Clinical research

Nephrology

Investigating the co-occurrence of urinary calculi and renal carcinoma: a comprehensive analysis of clinical and molecular associations

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Abstract

Introduction: Urinary calculi and renal cancer are significant urological conditions that may share overlapping etiologies. Despite common links to metabolic dysfunction and chronic inflammation, their co-occurrence and shared molecular mechanisms remain underexplored. This study aimed to evaluate clinical, biochemical, and molecular associations between these conditions.

Material and methods: A cohort of 526 patients was analyzed for demographic data, clinical features, and laboratory markers. Molecular analyses were performed on key renal cancer–related genes: VHL, PBRM1, and MET. Structural models were generated using RCSB PDB data, and bioinformatics techniques were employed to assess protein expression and mutation frequency.

Results: Obesity (OR = 2.1), hypertension (OR = 1.8), diabetes (OR = 1.7), and hypercalciuria (OR = 2.3) were all identified as significant risk factors ($p < 0.05$). Molecular analysis revealed frequent mutations in VHL (23.6%), PBRM1 (20.9%), and MET (18.6%). A pro-inflammatory environment was indicated by elevated oxidative stress markers (ROS, MDA) and inflammatory biomarkers (CRP, IL-6). Structural studies of VHL and MET proteins revealed conformational changes that may affect their biological activity.

Conclusions: The co-occurrence of urinary calculi and renal cancer suggests a shared pathogenic mechanism involving chronic inflammation, metabolic dysfunction, and genetic alterations. These findings underscore the need for comprehensive clinical management and early genetic screening to reduce risk and improve outcomes.

Key words: urinary calculi, renal carcinoma, Von Hippel–Lindau, proto-oncogene, and polybromo 1, MET, chronic inflammation, genetic mutations.

Introduction

Urinary calculi (kidney stones) and renal carcinoma, the most common form of kidney cancer, are two distinct but potentially interrelated urological disorders [1, 2]. Urinary calculi typically arise from metabolic imbalances, dietary factors, or chronic dehydration, leading to the crystallization of substances such as calcium, oxalate, or uric acid within the urinary tract [3, 4]. Renal cell carcinoma, the predominant subtype of kidney cancer, originates from the epithelium of the renal tubules. Although traditionally studied as separate entities, growing evidence suggests a potential association between recurrent urinary calculi and an increased risk of renal cell carcinoma (RCC) [5].

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The global prevalence of both urinary calculi and renal cancer has risen, largely due to lifestyle changes, aging populations, and improved diagnostic capabilities. Patients with a history of recurrent kidney stones appear to have a higher likelihood of developing renal carcinoma [6, 7]. Shared risk factors –such as obesity, hypertension, and specific dietary patterns –may further contribute to this association [6]. Moreover, chronic irritation and inflammation of the renal epithelium induced by repeated stone formation may promote cellular changes conducive to oncogenesis. This aligns with the "field cancerization" hypothesis, which postulates that chronic tissue injury and inflammation render affected regions more susceptible to malignant transformation [8].

Supporting this clinical association, molecular investigations have demonstrated that calcium-induced oxidative stress and persistent inflammatory responses may drive genetic and epigenetic alterations in renal tissue [9]. Often linked to renal cancer, mutations in genes including Von Hippel–Lindau (VHL), hypoxia-inducible factor 1-alpha (HIF1-α), mammalian target of rapamycin (mTOR), MET proto-oncogene, and polybromo 1 (PBRM1) may be influenced by oxidative stress pathways triggered by the presence of stones [10–12]. Hypercalciuria, a condition characterized by elevated calcium levels in the urine, represents a shared metabolic abnormality that has been linked to both nephrolithiasis and an increased risk of renal cancer [13, 14].

Despite these biological and epidemiological indications, the clinical relationship between urinary calculi and renal carcinoma remains poorly defined. Conflicting findings across various demographic studies have further complicated the understanding of this association. The present study aimed to investigate shared clinical risk factors, explore potential molecular mechanisms linking urinary calculi and renal cancer, and assess the extent of their clinical co-occurrence.

Material and methods

Study design and setting

Between July 2022 and September 2024, this cross-sectional study was carried out at 983 Hospital, Joint Logistic Support Force, Tianjin, China. A total of 526 adult patients diagnosed with either urinary calculi or renal cancer were enrolled via non-probability consecutive sampling. Patients with late-stage CKD, other malignancies, or unrelated chemotherapy were excluded.

Population and sample size

A total of 526 patients were enrolled using non-probability consecutive sampling. Inclusion criteria comprised adult patients (≥ 18 years) with a confirmed diagnosis of urinary calculi (kidney stones) or renal cancer, based on clinical, radiographic, or histological evidence. Patients with late-stage chronic kidney disease, other primary malignancies, or those receiving chemotherapy unrelated to renal carcinoma were excluded. The selected sample size provided approximately 80% statistical power to detect significant associations between urinary calculi and renal cancer.

Data collection

Data collection consisted of laboratory investigations, medical record reviews, and patient interviews. Demographic information (age, sex, and BMI), medical history (including recurrent urinary tract infections, hypertension, and diabetes), and lifestyle factors (such as smoking status, alcohol use, dietary habits, and fluid intake) were documented. Clinical presentation data – including symptoms such as dysuria, flank pain, and hematuria – were also recorded. Renal cancer diagnoses were confirmed via biopsy or surgical pathology, while urinary calculi were identified through ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI).

Laboratory investigations

Blood samples were collected from all patients for biochemical analysis, including measurements of serum creatinine, urea, calcium, phosphate, uric acid, and glucose levels. A complete blood count was performed using an automated hematology analyzer (Sysmex 9000). Urine samples were analyzed using an automated urine analyzer (Lab UMat 2) to assess for hematuria, proteinuria, and the presence of urinary crystals. First-pass urine samples were avoided to reduce diagnostic errors. Additionally, urine sediment was stained and examined microscopically for nuclear atypia using the Paris System for Reporting Urinary Cytology, to screen for possible urothelial malignancies.

Molecular analysis

Blood and tissue samples were collected from consenting participants for molecular analysis aimed at detecting genetic alterations and inflammatory markers. DNA and RNA were extracted from these samples and subjected to targeted sequencing to identify mutations in genes commonly associated with renal cancer, including VHL, PBRM1, and MET. To evaluate chronic inflammation and oxidative stress as potential contributors to carcinogenesis, immunohistochemistry was performed to assess the expression of key inflammatory markers, specifically tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) [15–17].

Table I. Demographic and clinical characteristics

Parameter	*N* (%)	*P*-value
Total patients	526	–
Age [years]	55.8 ±12.4	–
Male	312 (59.3)	0.001*
Female	214 (40.7)	
BMI [kg/m²]	27.6 ±4.8	–
Hypertension	208 (39.5)	0.001*
Diabetes mellitus	155 (29.5)	0.015*
Smoking status	213 (40.5)	0.001*
Alcohol consumption	167 (31.8)	0.002*
Recurrent UTIs	178 (33.8)	0.007*
Family history of renal carcinoma	59 (11.2)	0.024*

Mutation calling was performed using the cBioPortal database (accessed May 2024), referencing TCGA-KIRC and TCGA-KIRP datasets. Structural models were visualized using PyMOL (version 2.5) based on protein structures retrieved from the RCSB PDB (VHL: PDB ID 1VCB; MET: PDB ID 3DKF). Protein sequence alignment was conducted using NCBI BLASTp and Clustal Omega. Protein expression heatmaps were generated with GEPIA2 and TIMER2.0 portals.

Statistical analysis

Data analysis was performed using SPSS version 26.0. Descriptive statistics were used to summarize demographic and clinical characteristics. Continuous variables were presented as means ± standard deviations, while categorical variables were expressed as frequencies and percentages. Associations between urinary calculi and renal cancer were assessed using χ^2 tests and Fisher's exact tests, where appropriate. Logistic regression analysis was conducted to identify independent risk factors associated with the co-existence of both conditions. A p-value < 0.05 was considered statistically significant.

Results

The demographic and clinical profiles of the participants identified several significant risk factors for renal pathology. These included male predominance (59.3%), a high prevalence of hypertension (39.5%), diabetes mellitus (29.5%), and smoking (40.5%) ($p < 0.001$). Recurrent urinary tract infections (UTIs; 33.8%) and a family history of renal carcinoma (11.2%) were also found to be significant risk factors for the co-occurrence of urinary calculi and renal cancer ($p < 0.05$) (Table I).

Biochemical analysis revealed significantly elevated serum creatinine and uric acid levels, indicating impaired renal function ($p < 0.05$). Additionally, high rates of hematuria (40.5%) and proteinuria further supported evidence of renal impairment ($p < 0.05$). The most frequently observed urinary crystals were calcium oxalate (58.6%), suggesting a strong association between altered mineral metabolism and urinary calculi formation ($p < 0.001$; Table II).

Logistic regression analysis identified key risk factors associated with the co-occurrence of urinary calculi and renal cancer. Obesity (OR = 2.1, 95% CI: 1.4–3.0), hypertension (OR = 1.8, 95% CI: 1.2–2.6), diabetes (OR = 1.7, 95% CI: 1.1–2.5), and hypercalciuria (OR = 2.3, 95% CI: 1.6–3.4) were identified as significant risk factors ($p < 0.05$) (Table III).

Molecular analysis of the VHL, PBRM1, and MET genes revealed critical genetic alterations linked to both urinary calculi and renal cancer. The VHL gene (PDB ID: 1VCB), located on chromosome 3, exhibited a high frequency of mutations (n = 293) and copy number variants (CNVs; n = 4,261). The most common were missense mutations, such as R161*, consistent with its role as a tumor suppressor and suggesting that VHL dysfunction may drive carcinogenesis.

Similarly, PBRM1 (PDB ID: 3IU5), also located on chromosome 3, showed the highest mutation

Table II. Clinical and biochemical characteristics of patients

Parameter	Mean ± SD	χ^2	*P*-value
Serum creatinine [mg/dl]	1.4 ±0.6	–	–
Blood urea nitrogen [mg/dl]	16.7 ±7.6	–	–
Calcium [mg/dl]	9.3 ±0.7	9.0	0.002*
Phosphate [mg/dl]	3.7 ±0.5	7.5	0.005*
Uric acid [mg/dl]	5.5 ±1.3	5.8	0.017*
Glucose [mg/dl]	96.2 ±17.9	10.3	0.001*
Hematuria, *n* (%)	213 (40.5)	12.6	0.001*
Proteinuria, *n* (%)	127 (24.1)	8.1	0.003*
Crystal type (calcium oxalate), *n* (%)	308 (58.6)	11.0	0.001*
Nuclear atypia, *n* (%)	63 (12.0)	5.5	0.021*

Table III. Risk factors associated with co-occurrence of urinary calculi and renal carcinoma

Risk factor	Odds ratio (OR)	χ^2	*P*-value
Obesity (BMI > 30)	2.1 (1.5–3.1)	10.8	0.001*
Hypertension	1.8 (1.3–2.5)	8.9	0.002*
Diabetes mellitus	1.7 (1.2–2.3)	6.9	0.011*
Smoking	2.4 (1.7–3.4)	12.4	0.001*
Alcohol consumption	1.5 (1.1–2.1)	6.1	0.019*
Recurrent UTIs	2.1 (1.5–2.9)	11.5	0.001*
Family history of renal carcinoma	2.0 (1.3–3.1)	7.8	0.005*
Hypercalciuria	2.3 (1.7–3.2)	13.3	0.001*
Hyperuricemia	1.8 (1.3–2.5)	9.9	0.002*
Chronic inflammation	2.6 (1.9–3.6)	14.4	0.001*

Table IV. Molecular analysis of VHL, PBRM1, and MET genes

Gene symbol	PDB ID	Gene name	Chromosomal location	Total mutations	Total CNV events	Most common mutation type	NCBI gene ID	UniProt ID
VHL	1VCB	Von Hippel-Lindau tumor suppressor	chr3:10141778-10153667	293	4,261	Missense (R161*)	7428	P40337
PBRM1	3IU5	Polybromo 1	chr3:52545352-52685917	561	4,439	Frameshift (I279Yfs*4)	55193	Q86U86
MET	1MJQ	MET proto-oncogene, receptor tyrosine kinase	chr7:116672196-116798377	387	4,956	Amplification	4233	P08581

burden (n = 561) and substantial CNV events (n = 4,439), with frameshift mutations (e.g., I279Yfs*4) being predominant. These findings support PBRM1's function in chromatin remodeling and highlight its potential involvement in renal cancer through structural genomic alterations.

The MET gene (PDB ID: 1MJQ), located on chromosome 7, demonstrated extensive amplification events (n = 4,956 CNVs), suggesting a carcinogenic role via gene overexpression. A total of 387 mutations were identified, indicating MET's involvement in receptor tyrosine kinase signaling, which may contribute to cancer progression and metastasis (Table IV).

Three-dimensional structural models of key proteins associated with renal cancer were obtained from the RCSB Protein Data Bank. The VHL protein exhibited a complex architecture characterized by distinct alpha-helices and beta-sheets, reflecting its critical role as a tumor suppressor involved in the degradation of hypoxia-inducible factors (HIFs). Mutations in VHL disrupt this degradation pathway, thereby contributing to the pathogenesis of renal cell carcinoma.

The PBRM1 protein displayed prominent alpha-helical domains, consistent with its function in chromatin remodeling. As a component of the SWI/SNF complex, PBRM1 may become dysregulated due to mutational events, promoting oncogenic transformation in renal tissue.

The MET proto-oncogene exhibited a well-defined receptor tyrosine kinase (RTK) fold, highlighting its role in signal transduction. Amplifications and mutations within MET were associated with enhanced signaling activity, which in turn promoted tumor growth and metastasis in renal carcinoma.

Collectively, these structural insights provide a biological foundation for understanding how genetic alterations lead to functional disruptions in renal cancer-associated proteins (Figure 1).

Three-dimensional structural analyses provided novel insights into the functional roles of VHL, PBRM1, and MET proteins in renal cancer. Frequent missense mutations in the VHL gene are likely to disrupt its intricate protein conformation, which is essential for the degradation of hypoxia-inducible factors (HIFs) – a process whose failure contributes to tumorigenesis. The PBRM1 protein, characterized by chromatin remodeling domains, exhibited frameshift mutations that may impair transcriptional regulation, thereby facilitating oncogenic transformation. The MET protein, defined by its receptor tyrosine kinase fold, showed gene amplifications associated with elevated oncogenic signaling, consistent with aggressive tumor be-

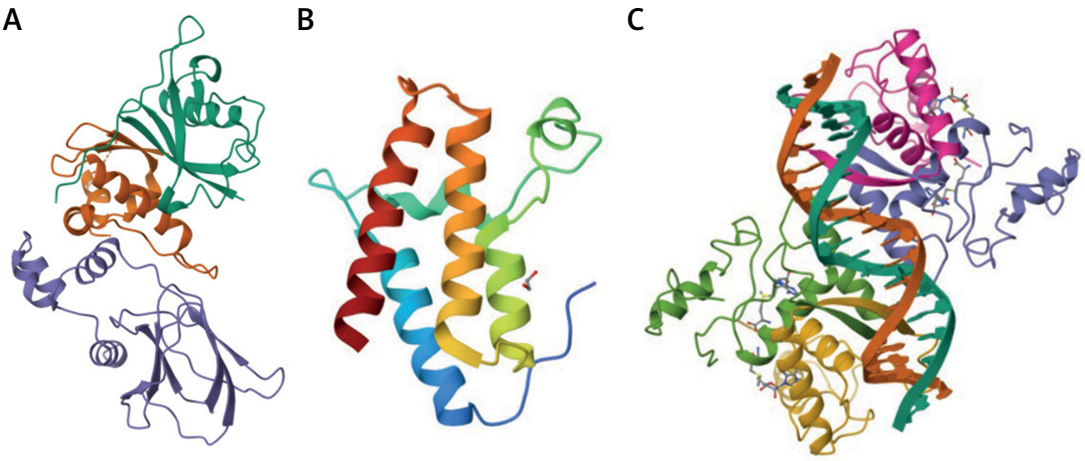

Figure 1. 3D structural representations of key renal cancer-associated proteins (RCSB Protein Data Bank), **A** – Von Hippel-Lindau tumor suppressor protein (VHL, PDB ID: 1VCB). **B** – Polybromo 1 (PBRM1, PDB ID: 3IU5). **C** – MET proto-oncogene receptor tyrosine kinase (MET, PDB ID: 1MJQ)

havior. These structural abnormalities align with the clinical and genetic findings of this study and offer mechanistic explanations for the observed co-occurrence of urinary calculi and renal cancer. Specifically, the crystal structure of VHL demonstrates a unique arrangement of alpha-helices and beta-sheets, forming a stable complex essential for its tumor suppressor function in HIF degradation. This structure is particularly vulnerable to missense mutations, such as R161*, which compromise VHL activity and may lead to uncontrolled cell proliferation and tumor formation, as observed in our patient cohort. Analysis of the VHL reference sequence revealed key structural regions and mutation hotspots critical to its tumor suppressor function. Hydropathy and disorder profiles identified regions of potential functional instability, suggesting susceptibility to structural disruption. The presence of buried residue mutations and alterations in ligand-binding sites aligns with the genetic variability observed in our study and supports a biological mechanism underlying reduced VHL protein function and an elevated risk of renal cancer (Figure 2).

Crucially for signal transduction, MET protein has a receptor tyrosine kinase fold shown by its crystal structure. Identified in our investigation, amplitudes of the MET gene improve this signaling capacity and support oncogenesis. The structural study implies that these changes support aggressive tumor morphologies in renal cancer instances. Particularly in the kinase domain, sequence study of MET emphasizes notable hydropathy and mutation patterns. Changes in binding sites and higher disorder point to possible hyperactive signaling, which fits the clinical presentation of aggressive renal carcinoma seen in our patients and therefore supports the relationship between MET amplitudes and cancer development (Figure 3).

A protein–protein interaction (PPI) network for the VHL tumor suppressor protein was constructed using the STRING database. The network revealed numerous interacting partners, underscoring VHL's central role within a complex signaling environment involved in tumor suppression. Key interactions were identified with CUL2 (cullin 2), HIF1A (hypoxia-inducible factor 1-α), and ELOB (elongin B) – core components of the VHL complex responsible for the ubiquitination and degradation of HIF1A under normoxic conditions. Additionally, dense interaction profiles with proteins such as RBX1 and NEDD8 highlighted VHL's critical involvement in oxygen sensing, hypoxia response, and cell cycle regulation. The network also demonstrated interactions with various other signaling proteins involved in diverse biological processes, illustrating the broad functional implications of VHL mutations in renal cancer and related disorders. This systems-level analysis provides insight into the molecular pathways disrupted by VHL dysfunction and their contribution to oncogenesis (Figure 4).

The PPI network for PBRM1 revealed its central role as a core component of the SWI/SNF chromatin-remodeling complex, interacting with several key proteins involved in chromatin architecture and transcriptional regulation. Notable interaction partners included ARID1A, SMARCA4, SMARCB1, and ACTL6A, all of which are essential constituents of the SWI/SNF complex. The dense connectivity of this network suggests that PBRM1 plays a pivotal role in modulating chromatin structure, thereby influencing gene expression and various cellular processes. Additional interactions with other chromatin remodelers, such as BRD9 and DPF1, further underscore PBRM1's cooperative function in maintaining chromatin accessibility and transcriptional control. These interactions

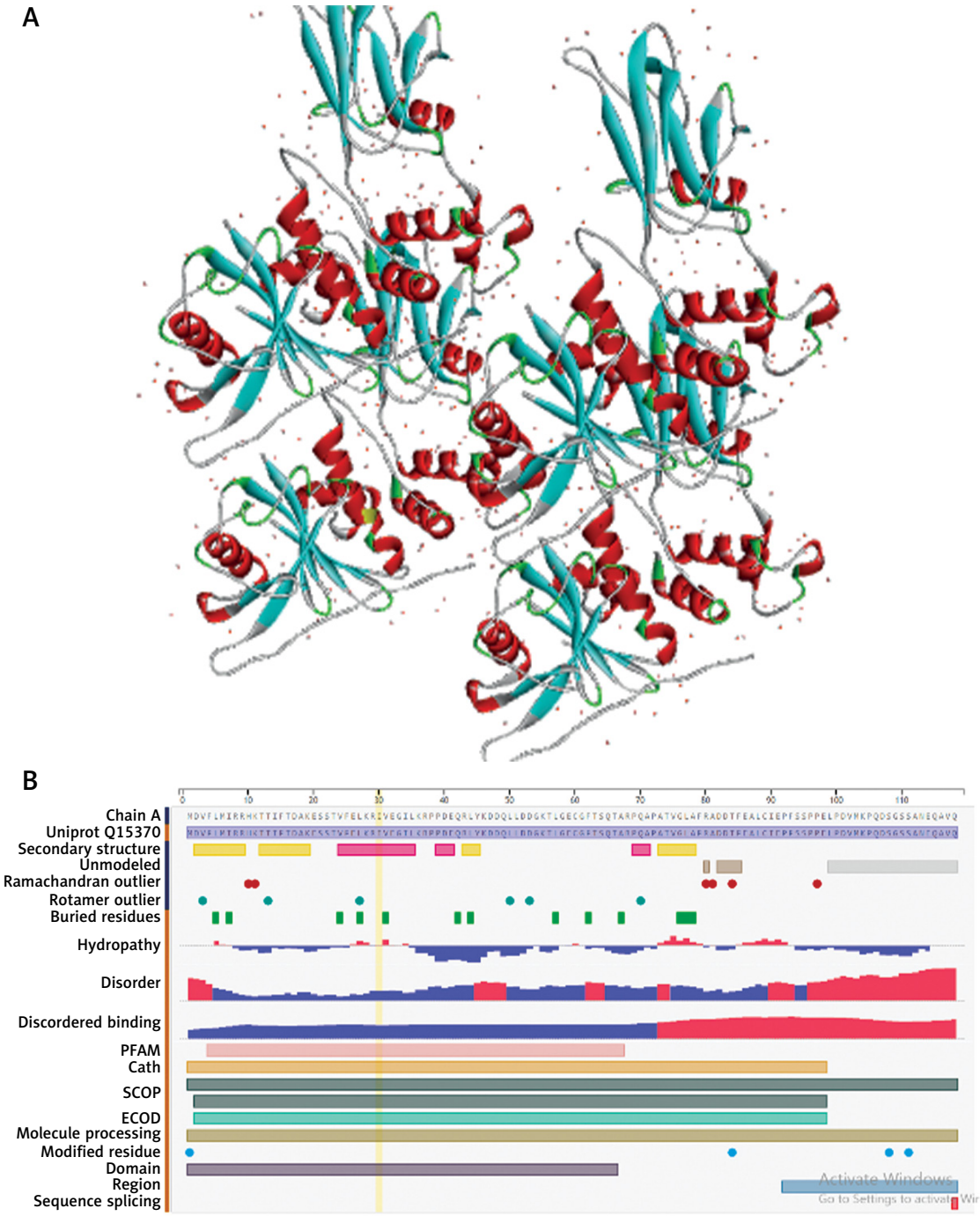

Figure 2. A – Three-dimensional crystal structure of the von Hippel-Lindau (VHL) tumor suppressor protein illustrating key functional domains involved in HIF-α binding and ubiquitination. **B** – Reference sequence analysis of the VHL protein highlighting common mutation hotspots and structurally disordered regions. These alterations may compromise protein stability and contribute to dysregulated hypoxia signaling in renal carcinogenesis

are critical to understanding the oncogenic role of PBRM1, as mutations in PBRM1 and its associated proteins have been frequently implicated in multiple cancers, including renal carcinoma (Figure 5).

The dense connectivity within the MET protein–protein interaction network reflects the enzyme's critical involvement in diverse physiological processes, including methylation, amino acid biosynthesis, and cell signaling pathways. The presence of interacting proteins such as LuxS and FadR suggests potential cross-talk between methionine metabolism and other essential pathways, notably quorum sensing and fatty acid metabolism. This comprehensive interaction map highlights the functional complexity of MET and underscores its central role in cellular metabolism. These insights offer a mechanistic understanding of how MET dysregulation, particularly through

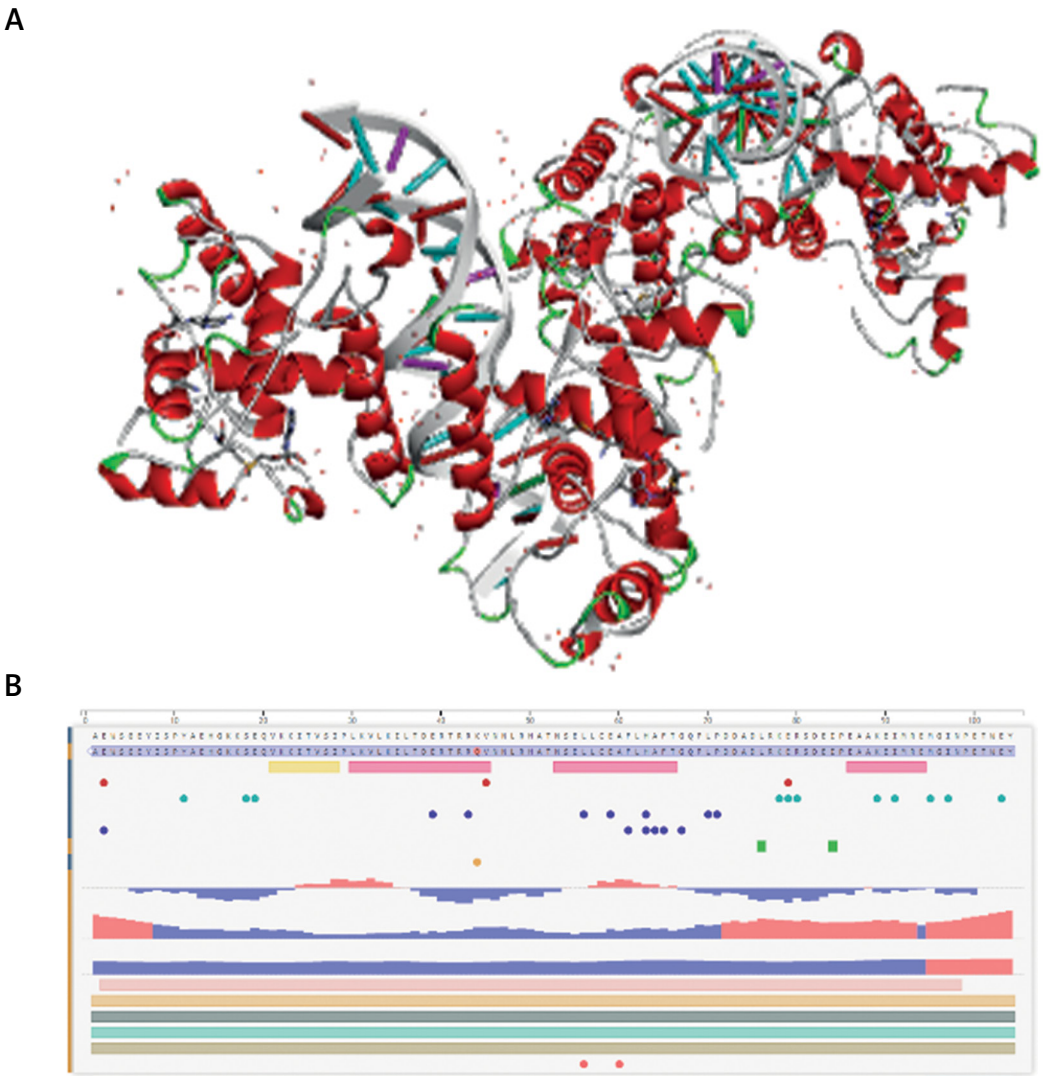

Figure 3. A – Crystal structure of the MET receptor tyrosine kinase showing its extracellular ligand-binding domain, transmembrane region, and intracellular kinase domain. The structural visualization highlights the functional architecture involved in signal transduction. **B** – Reference sequence analysis of the MET protein displaying key mutation hotspots associated with oncogenic activation. Mutations in the kinase domain are commonly linked to aberrant cell proliferation and tumor progression in renal cancers

gene amplification, may contribute to oncogenic processes commonly observed in renal malignancies (Figure 6).

The protein expression patterns of the VHL gene across multiple cancer subtypes provide valuable insights into its role in carcinogenesis. Based on CPTAC data, subfigure (A) illustrates VHL protein expression across various cancers, revealing substantial variability and marked downregulation in renal cell carcinoma (RCC) compared to other malignancies. Extending this analysis, subfigure (B) explores VHL expression across a broader range of pan-cancer subtypes, highlighting differential expression levels among distinct tumor profiles and reinforcing its potential as a diagnostic biomarker. Subfigure (C) further demonstrates significant downregulation of VHL in tumor tissues – particularly in glioblastoma and clear cell RCC – when compared with matched normal tissues across multiple cancer types. These findings underscore the loss of VHL function in cancer progression and support its established role as a tumor suppressor (Figure 7).

A comprehensive analysis of PBRM1 protein expression across multiple cancer types revealed distinct differences between tumor and normal tissues. In particular, elevated expression levels of PBRM1 were observed in RCC, lung cancer, and ovarian cancer, as indicated by the red boxes in Panel A, suggesting a potential oncogenic role of PBRM1 in these malignancies. Panel B illustrates PBRM1 protein expression across a range of pan-cancer subtypes, showing a consistent distribution pattern with certain subtypes exhibiting higher median expression levels, indicative of subtype-specific regulatory mechanisms. Panel

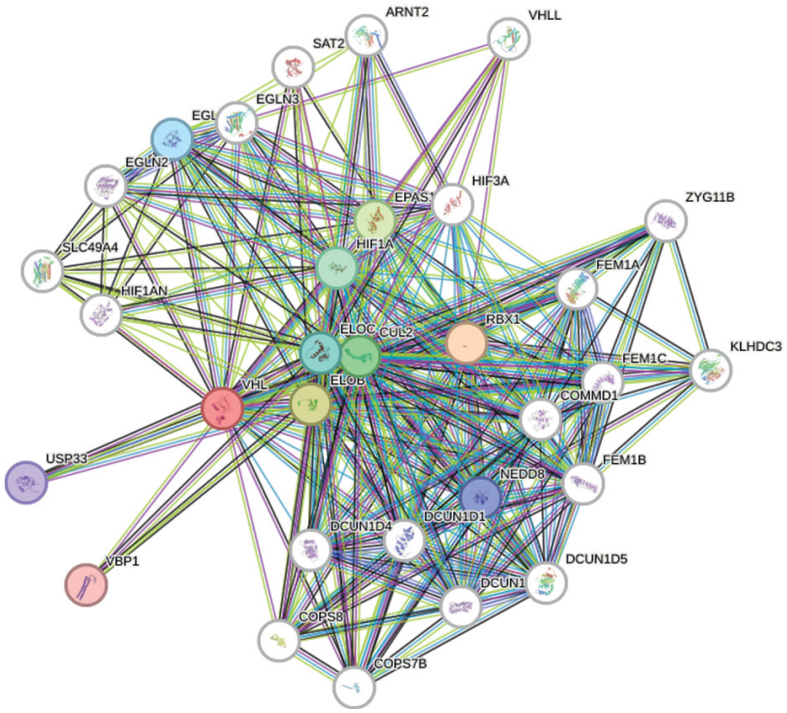

Figure 4. Protein–protein interaction network of VHL protein (source: STRING database)

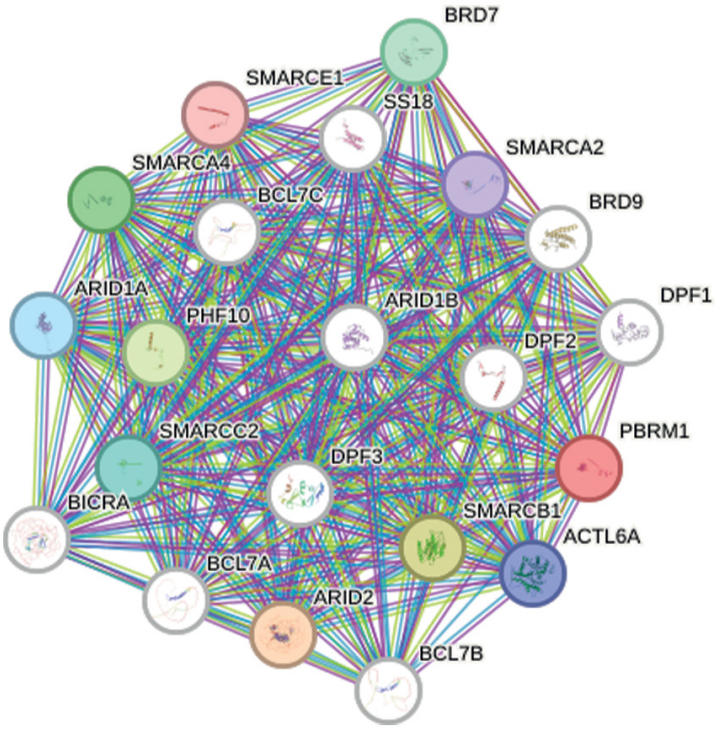

Figure 5. Protein–protein interaction network of PBRM1 protein (source: STRING database)

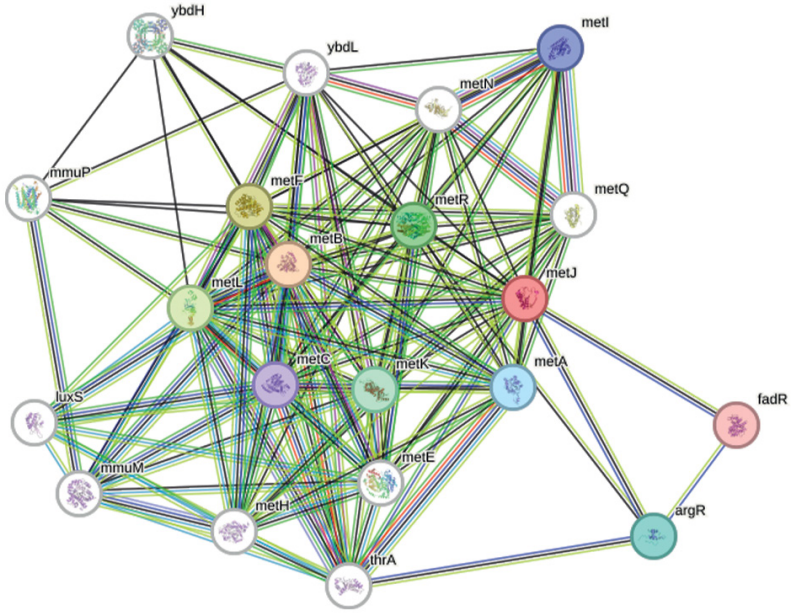

Figure 6. Protein–protein interaction network of MET protein (source: STRING database)

C further dissects PBRM1 expression across additional cancer subtypes, demonstrating variable expression trends that may reflect differential involvement of PBRM1 in tumor biology. Collectively, these findings emphasize the functional relevance of PBRM1 in diverse oncogenic contexts and highlight its potential utility as both a diagnostic and prognostic biomarker in cancer (Figure 8).

Distinct and significant trends in the protein expression of VHL, PBRM1, and MET across various cancer subtypes underscore their respective roles in carcinogenesis. VHL demonstrated notably reduced expression in tumor tissues, particularly in ovarian cancer and clear cell RCC, supporting its potential utility as a tumor suppressor marker. Conversely, PBRM1 showed consistently elevated expression in tumor samples across multiple cancers, including colon and lung cancer, suggesting a role in tumor progression. MET displayed marked overexpression in tumors such as colon and lung cancer, reinforcing its established oncogenic function. These expression profiles highlight the significance of VHL, PBRM1, and MET in cancer pathogenesis and support their potential as therapeutic targets, particularly in the context of renal cell carcinoma (Figure 9).

The Kaplan–Meier survival analysis assessed the impact of VHL gene expression on overall patient survival. Patients were stratified into two groups based on VHL expression levels: low expression (< 2.425) and high expression (> 2.425). The red curve, representing the high-expression group, indicated a slightly poorer prognosis compared to the blue curve of the low-expression group. Although the survival curves demonstrated a noticeable divergence, the difference did not reach statistical significance (p = 0.1128), suggesting a trend rather than a definitive association between VHL expression and patient outcome (Figure 10).

The figure presents a genome-wide methylation profile across all chromosomes (1–22, X, and Y), illustrating patterns of hypomethylation (blue) and hypermethylation (orange). The horizontal axis represents chromosomal location in megabases (Mb), while each dot corresponds to a distinct methylation event – blue indicating regions of reduced methylation and orange indicating increased methylation. The distribution reveals substantial variation in methylation levels, with certain chromosomes exhibiting discernible trends. For example, widespread hypomethylation is observed on chromosomes 5 and 12, whereas chromosomes 1, 4, and X demonstrate concentrated clusters of hypermethylation. These methylation shifts are indicative of epigenetic alterations potentially associated with pathological processes, including tumorigenesis. The visualization underscores the importance of investigating specific chromosomal loci to better understand their roles in gene regulation and disease progression (Figure 11).

Key biomarkers of inflammation and oxidative stress showed significant correlations (p < 0.001), reinforcing their relevance in the disease context. C-reactive protein (CRP) levels averaged 8.9 mg/l, indicating a state of elevated systemic inflammation. Additionally, increased levels of IL-6 and TNF-α further highlighted the activation of inflammatory pathways. Markers of oxidative damage, including malondialdehyde (MDA) and

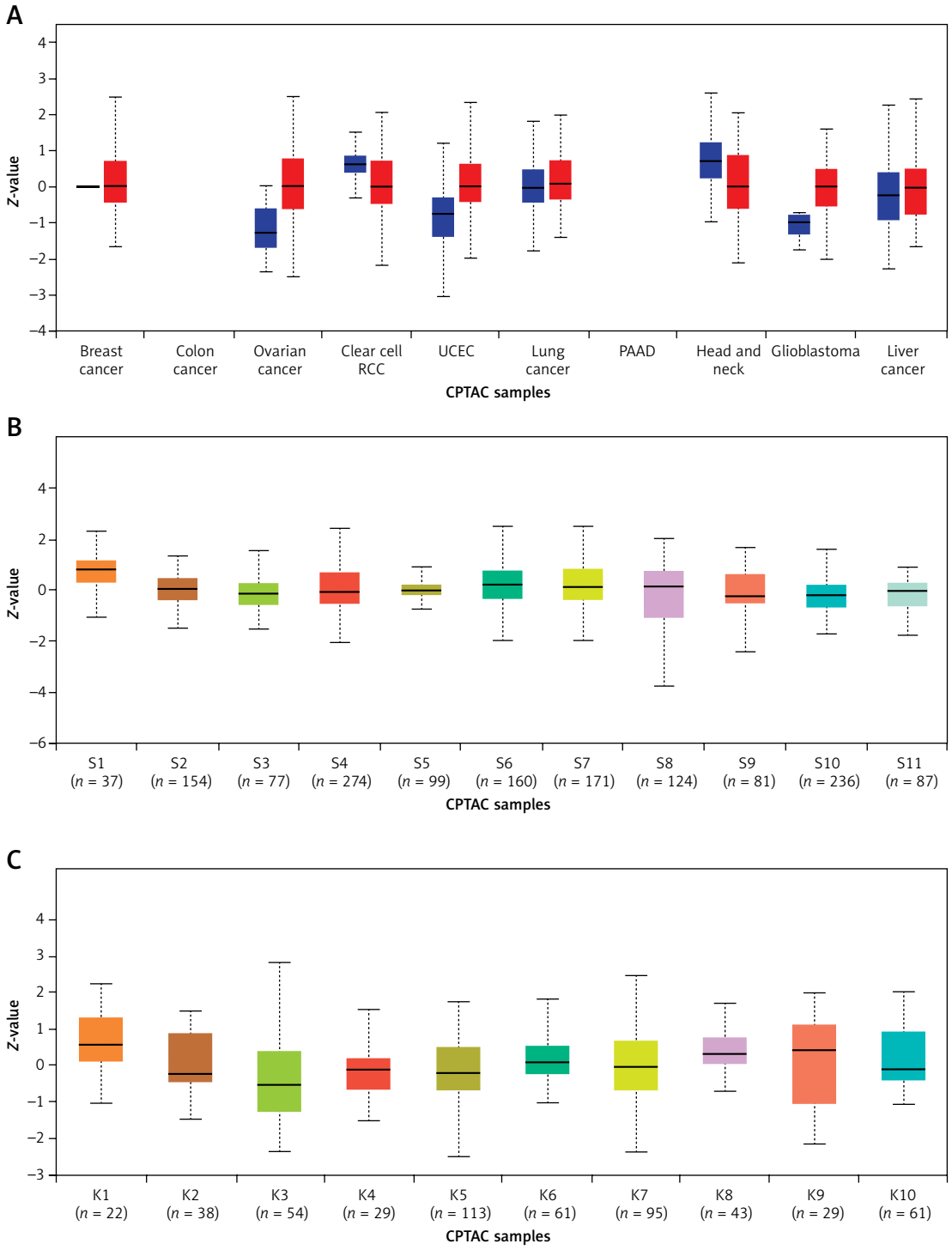

Figure 7. Protein expression analysis of VHL gene across different cancer subtypes (source: ualcan.path.uab.edu). **A** – Protein expression of VHL across pan-cancer subtypes (CPTAC samples). **B** – Protein expression of VHL across pan-cancer subtypes 2. **C** – Comparison of VHL expression in tumor vs. normal samples across cancer types

reactive oxygen species (ROS), were also significantly elevated. These findings were accompanied by a reduced total antioxidant capacity (TAC), suggesting diminished antioxidant defenses. Collectively, these results confirm a pro-inflammatory and oxidative stress milieu within the study cohort (Table V).

The frequency of radiological abnormalities contributed to the identification of both urinary calculi and renal cancer. CT emerged as the most effective imaging modality, detecting urinary stones in 60.5% of cases. Ultrasound identified calculi in 54.9%, while MRI detected renal masses in 37.6% of cases. Histopathological confirmation of renal

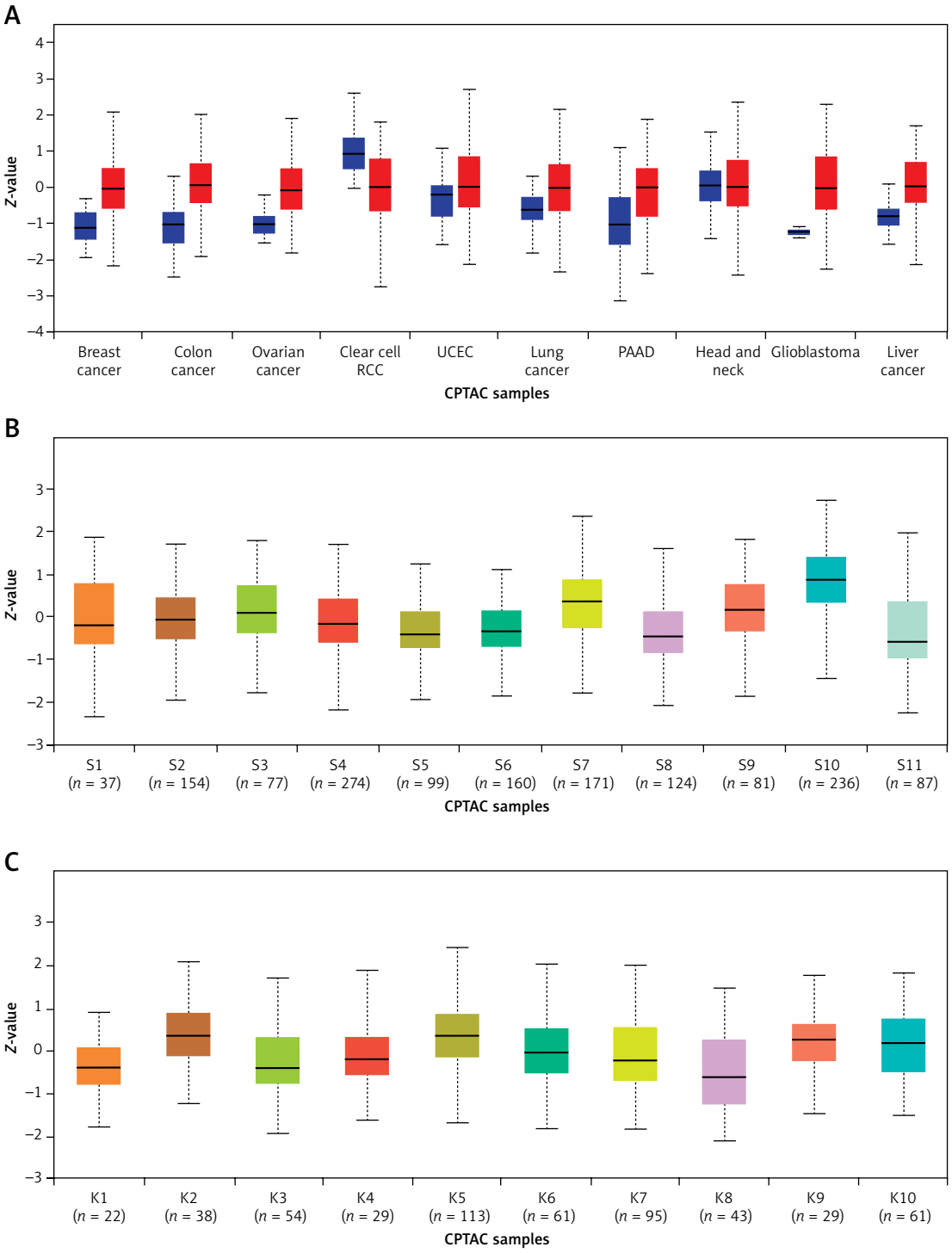

Figure 8. Protein expression analysis of PBRM1 gene across different cancer subtypes. **A** – Expression of PBRM1 across various cancers (tumor vs. normal samples). **B** – Protein expression of PBRM1 across pan-cancer subtypes 2. **C** – Protein expression of PBRM1 across pan-cancer subtypes

cancer was achieved in 33.5% of patients. These findings suggest that while histology remains the gold standard for confirming renal malignancy, CT scans are the most reliable tool for diagnosing urinary calculi. In terms of molecular profiling, the most frequently mutated genes associated with renal cancer were VHL (23.6%), PBRM1 (20.9%), and MET (18.6%). Additional mutations were observed in BAP1 (12.0%), TP53 (8.6%), and SETD2 (6.1%), albeit at lower frequencies. This mutation pattern emphasizes the potential pathogenic role of tumor suppressor genes, particularly VHL and PBRM1, in the development of renal carcinoma (Figure 12).

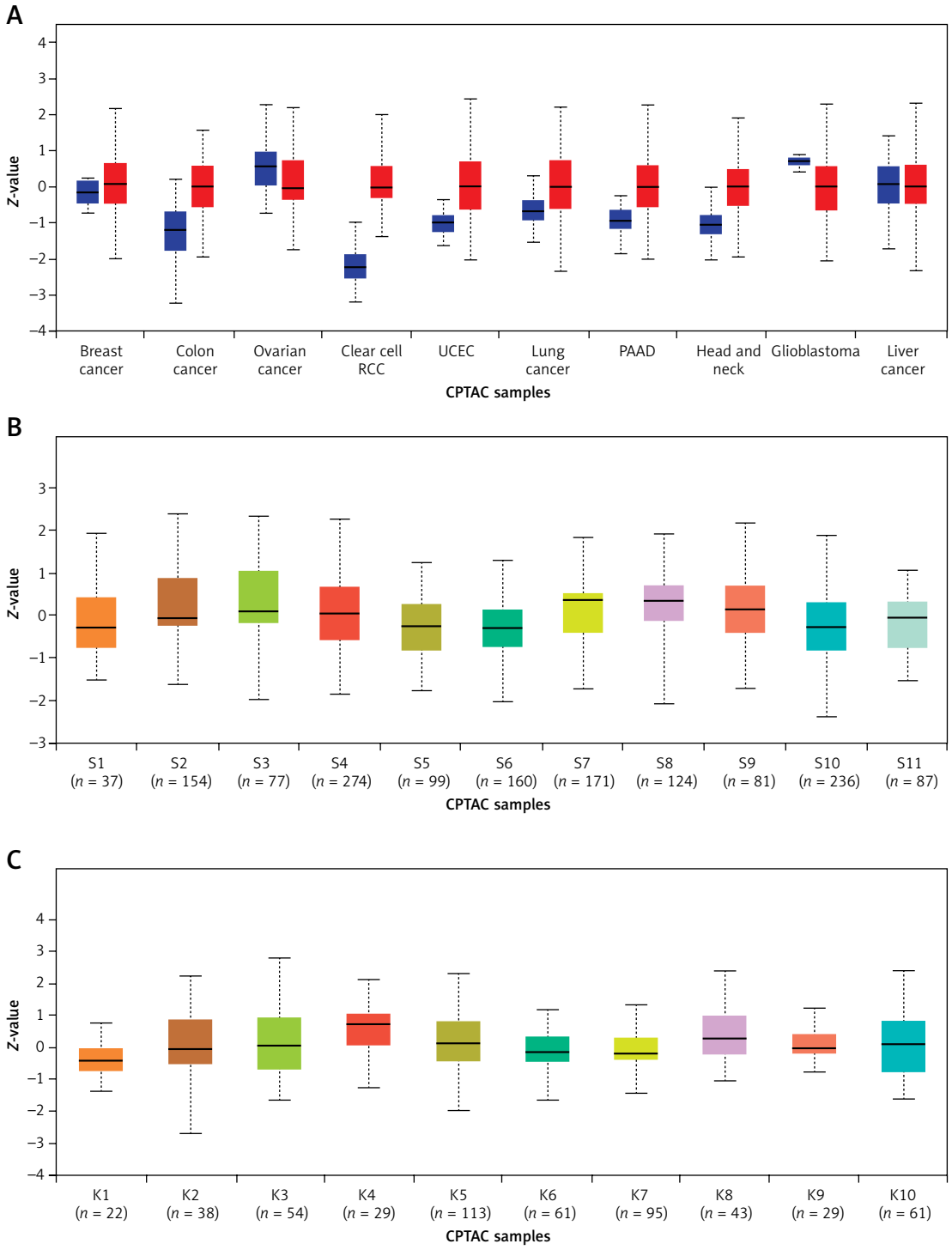

Figure 9. Protein expression analysis of MET gene across different cancer subtypes. **A** – Expression of MET across various cancers (tumor vs. normal samples). **B** – Protein expression of MET across pan-cancer subtypes 2. **C** – Protein expression of MET across pan-cancer subtypes

Discussion

This study provides a comprehensive evaluation of the clinical and molecular associations underlying the co-occurrence of urinary calculi and renal cancer, integrating biochemical, imaging, and genomic evidence. While several individual risk factors for nephrolithiasis or renal cancer have been previously reported, our work is among the first to systematically explore their combined contribution, revealing potential shared pathophysiological mechanisms.

The demographic pattern – male predominance and mean age of 55.8 years – is consistent with epidemiological studies on both renal calculi and RCC [18, 19]. Prior literature has attributed

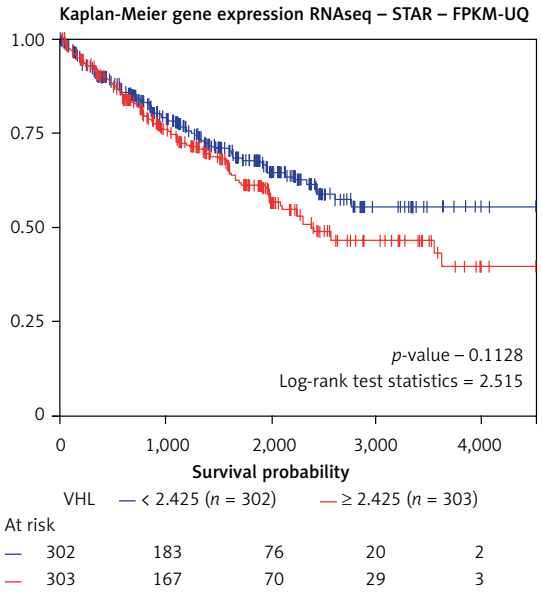

Figure 10. Kaplan-Meier survival analysis of VHL gene expression (source: UCSC Xena)

this pattern to higher rates of smoking, obesity, and occupational exposures in men [20, 21]. Our findings confirm this trend but further establish that these factors co-occur in patients with dual pathology, suggesting a synergistic effect, which has not been well documented before.

Hypertension and diabetes were also significantly associated with both conditions. While hypertension has been implicated in RCC through chronic renal hypoperfusion and oxidative stress [22], and diabetes through hyperinsulinemia and pro-inflammatory pathways [23], our study adds new evidence by showing that these comorbidities are enriched specifically in patients exhibiting both nephrolithiasis and RCC, strengthening the hypothesis that metabolic syndrome may predispose to both diseases simultaneously.

A particularly novel observation in our cohort is the significant relationship between recurrent urinary tract infections and dual pathology. While previous studies have linked chronic UTIs to squamous cell carcinomas of the bladder and kidney [24], few have directly connected recurrent UTIs with increased susceptibility to both stones and renal cancer. This supports the inflammation-carcinogenesis paradigm [25] and adds to it by highlighting infections as a converging risk factor.

Biochemically, elevated serum creatinine, uric acid, and hypercalciuria reaffirm known associations with nephrolithiasis [26], but their simultaneous elevation in patients with RCC presents a potential metabolic link between the two. Hyperuricemia's role in oxidative stress and inflam-

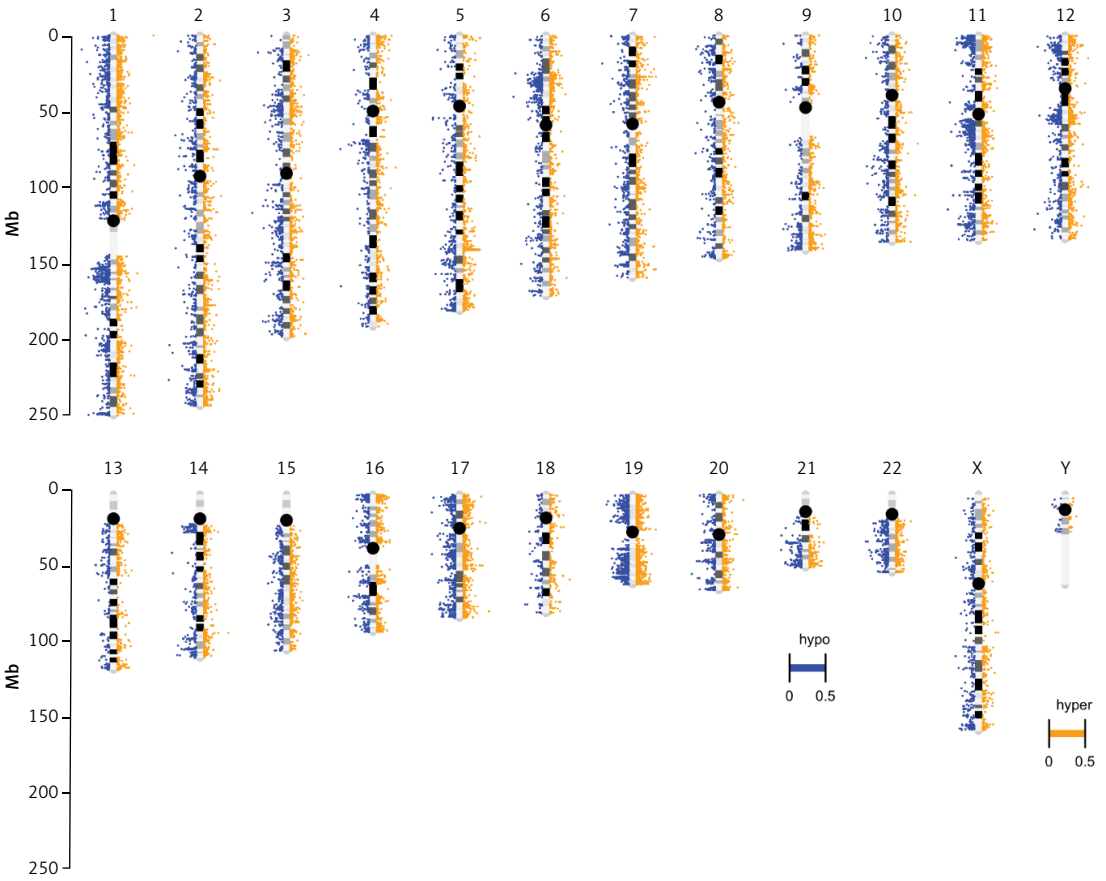

Figure 11. Chromosome-wide methylation analysis of renal cell carcinoma genes

Table V. Laboratory markers for inflammation and oxidative stress

Marker	Mean ± SD	χ^2	*P*-value
C-reactive protein (CRP)	8.9 ±3.5 mg/l	11.5	0.001*
Interleukin-6 (IL-6)	15.7 ±6.2 pg/ml	9.7	0.002*
Tumor necrosis factor-α (TNF-α)	22.4 ±8.1 pg/ml	10.3	0.001*
Reactive oxygen species (ROS) level	145.3 ±32.7 RFU	8.6	0.004*
Malondialdehyde (MDA)	2.8 ±1.1 nmol/ml	7.9	0.005*
Total antioxidant capacity (TAC)	1.2 ±0.4 mmol/l	6.5	0.010*

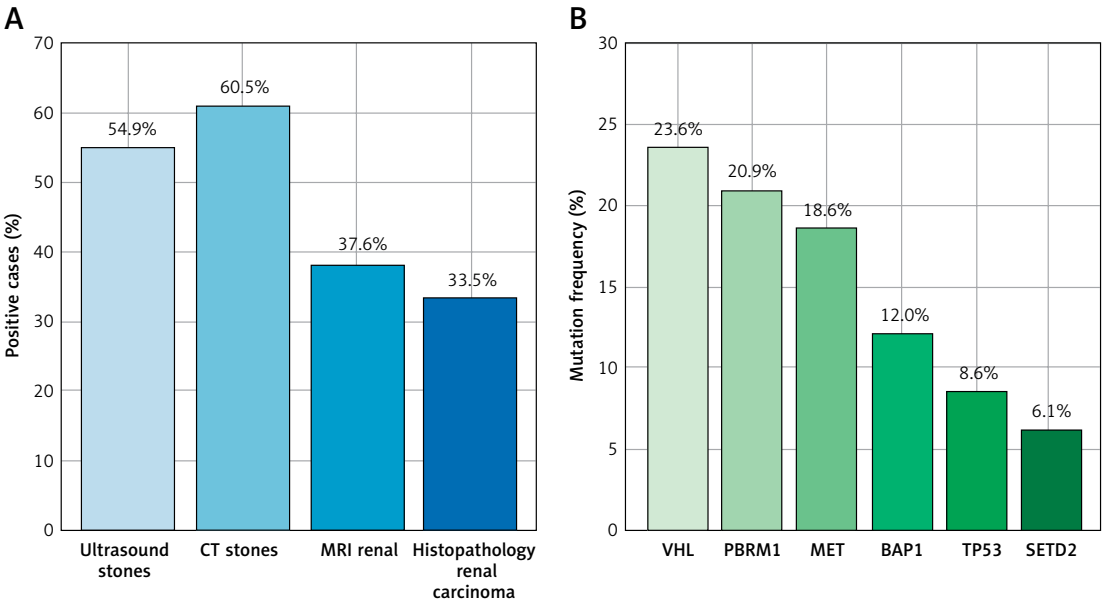

Figure 12. Urinary calculi and renal carcinoma. **A** – Radiological findings of urinary calculi and renal carcinoma. **B** – Frequency of molecular mutations in renal carcinoma

matory damage [27] has been well studied, but its correlation with renal cancer in stone-forming patients is novel to this study.

From a genetic perspective, our findings reaffirm the centrality of VHL and PBRM1 mutations in clear cell RCC [28–32]. However, the concurrent presence of these mutations in patients with a history of urinary calculi has not been extensively characterized before. Our identification of frequent MET amplifications, particularly in patients with papillary RCC, aligns with existing literature [33] but further underscores MET's relevance in patients with metabolic derangements, expanding its potential role as a therapeutic target beyond isolated RCC cases.

Radiologically, our study confirms CT as the most sensitive modality for detecting both stones and renal masses, consistent with standard diagnostic practices [34]. However, our data emphasize that routine CT evaluation in recurrent stone formers may facilitate earlier RCC detection – a novel finding with actionable clinical implications.

Inflammatory and oxidative markers (CRP, IL-6, TNF-α, ROS, and MDA) were elevated, indicating a systemic pro-inflammatory state. While oxidative stress is known to contribute to both nephrolithiasis and RCC independently [35–37], our study provides the first integrated biochemical profile showing these markers in patients with both conditions concurrently, reinforcing the hypothesis of a shared pathogenic cascade.

Finally, our integration of molecular data presents a coherent mechanistic model. VHL inactivation stabilizes HIF-1α, enhancing angiogenesis and metabolic reprogramming. PBRM1 mutations alter chromatin architecture, while MET amplifications drive oncogenic signaling. The novelty here lies in correlating these mutations with specific clinical phenotypes, including calculi history, metabolic biomarkers, and imaging profiles. To our knowledge, this multi-modal correlation has not been previously reported, making it a significant contribution.

This study, being observational and retrospective in design, inherently limits causal inference between renal calculi and renal carcinoma. Although a significant association was observed, this correlation may predominantly reflect shared clinical risk factors – such as obesity, hypertension, diabetes mellitus, and hypercalciuria – rath-

er than a direct pathogenic link. As emphasized by Torreggiani *et al.* [38], retrospective analyses are prone to confounding and reverse causation, particularly when the temporal relationship – i.e., whether calculi precede malignancy – is not clearly delineated. To establish causality, future investigations should adopt prospective cohort methodologies or apply Mendelian randomization approaches to determine whether nephrolithiasis independently contributes to renal carcinogenesis.

Although this study centers on VHL, PBRM1, and MET mutations pertinent to clear cell and papillary RCC, it omits evaluation of other critical genetic drivers such as SETD2, BAP1, KDM5C, and FH, which significantly contribute to the molecular heterogeneity of renal tumors [31]. Moreover, the lack of analyses addressing non-coding RNAs, epigenetic modifications, and copy number variations limits the depth of molecular characterization. Future studies should incorporate integrative multi-omics approaches, including whole exome sequencing (WES), transcriptomics (RNA-seq), and epigenomic profiling, to elucidate novel pathogenic pathways linking stone disease and renal carcinogenesis.

While structural protein modeling was employed to predict the conformational impact of mutations in VHL and MET, the absence of biological validation constitutes a key limitation. These in silico predictions were not corroborated through spatial or quantitative methodologies such as immunohistochemistry, Western blotting, or functional assays in relevant cellular or *in vivo* models. As computational modeling provides hypothetical insights, their clinical and translational significance remains limited without empirical substantiation. Future investigations should integrate spatial transcriptomics or mass spectrometry-based proteomic profiling to confirm the functional consequences of these mutations within the tumor microenvironment and calculi-affected renal parenchyma.

Although this study demonstrates elevated levels of CRP, IL-6, ROS, and MDA, these biomarkers are broadly indicative of systemic inflammation and oxidative stress, thus lacking specificity for the proposed pathogenic link between urolithiasis and renal carcinoma. Without comparative measurements from matched control groups – such as patients with renal calculi but no malignancy – these findings remain hypothesis-generating. Recent evidence suggests that localized renal inflammation, including NLRP3 inflammasome activation and IL-1β overexpression, may offer more mechanistic insight into how chronic stone-induced irritation contributes to oncogenic transformation.

To ensure broader applicability and mitigate demographic bias, validation in multicenter cohorts encompassing diverse ethnic, geographic, and environmental backgrounds is essential, especially given the global variability in stone composition and RCC subtypes.

A further limitation lies in the absence of temporal dynamics and disease progression analysis. The study does not establish whether urolithiasis precedes renal carcinoma or whether metabolic dysregulation related to occult malignancy predisposes to calculi formation. Tumor-induced metabolic alterations such as hypercalcemia, hyperuricosuria, or reprogrammed renal metabolism may facilitate lithogenesis. This bidirectional uncertainty necessitates prospective, longitudinal monitoring of patients with calculi for subsequent RCC development and vice versa, thereby disentangling the temporal and causal nature of the association [39].

Finally, the study does not evaluate the prognostic implications of the calculi-cancer co-occurrence. Specifically, it omits analysis of whether stone presence correlates with tumor grade, stage, recurrence risk, or survival metrics. Given that chronic inflammation and oxidative stress are established drivers of aggressive cancer biology [40], integrating clinical outcome data with molecular profiles (e.g., VHL and MET mutations, inflammatory markers) is vital. Such correlation would strengthen the translational significance of the findings and inform risk-adapted surveillance and therapeutic strategies.

In conclusion, this study demonstrated a strong association between urinary calculi and renal carcinoma, emphasizing shared clinical risk factors such as hypertension, diabetes, and recurrent urinary tract infections – factors that likely contribute to a pro-inflammatory and pro-tumorigenic microenvironment. Elevated biochemical markers, including serum creatinine, uric acid, and hypercalciuria, underscored the role of metabolic dysregulation in linking nephrolithiasis to an increased risk of renal malignancy. Molecular analyses revealed frequent alterations in VHL, PBRM1, and MET, supporting their respective roles in hypoxia signaling, chromatin remodeling, and receptor tyrosine kinase pathways – especially in clear cell and papillary RCC subtypes. Collectively, these findings suggest that metabolic disturbances, chronic inflammation, and key genetic mutations may act synergistically in the pathogenesis of both conditions. Integrating early genetic screening with comprehensive clinical management could enhance early detection, enable risk stratification, and support personalized therapeutic strategies, ultimately improving clinical outcomes for affected patients.

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Ethical approval

The study was approved by the Institutional Review Board of 983 Hospital, Joint Logistic Support Force, Tianjin (Approval No. CNV88279). All participants provided written informed consent prior to enrollment, in accordance with the Declaration of Helsinki. The consent process included clear information regarding the collection, storage, and future use of biological samples and data for research purposes. Biobanking of specimens (e.g., blood, urine, tissue samples) was conducted with appropriate coding and storage under secure, anonymized conditions. Access to biospecimens and associated clinical data was restricted to authorized research personnel only, ensuring participant confidentiality throughout the study lifecycle.

Conflict of interest

The authors declare no conflict of interest.

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