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# Prognostic evaluation and clinical application of lipid immune score in clear cell renal cell carcinoma

Guifen DONG[1], Bo YANG[2], Yan LÜ[1],Wei ZHONG[3],Wei LI[4],Xiaohui WANG[1],Zhiqiang WANG[4*]

*1.Hospital Infection Control Office, Shouguang Hospital of Traditional Chinese Medicine, Shouguang, China(SHTCM), 2.Department of critical care medicine, SHTCM 3.Thoracic surgery, SHTCM 4.Department of Urology, SHTCM, *Corresponding to TCMwangzhiqiang@163.com,https://orcid.org/0000-0003-1459-6602*

**Abstract**

Clear cell renal cell carcinoma (ccRCC) is the most common and aggressive subtype of renal cancer. Despite advances in treatment, its prognosis remains poor. In this study, we developed a lipid immune score (LIS) based on six genes (ADAM8, IQGAP2, SLC16A12, PYCR1, TOX3, and LRRC19) involved in lipid metabolism and immune response. These genes are differentially expressed in ccRCC and are associated with tumor progression and patient survival. The LIS shows potential for improving diagnosis, prognosis evaluation, and identifying therapeutic targets in ccRCC. Although promising, further validation and clinical standardization are needed.

**Keywords** Clear cell renal cell carcinoma; lipid immune score; ADAM8; IQGAP2; SLC16A12; PYCR1; TOX3; LRRC19

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## 1 Introduction

### 1.1 Epidemiology, Clinical Challenges, and Molecular Insights into ccRCC

Renal cell carcinoma (RCC) is one of the most common malignant tumors of the urinary system, with clear cell RCC (ccRCC) being the predominant pathological subtype, accounting for 60-85% of all renal malignancies[1]. Globally, RCC ranks sixth among the most frequently diagnosed cancers in men and eighth in women[2]. In China, the incidence of RCC has been steadily increasing year by year, making it a growing public health concern[3].

Currently, surgical intervention remains the most effective treatment for early-stage localized RCC, yielding a 5-year survival rate of approximately 69%. However, 30-50% of patients still experience recurrence or metastasis after surgery[4]. Despite advancements in the early diagnosis and treatment of kidney

cancer, around 60% of patients either present with metastatic disease at initial diagnosis or develop distant metastases during follow-up, posing a substantial threat to patient survival.

In terms of therapeutic response, the efficacy rate for advanced RCC has improved from roughly 30% during the targeted therapy era to 50 70% in the era of targeted immunotherapy combinations. Nonetheless, not all RCC patients benefit from these combination therapies, and many who respond initially eventually develop secondary drug resistance.

Further investigation reveals that renal cancer is a highly genetically heterogeneous malignancy. Tumor cells with different gene mutation profiles and genomic phenotypes exhibit diverse biological behaviors and variable sensitivity to treatments. Thus, elucidating the molecular characteristics and subtypes of RCC is essential to improving therapeutic outcomes and achieving precision medicine.

Milestone multi-omics studies conducted by The Cancer Genome Atlas (TCGA)[5] and the Clinical Proteomic Tumor Analysis Consortium (CPTAC)[6] have significantly expanded our understanding of ccRCC. The TCGA project offers the most comprehensive genomic landscape of ccRCC to date and highlights its association with invasive phenotypes and metabolic reprogramming. Additionally, proteomic profiling of 103 ccRCC samples by CPTAC has revealed tumor-specific proteomic and phosphoproteomic alterations, as well as distinct immune-related features.

## 1.2 Rationale for Constructing a Lipid Immune Score in ccRCC

In 2011, Cell expanded the six hallmark features of tumor cells to ten, identifying enhanced metabolic reprogramming as a critical characteristic of cancer. This reprogramming promotes rapid cell growth and proliferation, and is now recognized as an emerging hallmark of cancer. Recently, metabolic disorders involving fatty acids have been observed in various cancers, including renal cell carcinoma, breast cancer, prostate cancer, and lung cancer[7,8].

The correlation between dysregulated fatty acid metabolism, glucose metabolism disorders (known as the Warburg effect), and amino acid metabolism changes—particularly glutamine metabolism—and their impact on cancer cell function is increasingly recognized[9]. Abnormal cancer metabolism alters the fate of fatty acids, including the shift in ccRCC towards excessive lipid accumulation. Hypoxia-inducible factors (HIFs) have been identified as key regulators of fatty acid metabolism, playing a crucial role in the development of ccRCC.

As a result of excessive lipid and glycogen deposits, ccRCC cells exhibit malignant epithelial characteristics with clear cytoplasm. Lipid accumulation affects cellular energy homeostasis, lipid signaling, biofilm synthesis, and phenotypic transformation in ccRCC. Alterations in lipid metabolism enable tumor cells to survive under nutrient-deficient conditions[10].

Meanwhile, RCC is considered an immunogenic tumor, characterized by the presence of various inflammatory cells, including natural killer (NK) cells, dendritic cells (DCs), T cells, and macrophages. Tyrosine kinase inhibitors (TKIs), molecular targeted therapies, and immune checkpoint inhibitors (ICIs) have been recommended and widely studied in the treatment of advanced RCC[11].

However, due to the highly dynamic, regulated, and heterogeneous tumor microenvironment (TME) of RCC—which involves both glucose and lipid metabolism—these factors may contribute to resistance against TKIs and ICIs[12].

A growing body of evidence suggests that interactions between lipid metabolism and immune function within the ccRCC microenvironment may have important clinical implications. Nevertheless, reliable prognostic indicators based on the integration of lipid metabolism and immunity have yet to be established. Moreover, many previous studies have only relied on genomic profiling to characterize the prognostic features of ccRCC.

Therefore, we aim to construct a lipid immune score (LIS) based on genes related to immune function

and lipid metabolism, in order to guide personalized treatment strategies and improve survival prediction for clinical patients.

### 1.3 Key Genes Comprising the Lipid Immune Score and Their Functional Roles

The *lipid immune score* we constructed consists of six genes: **ADAM8**, **IQGAP2**, **SLC16A12**, **PYCR1**, **TOX3**, and **LRRC19**.

**ADAM8**: Belonging to the disintegrin and metalloproteinase families, ADAM8 is associated with tumor cell migration, invasion, and angiogenesis in various cancers. It may influence tumor progression by regulating extracellular matrix degradation and intercellular interactions[13].

**IQGAP2**: IQGAP2 is a scaffold protein involved in the regulation of the cytoskeleton and signal transduction pathways. It has been linked to tumor cell proliferation, migration, and invasion, and may play a key role in the development of clear cell renal cell carcinoma[14].

**SLC16A12**: This gene encodes a solute carrier family protein that primarily facilitates the transmembrane transport of various substances. It may participate in lipid metabolism, and its abnormal expression could disrupt lipid homeostasis in clear cell renal cell carcinoma, thereby influencing tumor growth and survival[15].

**PYCR1**: PYCR1 encodes a key enzyme in the biosynthetic pathway of proline, which is closely related to cellular energy metabolism and proliferation. Its overexpression may confer a growth advantage to tumor cells and contribute to the progression of clear cell renal cell carcinoma[16].

**TOX3**: TOX3 is a transcription factor involved in cellular differentiation and development. It may influence tumor biology by regulating downstream gene expression, and is potentially associated with the prognosis of clear cell renal cell carcinoma[17].

**LRRC19**: LRRC19 encodes a leucine-rich repeat-containing protein whose functions are not yet fully understood. However, aberrant expression has been observed in certain tumors, and it may be implicated in tumor development and the immune microenvironment[18].

## 2 Application in Clear Cell Renal Cell Carcinoma

Diagnostic markers: The expression levels of these genes differ between clear cell renal cell carcinoma (ccRCC) tissue and normal renal tissue. By detecting their expression in tissue or blood samples, they may serve as auxiliary diagnostic markers for ccRCC. For example, research has shown that ADAM8 is highly expressed in ccRCC tissue, and its expression level correlates with tumor stage and grade, making it a potential diagnostic indicator.

Prognostic assessment: Multiple studies have demonstrated that these genes are closely associated with the prognosis of ccRCC patients. High PYCR1 expression is often linked to poor prognosis, while TOX3 expression levels may be associated with disease-free survival and overall survival. Testing these genes can enable clinicians to more accurately assess patient prognosis and develop personalized treatment strategies.

Therapeutic targets: A deeper understanding of the functional mechanisms of these genes in ccRCC may facilitate the discovery of new therapeutic targets. For instance, inhibitors targeting ADAM8 may exert anti-tumor effects by inhibiting tumor cell migration and invasion. Regulating the function of SLC16A12 could affect tumor lipid metabolism, thereby suppressing tumor cell growth.

## 3 Clinical Evaluation

Personalized medicine: By assessing the expression of these genes, personalized treatment plans can be designed for each patient. For those with a poor prognosis, postoperative adjuvant therapies can be in-

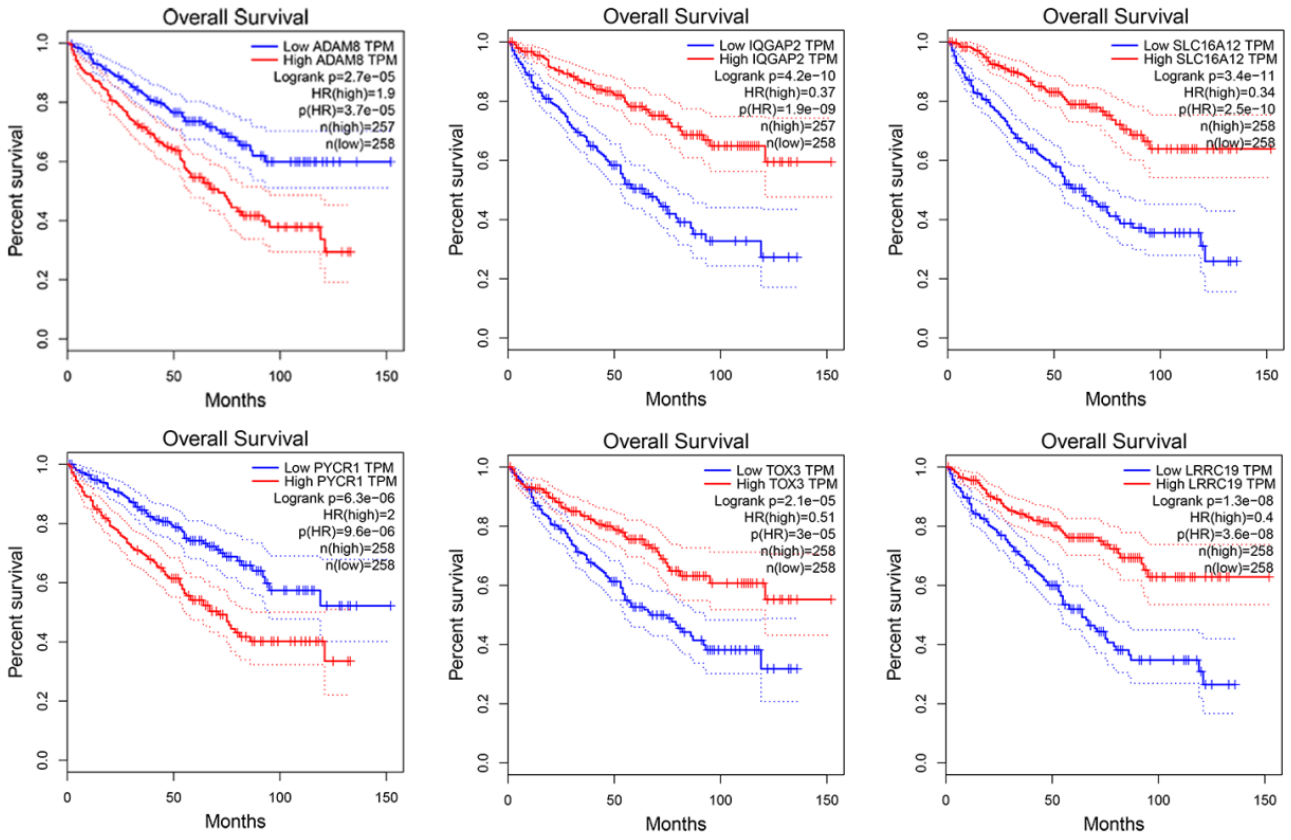


Figure1 ADAM8、IQGAP2、SLC16A12、PYCR1、TOX3、LRRC19

tensified. For patients with a more favorable prognosis, overtreatment can be avoided, thus reducing treatment-related side effects and healthcare costs.

Early diagnosis: As potential diagnostic biomarkers, these genes may assist in the early detection and diagnosis of ccRCC. Early diagnosis is critical for improving cure and survival rates. Genetic testing may offer greater sensitivity than imaging examinations, particularly in detecting small tumors that are otherwise difficult to identify.

Mechanism research: Investigating these genes can enhance our understanding of the pathogenesis of ccRCC and provide a theoretical foundation for developing novel treatments and drugs. For example, identifying the crucial role of PYCR1 in tumor cell energy metabolism may guide the development of metabolism-targeted therapies.

## 4 Limitations

Detection technology and cost: Currently, detecting the expression levels of these genes requires specialized equipment and trained personnel. The relatively high cost of detection limits its widespread clinical application. Additionally, variations in testing methods and standards among different laboratories may affect the accuracy and comparability of results.

Multifactorial influence: The occurrence and progression of clear cell renal cell carcinoma is a complex process influenced by multiple factors. Although these genes are closely associated with tumor prognosis and biological behavior, relying solely on genetic testing results may not fully or accurately predict a

patient's condition and response to treatment. Clinicians must also consider various factors such as patient age, sex, tumor stage, and grade to make comprehensive evaluations and clinical decisions.

Validation and optimization: While numerous studies have reported the potential clinical value of these genes in clear cell renal cell carcinoma, larger-scale clinical studies are needed to further validate and optimize their applications. For instance, determining the most effective gene combinations and testing methods could enhance the accuracy of diagnosis and prognosis prediction.

Lipid metabolism and immune-related genes (ADAM8, IQGAP2, SLC16A12, PYCR1, TOX3, and LRRC19) hold significant potential in the diagnosis, prognosis assessment, and identification of therapeutic targets for clear cell renal cell carcinoma. However, challenges remain in clinical translation and application, necessitating further research and refinement.

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