

In Silico Gene Expression Profiling Maps the Drivers of Pan-Cancer Progression [†]

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Abstract

Clear cell renal cell carcinoma (ccRCC), hepatocellular carcinoma (HCC), lung adenocarcinoma (LUAD), and pancreatic ductal adenocarcinoma (PDAC) are highly lethal cancers that share molecular mechanisms underlying tumor progression, yet common biomarkers across these cancers remain largely unexplored. Microarray datasets for the four cancers were analyzed to identify differentially expressed genes (DEGs) using adjusted $p < 0.05$ and $|\log_2 FC| > 1$ as significance thresholds. Disease-associated gene targets were collected from CTD, DISEASES, and GeneCards databases. Shared genes were identified across cancers, and functional enrichment analysis revealed their involvement in key cancer-related pathways, particularly the cell cycle. Protein–protein interaction networks identified ten candidate hub biomarkers (*HGF*, *CDK1*, *CCNB1*, *RRM2*, *KIF14*, *DCN*, *SERPINE1*, *CCNA2*, *DLGAP5*, and *MAD2L1*) consistently dysregulated across all four cancers. Survival analysis supported their potential as therapeutic targets, correlating with poor prognosis. These findings highlight candidate pan-cancer biomarkers for improved diagnosis and therapy.

Keywords: pan-cancer; differential gene expression; prognostic biomarkers; clear cell renal cell carcinoma (ccRCC); hepatocellular carcinoma (HCC); lung adenocarcinoma (LUAD); pancreatic ductal adenocarcinoma (PDAC)

1. Introduction

Clear cell renal cell carcinoma (ccRCC), hepatocellular carcinoma (HCC), lung adenocarcinoma (LUAD), and pancreatic ductal adenocarcinoma (PDAC) are among the most aggressive and lethal malignancies worldwide. ccRCC, a kidney cancer subtype, is often diagnosed late with limited treatment options [1]. HCC, the predominant category of primary liver cancer, is strongly associated with chronic liver diseases and has a poorer prognosis due to high recurrence rates [2]. LUAD, the most common non-small cell lung cancer, causes a large proportion of lung cancer deaths [3]. PDAC, representing the majority of pancreatic cancers, is notorious for its late diagnosis and rapid disease progression, making it one of the deadliest cancers [4].

Though these are the cancers that originate in unique organs and may have tissue-specific features, it has recently been revealed that they have shared mechanisms on the molecular level related to the tumor development that are cell cycle pathway dysregulation, evasion of apoptosis, and changes in tumor microenvironment interactions. Understanding these shared molecular alterations can provide critical insights into universal oncogenic processes, which are often overlooked when cancers are studied in isolation [5–7].



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Recent studies have identified numerous biomarkers within individual cancers, improving diagnosis and prognosis. In ccRCC, immune-stromal scores, SERPINE1, and urine proteomics-derived markers have been validated for survival prediction and non-invasive diagnosis [8–10]. For HCC, novel biomarkers for early detection and immunotherapy responsiveness have been explored [11]. Similarly, in LUAD, *CHAF1B* and *DDX52* have been reported as promising prognostic biomarkers [12,13]. In PDAC, beyond the conventional CA19-9, multi-marker panels and *hENT1* have demonstrated enhanced diagnostic sensitivity and predictive value for therapeutic response [14,15].

Although previous studies have advanced the discovery of cancer-specific biomarkers, integrative analyses to uncover common molecular signatures across different cancers remain limited. Pan-cancer analysis is critical to systematically identify shared biomarkers and therapeutic targets, which could enable broad-spectrum diagnostic and treatment strategies and improve patient outcomes. In this study, we aimed to identify key candidate hub biomarkers that are consistently dysregulated in ccRCC, HCC, LUAD, and PDAC by integrative analytical approach that may guide novel pan-cancer therapies.

2. Methods

2.1. Expression Data Acquisition

The study utilized four publicly available Gene Expression Omnibus (GEO) microarray datasets (<http://www.ncbi.nlm.nih.gov/geo> (accessed on 28 July 2025)) all generated using the Affymetrix Human Genome U133 Plus 2.0 Array (GPL570) platform, thereby minimizing platform-related technical variability across datasets. ccRCC dataset GSE36895 included 29 tumor and 23 normal samples ($n = 52$). PDAC dataset GSE15471 contained 39 tumor and 39 normal samples ($n = 78$). HCC dataset GSE84402 included 14 tumor and 14 normal samples ($n = 28$), while LUAD dataset GSE118370 comprised 6 tumor and 6 normal samples ($n = 12$).

2.2. Pancancer's Differential Expression Analysis

Differential expression analysis for each cancer dataset was performed independently using GEO2R, an online interface based on the “limma” Bioconductor package. Samples were divided into tumor and normal groups, and $\log_2$ transformation was applied automatically by GEO2R when required. DEGs were identified using an adjusted $p < 0.05$ (false discovery rate-corrected) and $\log_2$ fold change $|\log_2 FC| > 1$. Significant genes were downloaded for downstream analysis.

2.3. Identification of Shared Gene Targets Across Cancer Types

To identify shared gene targets among all selected cancer types, three publicly available databases were utilized including the Comparative Toxicogenomics Database (CTD), DISEASES, and GeneCards. For each cancer, cancer-related gene targets were extracted from the databases. Venn diagram analysis was used to identify overlapping genes across the three databases, producing refined gene sets per cancer. A four-way Venn diagram was then applied to determine genes shared across all four cancers, identifying potential pan-cancer molecular targets.

2.4. Functional Enrichment Analysis

ShinyGO (<http://bioinformatics.sdstate.edu/go/> (accessed on 30 July 2025)) was used for functional enrichment analysis of two gene cohorts: overlapped disease-associated gene targets derived from public databases and consensus differentially expressed genes (DEGs) present in at least three cancers. Gene Ontology (GO), including Biological Process (BP),

Molecular Function (MF), and Cellular Component (CC), along with Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis, were performed.

2.5. Hub Gene Identification via PPI Network Analysis

Hub genes were identified by intersecting DEGs with disease-associated gene targets from CTD, DISEASES, and GeneCards. The overlapping genes were used to construct a protein–protein interaction (PPI) network using STRING (<https://string-db.org/>) (accessed on 1 August 2025). The network was imported into Cytoscape (version 3.10.3) and analyzed with the CytoHubba plugin. Using the Degree algorithm, the top 10 hub genes with the highest interaction scores were selected.

2.6. Prognostic Validation Using KM Plotter

The prognostic value of the found hub genes was assessed using the Kaplan–Meier online tool (<http://kmplot.com>). The Pan-Cancer mRNA RNA-seq module was selected, and the previously identified 10 hub genes were input individually for survival analysis. For this study, four cancer types were specifically selected, including “Kidney renal clear cell carcinoma”, “Lung adenocarcinoma”, “Pancreatic ductal adenocarcinoma”, and “Liver hepatocellular carcinoma”. The detailed workflow diagram is shown in Figure 1.

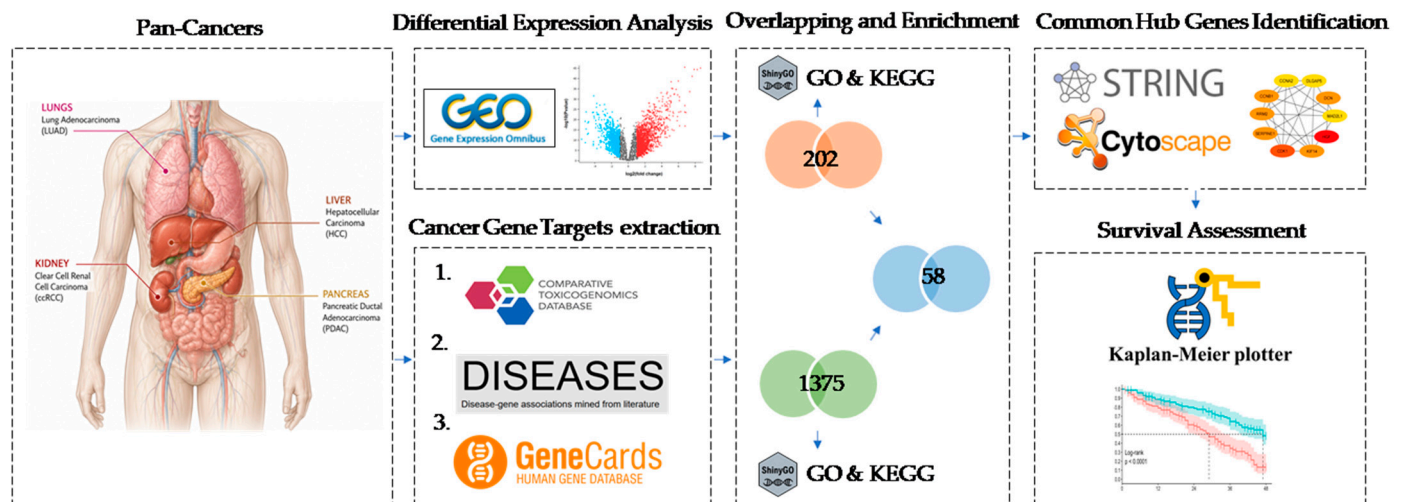


Figure 1. Graphical overview of the integrated cross-cancer biomarker discovery pipeline. In the overlapping and enrichment module, orange color represents consensus DEGs commonly dysregulated across three or more cancer types, while green represents the consolidated set of unique gene targets across cancers, whereas blue indicates the intersection of both groups.

3. Results and Discussion

3.1. Pan-Cancer Differentially Expressed Genes

Differential expression analysis was performed using GEO2R across four cancer types. In ccRCC, a total of 3540 genes were identified as differentially expressed out of 51,135 probes. Similarly, 1671 DEGs were identified in HCC (out of 52,978), 1447 DEGs in LUAD (out of 53,228), and 2654 DEGs in PDAC (out of 52,021), based on comparisons between tumor and normal tissue samples. The distribution of DEGs in each cancer type is visualized through volcano plots (Figure 2a–d). Subsequently, the DEGs from all four cancers were overlapped, resulting in a total of 202 genes that were commonly dysregulated across three or more cancer types, as illustrated in the Venn diagram (Figure 2f).

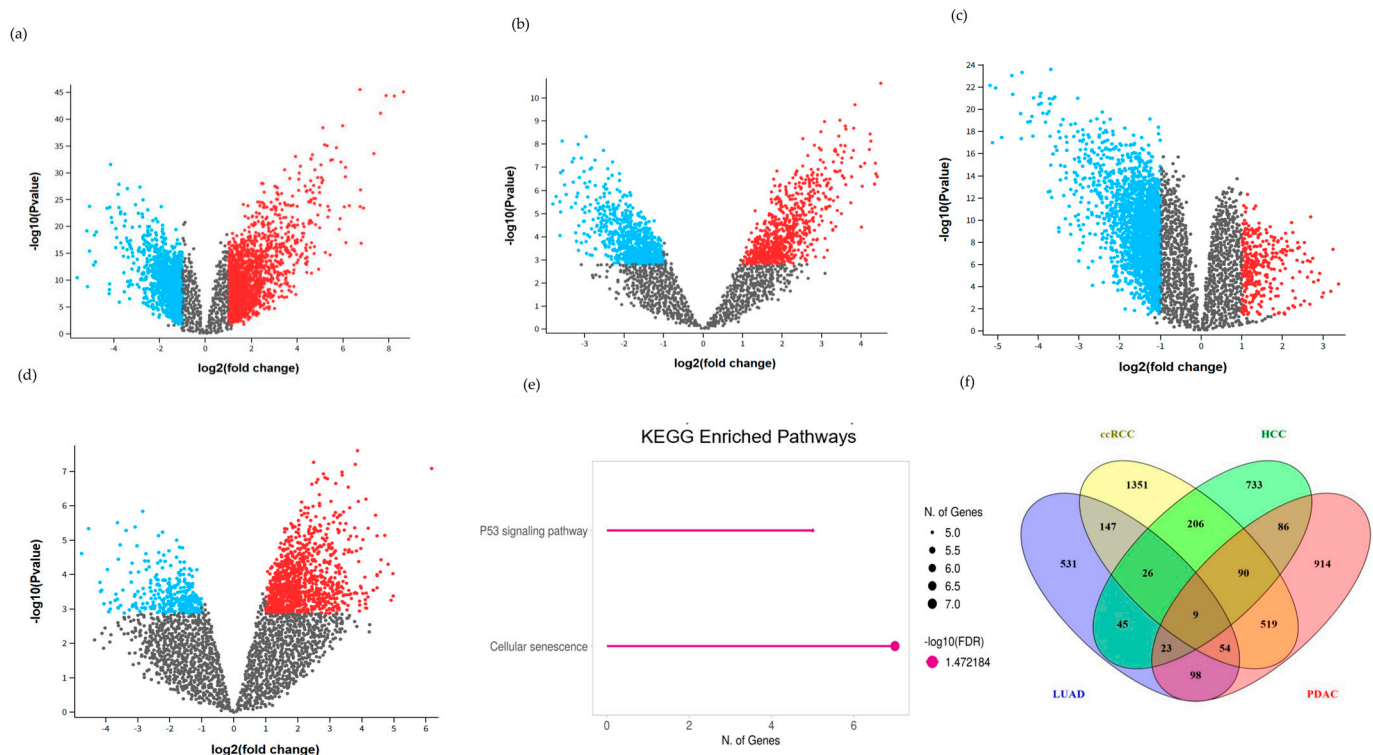


Figure 2. Volcano plots illustrating significantly upregulated and downregulated genes across four cancer types: (a) ccRCC, (b) HCC, (c) PDAC, and (d) LUAD. In the volcano plots, Red, blue, and gray represent upregulated, downregulated, and non-significant genes, respectively. (e) KEGG pathway enrichment analysis of common DEGs. (f) Venn diagram depicting the overlap of DEGs among the four cancer types.

3.2. Compilation of Target Genes from Public Databases

To compile disease-associated gene targets, data were retrieved from three public databases: CTD, DISEASES, and GeneCards. For each cancer type, gene targets obtained from these databases were overlapped to identify common targets. The Venn diagram analysis for ccRCC is shown in Figure 3a, while overlaps for HCC, LUAD, and PDAC are illustrated in Figure 3b–d, respectively. This integrative approach yielded a consolidated set of 1375 unique gene targets (Figure 3f).

3.3. Gene Ontology and KEGG Expressed Pathways

The 202 genes obtained from DEG analysis and 1375 unique gene targets obtained from public databases were subjected to GO and KEGG pathway analysis. The GO terms of DEG-derived genes were analyzed for BP, MF, and CC. The details of these GO terms are shown in Figure 4a. Furthermore, the GO term summary for the unique genes from public databases is presented in Figure 4b.

KEGG pathway analysis revealed that DEGs were predominantly enriched in critical tumorigenic pathways, including the p53 signaling pathway and cellular senescence (Figure 2e), indicating their involvement in cancer progression and cellular stress responses. Furthermore, the unique gene targets from public databases were significantly enriched in cancer-related pathways, demonstrating the functional significance of these genes (Figure 3e).

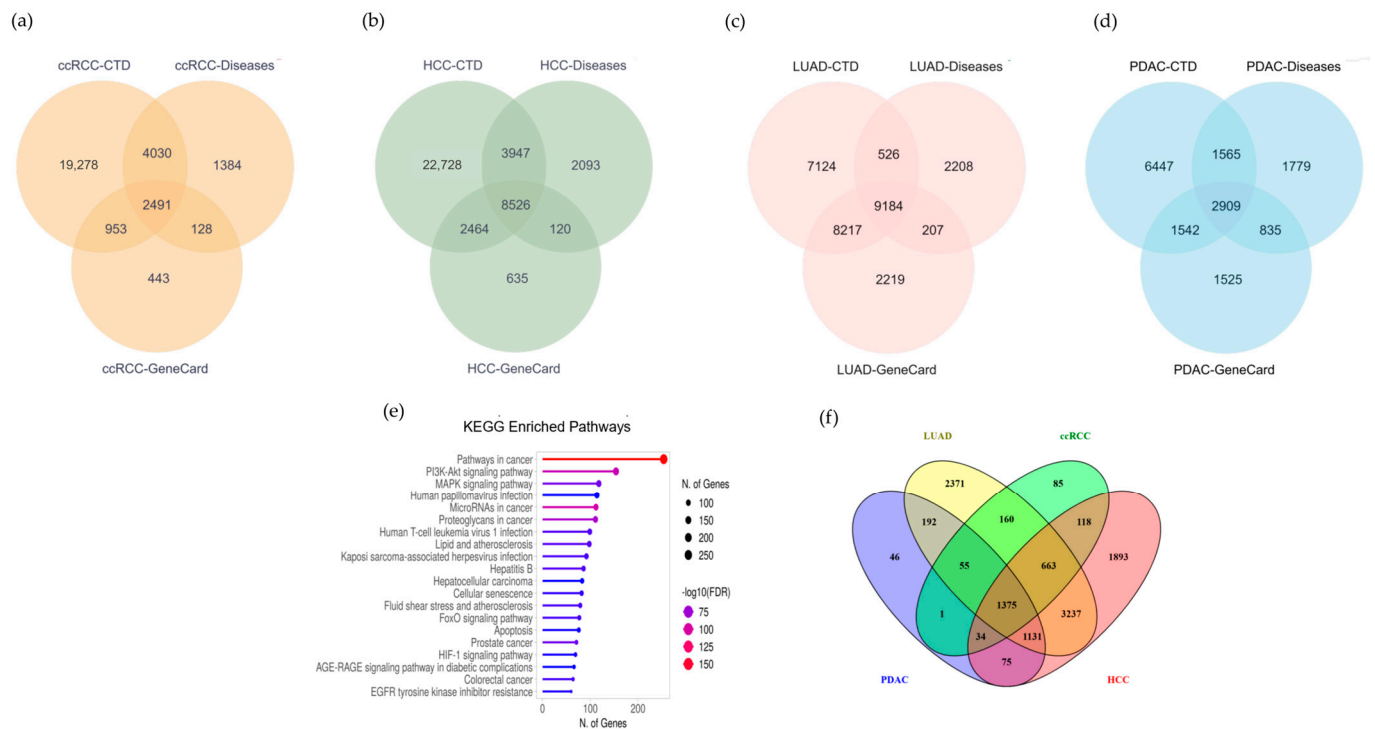


Figure 3. Common gene targets identified from public databases across different cancers: (a) ccRCC, (b) HCC, (c) LUAD, and (d) PDAC. (e) KEGG pathway enrichment of overlapping gene targets obtained from databases. (f) Venn diagram representing shared gene targets among ccRCC, HCC, LUAD, and PDAC.

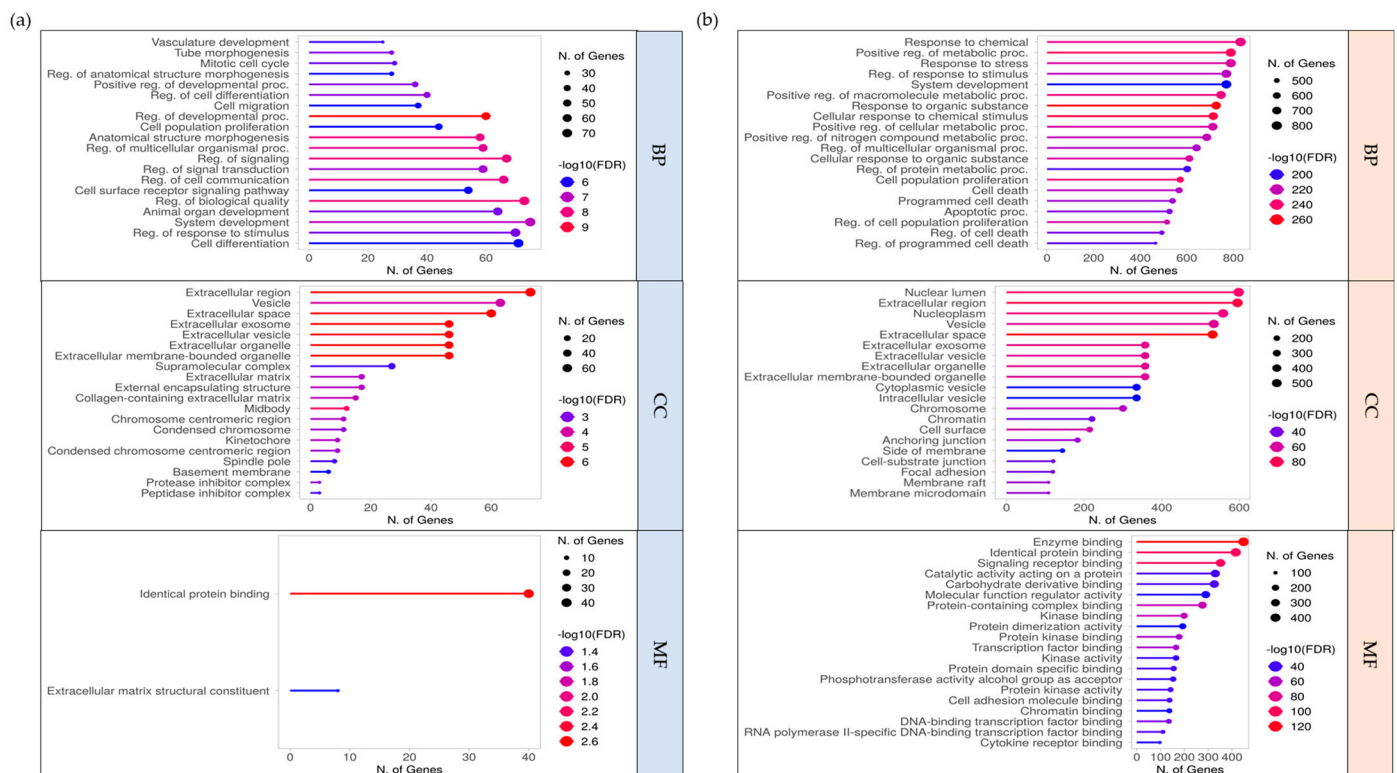


Figure 4. (a) Gene Ontology (GO) enrichment of unique DEGs across Biological Process (BP), Cellular Component (CC), and Molecular Function (MF). (b) GO enrichment of unique gene targets retrieved from public databases across the four cancer types.

3.4. Hub Biomarker Identification via PPI

For the identification of hub biomarkers common across the four selected cancers, reflecting an integrative molecular mechanism, the 202 DEGs were overlapped with the 1375 gene targets obtained from public databases, resulting in a refined set of 58 key genes. These genes were further subjected to PPI network construction using the STRING database, and the interaction data were visualized in Cytoscape. The CytoHubba plugin was employed to identify central hub genes based on the degree topological method. As a result, 10 hub genes were identified, including *HGF*, *CDK1*, *CCNB1*, *RRM2*, *KIF14*, *DCN*, *SERPINE1*, *CCNA2*, *DLGAP5*, and *MAD2L1*. These genes are considered potential key regulators within shared oncogenic pathways across multiple cancer types. The PPI network of hub genes is illustrated in Figure 5.

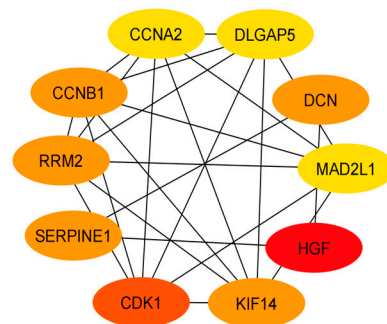


Figure 5. Protein–protein interaction (PPI) network of the top ten hub genes constructed using Cytoscape, highlighting key molecular interactions shared among ccRCC, HCC, LUAD, and PDAC.

3.5. Overall Survival Analysis of Hub Genes

The 10 hub genes were analyzed through KM plotter to assess their prognostic association with OS. The hazard ratios (HRs) and corresponding *p*-values are summarized in Table 1. Among these, *CDK1*, *CCNB1*, *RRM2*, *KIF14*, *CCNA2*, *DLGAP5*, and *MAD2L1* exhibited a strong association with poor prognosis ($HR > 2$, $p < 0.001$) across most cancer types, indicating their potential role as unfavorable prognostic biomarkers. For example, *CDK1* showed HR values of 2.24 ($p = 5.20 \times 10^{-8}$) in ccRCC, 2.17 ($p = 1.20 \times 10^{-5}$) in HCC, 2.65 ($p = 4.10 \times 10^{-6}$) in PDAC, and 1.94 ($p = 7.80 \times 10^{-6}$) in LUAD. Similarly, *RRM2* was significantly correlated with worse survival outcomes in all four cancers, with HR values exceeding 2.0 and highly significant *p*-values.

Table 1. Overall survival analysis of hub genes across pan-cancers.

Genes	Overall Survival							
	ccRCC		HCC		PDAC		LUAD	
	HR	<i>p</i> -Value	HR	<i>p</i> -Value	HR	<i>p</i> -Value	HR	<i>p</i> -Value
<i>HGF</i>	1.47	2.00×10^{-2}	0.78	1.80×10^{-1}	0.79	3.20×10^{-1}	0.49	3.20×10^{-4}
<i>CDK1</i>	2.24	5.20×10^{-8}	2.17	1.20×10^{-5}	2.65	4.10×10^{-6}	1.94	7.80×10^{-6}
<i>CCNB1</i>	2.21	2.30×10^{-7}	2.42	3.90×10^{-7}	1.89	2.50×10^{-3}	1.85	1.10×10^{-4}
<i>RRM2</i>	2.28	3.40×10^{-8}	2.13	2.80×10^{-5}	2.17	1.60×10^{-4}	2.04	1.20×10^{-6}
<i>KIF14</i>	2.32	3.30×10^{-8}	1.76	1.30×10^{-3}	2.43	2.50×10^{-5}	2.02	6.20×10^{-6}
<i>DCN</i>	1.48	1.10×10^{-2}	0.65	2.80×10^{-2}	1.33	1.80×10^{-1}	0.66	1.30×10^{-2}
<i>SERPINE1</i>	1.58	4.10×10^{-3}	1.61	8.80×10^{-3}	1.87	2.90×10^{-3}	1.59	2.80×10^{-3}
<i>CCNA2</i>	2.51	7.90×10^{-10}	1.96	1.10×10^{-4}	2.50	2.30×10^{-5}	1.86	3.00×10^{-5}
<i>DLGAP5</i>	2.42	4.60×10^{-9}	2.27	1.80×10^{-6}	2.56	9.90×10^{-6}	1.98	3.40×10^{-5}
<i>MAD2 L1</i>	1.71	7.70×10^{-4}	2.10	6.20×10^{-5}	1.88	2.60×10^{-3}	1.79	8.80×10^{-5}

On the other hand, *HGF* and *DCN* displayed variable prognostic impacts. *HGF* showed a significant association with poor prognosis in ccRCC (HR = 1.47, $p = 0.02$) and LUAD (HR = 0.49, $p = 0.00032$), while *DCN* demonstrated a protective effect in HCC (HR = 0.65, $p = 0.028$) and LUAD (HR = 0.66, $p = 0.013$).

3.6. Systematic Evidence of Hub Gene Involvement in Cancer Progression and Clinical Outcomes

Across ccRCC, HCC, LUAD, and PDAC, the ten identified hub genes demonstrate strong prognostic relevance, supporting their role as pan-cancer biomarkers. *CDK1* has been widely reported as a key prognostic and immunological marker associated with poor overall survival and tumor progression across multiple cancers, including the selected types [16,17].

Similarly, *CCNB1* is consistently associated with poor prognosis and aggressive tumor behavior in diverse malignancies [18,19]. *CCNA2*, *DLGAP5*, and *MAD2L1* are frequently co-regulated with *CDK1* and *CCNB1* and contribute to cell cycle dysregulation and chromosomal instability, leading to unfavorable clinical outcomes [20–22].

Finally, *RRM2*, *KIF14*, *SERPINE1*, *HGF*, and *DCN* have been individually reported as prognostic biomarkers across multiple cancers, supporting their role in tumor progression [9,23–26].

In our KM analysis, *CDK1*, *CCNB1*, *CCNA2*, *RRM2*, *KIF14*, *DLGAP5*, *CCNA2*, and *MAD2L1* consistently correlated with poorer overall survival (HR > 2; $p < 0.001$) across at least three cancers. Meanwhile, *HGF* and *DCN* exhibited variable prognostic effects, ranging from risk factors to protective biomarkers for our selected cancers. Collectively, these ten genes constitute a compelling set of shared oncogenic drivers and prognostic biomarkers across multiple malignancies, as supported by functional enrichment analyses, survival outcomes, and corroborative literature evidence. The findings support their potential as universal biomarkers for prognosis and merit further investigation as targets for pan-cancer therapeutic strategies.

4. Conclusions

This study identified ten driver genes (*HGF*, *CDK1*, *CCNB1*, *RRM2*, *KIF14*, *DCN*, *SERPINE1*, *CCNA2*, *DLGAP5*, and *MAD2L1*) as shared oncogenic drivers and prognostic biomarkers across ccRCC, HCC, LUAD, and PDAC. Integrating DEGs, functional enrichment, PPI networks, and survival analysis, these genes were shown to play key roles in cancer progression, particularly in cell cycle and tumor-related pathways.

Several genes were strongly associated with poor survival, highlighting their potential as universal biomarkers and therapeutic targets in pan-cancer contexts. Further experimental validation is recommended to confirm their clinical relevance.

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Abbreviations

The following abbreviations are used in this manuscript:

ccRCC	Clear Cell Renal Cell Carcinoma
HCC	Hepatocellular Carcinoma
LUAD	Lung Adenocarcinoma
PDAC	Pancreatic Ductal Adenocarcinoma
DEGs	Differentially Expressed Genes
GEO	Gene Expression Omnibus
CTD	Comparative Toxicogenomics Database
BP	Biological Process
MF	Molecular Function
CC	Cellular Component
KEGG	Kyoto Encyclopedia of Genes and Genomes
PPI	Protein–Protein Interaction
KM	Kaplan–Meier
HR	Hazard Ratio
OS	Overall Survival
logFC	Log Fold Change

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