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Key targets and mechanistic insights affecting radiotherapy effectiveness in renal carcinoma patients with concurrent renal failure

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► ***Original article***

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ABSTRACT

Background: To explore the key targets and regulatory mechanisms affecting the efficacy of radiotherapy (RT) in patients with renal carcinoma (RCC) complicated by renal failure. ***Materials and Methods:*** Differentially expressed genes (DEGs) (|log2FC|>2) in TCGA (n=537) and GEO data set (n=215) were screened by limma package in R software. Intersecting genes were accessed through the online site (InteractiVenn). The STRING and MCODE module of the Metascape website were used for key target screening and enriched pathway analysis. The preprocessCore R package was used for data normalization and batch effect processing. The survival/survminer R package was used to analyze the relationship between gene expression and patient survival. ***Results:*** High expression of ACADM, DLAT, SUCLA2 and SUCLG2 genes were all associated with significantly improved prognosis in renal cancer patients. The mOS time in the ACADM high expression group was 7.10 years [Hazard Ratio (HR) = 0.466, 95% Confidence Interval (CI): 0.353-0.615). The mOS time in the DLAT high expression group was 7.10 years (HR=0.489, 95% CI: 0.372-0.642). The mOS time in the SUCLA2 high expression group was 7.30 years (HR=0.458, 95% CI: 0.346-0.606). The mOS time in the SUCLG2 group was 7.00 years (HR=0.544, 95% CI: 0.415-0.715). ***Conclusion:*** The suppression of ACADM, DLAT, SUCLA2, and SUCLG2 can regulate fatty acid metabolism and tricarboxylic acid cycle-related pathways, which provides ideas for the prognosis of patients with RCC complicated by renal failure.

INTRODUCTION

Renal carcinoma (RCC) ranks among the most prevalent malignancies affecting the urinary system. There were 431,288 new cases of RCC and 179,368 deaths in 2020 in the whole world [1, 2]. According to pathological features, RCC is primarily divided into clear cell renal cell carcinoma (ccRCC) and non-clear cell renal cell carcinoma (nccRCC), with a higher proportion of ccRCC patients. The spread of awareness of medical checkups and advances in testing technology have reduced the mortality rate of RCC patients, but the treatment outcome is not as good as expected [3]. Heterogeneity and drug resistance result in objective remission rates of less than 40% in patients with advanced ccRCC treated with standard regimens [4, 5]. There is a complex bidirectional association between renal failure and RCC [6]. On the one hand, researchers believe that the high risk of RCC in patients with renal failure may be related to the long-term inflammatory microenvironment of the body, while metabolic disorders [7] and immune function inhibition leading to cell damage, DNA mutation and accumulation of toxic substances should not be ignored [8, 9]. On the other hand, RCC patients who have received clinical treatment are prone to show compensatory hypertrophy of renal units and overload of renal function, which can trigger the deterioration of renal function to form a "tumor-renal failure" cycle [10, 11]. Clinical evidence in patients with RCC complicated by renal failure is limited, and the key targets and mechanisms of onset of action that influence the prognosis of this group are currently unclear [12]. Surgery is the main treatment modality for kidney cancer patients, and non-surgical treatment modalities such as stereotactic body radiation therapy (SBRT) are also clinical options [13]. The combination of radiotherapy and immunotherapy has emerged as a research frontier, as radiotherapy modulates the tumor microenvironment to enhance immune cell recruitment and activation, synergizing with immune checkpoint inhibitors [14]. Clinical trials report promising disease control in metastatic RCC with combined radiotherapy and immunotherapy [15]. Furthermore, radiotherapy demonstrates efficacy in surgically ineligible locally advanced RCC, where SBRT achieves robust local control with minimal

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toxicity [16], and may be combined with tyrosine kinase inhibitors (TKIs) to amplify therapeutic outcomes [17]. However, renal failure patients with impaired kidney function often exhibit heightened oxidative stress, compromised DNA repair capacity, and dysregulated immune microenvironments, potentially exacerbating radiotherapy toxicities such as radiation nephritis or myelosuppression [18, 19]. Current clinical guidelines lack specific radiotherapy recommendations for this high-risk cohort, and systematic investigations into shared molecular targets between renal carcinoma radiotherapy resistance and renal failure progression remain absent, severely hindering the development of precision therapeutic strategies.

In this study, we integrated the transcriptomic data from TCGA and GEO databases to identify for the first time the prognostic targets affecting radiotherapy in patients with RCC and renal failure. These targets may become a "molecular bridge" connecting the resistance to RT in RCC and the progression of renal failure, providing a basis for optimizing the RT regimen for patients with renal failure combined with RCC and a new perspective for translational medicine.

MATERIALS AND METHODS

TCGA data selection

Transcriptomic data and clinical information for renal carcinoma samples were retrieved fromTCGA database (https://portal.gdc.cancer.gov). Gene expression data in transcripts per million (TPM) format were extracted and normalized using log2 (TPM + 1) transformation [20]. Samples with complete RNA sequencing (RNA-seq) data and clinical annotations were included for subsequent analyses.

GEO dataset processing

Data from the GEO database were downloaded in MINiML format.For datasets lacking normalization, log2 transformation was uniformly applied. Datasets lacking normalization were standardized using the normalize.quantiles function from the preprocess Core package in R/Bioconductor (http://www.bioconductor.org/packages/3.0/bioc/html/preprocessCore.html). Probes associated with multiple genes were excluded using platform annotation files, and the expression values for genes with multiple probes were averaged. The removeBatchEffect function from the limma package in R was utilized to correct batch effects [21].

Differential gene expression analysis

were identified using the limma package (v3.40.2) in R.Adjusted P-values were calculated to control false discovery rates (FDR) in TCGA and GTEx datasets. DEGs were identified by a |log2(fold change)| greater than 2 and an adjusted P-value less than 0.05. Gene expression heatmaps were created using the pheatmap package (v1.0.12) [22]. For visualization, genes with variance > 0.1 were prioritized. If the number of candidate genes exceeded 1,000, the top 25% of genes with the highest variance were selected.Statistical analyses were conducted using R (v4.0.3), with significance set at $P<0.05$.

Identification of overlapping DEGs

DEG lists from renal carcinoma and renal failure cohorts were imported into the InteractiVenn web tool (http://www.interactivenn.net/) to identify overlapping genes through interactive multi-set visualization. Overlapping genes were strictly validated by matching both gene symbols and Ensembl IDs to exclude false positives caused by annotation discrepancies.

STRING/Metascape functional analysis

PPI and functional annotations were developed using the STRING database (https://cn.string-db.org/) with high-confidence interactions (score ≥ 0.7). Core functional modules were identified using the MCODE algorithm with a score threshold of 3 or higher, and enriched pathways were determined with a false discovery rate (FDR) below 0.05. Pathway and process enrichment analyses were conducted using Metascape (https://metascape.org/gp/index.html) with the Gene Prioritization by Evidence Counting (GPEC) method. The parameters were set to a minimum overlap of 3, a P-value cutoff of 0.01, and a minimum enrichment of 1.5.

Survival analysis

Genes with high centrality scores in PPI networks were subjected to survival analysis in renal carcinoma patients. The log-rank test ($P < 0.05$) was used to evaluate survival differences between groups.Calculated hazard ratios (HRs) with 95% confidence intervals (CIs) and median survival times (years). The analyses utilized the survival and survminer packages (v4.0.3) in R [23].

RESULTS

DEGs in TCGA renal carcinoma radiotherapy cohort

Analysis of 26 radiotherapy-treated renal carcinoma samples and 128 adjacent normal tissues from TCGA identified 993 upregulated and 1,650 downregulated DEGs. Notably, genes such as *TMEM213, KCNJ1,* and *KNG1* exhibited significant expression changes in renal failure samples, suggesting their potential roles in renal pathology (figure 1A).

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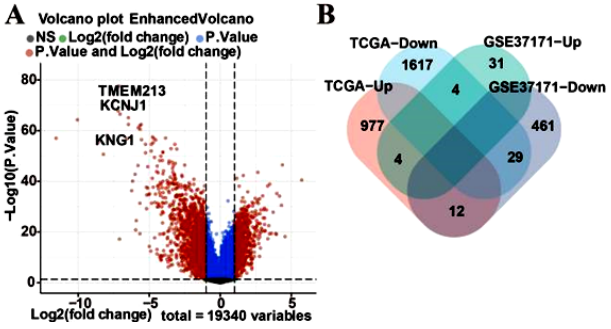

Figure 1. presents an intersection analysis of differentially expressed genes associated with RCC and renal failure (**A,** Volcano plot; **B,** Intersection of differentially expressed genes for RCC and renal failure).

Functional enrichment of TCGA radiotherapy-related DEGs

Gene Ontology (GO) enrichment analysis of TCGA radiotherapy-related differentially expressed genes (DEGs) indicated that upregulated genes were significantly linked to biological processes such as T-cell activation, leukocyte proliferation, and regulation of cell-cell adhesion. Molecular functions (MF) enriched cytokine binding, carbohydrate binding, and immune receptor activity. Cellular component (CC) analysis highlighted chromosomal centromeric regions, endoplasmic reticulum lumen, and secretory granule membranes. The top three pathways in terms of significance were shown in figure 2A. KEGG pathway analysis revealed that upregulated genes were enriched in the phagosome, cytokine-cytokine receptor interaction, and NF-κB signaling pathways. The more significant pathways were shown in figure 2B. Downregulated genes were linked to organic acid catabolism, kidney development, and sodium ion homeostasis, transmembrane transporter activity and mitochondrial matrix. The top three pathways in terms of significance were shown in figure 2C. KEGG pathways for downregulated genes included valine, leucine, and isoleucine degradation, carbon metabolism, and PPAR signaling. The more significant pathways were shown in figure 2D.

GEO renal failure DEGs

Analysis of dataset GSE37171 (GPL570 platform, 75 renal failures vs. 40 normal samples) identified 39 upregulated and 502 downregulated DEGs [24].

Overlapping DEGs between renal carcinoma and renal failure

Intersection analysis revealed 4 upregulated (*ZNF205, PLEKHN1, S100A8, and VWCE*) and 29 downregulated genes (*ACAD8, SUCLG2, BEX4, DLAT, PRMT6, TSPYL4, FOS, AK3, SGPP1, GPRASP1, CIPC, NR1D2, TBC1D4, SUCLA2, AMIGO2, ACADM, BLNK, MICU2, ARHGEF3, SGMS1, ATP6V1A, PTGER4, UBL3, GCH1, SACM1L, HLTF, KLHL2 and MAN1A1*) shared between renal carcinoma radiotherapy and renal failure cohorts (figure 1B).

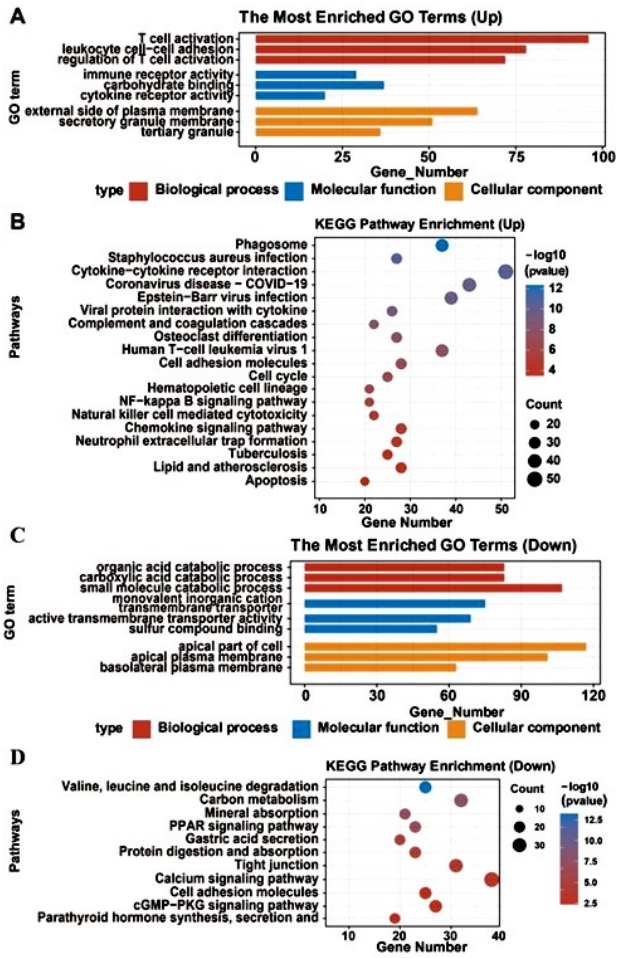

Figure 2. presents the functional and pathway enrichment analysis of genes differentially expressed due to RT in RCC. (**A,** GO analysis of up-regulated genes; B, KEGG analysis of up-regulated genes; **C,** GO analysis of down-regulated genes; **D,** KEGG analysis of down-regulated genes).

Core gene identification

STRINGanalysis identified ACADM, DLAT, SUCLA2, and SUCLG2 as hub genes with high node degrees (figure 3, table 1). These genes were prioritized as core regulators influencing radiotherapy outcomes in renal carcinoma patients with renal failure.

Table 1. Core genes identified via STRING database.

Node	Identifier	Node Degree
ACADM	9606.ENSP00000359871	3
DLAT	9606.ENSP00000280346	4
SUCLA2	9606.ENSP00000494360	4
SUCLG2	9606.ENSP00000419325	3

Note: Acyl-CoA Dehydrogenase Medium Chain, ACADM; Dihydrolipoamide S-Acetyltransferase, DLAT; Succinate-CoA Ligase ADP-Forming Subunit Beta, SUCLA2; Succinate-CoA Ligase GDP-Forming Subunit Beta, SUCLG2.

Pathway enrichment of core genes

GO-MF analysis enriched ligase activity, GTP binding, and calcium ion binding. GO-BP highlighted tricarboxylic acid (TCA) cycle, response

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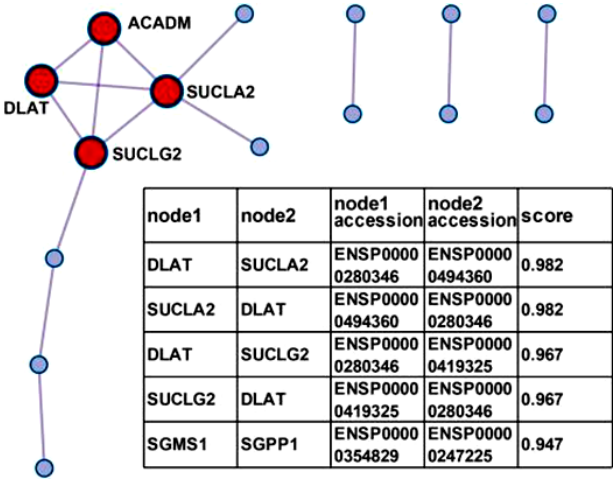
to lipopolysaccharide, and lipid modification. GO-CC terms included mitochondrial matrix and Golgi membrane. KEGG pathways showed significant enrichment in citrate cycle (TCA cycle) and metabolic pathways (table 2).



node1	node2	node1 accession	node2 accession	score
DLAT	SUCLA2	ENSP00000 0280346	ENSP00000 0494360	0.982
SUCLA2	DLAT	ENSP00000 0494360	ENSP00000 0280346	0.982
DLAT	SUCLG2	ENSP00000 0280346	ENSP00000 0419325	0.967
SUCLG2	DLAT	ENSP00000 0419325	ENSP00000 0280346	0.967
SGMS1	SGPP1	ENSP00000 0354829	ENSP00000 0247225	0.947

Figure 3. Core gene selection based on string database.

Table 2. Enriched pathways of core genes.

Category	Term ID	Description	LogP
GO-MF	GO:0016874	Ligase activity	-6.068
	GO:0005525	GTP binding	-3.198
	GO:0005509	Calcium ion binding	-2.259
GO-BP	GO:0006099	Tricarboxylic acid cycle	-6.234
	GO:0032496	Response to lipopolysaccharide	-3.311
	GO:0030258	Lipid modification	-3.099
	GO:0005975	Carbohydrate metabolic process	-2.872
	GO:0070482	Response to oxygen levels	-2.200
GO-CC	GO:0005759	Mitochondrial matrix	-4.730
	GO:0000139	Golgi membrane	-2.180
KEGG	hsa00020	Citrate cycle (TCA cycle)	-5.329
	hsa01100	Metabolic pathways	-3.257

Note: GO, Ontology; MF, Molecular Function; BP, Biological Process; CC, Cellular Component; KEGG, Kyoto Encyclopedia of Genes and Genomes; TCA, Tricarboxylic Acid cycle.

Prognostic significance of core genes

Survival analysis demonstrated that high expression of *ACADM* (median survival: 7.1 years; HR = 0.466, 95% CI: 0.353–0.615; P < 0.05; figure 4A), *DLAT* (HR = 0.489, 95% CI: 0.372–0.642; P < 0.05; figure 4B), *SUCLA2* (median survival: 7.3 years; HR = 0.458, 95% CI: 0.346–0.606; P < 0.05; figure 4C), and *SUCLG2* (median survival: 7.0 years; HR = 0.544, 95% CI: 0.415–0.715; P < 0.05; figure 4D) correlated with improved overall survival in renal carcinoma patients.

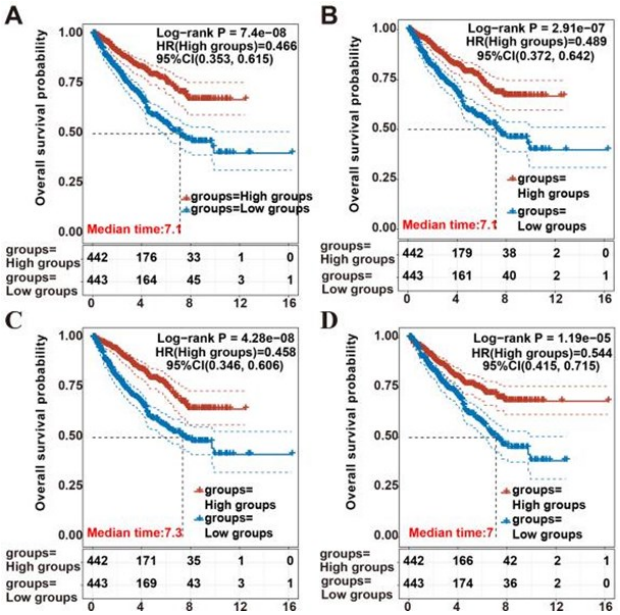


Figure 4. Survival analysis of ACADM, DLAT, SUCLA2, and SUCLG2 in TCGA RCC cohort (A, ACADM; B, DLAT; C, SUCLA2; D, SUCLG2).

DISCUSSION

We analyzed RT data from public databases of patients with RCC complicated by renal failure, and found that *ACADM, DLAT, SUCLA2 and SUCLG2* may affect patient prognosis by regulating the mitochondrial tricarboxylic acid cycle (TCA cycle) and energy metabolic pathways. Cancer patients with renal insufficiency may face higher toxicity and cardiovascular risks when receiving treatment, but individualized treatment strategies may help to reduce renal damage. Nouhaud *et al.* [25] concluded that patients with renal insufficiency may face a higher risk of toxicity when receiving tumor therapy, which in turn affects the tolerability and efficacy of the treatment. Zhang *et al.* [26] showed that patients with poorer renal function may be at a higher risk of cardiovascular events after receiving tumor therapy, and that certain radiotherapy techniques are able to reduce the risk of further renal damage. However, Ohno *et al.* [6, 27] suggested that in some cases surgery or targeted therapy could avoid the phenomenon of RT-induced deterioration of renal function. We believe that screening of key prognostic genes for RT in patients with RCC combined with renal failure

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would be beneficial to provide more clinical options.

Our results suggest the idea that ACADM and SUCLA2 may be targets that influence the prognosis of patients with RCC combined with renal failure. Ducasa *et al*. [28-30] concurred with our view, which may be due to the fact that deletion of ACADM and SUCLA2 can lead to the accumulation of lipotoxic metabolites (e.g., ceramides) in the mitochondria, which induces mitochondrial membrane potential collapse and ROS overproduction, which ultimately activates apoptotic signaling in renal tubular epithelial cells. In addition, Sukonina *et al*. [31] also suggested that DLAT may affect survival in patients with renal disease, which is related to the fact that low expression of DLAT may weaken renal antioxidant defenses by inhibiting pyruvate dehydrogenase activity and reducing NADH production. Together, the above mechanisms lead to renal tubular energy metabolism failure and interstitial fibrosis, which may be an important molecular basis for renal failure after radiotherapy in renal cancer patients. Our results showed that these four genes were significantly under-expressed in both the renal cancer radiotherapy group and the renal failure group, suggesting that the inhibition of their expression may drive both acidification of the tumor microenvironment and renal tubulointerstitial fibrosis, and serve as a key molecular hub linking renal cancer progression and renal failure.

The ACADM gene encodes medium chain acyl coenzyme A dehydrogenase (MCAD), whose deficiency is one of the most common mitochondrial fatty acid oxidation disorders. Nochi *et al*. [32] showed that cells from patients with MCAD deficiency are more resistant to oxidative stress, which may be related to their enhanced antioxidant system. The SUCLG2 gene encodes the β subunit, which is an essential component of the tricarboxylic acid cycle. Donti *et al*. [33] found that deletion of SUCLG2 leads to mitochondrial DNA depletion and defects in the multiple respiratory chain, thereby affecting mitochondrial energy metabolism. The results of Jackson *et al*. [34] suggested that DLAT and SUCLA2 are important components of the pyruvate dehydrogenase complex (PDC) and succinyl coenzyme A synthetase, which converts pyruvate to acetyl coenzyme A in cellular metabolism, thereby linking glycolysis and the tricarboxylic acid cycle (TCA cycle). When PDC function is impaired, cells may compensate for this metabolic defect by increasing glycolysis and oxidative phosphorylation [35]. Taken together, we suggest that the metabolic imbalance induced by these four genes may indirectly regulate immune cell epigenetic modification and inflammatory signaling activation by altering the abundance of mitochondrial metabolic intermediates (e.g., α-ketoglutarate, succinate), thus creating a vicious cycle of metabolic reprogramming and immune microenvironmental disruption.

Our findings revealed that GO and KEGG enrichment analysis of upregulated genes in the kidney cancer radiotherapy population compared to the normal population showed significant activation of T-cell activation (GO:0042110), cytokine-cytokine receptor interactions (hsa04060), and the NF-κB pathway (hsa04064), suggesting that renal cancer radiotherapy may remodel the tumor immune microenvironment through pro-inflammatory factor release. The results of Vanpouille *et al*. [36] demonstrated that radiotherapy induces immunogenic death of tumor cells, thereby promoting cross-presentation of tumor antigens and activation of effector T cells. In addition, Filatenkov *et al*. [37] found that radiotherapy could also enhance the infiltration and activity of effector T cells by altering the expression of cytokines and chemokines in the tumor microenvironment. Wu *et al*. [38] suggested that radiotherapy may affect the tumor immune microenvironment by altering the phenotype of tumor-associated macrophages (TAMs) from the pro-tumorigenic M2 type to the anti-tumorigenic M1 type.

We found that down-regulated genes in patients with RCC combined with renal failure were significantly enriched in the mitochondrial matrix (GO:0005759) and basement membrane (GO:0005604), which was highly consistent with the clinical renal tubular atrophy and abnormal mitochondrial morphology. The results of Tang et al. also showed that mitochondrial dysfunction plays an important role in the pathogenesis of chronic kidney disease (CKD) and and that the loss of mitochondrial mass Loss of control mechanisms may lead to mitochondrial damage and dysfunction, which may trigger cell death and tissue damage [39]. In addition to this, a study by Galvan *et al*. proposed that morphological changes in mitochondria may be due to dysregulation of mitochondrial fusion and division processes, which are critical in maintaining mitochondrial function and cellular health [40]. The findings of He *et al.* showing that a reduction in mitochondrial DNA copy number is associated with an increased risk of progression of chronic kidney disease further support the mitochondrial important role [41]. These studies are consistent with our findings.

Our survival analysis confirmed that high expression of ACADM, DLAT, SUCLA2, and SUCLG2 was significantly and positively correlated with patients' overall survival (HR = 0.466-0.544), suggesting that they could be used as novel biomarkers for the efficacy of radiotherapy and prognosis of renal function in renal cancer. The combination of immune checkpoint inhibitors with radiotherapy may enhance therapeutic efficacy, especially in those tumors carrying programmed death ligand 1 (PD-L1) [42]. The expression levels of these immune-related genes can be an important

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indicator for assessing the efficacy of radiotherapy. Thus, the results of Ren et al. showed the importance of IANGPTL3, IL2RA, PPARA, SHC1, TGFA and TNFSF14 in monitoring and predicting the prognosis of ccRCC [43]. The current study has not yet reached a unified conclusion and needs to be validated by animal and cellular experiments as well as large-scale cohort studies.

This study has some limitations. The first integrated GEO datasets were from different sequencing platforms, and batch effects may not have been completely eliminated despite the standardized process (RMA algorithm). Secondly the functional mechanisms of the target genes have not been validated by in vitro/in vivo experiments and independent clinical cohorts were not included to validate their causal relationship with the IBS-D phenotype. Finally, data association relies on published literature, which may miss negative results or emerging pathologic mechanisms, limiting the comprehensiveness of conclusions.

CONCLUSION

ACADM, DLAT, SUCLA2 and SUCLG2 may affect the prognosis of patients with RCC combined with renal failure. More clinical data and experiments are needed to validate the specific mechanisms of these genes in metabolic adaptive regulation and to explore combination therapy strategies targeting metabolic reprogramming.

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***Ethical compliance*:** This study utilized de-identified genomic data from open-access repositories (including TCGA and GEO), which were ethically sourced and contained no identifiable private information. As no human/animal experiments were conducted, institutional ethics approval was exempted per national guidelines. Analytical workflows adhered to FAIR data principles, ensuring methodological rigor and reproducibility. Stringent measures were implemented to prevent any ethical violations or data misuse during computational analyses.

***Conflict of interest* :** The authors declare that there are no potential conflicts of interest in this article. No AI assistance was used in the manuscript writing process.

***Author contributions*:** J.W., and P.G., conceived and designed the research framework. Z.W., performed data acquisition from TCGA and public repositories, while L.F., conducted bioinformatics analysis and statistical validation. J.W., and P.G., drafted the initial manuscript with critical input from J.Z., who supervised the methodological rigor. All authors collaboratively refined and approved the final manuscript version.

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