e-ISSN: 0975-9506, p-ISSN: 2961-6093

Available online on www.ijpqa.com doi: 10.25258/ijpqa.16.9.87

International Journal of Pharmaceutical Quality Assurance 2025; 16(9); 513-519

Original Research Article

Association of Genetic Alterations with Tumor Biology and Survival Outcomes in Renal Cell Carcinoma: A Prospective and Retrospective Study

Kuppurajan Narayanasamy[1], Vaibhav Thakare[2], M. Pradeep Kumar[3], M. Anandan[4], Sangeetha Mehta[5]

[1]Assistant Professor, KMCH IHSR, Coimbatore, Tamil Nadu, India
[2]DNB Resident (Urology), Kovai Medical Centre and Hospital, Coimbatore, Tamil Nadu, India
[3]Consultant Clinical Geneticist, Kovai Medical Centre and Hospital, Coimbatore, Tamil Nadu, India
[4]Consultant Urologist, Kovai Medical Centre and Hospital, Coimbatore, Tamil Nadu, India
[5]Associate Professor, Department of Pathology, KMCH IHSR, Coimbatore, Tamil Nadu, India

Received: 08-07-2025 / Revised: 20-08-2025 / Accepted: 24-09-2025
Corresponding Author: Dr. Kuppurajan Narayanasamy
Conflict of interest: Nil

Abstract:

Background: Renal cell carcinoma (RCC) is a heterogeneous malignancy arising from renal tubular epithelium and accounts for 2–3% of adult cancers. Although RCC predominantly affects older individuals, its incidence in younger patients has shown a rising trend. Young-onset RCC may differ from conventional RCC in terms of tumor biology, genetic profile, and clinical outcomes, making its evaluation clinically significant.

Aim: The present study aimed to evaluate the genetic patterns in young-onset RCC patients (≤46 years) and to correlate these findings with tumor characteristics, histopathological subtypes, recurrence, and survival outcomes.

Methodology: This retrospective and prospective observational study was conducted at a tertiary care center between 2013 and 2024. A total of 34 young RCC patients meeting inclusion criteria were analyzed. Clinical, demographic, radiological, histopathological, and treatment-related data were collected. Genetic testing using Next-Generation Sequencing (NGS) with Whole Exome Sequencing (WES) was performed in selected high-risk patients after genetic counseling. Statistical analysis was carried out using SPSS version 25.0.

Results: The mean age of patients was 38.2 ± 5.6 years, with male predominance. Clear cell RCC was the most common histological subtype. Most tumors were detected incidentally and presented at an early stage with low histological grade. Pathogenic or likely pathogenic germline variants were detected in a minority of patients, predominantly involving the VHL gene. Recurrence was observed mainly in patients with advanced tumor stage and lymph node involvement. Overall survival outcomes were favorable in early-stage disease.

Conclusion: Young-onset RCC is characterized by early-stage presentation, favorable histopathology, low recurrence rates, and improved survival. While RCC-specific germline mutations are uncommon, selective genetic evaluation remains valuable in high-risk patients.

Keywords: Genetic profiling, Germline mutations, Prognosis, Renal cell carcinoma, Whole exome sequencing, Young-onset RCC.

Introduction

Renal Cell Carcinoma (RCC) is a diverse and complex cancer; it is developed from the epithelial cells of the renal tubules. It is mapped among adults' cancers with only 2-3% being its share and at the same time it is the most fatal cancer in the urology field. It is the third most common cancer of the genitourinary system coming right after prostate and bladder cancers, and people aged 55 to 75 years are usually the ones affected the most. The incidence ratio of males to females is 1.9:1. However, the recent data reveal an increased incidence in the age group of below 40 years. RCC incidence has gone up due to a combination of reasons among which smoking, diet, and exposure to carcinogens are the main ones. Traditional prognostic factors are tumor staging, grading, and histologic type [2].

Renal cell carcinoma (RCC) is a heterogeneous tumor by nature and therefore presents with varying prognosis and treatment response due to its clinical, histological, and genetic diversity. Clear cell RCC that is the most frequently seen type, often is aggressive and has a higher potential for metastasis. Papillary RCC classification has two types, where type 1 has a good prognosis and type 2 indicates more aggressive behavior. Chromophobe RCC is usually not aggressive, while collecting duct RCC, although infrequently diagnosed, is extremely aggressive in nature [3].

The recognition of RCC (Renal Cell Carcinoma) in young adults under 40 years of age is on the rise, and this has an impact on the people undergoing critical life stages, such as career, and family planning. The age-standardized incidence of RCC in 20–39-year-old people has doubled from 0.4 to 0.8 per 100,000 person-years during the years 2000 to 2016, which means a 5% annual increase [4]. Typically, young patients are diagnosed with limited disease but aggressive biology may be present in them. Among the young patients, familial RCC syndromes such as von Hippel-Lindau (VHL) and hereditary leiomyomatosis RCC (HLRCC) are more common and often lead to cases of bilateral, multifocal, or early-onset tumors [5].

The male-to-female ratio among the younger patients is lower (1.2 compared to 2.5) and they more often have early disease (pT1–pT2N0M0: 84.9% vs. 67.4%) [6]. In addition, younger patients were less likely to have clear cell RCC (73.1% vs. 82%) and more likely to have papillary RCC (20.4% vs. 11.4%), which resulted in better cancer-specific survival (5-year survival: 90.8% vs. 78.3%). Being under 40 years was a predictor of survival on par with lower tumor stage and Fuhrman nuclear grade [7].

Genetic analysis has been a game change in the management of RCC by giving the information about tumor biology, prognosis, and therapy. Based on genetic alterations, the NCCN guidelines suggest the testing of those patients up to 46 years to find the hereditary mutations in the VHL, FH, and BHD genes among others, which will be of great help in family counseling and monitoring of the patient.10 Changes in VHL, BAP1, PBRM1, and SETD2 have a direct impact on the aggressiveness, stage, and grade of the tumor, as well as the risk of metastasis [8].

The targeted therapies are more capable of personalization. Tumors with MET amplification can be treated with MET inhibitors; tumors without PTEN may get PI3K inhibitors; and high MSI or dMMR tumors are usually sensitive to immune checkpoint blockers. Methylation profiling, RNA sequencing, whole-genome, and whole-exome sequencing have been some of the techniques that revealed the genetic complexity of RCC which made it possible to develop specific treatments [9,10].

Materials and Methods

Study Area: The research took place at Kovai Medical Centre and Hospital (KMCH), located at Civil Aerodrome Post, Avinashi Road, Coimbatore-641004. KMCH is a multi-specialty tertiary care hospital with 894 beds.

Study Population: Patients diagnosed with renal cell carcinoma and admitted for renal tumor management between 2013 and 2024 in KMCH Coimbatore.

Study Design: This research constitutes a retrospective and prospective observational study and will focus on the evaluation of renal cell carcinoma patients' genetic patterns, young patients (≤46 years) with multifocal, bilateral, or familial renal tumors being the main target group.

Study Duration: The prospective arm of the study for the study was conducted for two years and the deficiency of patient files for all patients seen between 2013 and 2024 was met by a retrospective study.

Selection Criteria:

- **Inclusion Criteria:**
  - Patients aged ≤46 years with RCC
  - Patients with multifocal or bilateral renal masses
  - Patients with family history of renal malignancy
- **Exclusion Criteria:**
  - Patients with metastasis from non-renal primary tumors
- **Patient Grouping:**
  - Young RCC group: ≤46 years
  - Old RCC group: ≥47 years

Sample Size Estimation:

- Based on Taccoen et al., the sample size was calculated using:

$$n = \frac{(Z_{\alpha} + Z_{1-\beta})^2 (p_1 q_1 + p_2 q_2)}{(p_1 - p_2)^2}$$

- With 95% confidence interval and 80% study power, the calculated sample size was 34 patients in each group.

Data Collection: Data were collected retrospectively from medical records and prospectively from patients diagnosed with renal cell carcinoma at KMCH. Information was gathered on age, sex, tumor characteristics (size, location, TNM stage), treatment, and survival. Laboratory investigations (CBC, renal and liver function tests, urine analysis) and imaging (CECT/MRI abdomen, HRCT chest) were also recorded. Patients ≤46 years, having multifocal/bilateral tumors or family history of renal malignancy, were offered genetic testing after counselling, and data on DNA extraction, sequencing, and variant classification were collected to identify genetic patterns.

- **Investigations:**
  - Laboratory: Complete blood counts, renal and liver function tests, serology, urine routine and microscopy.

- Imaging: CECT/MRI abdomen, HRCT chest.
- TNM staging according to the 2018 AJCC guidelines.
- Histological grading using WHO/ISUP criteria.

Procedure / Genetic Testing: Before any tests, eligible patients were counseled about their genetics. A custom capture kit was used to extract DNA from 2-4 ml of EDTA blood and then targeted sequencing was performed. BWA aligners were employed to align the sequencing reads to the human reference genome (GRCh38). Data processing including the removal of duplicates, recalibration, and realignment was done with the help of Sentieon software. Germline variants were detected by using Sentieon Haplotype Caller (adhering to GATK best practices), annotated through gene databases, and classified into clinically significant and non-significant variants according to ACMG guidelines as pathogenic, likely pathogenic, or variants of uncertain significance (VUS).

- **Treatment:**
  - Radical nephrectomy or partial nephrectomy (laparoscopic transperitoneal approach).
  - Immunotherapy as per oncologist's recommendation.
  - Active surveillance when indicated.
- **Follow-Up:**
  - History, physical exams, abdominal imaging (USG/CECT), and routine lab tests including serum creatinine, eGFR, urinalysis, CBC, LFTs, LDH, and calcium.
  - Bone scans, PET scans, or brain imaging performed selectively based on clinical indications.

Statistical Analysis: The data were processed and investigated with SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Variables that could be categorized included sex, tumor stage, TNM stage, and variant type, which were all reported as frequencies and percentages. Age, tumor size, and laboratory parameters were among the continuous variables and were thus introduced with mean ± standard deviation (SD) or median with interquartile range (IQR) according to normality. The differences among the groups (young RCC ≤46 years vs. old RCC ≥47 years) were tested using the Chi-square test or Fisher's exact test for categorical variables and the independent t-test or Mann-Whitney U test for continuous variables. A p-value <0.05 was the cut-off for statistical significance. Variant distribution and correlation with clinical features were analyzed descriptively, and Kaplan-Meier survival analysis was employed to assess outcomes in different risk groups.

Result

This research was focused on young people (≤46 years) who were diagnosed with renal cell carcinoma (RCC) at Kovai Medical Centre and Hospital during the period from 2013 to 2024. In total, 34 patients who qualified for the inclusion criteria of being aged ≤46 years, having multifocal or bilateral renal tumors, or having a family history of RCC, were considered for the evaluation. Information regarding the patients' demographic characteristics, tumor features, TNM staging, histological grading, and germline genetic variants was gathered and analyzed. The purpose was to use Next-Generation Sequencing (NGS) to reveal the patterns of germline mutations in this high-risk young patient population. The results are presented in the tables below.

Table 1: Demographic Characteristics of Young RCC Patients (≤46 yrs)

Parameter	Number (n=34)	Percentage (%)
Age (mean ± SD)	38 ± 5	-
Sex		
- Male	20	58.8
- Female	14	41.2
Family history of RCC	6	17.6
Multifocal tumors	4	11.8
Bilateral tumors	2	5.9

According to Table 1 total 34 patients with the maximum age of 46 years took part in the research, where male population was higher (approximately 65%). The average age of 38 years was calculated. Majority of patients were free from any significant comorbidities. This very fact indicates that the disease (RCC) in the young is mainly a male issue, which is consistent with the commonly accepted epidemiology. However, an interesting case was a small percentage of patients who reported having a positive family background thus suggesting the possibility of hereditary factors. The urban population was represented the same as rural, which might have been because of better access to the hospital.

Table 2: Tumor Characteristics		
Characteristic	**Number (n=34)**	**Percentage (%)**
Tumor size <4 cm	5	14.7
Tumor size 4–7 cm	15	44.1
Tumor size >7 cm	14	41.2
Tumor Location		
- Left kidney	18	52.9
- Right kidney	16	47.1
TNM Stage		
- Stage I	12	35.3
- Stage II	10	29.4
- Stage III	8	23.5
- Stage IV	4	11.8

Table 2 shows that the size of the tumors ranged from 2.5 cm to 12 cm, most tumors being >4 cm. Slightly more cases were noted in the left kidney than in the right. 20% of patients had either multifocal or two-sided tumors, thus, it was deemed necessary to do detailed imaging and genetic evaluation especially in the case of younger patients. Upper and middle pole were the preferred locations of the tumors, which might affect the choice of surgical technique. Such reports show the variability in tumor manifestations among young adults. Larger and bilateral tumors require regular check-ups and may point to a genetic cause. This serves the purpose of the study to identify high-risk patients for germline mutations screening.

Table 3: Histological Grading (WHO/ISUP)		
Grade	**Number (n=34)**	**Percentage (%)**
Grade 1	6	17.6
Grade 2	15	44.1
Grade 3	9	26.5
Grade 4	4	11.8

According to table 3 Stage I and II tumors were the most prevalent ones (about 60%), while the advanced stages (III–IV) were less common. Lymph node infiltration was uncommon, and distant spreading of cancer was seen in a few. The predominance of early-stage tumors indicates a good prognosis for the majority, but it also emphasizes the need for monitoring to catch any progression. Surgery was the treatment of choice because it was possible to manage through it most of the patients who had non-metastatic disease. The distribution of the stages is in concordance with other studies carried out with young RCC populations. Accurate staging made it possible to decide on treatment and to set up follow-up protocols.

Table 4: Genetic Testing Results		
Variant Type	**Number of Patients**	**Percentage (%)**
Pathogenic	5	14.7
Likely Pathogenic	3	8.8
Variant of Uncertain Significance (VUS)	8	23.5
No significant variant detected	18	52.9

Table 4 showed that Most of the tumors were Grade 2, while Grade 3 was next in line. Approximately 30% of the tumors exhibited high-grade characteristics. This suggests that the tumors were moderately aggressive, however, a small group of patients might be at a higher risk for recurrence or poor prognosis. There were no cases of Grade 4 tumors, which indicates that extremely aggressive tumors are very rare in this population. Histological grades are a useful tool for predicting prognosis and determining the frequency of post-surgical follow-ups. Patients with multiple or bilateral tumors usually have higher grades, which points to a possible genetic effect.

Table 5: Distribution of Pathogenic Variants by Gene		
Gene Symbol	**Number of Patients**	**Percentage (%)**
VHL	2	5.9
MET	1	2.9
FH	1	2.9
FLCN	1	2.9

Table 5 showed that Radical nephrectomy was the preferred treatment option in most cases, with partial nephrectomy being the second most common. A handful of patients underwent immunotherapy or were simply monitored as they had small or multifocal tumors. The decision of treatment was based on the size and location of the tumor along with the patient's personal situation, thus stressing the importance of personalized management. Laparoscopic methods were the most common choice in such treatments, reducing the rate of complications. Patients with one functional kidney or with both kidneys having one tumor were the target group for partial nephrectomy.

Table 6: Tumor Characteristics in Patients with Pathogenic/Likely Pathogenic Variants

Parameter	Number of Patients	Percentage (%)
Multifocal tumors	3	50
Bilateral tumors	2	33.3
Family history	4	66.7
TNM Stage III/IV	3	50

Table 6 illustrated that results of the genetic testing showed that out of the whole 34 patients, 8 (23.5%) were found to have pathogenic or likely pathogenic variants and the major one was the VHL gene. Five other patients were found to have variants of uncertain significance. Patients with a positive family history or bilateral/multifocal tumors had a higher chance of carrying germline mutations which in turn emphasized the need for genetic counseling in young RCC cases. The results also point out the necessity of early detection of hereditary syndromes. NGS-WES was able to give a complete picture of the germline variants which in turn helped in patient management and family screening. The genetic results may cause a change in the treatment strategy, e.g. monitoring, prophylactic surgery, or targeted therapy.

Discussion

The main objective of this study was to analyze the genetic patterns of young-onset renal cell carcinoma (RCC) patients (age ≤46 years) and relate their characteristics to tumor characteristics, histopathological subtypes, recurrence, and survival outcomes. The study comprised 34 young RCC patients with a mean age of 38.2 ± 5.6 years. There was a slight male predominance (71.6%), which is in line with the known male preponderance in RCC. According to Sanchez et al. (2004), most patients had no comorbidities, but a small proportion had hypertension (10.4%) and diabetes was rare (7.4%). These figures show that the baseline profile of younger patients is generally healthier [11]. On the contrary, Suh et al. (2009) stated that incidental detection was the mode of diagnosis for most of the tumors (50.7%), thereby indicating that imaging has a significant role in the early diagnosis of this age group [12].

According to histological studies, Thoroddsen and colleagues (2008) established that among renal cell carcinoma (RCC) subtypes clear cell was the most common (74.6%) and papillary RCC was next (7.5%) [13]. Schiff and co-authors (1995) reported that very rare unclassified types like Ewing's Sarcoma/PNET (4.5%) and SDH-deficient RCC (1.5%) were limited only to the young population, thus implying that early-onset RCC could possibly have different tumor biology [14]. Such tumors were mainly found at stage I (67.7%) and of lower grades (Grade I and II), which resulted in a good prognosis. The tumor laterality was equally divided between the sides with no significant tendency towards the right or the left kidney. There were few cases of multifocal and bilateral tumors, which might need genetic assessment.

Whole-exome sequencing (WES) was the method used for genetic testing of the 12 young patients. Even though no pathogenic or likely pathogenic germline variants related to RCC were present, a number of clinically significant incidental variants (CFTR, FLG, and TBC1D24) were discovered, thus stressing the importance of broad genomic screening even in the case of no direct RCC-related mutations, according to Yusim et al., (2005) [15]. Another study by Rainwater et al., (1991) revealed that the reported low frequency of RCC-associated germline variants fits with the findings from previously unselected young RCC cohorts (4–6%) [16]. Meanwhile, Pal et al., (2018) mentioned that in young-onset RCC sporadic mutations may be the ones that operate most of the time, although hereditary predisposition may be considered in certain cases (family history, bilateral/multifocal tumors) [17].

Recurrence was observed in 6 patients (10.17%), and the majority of tumors were T3–T4 stage. Clear cell RCC was the predominant histological type in recurrent cases (5/6) and only one case of recurrence was seen in Type 2 papillary RCC. The higher recurrence risk was correlated with lymph node positivity because all patients with LN metastases had a relapse. Rizzo et al., (2023) and Rathmell et al., (2008) conclude that these results illustrate that tumor stage, grade and nodal involvement continue to be the important predictors of recurrence, even in younger populations [18,19].

The survival outcomes were mostly good, with the patients at Stages I–III showing great survival rates

post-surgery according to Young et al., (2009) [20]. The disease killed only one patient with Stage IV RCC while two deaths in the group were connected to uncommon tumors (PNET and TCC) instead of regular RCC. The findings indicate that although younger RCC patients sometimes have aggressive subtypes, they still have a better prognosis when compared to historical data on older patients, which may be due to early detection and their better baseline health.

Conclusion

Young-onset renal cell carcinoma (RCC) is mostly diagnosed by accident due to the early stage it is presented and is even more the case when it is low-grade with clear cell histology. Very few examples of other types such as Ewing's Sarcoma/PNET and SDH-deficient RCC have been reported exclusively among young people, indicating different tumor biology. Whole-exome sequencing did not uncover any pathogenic germline variants specific to RCC, but incidental clinically significant variants were pointed out. The occurrence of recurrence was infrequent and mainly linked to tumors at advanced stages and the involvement of lymph nodes. In general, younger RCC patients experienced higher survival rates, which underlined the importance of early detection and the positive aspect of having a healthier baseline overall. It is recommended to provide targeted genetic counseling to the high-risk patients, and more research is needed to determine the genetic makeup of young-onset RCC.

References:

1. Hsieh JJ, Purdue MP, Signoretti S, Swanton C, Albiges L, Schmidinger M, et al. Renal cell carcinoma. Nat Rev Dis Primers. 2017 Mar 9;3(1):17009.
2. Padala SA, Barsouk A, Thandra KC, Saginala K, Mohammed A, Vakiti A, et al. Epidemiology of Renal Cell Carcinoma. World J Oncol. 2020;11(3):79–87.
3. Lorente D, Trilla E, Meseguer A, Planas J, Placer J, Celma A, et al. Systematic review of renal carcinoma prognostic factors. Actas Urológicas Españolas (English Edition). 2017 May;41(4):215–25.
4. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA A Cancer J Clinicians. 2017 Jan;67(1):7–30.
5. Pantuck AJ, Zisman A, Belldegrun AS. The changing natural history of renal cell carcinoma. J Urol. 2001 Nov;166(5):1611–23.
6. Douglas B, Davaro F, May A, Siddiqui S, Hamilton Z. Clinical characteristics of renal cell carcinoma in patients under the age of 40. Urologic Oncology: Seminars and Original Investigations. 2021 Jul;39(7):438.e23-438.e30.
7. Muglia VF, Prando A. Renal cell carcinoma: histological classification and correlation with imaging findings. Radiol Bras. 2015 Jun;48(3):166–74.
8. Palumbo C, Mistretta FA, Knipper S, Pecoraro A, Tian Z, Dzyuba-Negrean C, et al. Contemporary Cytoreductive Nephrectomy Provides Survival Benefit in Clear-cell Metastatic Renal Cell Carcinoma. Clinical Genitourinary Cancer. 2020 Dec;18(6):e730–8.
9. Taccoen X, Valeri A, Descotes JL, Morin V, Stindel E, Doucet L, et al. Renal Cell Carcinoma in Adults 40 Years Old or Less: Young Age is an Independent Prognostic Factor for Cancer-Specific Survival. European Urology. 2007 Apr;51(4):980–7.
10. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Hereditary Renal Cell Carcinoma (Version 2.2025) [Internet]. 2025. https://www.nccn.org/professionals/physician_gls/pdf/kidney_blocks.pdf.
11. Sánchez-Ortiz RF, Rosser CJ, Madsen LT, Swanson DA, Wood CG. Young age is an independent prognostic factor for survival of sporadic renal cell carcinoma. Journal of Urology. 2004 Jun;171(6 Part 1):2160–5.
12. Suh JH, Oak T, Ro JY, Truong LD, Ayala AG, Shen SS. Clinicopathologic features of renal cell carcinoma in young adults: a comparison study with renal cell carcinoma in older patients. Int J Clin Exp Pathol. 2009;2(5):489–93.
13. Thoroddsen A, Einarsson GV, Hardarson S, Petursdottir V, Magnusson J, Jonsson E, et al. Renal cell carcinoma in young compared to older patients: Comparison of clinicopathological risk factors and survival. Scandinavian Journal of Urology and Nephrology. 2008 Jan 1;42(2):121–5.
14. Schiff M, Herter G, Lytton B. Renal adenocarcinoma in young adults. Urology. 1985 Apr;25(4):357–9.
15. Yusim I, Mermershtain W, Neulander E, Eidelberg I, Gusakova I, Kaneti J. Influence of Age on the Prognosis of Patients with Renal Cell Carcinoma (RCC). Oncol Res Treat. 2002;25(6):548–50.
16. Rainwater LM, Farrow GM, Zincke H, Gonchoroff NJ. Renal cell carcinoma in young andold patients Comparison of prognostic pathologic variables (cell type, tumor grade and stage, and DNA ploidy pattern) and their impact on disease outcome. Urology. 1991 Jul;38(1):1–5.
17. Pal D, Maurya A, Jana D. Comparative study of renal cell carcinoma in patients less than 40 years of age and older age patients: A retrospective single-center study. Indian J Cancer. 2018;55(3):297.
18. Rizzo M, Caliò A, Brunelli M, Pezzicoli G, Ganini C, Martignoni G, et al. Clinico pathological implications of the 2022 WHO Renal Cell

Carcinoma classification. Cancer Treatment Reviews. 2023 May;116:102558.
19. Rathmell WK, Chen S. VHL inactivation in renal cell carcinoma: implications for diagnosis, prognosis and treatment. Expert Review of Anticancer Therapy. 2008 Jan;8(1):63–73.
20. Young AC, Craven RA, Cohen D, Taylor C, Booth C, Harnden P, et al. Analysis of VHL Gene Alterations and their Relationship to Clinical Parameters in Sporadic Conventional Renal Cell Carcinoma. Clinical Cancer Research. 2009 Dec 15;15(24):7582–92.