

Correlation of Genetic Patterns with Tumor Biology and Survival Outcome in Renal Cell Carcinoma: A Combined Prospective and Retrospective Study

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Abstract:

Background: Renal cell carcinoma (RCC) is a heterogeneous malignancy with diverse genetic alterations, variable tumor biology, and differences in clinical presentation across age groups. Although age-related clinical patterns are recognized, the clinical utility of genetic testing across different tumor characteristics remains incompletely defined.

Aim: To evaluate the association between genetic patterns, tumor biology, and clinical outcomes in RCC, and to assess the role of selective genetic testing based on tumor laterality and focality.

Methodology: This study included RCC patients treated between 2013 and 2024 in the retrospective cohort and newly diagnosed cases enrolled prospectively. Comprehensive clinical, demographic, radiological, surgical, pathological, and genetic data were collected. Whole-exome sequencing was performed in patients aged ≤ 46 years and those with familial, bilateral, or multifocal renal tumors. Statistical analysis was conducted using SPSS version 22, with a significance threshold of $p < 0.05$.

Results: A total of 167 patients were analyzed. Older patients demonstrated a higher burden of comorbidities, whereas younger patients more frequently presented with early-stage disease. Clinical presentation, tumor laterality, and surgical approaches were comparable between age groups. Pathogenic genetic mutations were predominantly identified in patients with bilateral multifocal tumors and in rare aggressive histological subtypes such as primitive neuroectodermal tumor and SDH-deficient RCC. No pathogenic genetic alterations were detected in bilateral unifocal tumors.

Conclusion: The diagnostic yield of genetic testing appears higher in selected high-risk RCC subgroups, particularly bilateral multifocal tumors and rare aggressive variants. A selective, risk-based approach to genetic evaluation may aid in risk stratification and individualized patient management.

Keywords: Renal Cell Carcinoma, Genetics, Tumor Biology, Survival Outcomes, Age Groups, Molecular Profiling.

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Introduction

Renal cell carcinoma (RCC) is one of the most clinically heterogeneous malignancies of the genitourinary system, characterized by a wide range of histopathological subtypes, diverse biological behavior, and variable responses to treatment [1]. Over the past decade, the global incidence of RCC has shown a steady increase, largely attributable to improved imaging-based detection and partially to changing lifestyle factors such as obesity, hypertension, and tobacco use. Despite advances in surgical techniques and the introduction of targeted and immune-based therapies, RCC continues to account for a

substantial proportion of cancer-related mortality, with many patients presenting at advanced stages or experiencing disease recurrence following definitive treatment [2].

The intrinsic molecular heterogeneity of RCC contributes significantly to its clinical complexity, as multiple genetic alterations are involved in tumor initiation, progression, angiogenesis, and metastasis across different subtypes. Genetic mutations involving the VHL, PBRM1, SETD2, BAP1, PI3K/AKT/mTOR, and HIF pathways play a central role in determining tumor biology, including

aggressiveness, tumor microenvironment interactions, response to therapy, and overall clinical outcomes [3]. These molecular alterations give rise to a broad spectrum of phenotypic behavior, ranging from indolent, low-grade tumors to highly aggressive variants associated with poor prognosis.

Understanding the relationship between genetic patterns and tumor biology has therefore become a major focus of contemporary RCC research, particularly in the context of individualized risk stratification and precision-based therapeutic approaches [4]. Conventional prognostic models based solely on clinical and pathological parameters (such as tumor size, stage, grade, and metastatic status) are often insufficient to capture the underlying molecular complexity of the disease. Recent advances in genomic profiling have demonstrated that specific mutations are associated with distinct patterns of tumor growth, metastatic potential, and treatment response [5]. For instance, angiogenic signatures linked to VHL inactivation form the basis for VEGF-targeted therapies, while BAP1 loss has been associated with high-grade tumors, early metastasis, and poorer outcomes. In contrast, PBRM1 mutations have been correlated with relatively favorable prognoses and increased responsiveness to immunotherapy [6]. These findings underscore the importance of integrating genetic information with traditional clinical evaluation to improve prognostication and guide personalized management. However, much of the existing evidence is derived from retrospective or single-center studies with heterogeneous populations, limited sample sizes, and incomplete longitudinal follow-up, thereby restricting broader clinical applicability.

Survival outcomes in RCC are influenced not only by the genetic makeup of the tumor but also by complex interactions between tumor cells, stromal components, immune infiltrates, and the surrounding tumor microenvironment [7]. The evolving paradigm of precision oncology necessitates integrated approaches that link genomic alterations with phenotypic behavior, biological pathways, therapeutic response, and long-term clinical outcomes. A combined prospective and retrospective study design offers a unique advantage in this context, enabling systematic evaluation of historical clinical and genetic data while validating findings in a contemporary patient cohort managed using standardized diagnostic, therapeutic, and follow-up protocols. Such an approach enhances statistical power and allows for more robust assessment of disease patterns and outcomes.

Given these existing gaps and the ongoing need to translate genomic insights into routine clinical practice, studies examining the association between genetic patterns, tumor biology, and clinical outcomes in RCC are of considerable clinical relevance. The present study aims to provide a comprehensive

understanding of RCC behavior across different patient populations by analyzing molecular alterations alongside histopathological features, radiological findings, and longitudinal outcomes. By bridging molecular and clinical domains, this research seeks to contribute to improved risk stratification, optimized treatment strategies, and more personalized management of patients with renal cell carcinoma.

Methodology

Study Design: This study followed a combined prospective and retrospective observational design to assess the correlation between genetic patterns, tumor biology, and clinical outcomes in patients with renal cell carcinoma (RCC). The retrospective arm included patients treated between 2013 and 2024, while the prospective arm comprised newly diagnosed RCC patients enrolled during the study period. This design enabled a comprehensive evaluation of clinical characteristics, genetic variants, management patterns, and outcomes across different age groups.

Study Area: The study was conducted in the Department of Urology, Kovai Medical Center & Hospital (KMCH), Coimbatore, a 894-bed tertiary care multispecialty hospital located at Civil Aerodrome Post, Avinashi Road, Coimbatore-641004. KMCH serves as a major referral center for renal malignancies and is equipped with advanced diagnostic, surgical, and genomic facilities required for the conduct of this study.

Study Duration: The study was carried out over a period of two years, which included retrospective data collection and analysis of cases treated from 2013 to 2024, along with active enrollment, follow-up, and documentation of patients in the prospective cohort during the study timeline.

Study Participants: The study population consisted of patients admitted and treated for renal tumors at KMCH during the study period.

Inclusion Criteria:

- Patients diagnosed with renal cell carcinoma (RCC).
- Patients aged ≤ 46 years with bilateral or multifocal renal masses, or those with a family history of renal malignancy, were selected for genetic evaluation.

Exclusion Criteria:

- Patients with metastatic lesions originating from non-renal primary tumors.
- Retrospective cases with incomplete clinical data and prospective cases unwilling to provide informed consent.

Sample Size: Sample size estimation was based on the methodology described by Taccoen et al. 2007

[8] in a retrospective study evaluating RCC in adults aged ≤ 40 years. Using the formula:

$$n = \frac{(Z_{\alpha} + Z_{1-\beta})^2 (p_1q_1 + p_2q_2)}{(p_1 - p_2)^2}$$

with $Z = 1.96$ corresponding to a 95% confidence level and 80% study power, the calculated minimum sample size was 34 patients per group, yielding a total of 68 patients. However, all eligible patients meeting the inclusion criteria during the study period were included to enhance the statistical power of the analysis. Participants were categorized into a Young RCC group (≤ 46 years) and an Old RCC group (≥ 47 years).

Procedure: Retrospective data were obtained from electronic medical records, imaging archives, operative registers, and oncology follow-up records. Data collection was performed using a structured proforma capturing demographic details, clinical presentation, laboratory parameters, radiological findings, tumor characteristics, treatment modalities, and outcomes. All patients underwent standard diagnostic evaluations including complete blood counts, renal and liver function tests, urine microscopy, contrast-enhanced CT (CECT) or MRI of the abdomen, and high-resolution CT (HRCT) of the chest.

Treatment modalities such as radical nephrectomy, partial nephrectomy, immunotherapy, or active surveillance were documented. Pre-test genetic counseling was provided to eligible patients aged ≤ 46 years and those with familial, bilateral, or multifocal renal tumors. Genetic analysis was performed using whole-exome sequencing (WES). DNA extracted from EDTA-anticoagulated blood samples was aligned to the GRCh38 reference genome, followed by variant calling using the Sentieon Haplotype Caller. Variants were classified according to the American College of Medical Genetics and Genomics (ACMG) guidelines.

Tumor staging was assigned based on the 2018 American Joint Committee on Cancer (AJCC) TNM classification, and tumor grading was performed according to the ISUP/WHO criteria. Follow-up included periodic clinical assessment, renal function monitoring, and imaging surveillance as per risk-stratified protocols recommended by the National Comprehensive Cancer Network (NCCN).

Statistical Analysis: All collected data were entered into a standardized proforma and tabulated using Microsoft Excel before being exported for statistical analysis. Statistical evaluation was performed using SPSS software version 22. Categorical variables were summarized as frequencies and percentages, while continuous variables were expressed as mean \pm standard deviation (SD). Associations between categorical variables were analyzed using the Chi-square test or Fisher's exact test, as appropriate. A p-value of < 0.05 was considered statistically significant. Regression analysis was additionally performed to identify independent factors influencing RCC recurrence.

Result

As shown in Table 1, a statistically significant difference was observed in the age distribution between the younger and older renal tumor patients ($p < 0.0001$). Among patients in the older age group ($n = 100$), the majority belonged to the 47–60 years (48%) and 61–80 years (47%) age brackets, with a small proportion aged above 80 years (5%). In contrast, patients in the younger age group ($n = 67$) were predominantly in the 31–40 years age range (53.7%), followed by those aged 41–46 years (37.3%), while only 9% were aged between 20 and 30 years. This distribution indicates that renal tumors in younger patients predominantly occur during early to mid-adulthood, whereas in older patients they are more common in late adulthood, reflecting a significant age-related variation in disease occurrence.

Table 1: Demographic Analysis of Renal Tumor Patients (Age Distribution)

Age Group (Years)	Old Age Group (n = 100)	Age Group (Years)	Young Age Group (n = 67)	p-value
47–60	48 (48%)	20–30	6 (9%)	
61–80	47 (47%)	31–40	36 (53.7%)	<0.0001
>80	5 (5%)	41–46	25 (37.3%)	

Table 2 demonstrates that the pattern of clinical presentation was comparable between the two age groups. Incidental detection was slightly more frequent among younger patients (50.75%) compared to older patients (47%), whereas symptomatic presentation was marginally higher in the older age

group (53%) than in the younger group (49.25%). However, this difference was not statistically significant ($p = 0.75$), indicating that age was not a determining factor in whether RCC was detected incidentally or through symptoms.

S. No.	Clinical Presentation	Young Age (n = 67)	Old Age (n = 100)	p-value
1	Incidental	34 (50.75%)	47 (47%)	0.75
2	Symptomatic	33 (49.25%)	53 (53%)	

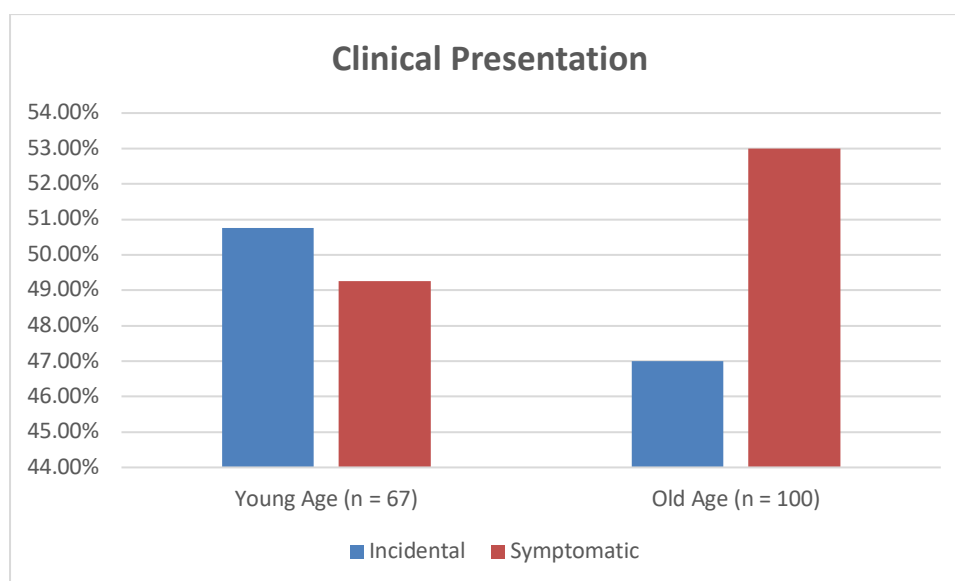


Figure 2: Clinical Presentation

As summarized in Table 3, incidental detection remained the most common mode of presentation in both age groups, with no statistically significant difference observed. Loin pain was reported more frequently in the older age group (34%) compared to the younger group (20.90%), though this difference did not reach statistical significance ($p = 0.09$). The incidence of haematuria was also comparable

between older (19%) and younger patients (13.43%) ($p = 0.46$). Back pain was reported exclusively in the younger group (4.48%), while weight loss was observed at similar low frequencies in both groups. Overall, none of the symptomatic variables showed statistically significant differences between the two age groups.

S. No.	Symptomatic Presentation	Old Age (n=100)	Young Age (n=67)	p-Value
1	Loin Pain	34 (34%)	14 (20.90%)	0.09
2	Haematuria	19 (19%)	9 (13.43%)	0.46
3	Back Pain	—	3 (4.48%)	0.12
4	Weight Loss	3 (3%)	2 (2.99%)	1
5	Incidental Finding	47 (47%)	34 (50.75%)	0.75

Table 4 highlights differences in comorbidity profiles between older and younger RCC patients. Type 2 diabetes mellitus (T2DM) and systemic hypertension were numerically more prevalent in the older age group, affecting 43% and 50% of patients, respectively. In contrast, the prevalence of T2DM

(7.4%) and hypertension (10.4%) was considerably lower among younger patients. Although the difference in hypertension prevalence was not statistically significant ($p = 0.76$), the numerical trend suggests an increased burden of comorbidities with advancing age.

S. No.	Comorbidity	Old Age (n = 100)	Young Age (n = 67)	p-value
1	T2DM	43 (43%)	5 (7.4%)	—
2	SHTN	50 (50%)	7 (10.4%)	0.76

As shown in Table 5, tumor laterality was similarly distributed between the two age groups, with no statistically significant association observed. In the older age group, left-sided tumors were slightly more common (52%) than right-sided tumors (46%),

while bilateral tumors were rare (2%). In the younger age group, right- and left-sided tumors were equally distributed (48% each), with bilateral involvement seen in 4% of cases. These findings

indicate that tumor laterality was independent of patient age.

S. No.	Laterality	Old Age (n = 100)	Young Age (n = 67)	p-Value
1	Right	46 (46%)	32 (48%)	0.6
2	Left	52 (52%)	32 (48%)	0.70
3	Bilateral	2 (2%)	3 (4%)	

Table 6 shows that laparoscopic surgery was the most commonly employed surgical approach in both age groups, accounting for 82% of procedures in older patients and 77.6% in younger patients. Open surgery was performed in 11% of older patients and 13.4% of younger patients, with no statistically

significant difference between the groups ($p = 0.78$). Robotic surgery was utilized less frequently and at comparable rates in both groups. Overall, the choice of surgical approach did not differ significantly with age.

S. No.	Surgical Approach	Old Age (n=100)	Young Age (n=67)	p-value
1	Laparoscopic	82 (82%)	52 (77.6%)	—
2	Open	11 (11%)	9 (13.4%)	0.78
3	Robotic	7 (7%)	6 (9%)	—

- **Genetic Findings According to Tumor Laterality and Focality**

Genetic evaluation was performed in selected patients based on predefined criteria, including younger age, family history, and tumor characteristics. Among patients with unilateral renal tumors, pathogenic genetic mutations were identified in three cases, comprising two cases of primitive neuroectodermal tumor (PNET) and one case of succinate dehydrogenase (SDH)-deficient renal cell carcinoma. No pathogenic mutations were detected in patients with bilateral unifocal renal tumors. In contrast, pathogenic genetic alterations were identified in three patients with bilateral multifocal renal tumors. These findings indicate a higher diagnostic yield of genetic testing in bilateral multifocal tumors and in rare aggressive histological variants compared to unilateral or bilateral unifocal RCC.

Discussion

The present study provides a comprehensive comparison of the clinical, pathological, and demographic characteristics of renal cell carcinoma (RCC) between younger and older patient populations, highlighting both distinct age-related differences and several important similarities. A marked difference in age distribution was observed between the two groups, consistent with earlier reports by Sanchez-Ortiz et al. (2004) [9] and Denzinger et al. (2007) [10], which demonstrated that although RCC predominantly affects older individuals, a significant proportion of cases also occur in younger adults. The lower mean age in the younger cohort suggests that differing environmental exposures, genetic predispositions, or alternative carcinogenic mechanisms may contribute to tumor development in this population. Despite this age disparity, the

male predominance observed in both groups aligns with previous findings by Pal DK (2018) [11], reinforcing the established sex distribution of RCC across age groups.

Despite demographic differences, clinical presentation patterns were largely comparable between younger and older patients. Incidental detection was the most common mode of diagnosis in both groups, reflecting increased utilization of imaging modalities, a trend similarly reported by Klatte et al. (2019) [12]. Symptomatic presentations such as loin pain and hematuria did not show statistically significant age-related differences, supporting observations that RCC symptomatology is more closely related to tumor burden than patient age. Constitutional symptoms, including weight loss, were also infrequent and similarly distributed, indicating that the clinical course of symptom development follows a broadly consistent pattern across different age groups.

In contrast, comorbidity burden differed notably between the two populations. Older patients demonstrated a higher prevalence of type 2 diabetes mellitus and systemic hypertension, findings that are consistent with reports by Chow et al. (2010) [13], who highlighted the clustering of metabolic disorders in elderly RCC populations. Although hypertension did not reach statistical significance in the present study, its higher numerical prevalence among older patients reflects the expected accumulation of vascular and metabolic risk factors with advancing age. Younger patients exhibited a markedly lower prevalence of these comorbidities, consistent with observations by Ljungberg et al. (2019) [14]. These differences have important clinical implications, as comorbid conditions can influence perioperative risk, suitability for nephron-sparing procedures, and postoperative renal outcomes.

Tumor laterality did not differ significantly between age groups, a finding consistent with Bafadni et al. (2024) [15], who reported that laterality patterns in RCC are largely independent of patient age. Although some studies, such as Hamano et al. (2002) [16], have suggested subtle differences in detection patterns or biological behavior between right- and left-sided tumors, such associations were not evident in the present cohort. This suggests that anatomical tumor location may have limited age-specific relevance, though larger studies may be required to further explore this aspect.

Surgical management strategies were also similar between younger and older patients. Laparoscopic radical nephrectomy was the most commonly employed approach in both groups, reflecting the widespread adoption of minimally invasive techniques, as previously emphasized by Gillett et al. (2005) [17]. Partial nephrectomy was performed less frequently, likely due to tumor size and complexity rather than patient age. These findings are consistent with contemporary surgical practices outlined by Campbell et al. (2021) [18], which emphasize tumor-related factors as the primary determinants of surgical approach. The similarity in surgical modality selection further supports the notion that treatment decisions in RCC are predominantly driven by tumor characteristics rather than chronological age.

Histopathological subtype distribution was broadly similar across age groups, with clear cell RCC remaining the predominant subtype, in accordance with classical descriptions by Motzer et al. (2015) [19]. However, rare aggressive tumors such as Ewing sarcoma/primitive neuroectodermal tumor (PNET) and SDH-deficient RCC were observed predominantly in the younger cohort. Previous studies have reported an association between these rare subtypes and hereditary or germline-driven mechanisms, suggesting that younger patients may exhibit distinct molecular pathways despite similar overall histological patterns.

A key finding of the present study is the differential diagnostic yield of genetic testing based on tumor laterality and focality. Pathogenic genetic alterations were identified primarily in patients with bilateral multifocal tumors and in rare aggressive histological variants, while no mutations were detected in bilateral unifocal tumors. Unilateral tumors demonstrated pathogenic mutations only in uncommon histological subtypes. These observations suggest that the clinical utility of genetic testing may be higher in selected high-risk subgroups rather than in the broader RCC population. Accordingly, the findings support consideration of a selective, risk-based genetic testing approach aimed at improving risk stratification, identifying hereditary RCC syndromes, and facilitating appropriate family screening, while minimizing unnecessary testing in low-risk cases.

Differences in tumor staging were also evident between the two age groups. Younger patients more frequently presented with Stage I disease, consistent with findings by Sanchez-Ortiz et al. (2004), who attributed earlier-stage presentation partly to incidental detection. Conversely, older patients demonstrated a higher proportion of Stage III and IV disease, as previously reported by Denzinger et al. (2007). These stage differences may partially explain survival variations observed in earlier comparative studies, although survival analysis was not the primary focus of the present investigation.

Overall, the present study confirms that while age significantly influences comorbidity burden and tumor stage, most core clinical and pathological characteristics of RCC (including presentation, laterality, histological distribution, and surgical management) remain largely consistent across age groups. The subtle yet clinically relevant differences observed in staging, comorbidities, and rare tumor variants point toward underlying biological and molecular heterogeneity. Future studies incorporating comprehensive genomic profiling and long-term outcome analysis may further elucidate age-specific patterns and refine precision-based management strategies in renal cell carcinoma.

Conclusion

The present study highlights distinct age-related differences in renal cell carcinoma while demonstrating several shared clinical characteristics between younger and older patients. Younger individuals more frequently presented with early-stage disease and a lower burden of comorbidities, whereas older patients exhibited higher rates of diabetes, hypertension, and advanced tumor stages. Despite these differences, clinical presentation, tumor laterality, and surgical management were largely comparable across age groups. Genetic evaluation in selected patients revealed that pathogenic mutations were predominantly identified in those with bilateral multifocal tumors and in rare aggressive histological subtypes such as primitive neuroectodermal tumor and SDH-deficient renal cell carcinoma. In contrast, unilateral and bilateral unifocal tumors showed a low diagnostic yield for pathogenic genetic alterations. These findings suggest that the clinical utility of genetic testing appears greater in specific high-risk subgroups rather than across all RCC patients. Accordingly, a selective, risk-based approach to genetic evaluation may be considered to improve risk stratification, facilitate family screening, and support individualized patient management, thereby contributing to precision oncology in renal cell carcinoma.

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