., Chen, F. and Wang, T.-B. (2022). ANLN Serves as an Oncogene in Bladder Urothelial Carcinoma via Activating JNK Signaling Pathway. *Urologia Internationalis*, 107(3), pp.310–320. doi:https://doi.org/10.1159/000524204.

Chen, W.-J., He, D.-S., Tang, R.-X., Ren, F.-H. and Chen, G. (2015). Ki-67 is a Valuable Prognostic Factor in Gliomas: Evidence from a Systematic Review and Meta-analysis. *Asian Pacific Journal of Cancer Prevention*, 16(2), pp.411–420. doi:https://doi.org/10.7314/apjcp.2015.16.2.411.

Chen, X., Zhao, H., Chen, C., Li, J., He, J., Fu, X. and Zhao, H. (2019). The HPA/SDC1 axis promotes invasion and metastasis of pancreatic cancer cells by activating EMT via FGF2 upregulation. *Oncology Letters*. doi:https://doi.org/10.3892/ol.2019.11121.

Chin, C.-H., Chen, S.-H., Wu, H.-H., Ho, C.-W., Ko, M.-T. and Lin, C.-Y. (2014). cytoHubba: identifying hub objects and sub-networks from complex interactome. *BMC Systems Biology*, 8(Suppl 4), p.S11. doi:https://doi.org/10.1186/1752-0509-8-s4-s11.

Christenson, E.S., Jaffee, E. and Azad, N.S. (2020). Current and emerging therapies for patients with advanced pancreatic ductal adenocarcinoma: a bright future. *The Lancet Oncology*, [online] 21(3), pp.e135–e145. doi:https://doi.org/10.1016/S1470-2045(19)30795-8.

Chung, M.-H., Aimaier, R., Yu, Q., Li, H., Li, Y., Wei, C., Gu, Y., Wang, W., Guo, Z., Long, M., Li, Q. and Wang, Z. (2023). RRM2 as a novel prognostic and therapeutic target of NF1-associated MPNST. *Cellular Oncology*. doi:https://doi.org/10.1007/s13402-023-00819-4.

Copello, V.A. and Burnstein, K.L. (2022). The kinesin KIF20A promotes progression to castration-resistant prostate cancer through autocrine activation of the androgen receptor. *Oncogene*, 41(20), pp.2824–2832. doi:https://doi.org/10.1038/s41388-022-02307-9.

D'Arcy, C., Zimmermann, C.C., Espinoza-Sanchez, N.A., Greve, B., Schmidt, A., Kiesel, L., von Wahlde, M.-K. and Götte, M. (2022). The heparan sulphate proteoglycan Syndecan-1 (CD138) regulates tumour progression in a 3D model of ductal carcinoma in situ of the breast. *IUBMB life*, [online] 74(10), pp.955–968. doi:https://doi.org/10.1002/iub.2623.

Das, S., Kundu, M., Hassan, A., Parekh, A., Jena, B.Ch., Mundre, S., Banerjee, I., Yetirajam, R., Das, C.K., Pradhan, A.K., Das, S.K., Emdad, L., Mitra, P., Fisher, P.B. and Mandal, M. (2023). A novel computational predictive biological approach distinguishes Integrin β1 as a salient biomarker for breast cancer chemoresistance. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, [online] 1869(6), p.166702. doi:https://doi.org/10.1016/j.bbadis.2023.166702.

Davis, S. and Meltzer, P.S. (2007). GEOquery: a bridge between the Gene Expression Omnibus (GEO) and BioConductor. *Bioinformatics*, 23(14), pp.1846–1847. doi:https://doi.org/10.1093/bioinformatics/btm254.

Ding, X., Chen, L., Xu, D., Yu, Y., Tao, X., Fan, Y. and Huang, Y. (2022). Pan-Cancer Analysis of BUB1B/hsa-miR-130a-3p Axis and Identification of Circulating hsa-miR-130a-3p as a Potential Biomarker for Cancer Risk Assessment. *Evidence-Based Complementary and Alternative Medicine*, 2022, pp.1–15. doi:https://doi.org/10.1155/2022/3261300.

Dong, S., Men, W., Yang, S. and Xu, S. (2020). Identification of lung adenocarcinoma biomarkers based on bioinformatic analysis and human samples. *Oncology Reports*. doi:https://doi.org/10.3892/or.2020.7526.

Duan, J., Huang, W. and Shi, H. (2016). Positive expression of KIF20A indicates poor prognosis of glioma patients. *OncoTargets and Therapy*, Volume 9, pp.6741–6749. doi:https://doi.org/10.2147/ott.s115974.

Elad-Sfadia, G., Haklai, R., Balan, E. and Kloog, Y. (2004). Galectin-3 Augments K-Ras Activation and Triggers a Ras Signal That Attenuates ERK but Not Phosphoinositide 3-Kinase Activity*. *Journal of Biological Chemistry*, [online] 279(33), pp.34922–34930. doi:https://doi.org/10.1074/jbc.M312697200.

Eltawil, K.M., Renfrew, P.D. and Molinari, M. (2012). Meta-analysis of Phase III randomized trials of molecular targeted therapies for advanced pancreatic cancer. *HPB*, 14(4), pp.260–268. doi:https://doi.org/10.1111/j.1477-2574.2012.00441.x.

Fang, Y., Yu, H., Liang, X., Xu, J. and Cai, X. (2014). Chk1-induced CCNB1 overexpression promotes cell proliferation and tumor growth in human colorectal cancer. *Cancer Biology & Therapy*, 15(9), pp.1268–1279. doi:https://doi.org/10.4161/cbt.29691.

Fu, H., Li, K., Wang, S. and Li, Y. (2022). High expression of CCNB1 driven by ncRNAs is associated with a poor prognosis and tumor immune infiltration in breast cancer. *Aging*, 14(16), pp.6780–6795. doi:https://doi.org/10.18632/aging.204253.

Ganguly, K., Cox, J.L., Ghersi, D., Grandgenett, P.M., Hollingsworth, M.A., Jain, M., Kumar, S. and Batra, S.K. (2022). Mucin 5AC–Mediated CD44/ITGB1 Clustering Mobilizes Adipose-Derived Mesenchymal Stem Cells to Modulate Pancreatic Cancer Stromal Heterogeneity. *Gastroenterology*, 162(7), pp.2032-2046.e12. doi:https://doi.org/10.1053/j.gastro.2022.02.032.

Geng, Q.-S., Huang, T., Li, L.-F., Shen, Z.-B., Xue, W.-H. and Zhao, J. (2022). Over-Expression and Prognostic Significance of FN1, Correlating With Immune Infiltrates in Thyroid Cancer. *Frontiers in Medicine*, 8. doi:https://doi.org/10.3389/fmed.2021.812278.

Gritsko, T.M., Coppola, D., Paciga, J.E., Yang, L., Sun, M., Shelley, S.A., Fiorica, J.V., Nicosia, S.V. and Cheng, J.Q. (2003). Activation and Overexpression of Centrosome Kinase BTAK/Aurora-A in Human Ovarian Cancer1. *Clinical Cancer Research*, [online] 9(4), pp.1420–1426. Available at: https://aacrjournals.org/clincancerres/article/9/4/1420/202363/Activation-and-Overexpression-of-Centrosome-Kinase [Accessed 9 May 2023].

Gu, Y., Tang, S., Wang, Z., Cai, L., Lian, H., Shen, Y. and Zhou, Y. (2021). A pan-cancer analysis of the prognostic and immunological role of β-actin (ACTB) in human cancers. *Bioengineered*, 12(1), pp.6166–6185. doi:https://doi.org/10.1080/21655979.2021.1973220.

Gu, Y.-L., Lan, C., Pei, H., Yang, S.-N., Liu, Y.-F. and Xiao, L.-L. (2015). Applicative Value of Serum CA19-9, CEA, CA125 and CA242 in Diagnosis and Prognosis for Patients with Pancreatic Cancer Treated by Concurrent Chemoradiotherapy. *Asian Pacific Journal of Cancer Prevention*, 16(15), pp.6569–6573. doi:https://doi.org/10.7314/apjcp.2015.16.15.6569.

Guo, C., Liu, S., Wang, J., Sun, M.-Z. and Greenaway, F.T. (2013). ACTB in cancer. *Clinica Chimica Acta*, 417, pp.39–44. doi:https://doi.org/10.1016/j.cca.2012.12.012.

Guo, E., Mao, X., Wang, X., Guo, L., An, C., Zhang, C., Song, K., Wang, G., Duan, C., Zhang, X., Yang, X., Yuan, Z., Sun, J., Li, X., Yang, W., Meng, H. and Miao, S. (2021). Alternatively spliced ANLN isoforms synergistically contribute to the progression of head and neck squamous cell carcinoma. *Cell Death & Disease*, 12(8). doi:https://doi.org/10.1038/s41419-021-04063-2.

Guo, Q., Furuta, K., Lucien, F., Gutierrez Sanchez, L.H., Hirsova, P., Krishnan, A., Kabashima, A., Pavelko, K.D., Madden, B., Alhuwaish, H., Gao, Y., Revzin, A. and Ibrahim, S.H. (2019). Integrin β1-enriched extracellular vesicles mediate monocyte adhesion and promote liver inflammation in murine NASH. *Journal of Hepatology*, 71(6), pp.1193–1205. doi:https://doi.org/10.1016/j.jhep.2019.07.019.

Henning, C., Branopolski, A., Follert, P., Lewandowska, O., Ayhan, A., Benkhoff, M., Flögel, U., Kelm, M., Heiss, C. and Lammert, E. (2021). Endothelial β1 Integrin-Mediated Adaptation to Myocardial Ischemia. *Thrombosis and Haemostasis*, 121(06), pp.741–754. doi:https://doi.org/10.1055/s-0040-1721505.

Hickson, Gilles R.X. and O'Farrell, Patrick H. (2008). Anillin: a pivotal organizer of the cytokinetic machinery. *Biochemical Society Transactions*, 36(3), pp.439–441. doi:https://doi.org/10.1042/bst0360439.

Hruban, R.H., Petersen, G.M., Ha, P.K. and Kern, S.E. (1998). Genetics of Pancreatic Cancer. *Surgical Oncology Clinics of North America*, 7(1), pp.1–23. doi:https://doi.org/10.1016/s1055-3207(18)30282-5.

Hung, Y.-H., Hsu, M.-C., Chen, L.-T., Hung, W.-C. and Pan, M.-R. (2019). Alteration of Epigenetic Modifiers in Pancreatic Cancer and Its Clinical Implication. *Journal of Clinical Medicine*, 8(6), p.903. doi:https://doi.org/10.3390/jcm8060903.

Iacobuzio-Donahue, C.A., Maitra, A., Mari Broman Olsen, Lowe, A.W., Heek, van, Christophe Rosty, Walter, K., Sato, N., Parker, A.R., Ashfaq, R., Jaffee, E.M., Ryu, B., Jones, J., Eshleman, J.R., Yeo, C.J., Cameron, J.L., Kern, S.E., Hruban, R.H., Brown, P.O. and Goggins, M. (2003). Exploration of Global Gene Expression Patterns in Pancreatic Adenocarcinoma Using cDNA Microarrays. *American Journal of Pathology*, 162(4), pp.1151–1162. doi:https://doi.org/10.1016/s0002-9440(10)63911-9.

Idichi, T., Seki, N., Kurahara, H., Yonemori, K., Osako, Y., Arai, T., Okato, A., Kita, Y., Arigami, T., Mataki, Y., Kijima, Y., Maemura, K. and Natsugoe, S. (2017). Regulation of actin-binding protein ANLN by antitumor miR-217 inhibits cancer cell aggressiveness in pancreatic ductal adenocarcinoma. *Oncotarget*, [online] 8(32), pp.53180–53193. doi:https://doi.org/10.18632/oncotarget.18261.

Inari, H., Suganuma, N., Kawachi, K., Yoshida, T., Yamanaka, T., Nakamura, Y., Yoshihara, M., Nakayama, H., Masudo, K., Oshima, T., Yokose, T., Rino, Y., Shimizu, S., Miyagi, Y. and Masuda, M. (2017). Clinicopathological and prognostic significance of Ki-67 immunohistochemical expression of distant metastatic lesions in patients with metastatic breast cancer. *Breast Cancer*, 24(6), pp.748–755. doi:https://doi.org/10.1007/s12282-017-0774-z.

Izadi, S., Nikkhoo, A., Hojjat-Farsangi, M., Namdar, A., Azizi, G., Mohammadi, H., Yousefi, M. and Jadidi-Niaragh, F. (2020). CDK1 in Breast Cancer: Implications for Theranostic Potential. *Anti-Cancer Agents in Medicinal Chemistry*, 20(7), pp.758–767. doi:https://doi.org/10.2174/1871520620666200203125712.

Janczyk, P.Ł., Żyłkiewicz, E., De Hoyos, H., West, T., Matson, D.R., Choi, W.-C., Young, H.M.R., Derewenda, Z.S. and Stukenberg, P.T. (2023). Aurora A phosphorylates Ndel1 to reduce the levels of Mad1 and NuMA at spindle poles. *Molecular Biology of the Cell*, 34(1). doi:https://doi.org/10.1091/mbc.e21-09-0438.

Jemal, A., Siegel, R., Ward, E., Hao, Y., Xu, J. and Thun, M.J. (2009). Cancer Statistics, 2009. *CA: A Cancer Journal for Clinicians*, 59(4), pp.225–249. doi:https://doi.org/10.3322/caac.20006.

Jiang, A., Zhou, Y., Gong, W., Pan, X., Gan, X., Wu, Z., Liu, B., Qu, L. and Wang, L. (2022). CCNA2 as an Immunological Biomarker Encompassing Tumor Microenvironment and Therapeutic Response in Multiple Cancer Types. *Oxidative Medicine and Cellular Longevity*, 2022, pp.1–35. doi:https://doi.org/10.1155/2022/5910575.

Jiang, P., Zhang, M., Gui, L. and Zhang, K. (2020). Expression patterns and prognostic values of the *cyclin-dependent kinase 1* and *cyclin A2* gene cluster in pancreatic adenocarcinoma. *Journal of International Medical Research*, 48(12), p.030006052093011. doi:https://doi.org/10.1177/0300060520930113.

Jiao, C.Y., Feng, Q.C., Li, C.X., Wang, D., Han, S., Zhang, Y.D., Jiang, W.J., Chang, J., Wang, X. and Li, X.C. (2021). BUB1B promotes extrahepatic cholangiocarcinoma progression via JNK/c-Jun pathways. *Cell Death & Disease*, 12(1). doi:https://doi.org/10.1038/s41419-020-03234-x.

Jimeno, A. (2006). Molecular biomarkers: their increasing role in the diagnosis, characterization, and therapy guidance in pancreatic cancer. *Molecular Cancer Therapeutics*, 5(4), pp.787–796. doi:https://doi.org/10.1158/1535-7163.mct-06-0005.

Jin, C.-Y., Du, L., Nuerlan, A-Han., Wang, X.-L., Yang, Y.-W. and Guo, R. (2020). High expression of RRM2 as an independent predictive factor of poor prognosis in patients with lung adenocarcinoma. *Aging*, 13(3), pp.3518–3535. doi:https://doi.org/10.18632/aging.202292.

Jin, Z., Tao, S., Zhang, C., Xu, D. and Zhu, Z. (2022). KIF20A promotes the development of fibrosarcoma via PI3K-Akt signaling pathway. *Experimental Cell Research*, 420(1), p.113322. doi:https://doi.org/10.1016/j.yexcr.2022.113322.

Kaitetzidou, E., Katsiadaki, I., Lagnel, J., Antonopoulou, E. and Sarropoulou, E. (2019). Unravelling paralogous gene expression dynamics during three-spined stickleback embryogenesis. *Scientific Reports*, 9(1). doi:https://doi.org/10.1038/s41598-019-40127-2.

Kanehisa, M. and Goto, S. (2000). KEGG: Kyoto Encyclopedia of Genes and Genomes. *Nucleic Acids Research*, 28(1), pp.27–30. doi:https://doi.org/10.1093/nar/28.1.27.

Kim, V.M. and Ahuja, N. (2015). Early detection of pancreatic cancer. *Chinese journal of cancer research = Chung-kuo yen cheng yen chiu*, [online] 27(4), pp.321–31. doi:https://doi.org/10.3978/j.issn.1000-9604.2015.07.03.

Klebig, C., Korinth, D. and Meraldi, P. (2009). Bub1 regulates chromosome segregation in a kinetochore-independent manner. *The Journal of Cell Biology*, 185(5), pp.841–858. doi:https://doi.org/10.1083/jcb.200902128.

Kleeff, J., Korc, M., Apte, M., La Vecchia, C., Johnson, C.D., Biankin, A.V., Neale, R.E., Tempero, M., Tuveson, D.A., Hruban, R.H. and Neoptolemos, J.P. (2016). Pancreatic cancer. *Nature Reviews Disease Primers*, [online] 2(1). doi:https://doi.org/10.1038/nrdp.2016.22.

Klein, A.P. (2012). Identifying people at a high risk of developing pancreatic cancer. *Nature Reviews Cancer*, 13(1), pp.66–74. doi:https://doi.org/10.1038/nrc3420.

Kumar, D., Abdulovic, A.L., Viberg, J., Nilsson, A.K., Kunkel, T.A. and Chabes, A. (2010). Mechanisms of mutagenesis in vivo due to imbalanced dNTP pools. *Nucleic Acids Research*, 39(4), pp.1360–1371. doi:https://doi.org/10.1093/nar/gkq829.

Law, C.W., Chen, Y., Shi, W. and Smyth, G.K. (2014). voom: precision weights unlock linear model analysis tools for RNA-seq read counts. *Genome Biology*, 15(2), p.R29. doi:https://doi.org/10.1186/gb-2014-15-2-r29.

Li, J., Qian, W.-P. and Sun, Q.-Y. (2019). Cyclins regulating oocyte meiotic cell cycle progression†. *Biology of Reproduction*, 101(5), pp.878–881. doi:https://doi.org/10.1093/biolre/ioz143.

Li, S., Pritchard, D.M. and Yu, L.-G. (2023). Galectin-3 promotes secretion of proteases that decrease epithelium integrity in human colon cancer cells. *Cell Death & Disease*, 14(4). doi:https://doi.org/10.1038/s41419-023-05789-x.

Li, Y., Sun, C., Tan, Y., Zhang, H., Li, Y. and Zou, H. (2021). ITGB1 enhances the Radioresistance of human Non-small Cell Lung Cancer Cells by modulating the DNA damage response and YAP1-induced Epithelial-mesenchymal Transition. *International Journal of Biological Sciences*, 17(2), pp.635–650. doi:https://doi.org/10.7150/ijbs.52319.

Li, Z., He, S., Liu, J., Zhi, X., Yang, L., Zhang, J., Zhao, R., Zhang, R., Li, L. and Wang, W. (2022). High expression of SDC1 in stromal cells is associated with good prognosis in colorectal cancer. *Anti-Cancer Drugs*, 34(4), pp.479–482. doi:https://doi.org/10.1097/cad.0000000000001441.

Lian, Y.-F., Huang, Y.-L., Wang, J.-L., Deng, M.-H., Xia, T.-L., Zeng, M.-S., Chen, M.-S., Wang, H.-B. and Huang, Y.-H. (2018). Anillin is required for tumor growth and regulated by miR-15a/miR-16-1 in HBV-related hepatocellular carcinoma. *Aging*, 10(8), pp.1884–1901. doi:https://doi.org/10.18632/aging.101510.

Liang, B., Zhou, Y., Jiao, J., Xu, L., Yan, Y., Wu, Q., Tong, X. and Yan, H. (2022). Integrated Analysis of Transcriptome Data Revealed AURKA and KIF20A as Critical Genes in Medulloblastoma Progression. *Frontiers in Oncology*, 12. doi:https://doi.org/10.3389/fonc.2022.875521.

Liao, Y., Liao, Y., Li, J., Li, J., Fan, Y. and Xu, B. (2018). Polymorphisms in AURKA and AURKB are associated with the survival of triple-negative breast cancer patients treated with taxane-based adjuvant chemotherapy. *Cancer Management and Research*, Volume 10, pp.3801–3808. doi:https://doi.org/10.2147/cmar.s174735.

Lima, T., Macedo-Silva, C., Felizardo, D., Fraga, J., Carneiro, I., Jerónimo, C., Henrique, R., Fardilha, M. and Vitorino, R. (2023). Gal-3 Protein Expression and Localization in Prostate Tumours. *Current Oncology*, 30(3), pp.2729–2742. doi:https://doi.org/10.3390/curroncol30030206.

Liu, B., Su, J., Fan, B., Ni, X. and Jin, T. (2023). High expression of KIF20A in bladder cancer as a potential prognostic target for poor survival of renal cell carcinoma. *Medicine*, 102(2), p.e32667. doi:https://doi.org/10.1097/md.0000000000032667.

Liu, F.-T. and Rabinovich, G.A. (2005). Galectins as modulators of tumour progression. *Nature Reviews Cancer*, 5(1), pp.29–41. doi:https://doi.org/10.1038/nrc1527.

Lu, Q., Xie, Z., Yan, C., Ding, Y., Ma, Z., Wu, S., Qiu, Y., Cossette, S.M., Bordas, M., Ramchandran, R. and Zou, M.-H. (2018). SNRK (Sucrose Nonfermenting 1-Related Kinase) Promotes Angiogenesis In Vivo. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 38(2), pp.373–385. doi:https://doi.org/10.1161/atvbaha.117.309834.

Luo, Y., Ren, F., Liu, Y., Shi, Z., Tan, Z., Xiong, H., Dang, Y. and Chen, G. (2015). Clinicopathological and prognostic significance of high Ki-67 labeling index in hepatocellular carcinoma patients: a meta-analysis. *International Journal of Clinical and Experimental Medicine*, [online] 8(7), pp.10235–10247. Available at: https://pubmed.ncbi.nlm.nih.gov/26379815/ [Accessed 9 May 2023].

Magnusson, K., Gremel, G., Rydén, L., Pontén, V., Uhlén, M., Dimberg, A., Jirström, K. and Pontén, F. (2016). ANLN is a prognostic biomarker independent of Ki-67 and essential for cell cycle progression in primary breast cancer. *BMC Cancer*, 16 (1). doi:https://doi.org/10.1186/s12885-016-2923-8.

Melief, C.J.M. (2022). Two types of biomarker-dependent chemo-immunotherapy for pancreatic cancer? *Cell Reports Medicine*, 3(10), p.100788. doi:https://doi.org/10.1016/j.xcrm.2022.100788.

Messadi, D.V. (2013). Diagnostic aids for detection of oral precancerous conditions. *International Journal of Oral Science*, [online] 5(2), pp.59–65. doi:https://doi.org/10.1038/ijos.2013.24.

Mimeault, M., Brand, R.E., Sasson, A.A. and Batra, S.K. (2005). Recent Advances on the Molecular Mechanisms Involved in Pancreatic Cancer Progression and Therapies. *Pancreas*, 31(4), pp.301–316. doi:https://doi.org/10.1097/01.mpa.0000175893.04660.1b.

Mishra, D., Mishra, A., Nand Rai, S., Vamanu, E. and Singh, M.P. (2023). Demystifying the Role of Prognostic Biomarkers in Breast Cancer through Integrated Transcriptome and Pathway Enrichment Analyses. *Diagnostics*, 13(6), p.1142. doi:https://doi.org/10.3390/diagnostics13061142.

Morgan, D.O. (1995). Principles of CDK regulation. *Nature*, 374(6518), pp.131–134. doi:https://doi.org/10.1038/374131a0.

Mori, Y., Inoue, Y., Taniyama, Y., Tanaka, S. and Terada, Y. (2015). Phosphorylation of the centrosomal protein, Cep169, by Cdk1 promotes its dissociation from centrosomes in mitosis. *Biochemical and Biophysical Research Communications*, 468(4), pp.642–646. doi:https://doi.org/10.1016/j.bbrc.2015.11.004.

NAKANO, T., OHNO, T., ISHIKAWA, H., SUZUKI, Y. and TAKAHASHI, T. (2010). Current Advancement in Radiation Therapy for Uterine Cervical Cancer. *Journal of Radiation Research*, 51(1), pp.1–8. doi:https://doi.org/10.1269/jrr.09132.

Nantajit, D., Fan, M., Duru, N., Wen, Y., Reed, J.C. and Li, J.J. (2010). Cyclin B1/Cdk1 Phosphorylation of Mitochondrial p53 Induces Anti-Apoptotic Response. *PLoS ONE*, 5(8), p.e12341. doi:https://doi.org/10.1371/journal.pone.0012341.

Newlaczyl, A.U. and Yu, L.-G. (2011). Galectin-3 – A jack-of-all-trades in cancer. *Cancer Letters*, [online] 313(2), pp.123–128. doi:https://doi.org/10.1016/j.canlet.2011.09.003.

Niméus-Malmström, E., Koliadi, A., Ahlin, C., Holmqvist, M., Holmberg, L., Amini, R.-M. ., Jirström, K., Wärnberg, F., Blomqvist, C., Fernö, M. and Fjällskog, M.-L. . (2010). Cyclin B1 is a prognostic proliferation marker with a high reproducibility in a population-based lymph node negative breast cancer cohort. *International Journal of Cancer*, p.NA-NA. doi:https://doi.org/10.1002/ijc.25091.

Omar, I.S., Mat Adenan, N.A., Godoy, A., Teo, I.H., Gunasagran, Y. and Chung, I. (2022). Aberrant upregulation of CDK1 contributes to medroxyprogesterone acetate (MPA) resistance in cancer-associated fibroblasts of the endometrium. *Biochemical and Biophysical Research Communications*, 628, pp.133–140. doi:https://doi.org/10.1016/j.bbrc.2022.08.088.

Ott, J.J., Ullrich, A. and Miller, A.B. (2009). The importance of early symptom recognition in the context of early detection and cancer survival. *European Journal of Cancer*, 45(16), pp.2743–2748. doi:https://doi.org/10.1016/j.ejca.2009.08.009.

Pankov, R. (2002). Fibronectin at a glance. *Journal of Cell Science*, [online] 115(20), pp.3861–3863. doi:https://doi.org/10.1242/jcs.00059.

Plenary Presentations. (2021). *International Journal of Rheumatic Diseases*, 24(S2), pp.5–120. doi:https://doi.org/10.1111/1756-185x.14199.

Poncette, L., Bluhm, J. and Blankenstein, T. (2022). The role of CD4 T cells in rejection of solid tumors. *Current Opinion in Immunology*, 74, pp.18–24. doi:https://doi.org/10.1016/j.coi.2021.09.005.

Rahib, L., Smith, B.D., Aizenberg, R., Rosenzweig, A.B., Fleshman, J.M. and Matrisian, L.M. (2014). Projecting Cancer Incidence and Deaths to 2030: The Unexpected Burden of Thyroid, Liver, and Pancreas Cancers in the United States. *Cancer Research*, 74(11), pp.2913–2921. doi:https://doi.org/10.1158/0008-5472.can-14-0155.

Ravindran Menon, D., Luo, Y., Arcaroli, J.J., Liu, S., KrishnanKutty, L.N., Osborne, D.G., Li, Y., Samson, J.M., Bagby, S., Tan, A.-C., Robinson, W.A., Messersmith, W.A. and Fujita, M. (2018). CDK1 Interacts with Sox2 and Promotes Tumor Initiation in Human Melanoma. *Cancer Research*, 78(23), pp.6561–6574. doi:https://doi.org/10.1158/0008-5472.can-18-0330.

Ren, L., Yang, Y., Li, W., Zheng, X., Liu, J., Li, S., Yang, H., Zhang, Y., Ge, B., Zhang, S., Fu, W., Dong, D., Du, G. and Wang, J. (2022). CDK1 serves as a therapeutic target of adrenocortical carcinoma via regulating epithelial–mesenchymal transition, G2/M phase transition, and PANoptosis. *Journal of Translational Medicine*, 20(1). doi:https://doi.org/10.1186/s12967-022-03641-y.

Ren, X., Chen, X., Ji, Y., Li, L., Li, Y., Qin, C. and Fang, K. (2020). Upregulation of KIF20A promotes tumor proliferation and invasion in renal clear cell carcinoma and is associated with adverse clinical outcome. *Aging*, 12(24), pp.25878–25894. doi:https://doi.org/10.18632/aging.202153.

Riquelme, E., Maitra, A. and McAllister, F. (2018). Immunotherapy for Pancreatic Cancer: More Than Just a Gut Feeling. *Cancer Discovery*, 8(4), pp.386–388. doi:https://doi.org/10.1158/2159-8290.cd-18-0123.

Ritchie, M.E., Phipson, B., Wu, D., Hu, Y., Law, C.W., Shi, W. and Smyth, G.K. (2015). limma powers differential expression analyses for RNA-sequencing and microarray studies. *Nucleic Acids Research*, 43(7), pp.e47–e47. doi:https://doi.org/10.1093/nar/gkv007.

Rong, M.-H., Li, J.-D., Zhong, L.-Y., Huang, Y.-Z., Chen, J., Xie, L.-Y., Qin, R.-X., He, X.-L., Zhu, Z.-H., Huang, S.-N. and Zhou, X.-G. (2021). CCNB1 promotes the development of hepatocellular carcinoma by mediating DNA replication in the cell cycle. *Experimental Biology and Medicine*, p.153537022110491. doi:https://doi.org/10.1177/15353702211049149.

Ryan, D.P., Hong, T.S. and Bardeesy, N. (2014). Pancreatic adenocarcinoma. *The New England journal of medicine*, [online] 371(11), pp.1039–49. doi:https://doi.org/10.1056/NEJMra1404198.

Schek, N., Hall, B.L. and Finn, O.J. (1988). Increased glyceraldehyde-3-phosphate dehydrogenase gene expression in human pancreatic adenocarcinoma. *Cancer Research*, 48(22), pp.6354–9.

Scholzen, T. and Gerdes, J. (2000). The Ki-67 protein: From the known and the unknown. *Journal of Cellular Physiology*, [online] 182(3), pp.311–322. doi:https://doi.org/10.1002/(sici)1097-4652(200003)182:3%3C311::aid-jcp1%3E3.0.co;2-9.

Sekino, Y., Han, X., Kobayashi, G., Babasaki, T., Miyamoto, S., Kobatake, K., Kitano, H., Ikeda, K., Goto, K., Inoue, S., Hayashi, T., Teishima, J., Sakamoto, N., Sentani, K., Oue, N., Yasui, W. and Matsubara, A. (2021). BUB1B Overexpression Is an Independent Prognostic Marker and Associated with CD44, p53, and PD-L1 in Renal Cell Carcinoma. *Oncology*, 99(4), pp.240–250. doi:https://doi.org/10.1159/000512446.

Shannon, P. (2003). Cytoscape: A Software Environment for Integrated Models of Biomolecular Interaction Networks. *Genome Research*, [online] 13(11), pp.2498–2504. doi:https://doi.org/10.1101/gr.1239303.

Sharp, D.J., Rogers, G.C. and Scholey, J.M. (2000). Microtubule motors in mitosis. *Nature*, 407(6800), pp.41–47. doi:https://doi.org/10.1038/35024000.

Shen, C., Li, W. and Wang, Y. (2023). Research on the oncogenic role of the house-keeping gene GAPDH in human tumors. *Translational cancer research*, [online] 12(3), pp.525–535. doi:https://doi.org/10.21037/tcr-22-1972.

Sherif Abdelaziz Ibrahim, Gadalla, R., El-Ghonaimy, E.A., Omnia Samir, Mohamed, Hassan, H., Greve, B., El-Shinawi, M., Mona Mostafa Mohamed and Götte, M. (2017). Syndecan-1 is a novel molecular marker for triple negative inflammatory breast cancer and modulates the cancer stem cell phenotype via the IL-6/STAT3, Notch and EGFR signaling pathways. *Molecular Cancer*, 16(1). doi:https://doi.org/10.1186/s12943-017-0621-z.

Sherman, B.T., Hao, M., Qiu, J., Jiao, X., Baseler, M.W., Lane, H.C., Imamichi, T. and Chang, W. (2022). DAVID: a Web Server for Functional Enrichment Analysis and Functional Annotation of Gene Lists (2021 update). *Nucleic Acids Research*, 50 (W1). doi:https://doi.org/10.1093/nar/gkac194.

Shi, H., Xu, H., Chai, C., Qin, Z. and Zhou, W. (2022). Integrated bioinformatics analysis of potential biomarkers for pancreatic cancer. *Journal of Clinical Laboratory Analysis*. doi:https://doi.org/10.1002/jcla.24381.

Shi, L., Liu, B., Shen, D., Yan, P., Zhang, Y., Tian, Y., Hou, L., Jiang, G., Zhu, Y., Liang, Y., Liang, X., Shen, B., Yu, H., Zhang, Y., Wang, Y., Guo, X. and Cai, X. (2021). A tumor-suppressive circular RNA mediates uncanonical integrin degradation by the proteasome in liver cancer. *Science Advances*, 7(13). doi:https://doi.org/10.1126/sciadv.abe5043.

Shibata, O., Kamimura, K., Tanaka, Y., Ogawa, K., Owaki, T., Oda, C., Morita, S., Kimura, A., Abe, H., Ikarashi, S., Hayashi, K., Yokoo, T. and Terai, S. (2022). Establishment of a pancreatic cancer animal model using the pancreas-targeted hydrodynamic gene delivery method. *Molecular Therapy - Nucleic Acids*, 28, pp.342–352. doi:https://doi.org/10.1016/j.omtn.2022.03.019.

Shimoyama, S., Gansauge, F., Gansauge, S., Oohara, T. and Beger, H.G. (1995). Altered expression of extracellular matrix molecules and their receptors in chronic pancreatitis and pancreatic adenocarcinoma in comparison with normal pancreas. *International journal of pancreatology*, 18(3), pp.227–234. doi:https://doi.org/10.1007/bf02784946.

Shin, J.U., Lee, C.H., Lee, K.T., Lee, J.K., Lee, K.H., Kim, K.M., Kim, K.-M., Park, S.-M. and Rhee, J.C. (2012). Prognostic significance of ATM and cyclin B1 in pancreatic neuroendocrine tumor. *Tumor Biology*, 33(5), pp.1645–1651. doi:https://doi.org/10.1007/s13277-012-0420-5.

Singh, K., Pruski, M., Bland, R., Younes, M., Guha, S., Thosani, N., Maitra, A., Cash, B.D., McAllister, F., Logsdon, C.D., Chang, J.T. and Bailey-Lundberg, J.M. (2021). Kras mutation rate precisely orchestrates ductal derived pancreatic intraepithelial neoplasia and pancreatic cancer. *Laboratory Investigation*, [online] 101(2), pp.177–192. doi:https://doi.org/10.1038/s41374-020-00490-5.

Song, Y., Zhao, C., Dong, L., Fu, M., Xue, L., Huang, Z., Tong, T., Zhou, Z., Chen, A., Yang, Z., Lu, N. and Zhan, Q. (2007). Over-expression of cyclin B1 in human esophageal squamous cell carcinoma cells induces tumor cell invasive growth and metastasis. *Carcinogenesis*, 29(2), pp.307–315. doi:https://doi.org/10.1093/carcin/bgm269.

Szatmári, T., Mundt, F., Kumar-Singh, A., Möbus, L., Ötvös, R., Hjerpe, A. and Dobra, K. (2017). Molecular targets and signaling pathways regulated by nuclear translocation of syndecan-1. *BMC Cell Biology*, 18(1). doi:https://doi.org/10.1186/s12860-017-0150-z.

Szklarczyk, D., Franceschini, A., Wyder, S., Forslund, K., Heller, D., Huerta-Cepas, J., Simonovic, M., Roth, A., Santos, A., Tsafou, K.P., Kuhn, M., Bork, P., Jensen, L.J. and von Mering, C. (2015). STRING v10: protein-protein interaction networks, integrated over the tree of life. *Nucleic acids research*, [online] 43(Database issue), pp.D447-52. doi:https://doi.org/10.1093/nar/gku1003.

Szklarczyk, D., Gable, A.L., Lyon, D., Junge, A., Wyder, S., Huerta-Cepas, J., Simonovic, M., Doncheva, N.T., Morris, J.H., Bork, P., Jensen, L.J. and Mering, C. von (2019). STRING v11: protein–protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets. *Nucleic Acids Research*, 47(Database issue), pp.D607–D613. doi:https://doi.org/10.1093/nar/gky1131.

Tang, Z., Li, C., Kang, B., Gao, G., Li, C. and Zhang, Z. (2017). GEPIA: a web server for cancer and normal gene expression profiling and interactive analyses. *Nucleic Acids Research*, 45(W1), pp.W98–W102. doi:https://doi.org/10.1093/nar/gkx247.

Tian, Y., Ma, Z., Chen, Z., Li, M., Wu, Z., Hong, M., Wang, H., Svatek, R., Rodriguez, R. and Wang, Z. (2016). Clinicopathological and Prognostic Value of Ki-67 Expression in Bladder Cancer: A Systematic Review and Meta-Analysis. *PLOS ONE*, 11 (7), p.e0158891. doi:https://doi.org/10.1371/journal.pone.0158891.

Topalovski, M. and Brekken, R.A. (2016). Matrix control of pancreatic cancer: New insights into fibronectin signaling. *Cancer Letters*, [online] 381(1), pp.252–258. doi:https://doi.org/10.1016/j.canlet.2015.12.027.

Verhey, K.J. and Hammond, J.W. (2009). Traffic control: regulation of kinesin motors. *Nature reviews. Molecular cell biology*, [online] 10(11), pp.765–77. doi:https://doi.org/10.1038/nrm2782.

Visse, R. and Nagase, H. (2003). Matrix Metalloproteinases and Tissue Inhibitors of Metalloproteinases. *Circulation Research*, 92(8), pp.827–839. doi:https://doi.org/10.1161/01.res.0000070112.80711.3d.

Von Hoff, D.D., Ervin, T., Arena, F.P., Chiorean, E.G., Infante, J., Moore, M., Seay, T., Tjulandin, S.A., Ma, W.W., Saleh, M.N., Harris, M., Reni, M., Dowden, S., Laheru, D., Bahary, N., Ramanathan, R.K., Tabernero, J., Hidalgo, M., Goldstein, D. and Van Cutsem, E. (2013). Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *The New England journal of medicine*, [online] 369(18), pp.1691–703. doi:https://doi.org/10.1056/NEJMoa1304369.

Waltera, A., Schulz, D., Schaefer, N., Stoeckl, S., Pion, E., Haerteis, S., Reichert, T.E., Ettl, T. and Bauer, R.J. (2023). Opposing MMP-9 Expression in Mesenchymal Stromal Cells and Head and Neck Tumor Cells after Direct 2D and 3D Co-Culture. *International Journal of Molecular Sciences*, 24(2), p.1293. doi:https://doi.org/10.3390/ijms24021293.

Wang, B., Zhang, X., Li, C., Liu, N., Hu, M. and Gong, Z. (2021a). ANLN promotes carcinogenesis in oral cancer by regulating the PI3K/mTOR signaling pathway. *Head & Face Medicine*, 17(1). doi:https://doi.org/10.1186/s13005-021-00269-z.

Wang, G., Shen, W., Cui, L., Chen, W., Hu, X. and Fu, J. (2016). Overexpression of Anillin (ANLN) is correlated with colorectal cancer progression and poor prognosis. *Cancer Biomarkers*, 16(3), pp.459–465. doi:https://doi.org/10.3233/cbm-160585.

Wang, S., Wang, X., Wu, Z., Yang, Q., Xiong, H., Xiao, Y., Li, H. and Sun, Z. (2020). Overexpression of RRM2 is related to poor prognosis in oral squamous cell carcinoma. *Oral Diseases*, 27(2), pp.204–214. doi:https://doi.org/10.1111/odi.13540.

Wang, S., Zheng, Y., Yang, F., Zhu, L., Zhu, X.-Q., Wang, Z.-F., Wu, X.-L., Zhou, C.-H., Yan, J.-Y., Hu, B.-Y., Kong, B., Fu, D.-L., Bruns, C., Zhao, Y., Qin, L.-X. and Dong, Q.-Z. (2021b). The molecular biology of pancreatic adenocarcinoma: translational challenges and clinical perspectives. *Signal Transduction and Targeted Therapy*, 6(1). doi:https://doi.org/10.1038/s41392-021-00659-4.

Wang, Y., Schughart, K., Pelaia, T.M., Chew, T., Kim, K., Karvunidis, T., Knippenberg, B., Teoh, S., Phu, A.L., Short, K.R., Iredell, J., Thevarajan, I., Audsley, J., Macdonald, S., Burcham, J., Tang, B., McLean, A. and Shojaei, M. (2023). Pathway and Network Analyses Identify Growth Factor Signaling and MMP9 as Potential Mediators of Mitochondrial Dysfunction in Severe COVID-19. *International Journal of Molecular Sciences*, 24(3), p.2524. doi:https://doi.org/10.3390/ijms24032524.

Williams, G.L., Roberts, T.M. and Gjoerup, O.V. (2007). Bub1: Escapades in a Cellular World. *Cell Cycle*, 6(14), pp.1699–1704. doi:https://doi.org/10.4161/cc.6.14.4493.

Wu, L., Yin, L., Ma, L., Yang, J., Yang, F., Sun, B. and Nianzeng, X. (2022). Comprehensive bioinformatics analysis of ribonucleoside diphosphate reductase subunit M2(RRM2) gene correlates with prognosis and tumor immunotherapy in pancancer. *Aging*, [online] 14(19), pp.7890–7905. doi:https://doi.org/10.18632/aging.204315.

Wu, S., Liao, P., Yan, L., Zhao, Q., Xie, Z., Dong, J. and Sun, H. (2021a). Correlation of MKI67 with prognosis, immune infiltration, and T cell exhaustion in hepatocellular carcinoma. *BMC Gastroenterology*, 21(1). doi:https://doi.org/10.1186/s12876-021-01984-2.

Wu, T., Hu, E., Xu, S., Chen, M., Guo, P., Dai, Z., Feng, T., Zhou, L., Tang, W., Zhan, L., Fu, X., Liu, S., Bo, X. and Yu, G. (2021b). clusterProfiler 4.0: A universal enrichment tool for interpreting omics data. *The Innovation*, 2(3), p.100141. doi:https://doi.org/10.1016/j.xinn.2021.100141.

Xing, H., Wang, J., Wang, Y., Tong, M., Hu, H., Huang, C. and Li, D. (2018). Diagnostic Value of CA 19-9 and Carcinoembryonic Antigen for Pancreatic Cancer: A Meta-Analysis. *Gastroenterology Research and Practice*, 2018, pp.1–9. doi:https://doi.org/10.1155/2018/8704751.

Xiong, D., Zeng, C., Jiang, L., Luo, D. and Chen, G. (2019). Ki-67/MKI67 as a Predictive Biomarker for Clinical Outcome in Gastric Cancer Patients: an Updated Meta-analysis and Systematic Review involving 53 Studies and 7078 Patients. *Journal of Cancer*, 10(22), pp.5339–5354. doi:https://doi.org/10.7150/jca.30074.

Xu, Y., Wang, S., Xu, B., Lin, H., Zhan, N., Ren, J., Song, W., Han, R., Cheng, L., Zhang, M. and Zhang, X. (2023). AURKA, TOP2A and MELK are the key genes identified by WGCNA for the pathogenesis of lung adenocarcinoma. *Oncology Letters*, 25(6). doi:https://doi.org/10.3892/ol.2023.13824.

Yablecovitch, D., Ben-Horin, S., Picard, O., Yavzori, M., Fudim, E., Nadler, M., Levy, I., Sakhnini, E., Lang, A., Engel, T., Lahav, M., Saker, T., Neuman, S., Selinger, L., Dvir, R., Raitses-Gurevich, M., Golan, T. and Laish, I. (2022). Serum Syndecan-1: A Novel Biomarker for Pancreatic Ductal Adenocarcinoma. *Clinical and Translational Gastroenterology*, 13(5), p.e00473. doi:https://doi.org/10.14309/ctg.0000000000000473.

Yadav, S., Masud, M.K., Islam, Md.N., Gopalan, V., Lam, A.K., Tanaka, S., Nguyen, N.-T., Hossain, Md.S.A., Li, C., Yamauchi, Md.Y. and Shiddiky, M.J.A. (2017). Gold-loaded nanoporous iron oxide nanocubes: a novel dispersible capture agent for tumor-associated autoantibody analysis in serum. *Nanoscale*, 9(25), pp.8805–8814. doi:https://doi.org/10.1039/c7nr03006a.

Yang, J., Xu, R., Wang, C., Qiu, J., Ren, B. and You, L. (2021). Early screening and diagnosis strategies of pancreatic cancer: a comprehensive review. *Cancer Communications*, 41(12). doi:https://doi.org/10.1002/cac2.12204.

Yang, R.-Y., Rabinovich, G.A. and Liu, F.-T. (2008). Galectins: structure, function and therapeutic potential. *Expert Reviews in Molecular Medicine*, 10. doi:https://doi.org/10.1017/s1462399408000719.

Yang, Y., Li, S., Cao, J., Li, Y., Hu, H. and Wu, Z. (2019). RRM2 Regulated By LINC00667/miR-143-3p Signal Is Responsible For Non-Small Cell Lung Cancer Cell Progression. *OncoTargets and Therapy*, Volume 12, pp.9927–9939. doi:https://doi.org/10.2147/ott.s221339.

You, Q., Fang, T., Yin, X., Wang, Y., Yang, Y., Zhang, L. and Xue, Y. (2021). Serum CD4 Is Associated with the Infiltration of CD4+T Cells in the Tumor Microenvironment of Gastric Cancer. *Journal of Immunology Research*, 2021, pp.1–13. doi:https://doi.org/10.1155/2021/6539702.

Zahra Sahafnejad, Shahin Ramazi and Abdollah Allahverdi (2023). An Update of Epigenetic Drugs for the Treatment of Cancers and Brain Diseases: A Comprehensive Review. *Genes*, [online] 14(4), pp.873–873. doi:https://doi.org/10.3390/genes14040873.

Zeng, S., Yu, X., Ma, C., Song, R., Zhang, Z., Zi, X., Chen, X., Wang, Y., Yu, Y., Zhao, J., Wei, R., Sun, Y. and Xu, C. (2017). Transcriptome sequencing identifies ANLN as a promising prognostic biomarker in bladder urothelial carcinoma. *Scientific Reports*, 7(1). doi:https://doi.org/10.1038/s41598-017-02990-9.

Zeng, Y. and Fan, R. (2022). Identification and verification of CCNB1 as a potential prognostic biomarker by comprehensive analysis. *Scientific Reports*, [online] 12(1). doi:https://doi.org/10.1038/s41598-022-20615-8.

Zhang, C., Fang, Z., Xiong, Y., Li, J., Liu, L., Li, M., Zhang, W. and Wan, J. (2010). Copy number increase of aurora kinase A in colorectal cancers: a correlation with tumor progression. *Acta Biochimica et Biophysica Sinica*, 42(11), pp.834–838. doi:https://doi.org/10.1093/abbs/gmq088.

Zhang, H., Chen, G., Chen, S., Fu, Z., Zhou, H., Feng, Z., Mo, J., Li, C. and Liu, J. (2021). Overexpression of cyclin-dependent kinase 1 in esophageal squamous cell carcinoma and its clinical significance. *FEBS Open Bio*, 11(11), pp.3126–3141. doi:https://doi.org/10.1002/2211-5463.13306.

Zhang, X., Li, L., Huang, S., Liao, W., Li, J., Huang, Z., Huang, Y. and Lian, Y. (2022). Comprehensive Analysis of ANLN in Human Tumors: A Prognostic Biomarker Associated with Cancer Immunity. *Oxidative Medicine and Cellular Longevity*, 2022, pp.1–14. doi:https://doi.org/10.1155/2022/5322929.

Zhang, X.-X., Luo, J.-H. and Wu, L.-Q. (2022). FN1 overexpression is correlated with unfavorable prognosis and immune infiltrates in breast cancer. *Frontiers in Genetics*, 13. doi:https://doi.org/10.3389/fgene.2022.913659.

Zhou, L., Li, J., Zhao, Y.-P., Cui, Q.-C., Zhou, W.-X., Guo, J.-C., You, L., Wu, W.-M. and Zhang, T.-P. (2014). The prognostic value of Cyclin B1 in pancreatic cancer. *Medical Oncology*, 31(9). doi:https://doi.org/10.1007/s12032-014-0107-4.