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Cross-Tissue Regulatory Network Analyses Reveal Novel Susceptibility Genes and Potential Mechanisms for Endometriosis

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Simple Summary: Endometriosis (EMT) is a chronic gynecological disease affecting millions of women. Nevertheless, the precise mechanisms underlying this disorder remain largely unexplored. In this study, we conducted transcriptome-wide association study (TWAS) analyses to uncover novel susceptibility genes linked to EMT. In addition, we employed Mendelian randomization (MR) and colocalization analyses to delve into the causal associations between candidate genes across different tissues and EMT. Moreover, to elucidate the mechanisms by which these genes influence the risk of EMT, we conducted two-sample network MR analyses to assess the mediating roles of modifiable risk factors in the causal pathways connecting identified genes across tissues and EMT. Our findings revealed that expression levels of several genes, including CISD2, EFRB, GREB1, IMMT, SULT1E1, and UBE2D3, across various tissues influenced the risk of EMT, with blood lipids levels and hip circumference serving as mediators in these associations. These findings contribute to a deeper understanding of the tissue-specific transcriptional regulatory mechanisms associated with EMT, offering insights that may enhance the management and treatment strategies for EMT.

Abstract: Endometriosis (EMT) is a common gynecological disease with a strong genetic component, while its precise etiology remains elusive. This study aims to integrate transcriptome-wide association study (TWAS), Mendelian randomization (MR), and bioinformatics analyses to reveal novel putatively causal genes and potential mechanisms. We obtained summary-level data of the Genotype-Tissue Expression Project (GTEx), v8 expression quantitative loci (eQTL) data, and the genome-wide association study (GWAS) data of EMT and its subtypes from the R11 release results of the FinnGen consortium for analysis. GWAS data of modifiable risk factors were collected from IEU Open GWAS. Cross-tissue TWAS analyses were performed using the unified test for molecular signature (UTMOST), while functional summary-based imputation (FUSION) was employed for single-tissue TWAS analyses. Furthermore, we also conducted multi-marker analysis of genomic annotation (MAGMA) analyses to validate the significant associations. Subsequent Mendelian randomization (MR) and colocalization analysis elucidated the causal associations between the identified genes across various tissues and EMT. To further delve into mechanisms, two-sample network MR analyses were conducted. At last, bioinformatics analyses were employed to enhance our understanding of the functional implications and expression patterns of these identified genes. For EMT, 22 significant gene signals were identified by UTMOST, 615 by FUSION, and 354 by MAGMA. Ultimately, six genes, including CISD2, EFRB, GREB1, IMMT, SULT1E1, and UBE2D3, were identified as candidate susceptibility genes for EMT. Through similar procedures, we identified GREB1, IL1A, and SULT1E1 for EMT of the ovary, and we identified GREB1 for EMT of the pelvic peritoneum, EMT of rectovaginal septum and vagina, and deep EMT. In MR analyses, the expression of IMMT in

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Proteome-Wide Mendelian Randomization and Colocalization Analysis Identify Therapeutic Targets for Knee and Hip Osteoarthritis

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Abstract: Osteoarthritis (OA) is a common degenerative disease. Although some biomarkers and drug targets of OA have been discovered and employed, limitations and challenges still exist in the targeted therapy of OA. Mendelian randomization (MR) analysis has been regarded as a reliable analytic method to identify effective therapeutic targets. Thus, we aimed to identify novel therapeutic targets for OA and investigate their potential side effects based on MR analysis. In this study, two-sample MR, colocalization analysis, summary-data-based Mendelian randomization (SMR) and Mendelian randomization phenome-wide association study (MR-PheWAS) were conducted. We firstly analyzed data from 4907 plasma proteins to identify potential therapeutic targets associated with OA. In addition, blood expression quantitative trait loci (eQTLs) data sources were used to perform additional validation. A protein–protein interaction (PPI) network was also constructed to delve into the interactions among identified proteins. Then, MR-PheWASs were utilized to assess the potential side effects of core therapeutic targets. After MR analysis and FDR correction, we identified twelve proteins as potential therapeutic targets for knee OA or hip OA. Colocalization analysis and additional validation supported our findings, and PPI networks revealed the interactions among identified proteins. Finally, we identified MAPK3 (OR = 0.855, 95% CI: 0.791–0.923, $p = 6.88 \times 10^{-5}$) and GZMK (OR = 1.278, 95% CI: 1.131–1.444, $p = 8.58 \times 10^{-5}$) as the core therapeutic targets for knee OA, and ITIH1 (OR = 0.847, 95% CI: 0.784–0.915, $p = 2.44 \times 10^{-5}$) for hip OA. A further MR phenome-wide association study revealed the potential side effects of treatments targeting MAPK3, GZMK, and ITIH1. This comprehensive study indicates twelve plasma proteins with potential roles in knee and hip OA as therapeutic targets. This advancement holds promise for the progression of OA drug development, and paves the way for more efficacious treatments of OA.

Keywords: GWAS; mendelian randomization; osteoarthritis; plasma proteins; therapeutic targets

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1. Introduction

Osteoarthritis (OA) is the most common degenerative disorder of the joint, which typically involves lesions in articular cartilage, subchondral bone, ligaments, capsule, and synovial membrane [1]. According to the statistics from the epidemiology and register center in Lund university, in 2012, the proportion of OA patients in the Skåne region of southern Sweden was 26.6%. It is estimated that by 2032, the proportion will increase from 26.6% to 29.5% for OA, from 13.8% to 15.7% for knee OA, and from 5.8 to 6.9% for hip OA [2,3]. In recent years, the number of OA patients has been continuously increasing, bringing significant economic burden to society. In high-income countries, the medical expenses for OA account for 1~2.5% of the gross domestic product [3]. Among all OA, knee and hip OA are the most common, posing a threat to the health of millions of people [4].

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Diabetology & Metabolic Syndrome

RESEARCH Open Access

Construction and evaluation of sarcopenia risk prediction model for patients with diabetes: a study based on the China health and retirement longitudinal study (CHARLS)

Mingrui Zou[1,2,3] and Zhenxing Shao[1,2*]

Abstract

Purpose Sarcopenia is a common complication of diabetes. Nevertheless, precise evaluation of sarcopenia risk among patients with diabetes is still a big challenge. The objective of this study was to develop a nomogram model which could serve as a practical tool to diagnose sarcopenia in patients with diabetes.

Methods A total of 783 participants with diabetes from China Health and Retirement Longitudinal Study (CHARLS) 2015 were included in this study. After oversampling process, 1,000 samples were randomly divided into the training set and internal validation set. To mitigate the overfitting effect caused by oversampling, data of CHARLS 2011 were utilized as the external validation set. Least absolute shrinkage and selection operator (LASSO) regression analysis and multivariate logistic regression analysis were employed to explore predictors. Subsequently, a nomogram was developed based on the 9 selected predictors. The model was assessed by area under receiver operating characteristic (ROC) curves (AUC) for discrimination, calibration curves for calibration, and decision curve analysis (DCA) for clinical efficacy. In addition, machine learning models were constructed to enhance the robustness of our findings and evaluate the importance of the predictors.

Results 9 factors were selected as predictors of sarcopenia for patients with diabetes. The nomogram model exhibited good discrimination in training, internal validation and external validation sets, with AUC of 0.808, 0.811 and 0.794. machine learning models revealed that age and hemoglobin were the most significant predictors. Calibration curves and DCA illustrated excellent calibration and clinical applicability of this model.

Conclusion This comprehensive nomogram presented high clinical predictability, which was a promising tool to evaluate the risk of sarcopenia in patients with diabetes.

Keywords Prediction model, Sarcopenia, Diabetes, Nomogram, CHARLS

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Identify novel therapeutic targets for type II diabetes and periodontitis: insights from single-cell analysis and Mendelian randomization analysis

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Background: Periodontitis is a common complication of type II diabetes (T2D). However, the existing research cannot fully elucidate the association between them, let alone identify therapeutic targets for precise treatment of diabetic periodontitis. Therefore, we employed integrated genetic approaches such as single-cell analysis, Mendelian randomization (MR) analysis and colocalization analysis to uncover novel therapeutic targets for T2D and periodontitis.

Methods: This study integrated single-cell analysis, MR analysis, colocalization analysis, phenotype scanning, cell-cell communication analysis and metabolic pathway activity analysis to unveil novel therapeutic targets for periodontitis and T2D. We firstly identified core cell clusters of T2D and periodontitis, and important marker genes were selected. The causal associations between these genes and the two diseases were evaluated through MR analysis. Reverse MR analysis, colocalization analysis, additional validation and phenotype scanning further supported our findings. Finally, cell-cell communication analysis and metabolic pathway activity analysis were employed to preliminarily investigate the mechanisms of the observed causal associations.

Results: Through analysis of scRNA-seq data, we identified classical monocytes and intermediate monocytes as core cell subclusters. Differential analysis identified 221 differentially expressed genes (DEGs). MR analysis identified 13 genes exhibiting causal associations with T2D, and 11 causal genes with periodontitis. Colocalization analysis, reverse MR analysis, additional validation and phenotype scanning further enhanced the robustness of our results. Finally, we identified NCF1 as the core therapeutic target for T2D (OR = 1.09, 95% CI: 1.03-1.14, $p = 1.85 \times 10^{-3}$) and LRRC25 for T2D (OR = 0.96, 95% CI: 0.93-0.99, $p = 3.44 \times 10^{-2}$) and periodontitis (OR = 0.92, 95% CI: 0.84-0.99, $p = 4.45 \times 10^{-2}$). At last, cell-cell communication analysis indicated significant differences in functions and metabolic pathway activity between monocytes expressing or not expressing the core causal genes, which preliminarily interpreted the observed causal associations.

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Systematic Review

Therapeutic Potential of Exosomes in Tendon and Tendon–Bone Healing: A Systematic Review of Preclinical Studies

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Abstract: Exosomes have been proven to play a positive role in tendon and tendon–bone healing. Here, we systematically review the literature to evaluate the efficacy of exosomes in tendon and tendon–bone healing. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, a systematic and comprehensive review of the literature was performed on 21 January 2023. The electronic databases searched included Medline (through PubMed), Web of Science, Embase, Scopus, Cochrane Library and Ovid. In the end, a total of 1794 articles were systematically reviewed. Furthermore, a "snowball" search was also carried out. Finally, forty-six studies were included for analysis, with the total sample size being 1481 rats, 416 mice, 330 rabbits, 48 dogs, and 12 sheep. In these studies, exosomes promoted tendon and tendon–bone healing and displayed improved histological, biomechanical and morphological outcomes. Some studies also suggested the mechanism of exosomes in promoting tendon and tendon–bone healing, mainly through the following aspects: (1) suppressing inflammatory response and regulating macrophage polarization; (2) regulating gene expression, reshaping cell microenvironment and reconstructing extracellular matrix; (3) promoting angiogenesis. The risk of bias in the included studies was low on the whole. This systematic review provides evidence of the positive effect of exosomes on tendon and tendon–bone healing in preclinical studies. The unclear-to-low risk of bias highlights the significance of standardization of outcome reporting. It should be noted that the most suitable source, isolation methods, concentration and administration frequency of exosomes are still unknown. Additionally, few studies have used large animals as subjects. Further studies may be required on comparing the safety and efficacy of different treatment parameters in large animal models, which would be conducive to the design of clinical trials.

Keywords: exosomes; extracellular vesicles; regenerative medicine; tendon healing; tendon–bone healing

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1. Introduction

Tendons are structures composed of fibrous connective tissue that transmit power from muscles to bones. Although tendons can withstand different loadings, their damage is extremely severe. Due to the lack of blood vessels, the regeneration ability of tendons is poor. Therefore, tendon repair is a huge challenge in medicine. Tendon or ligament injuries are common. In the United States, every year there are more than 300,000 patients who require surgery to repair tendons or ligaments, and the number is growing as the population grows and sports are becoming more popular [1,2].

Common tendon injury can be divided into chronic injury caused by degeneration and acute injury caused by direct rupture, both of which significantly change the structure and function of the tendon. In severe cases, the tendon–bone interface is also damaged [3]. Generally, four stages take place in tendon or tendon–bone healing. The first stage is the inflammation stage, when macrophages are recruited to the injured site and vascular

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Research Paper

Two-Sample Network Mendelian Randomization and Single-Cell Analysis Reveal the Causal Associations and Underlying Mechanisms Between Antihypertensive Drugs and Kidney Cancer

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Abstract

Background: Antihypertensive drugs represent the most widely used drugs worldwide. However, the association between antihypertensive drugs and the risk of kidney cancer remains unclear. This study innovatively integrates multi-omics and causal inference approaches to investigate the long-term effects and potential mechanisms of 12 antihypertensive drug classes on kidney cancer risk.

Methods: In this study, novel approaches including two-sample mendelian randomization (MR), summary-data-based mendelian randomization (SMR), two-step network MR, and single-cell transcriptomic analysis were employed. Single nucleotide polymorphisms (SNPs) were obtained from genome-wide association studies (GWASs) to proxy exposures and outcomes. The cis-expression quantitative trait loci (cis-eQTL) as the proxies of exposure were also obtained. MR estimates were generated using the inverse-variance weighted method or Wald ratio method. Sensitivity analyses were undertaken to interrogate the robustness of the main findings. Two-step network MR and single-cell analysis were specifically designed to dissect pathway-level mediation and expression patterns of identified targets.

Results: In the main analysis, genetically proxied calcium-channel blockers (odds ratio [OR]: 0.95, 95% confidence interval [CI]: 0.91-0.99, p=0.021) and vasodilator antihypertensives (OR: 0.86, 95% CI: 0.76-0.97, p=0.018) were suggestively associated with decreased risk of kidney cancer, whereas genetically proxied angiotensin-converting enzyme inhibitors (OR: 1.13, 95% CI: 1.00-1.27, p=0.043) was suggestively associated with increased risk of kidney cancer. Genetically proxied antiadrenergic agents (OR=0.94, 95% CI: 0.90-0.99, p=0.021) and centrally acting antihypertensives (OR=0.93, 95% CI: 0.88-0.98, p=0.010) were suggestively associated with a decreased risk of clear cell renal cell carcinoma. SMR analysis revealed that these suggestively significant associations might be driven by *CACNA1C*, *CALM1*, *ACE*, and *LTA4H*. Upon two-step network MR analyses, 10 pathways with directional consistency were identified, and the mediation proportion ranged from 3.22% to 7.12%. The influence of antihypertensive drugs on kidney cancer risk might be associated with their regulation of levels of blood cells and lipids. Single-cell analysis further revealed the expression patterns of the four identified targets in peripheral blood and tumor infiltrating immune cells.

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Novel Protein Biomarkers and Therapeutic Targets for Type 1 Diabetes and Its Complications: Insights from Summary-Data-Based Mendelian Randomization and Colocalization Analysis

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Abstract: Millions of patients suffer from type 1 diabetes (T1D) and its associated complications. Nevertheless, the pursuit of a cure for T1D has encountered significant challenges, with a crucial impediment being the lack of biomarkers that can accurately predict the progression of T1D and reliable therapeutic targets for T1D. Hence, there is an urgent need to discover novel protein biomarkers and therapeutic targets, which holds promise for targeted therapy for T1D. In this study, we extracted summary-level data on 4907 plasma proteins from 35,559 Icelanders and 2923 plasma proteins from 54,219 UK participants as exposures. The genome-wide association study (GWAS) summary statistics on T1D and T1D with complications were obtained from the R9 release results from the FinnGen consortium. Summary-data-based Mendelian randomization (SMR) analysis was employed to evaluate the causal associations between the genetically predicted levels of plasma proteins and T1D-associated outcomes. Colocalization analysis was utilized to investigate the shared genetic variants between the exposure and outcome. Moreover, transcriptome analysis and a protein–protein interaction (PPI) network further illustrated the expression patterns of the identified protein targets and their interactions with the established targets of T1D. Finally, a Mendelian randomization phenome-wide association study evaluated the potential side effects of the identified core protein targets. In the primary SMR analysis, we identified 72 potential protein targets for T1D and its complications, and nine of them were considered crucial protein targets. Within the group were five risk targets and four protective targets. Backed by evidence from the colocalization analysis, the protein targets were classified into four tiers, with MANSC4, CTRB1, SIGLEC5 and MST1 being categorized as tier 1 targets. Delving into the DrugBank database, we retrieved 11 existing medications for T1D along with their therapeutic targets. The PPI network clarified the interactions among the identified potential protein targets and established ones. Finally, the Mendelian randomization phenome-wide association study corroborated MANSC4 as a reliable target capable of mitigating the risk of various forms of diabetes, and it revealed the absence of adverse effects linked to CTRB1, SIGLEC5 and MST1. This study unveiled many protein biomarkers and therapeutic targets for T1D and its complications. Such advancements hold great promise for the progression of drug development and targeted therapy for T1D.

Keywords: GWAS; Mendelian randomization; plasma proteins; therapeutic targets; type 1 diabetes

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Authors: Mingrui Zou, Ruiyi Deng, Haode Liu, Jianhui Qiu, Peidong Tian, Jiaheng Shang, Jingcheng Zhou, Xueying Li, Lin Cai, Yizhou Wang and Kan Gong
Contact name/email: Prof. Kan Gong <kan.gong@bjmu.edu.cn>

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7 results

Page 1 of 1

Did you mean ***minghui zou*** *AND Peking University* (9 results)?

1 Cite

Two-Sample Network Mendelian Randomization and Single-Cell Analysis Reveal the Causal Associations and Underlying Mechanisms Between Antihypertensive Drugs and Kidney Cancer.

J Cancer | 3.2 | Q2 | 2025

Deng R, **Zou M**, Qiu J, Shang J, Yu C, Tian P, Wang Y, Cai L, Zhou J, Gong K.

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2 Cite

Identify novel therapeutic targets for type II diabetes and periodontitis: insights from single-cell analysis and Mendelian randomization analysis.

Front Endocrinol (Lausanne) | 4.6 | Q1 | 2024

Zou M, Yang J.

DOI: 10.3389/fendo.2024.1410537

PMID: 39544234

Abstract | Times Cited: 0 | Heat: 128 | Tags:

3 Cite

Cross-Tissue Regulatory Network Analyses Reveal Novel Susceptibility Genes and Potential Mechanisms for Endometriosis.

Biology (Basel) | 3.5 | Q1 | 2024

Zou M, Lin M, Hu KL, Li R.

DOI: 10.3390/biology13110871

PMID: 39596826

Abstract | Times Cited: 1 | Heat: 124 | Tags:

4 Cite

Construction and evaluation of sarcopenia risk prediction model for patients with diabetes: a study based on the China health and retirement longitudinal study (CHARLS).

Diabetol Metab Syndr | 3.9 | Q2 | 2024

Zou M, Shao Z.

DOI: 10.1186/s13098-024-01467-w

PMID: 39285494

Abstract | Times Cited: 2 | Heat: 450 | Tags:

5 Cite

Novel Protein Biomarkers and Therapeutic Targets for Type 1 Diabetes and Its Complications: Insights from Summary-Data-Based Mendelian Randomization and Colocalization Analysis.

Pharmaceuticals (Basel) | 4.8 | Q1 | 2024

Zou M, Yang J.

DOI: 10.3390/ph17060766

PMID: 38931433

Abstract | Times Cited: 1 | Heat: 303 | Tags:

6 Cite

Proteome-Wide Mendelian Randomization and Colocalization Analysis Identify Therapeutic Targets for Knee and Hip Osteoarthritis.

Biomolecules | 4.8 | Q1 | 2024

Zou M, Shao Z.

DOI: 10.3390/biom14030355

PMID: 38540773

Abstract | Times Cited: 8 | Heat: 1199 | Tags:

7 Cite

Therapeutic Potential of Exosomes in Tendon and Tendon-Bone Healing: A Systematic Review of Preclinical Studies.

J Funct Biomater | 5.2 | Q1 | 2023 | Review

Zou M, Wang J, Shao Z.

DOI: 10.3390/jfb14060299

PMID: 37367263

Abstract | Times Cited: 9 | Heat: 331 | Tags:

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Las Vegas

Single-cell endoplasmic reticulum stress patterns guide intercellular communication of tumor microenvironment that influence the progression and prognosis of clear cell renal cell carcinoma

Mingrui Zou, Zedan Zhang, Ruiyi Deng, Tao Liu, Yizhou Wang AND Kan Gong*
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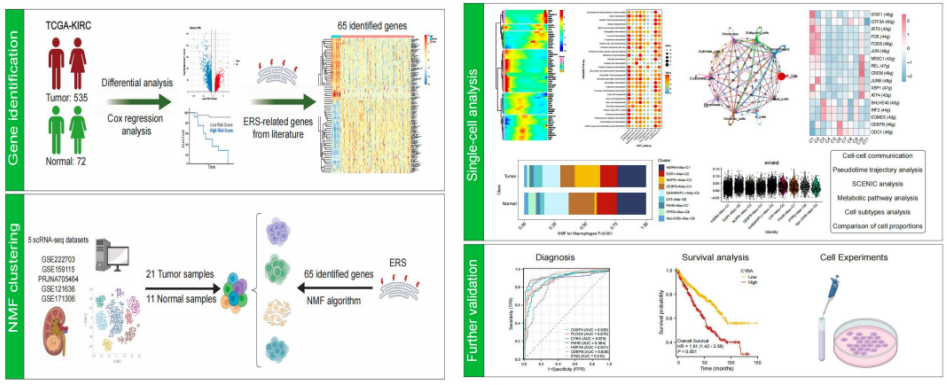
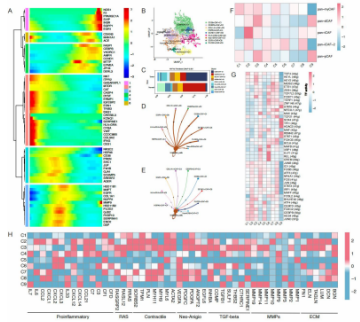
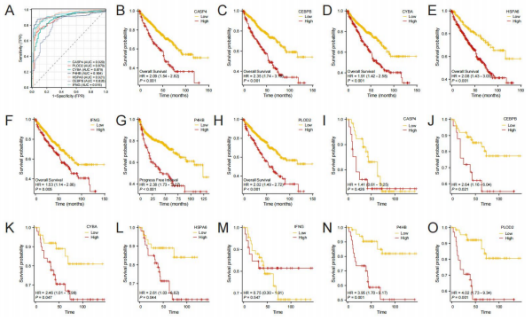
Introduction & objectives: Endoplasmic reticulum stress (ERS) typically manifests as protein folding dysfunction, which has been demonstrated to play important roles in the progression and prognosis of various cancers. For clear cell renal cell carcinoma (ccRCC), studies have indicated that ERS-related pathways were highly activated continuously, aiding the proliferation and metastasis of tumor cells. However, the specific functions and mechanisms of ERS in the tumor microenvironment (TME) of ccRCC remain elusive.

Materials & methods: A total of 104,559 single cells were obtained for analysis from 32 samples through single-cell RNA sequencing (scRNA-seq). 65 core ERS-related genes were selected for reanalyzing the scRNA data by nonnegative matrix factorization (NMF) algorithm. Pseudo-time trajectory analysis, SCENIC analysis, Cell-cell communication analysis and other Functional enrichment analysis were conducted to investigate the biological functions of novel identified TME subclusters. Survival analysis was performed to evaluate the predictive value of key cell clusters and genes for prognosis.







Results: We identified 65 ERS-related genes for formal analysis, which presented differential expression and prognostic significance. Cells including fibroblasts, Macrophages, endothelial cells, T cells and B cells, were respectively classified into various cell clusters based on marker genes and biological processes. Moreover, our findings suggested that ERS might be closely linked to the biological and clinical features of ccRCC, as well as the pseudotime trajectory of each TME cell subclusters. Notably, CellChat analysis demonstrated that ERS-related cell clusters exhibited diverse and extensive interactions with malignant tumor epithelial cells. Furthermore, there were significant differences in the proportions of different cell clusters between tumor and control group. Cell clusters related to ERS and not related to ERS also demonstrated different transcription factor activity. Additionally, bulk-seq analysis also revealed that ERS-related cell clusters had significant prognostic value for ccRCC patients, with the top marker genes demonstrating excellent diagnostic performance and prognostic significance.

Conclusions: Our study firstly revealed the ERS mediated intercellular communication of TME that may influence the progression and prognosis of ccRCC.

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肾癌患者发生第二原发恶性肿瘤的风险因素及预后分析：一项基于大规模人群的回顾性队列研究和孟德尔随机化分析

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目的 随着肾癌诊疗技术的进步和患者生存率的提高，第二原发恶性肿瘤（SPM）的发病率呈上升趋势，成为威胁肾癌幸存者健康的重大问题。然而，目前对于肾癌患者发生SPM的风险和预后因素仍缺乏高质量临床证据的支持。本研究旨在确定第一原发肾癌后与SPM相关的风险和预后因素，并构建列线图为优化肾癌患者的管理和治疗提供证据。

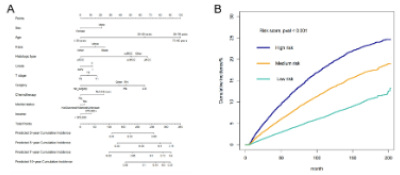

图1. SPM危险因素的评估（A）列线图（B）不同SPM风险患者的累积发病率曲线

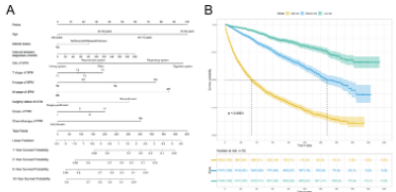

图2. 罹患SPM的肾癌患者总生存率（OS）的评估（A）用于预测罹患SPM的肾癌患者的1年、3年、5年和10年OS的列线图（B）不同风险的罹患SPM的肾癌患者的OS的Kaplan-Meier分析

方法 从美国Surveillance, Epidemiology, and End Results（SEER）数据库中筛选出2000-2020年诊断为第一原性肾癌的患者。构建竞争风险模型以确定患者发生SPM的危险因素。采用Cox回归分析筛选影响发生SPM的肾癌患者的预后相关的因素。构建列线图以预测患者发生SPM的风险和预后。C指数、受试者操作特征曲线（ROC）下面积（AUC）、校准曲线、决策曲线分析（DCA）被用于模型评价。最后，使用标准化发病率（SIR）和孟德尔随机化（MR）分析来评估发生SPM的相对风险以及肾癌与其他癌症之间的因果关系。

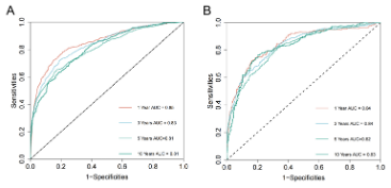

图3. 预后列线图的ROC曲线及AUC值（A）训练集（B）验证集

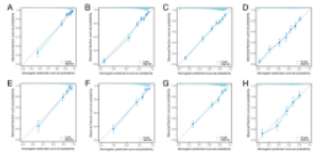

图4. 预后列线图的校准曲线（A-D）训练集中罹患SPM的肾癌患者的1年、3年、5年和10年OS的列线图的校准曲线（E-H）验证集中罹患SPM的肾癌患者的1、3、5和10年OS的列线图的校准曲线

结果 共纳入72408例肾癌患者，其中8583 (11.9%)名患者罹患SPM。年龄、性别、种族、婚姻状况、收入、组织学类型、病理分级、T分期、手术方式和化疗被确定为肾癌患者患SPM的独立危险因素。年龄、婚姻状况、诊断时间间隔、SPM的部位、SPM的TNM分期、SPM的手术状态、肾癌的病理分级和肾癌的化疗被确定为患有SPM的肾癌患者的独立预后因素。基于筛选出的变量构建列线图。竞争风险模型的C指数为：训练集0.634（95%CI：0.633-0.635），验证集0.642 (95%CI：0.641-0.643)。预后模型的C指数为：训练集0.782（95%CI：0.769-0.796），验证集0.784（95%CI：0.763-0.806）。ROC的AUC、校准曲线和DCA证明模型具有良好的准确性和临床适用性。MR分析表明，肾癌可能会增加患胃癌（OR = 1.14, 95% CI: 1.03-1.26）、结直肠癌（OR = 1.22, 95% CI: 1.03-1.44）、肺癌（OR = 1.34, 95% CI: 1.18-1.51）、前列腺癌（OR = 1.13, 95% CI: 1.03-1.24）、膀胱癌（OR = 1.28, 95% CI: 1.03-1.61）、皮肤癌（OR = 1.10, 95% CI: 1.03-1.18）以及眼部癌症（OR = 2.83, 95% CI: 1.30-6.17）的风险。

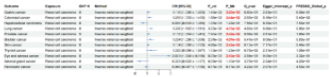

图5. 肾癌与其他癌症的的孟德尔随机化分析结果

结论 本研究利用SEER数据库成功地构建并验证了预测肾癌患者患SPM风险及预后的列线图。此外，MR分析明确了肾癌与其他癌症之间的因果关系。这些发现为优化肾癌患者的管理和治疗提供了临床证据。

Risk-based screen and prognostic analysis for second primary malignancies in kidney cancer patients: A retrospective cohort study based on large-scale population and mendelian randomization analysis

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Department of Urology, Peking University First Hospital, Beijing, China
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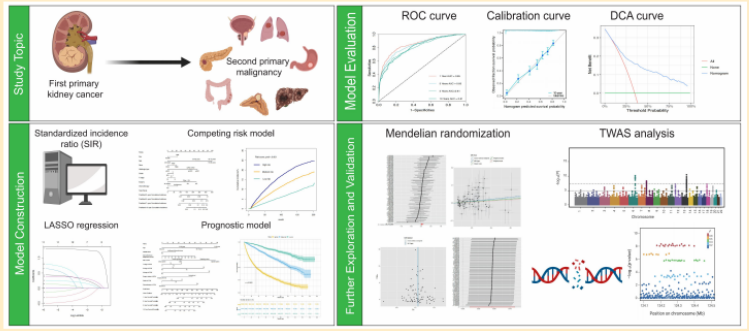
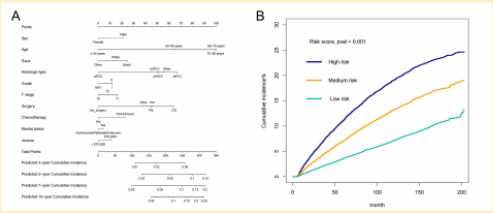
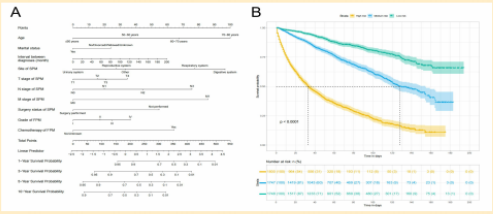


Introduction & objectives: Second primary malignancy (SPM) significantly impacts the survival of patients. This study endeavors to identify risk and prognostic factors of developing SPM after the first primary renal cell carcinoma (FPRCC), develop nomograms and delve into potential mechanisms to optimize treatment strategies.

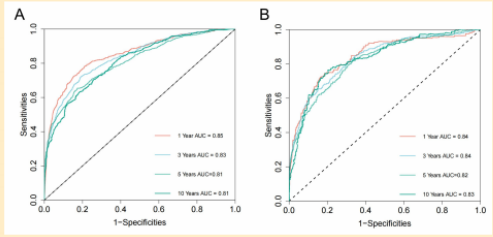
Materials & methods: Data of patients diagnosed with FPRCC between 2000 and 2020 from the SEER database were analyzed. Standardized incidence ratio (SIR) was calculated to assess the relative risk of developing SPM in FPRCC patients. Competing risk model as well as cox regression analyses were employed to identify independent risk and prognostic factors, and nomograms were constructed and evaluated based on these findings. Finally, to understand how FPRCC influence the risk of developing SPM, we carried out mendelian randomization (MR) and transcriptome-wide association study (TWAS) analyses (NCT06531629).

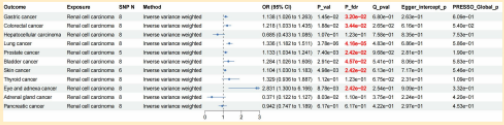




Results: A total of 72408 patients were included in the competing risk model, and 5295 patients were included to explore their prognosis. Risk distribution analysis revealed that FPRCC patients exhibited higher SPM risk than general population (SIR = 1.42, 95% CI: 1.40-1.44). Independent predictive factors were identified for model construction, and nomograms were developed, which were demonstrated to exhibit excellent performance. MR analysis revealed that RCC might causally increase the risk of gastric cancer, colorectal cancer, lung cancer, prostate cancer, bladder cancer, skin cancer and eye and adnexa cancer. TWAS analyses identified 19 causal susceptibility genes (PSCA, LYNX1, PM20D1, NOL10, TMEM17, SETD9, GNMT, L3MBTL3, AGAP4, HAUS4, TELO2, WFDC3, SEPT2, C10orf32, RBM6, DNAJC18, SPIRE2, CPNE1, ERAP2) associated with 4 cancers.

Conclusion: This study successfully established nomograms, delving into the potential mechanisms of developing SPM after FPRCC. All these findings will promote the optimization of individual treatment strategies.





EAU25 MADRID, SPAIN 21-24 March 2025

汇报人	项目导师	项目名称	拟推荐项目级别
邹明瑞	龚侃	基于多组学数据的肾细胞癌肿瘤微环境中内质网应激机制研究	国家级 重点支持领域项目
雷又览	康磊	靶向成纤维细胞激活蛋白的PET/CT显像在IgA肾病的临床价值研究	国家级 重点支持领域项目
邓涵晴	张建华	基于68Ga-N188 PET/CT 精准诊疗胰腺癌的临床转化	国家级 重点支持领域项目
顾赛娅	姜玉武	基于MySQL建立一个实时更新的儿童癫痫共患病相关单基因数据库	国家级 重点支持领域项目
王文质	汪旸	皮肤T细胞淋巴瘤	市级 重点支持领域项目
许李智	杨尹默	利用多重免疫组化探究早/晚期发生肝转移胰腺癌的肿瘤微环境差异	市级 重点支持领域项目
张翔捷	燕太强	遗传性多发骨软骨瘤病家系新突变位点鉴定及致病机制研究	市级 重点支持领域项目
胡智文	杨莉	急性肾损伤进程中脾脏髓系细胞亚群的单细胞时序动态图谱	市级 重点支持领域项目
孙亮亮	张卓莉,高岱	系统性红斑狼疮不同抗核抗体谱组合临床意义的研究	市级 重点支持领域项目
李佳怡	宋营改	皮肤癣菌耐药突变的分子检测研究	市级 重点支持领域项目
刘昱飞	杨莉	小鼠肾脏病理组学分析工具研发及肾损伤病理组学图谱构建	市级 重点支持领域项目
马喆	李昂	以代谢热整合法为基础的糖尿病无创筛查模型的构建	市级 重点支持领域项目
杨济宇	李学松	机器人双侧回肠代输尿管术的手术策略和中期随访结果	市级 重点支持领域项目
王谷天	张杨	探究基于TKIs单药及靶免联合的抗肿瘤治疗方案对糖代谢的影响	市级 重点支持领域项目

主持国家级大创

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2025年6月25日