

## A Hospital-Based Study to Assess the Impact of Diabetes and Chronic Kidney Disease on Outcomes for Small Renal Masses: An Observational Study

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Conflict of interest: Nil

### Abstract

**Aim:** The aim of the present study was to investigate the relationship between DM, CKD, and other risk factors affecting the rate of progression to delayed intervention (DI) and overall survival (OS).

**Material & Methods:** The present study was conducted in the Department of Urology, ESICMCH, Bihta, Patna, Bihar, India. Our study identified 100 patients on AS protocols for SRMs within the small kidney tumor database who met the inclusion/exclusion criteria. A waiver of consent was obtained before study start. The procedures adhered to the ethical guidelines of Declaration of Helsinki and its amendments.

**Results:** Gender was closely distributed with 55 male patients (55%) and 45 (45%) females. There were 11 patients less than age 60 years who opted for AS versus initial surgical intervention. DM was present in 35 (35%) of the patients. Following placement on AS, 15 (15%) patients died. In total, 25 (25%) patients crossed over to DI. On average, DI patients were significantly younger at 69.5 years old as compared to 76.6 among non-crossover patients ( $P = 0.01$ ). DI patients had a faster tumor GR of 0.44 cm/year (SD 0.35) as compared to 0.11 cm/year (SD 0.10;  $P = 0.01$ ). DI patients had a higher mean eGFR at 78.3 mL/min/1.73 m<sup>2</sup> (SD 22.44) as compared to 63.8 mL/min/1.73 m<sup>2</sup> (SD 22.6) among non-DI patients ( $P = 0.01$ ). There was a trend toward larger tumors and the likelihood of intervention in cross-over patients (mean size = 2.55 cm,  $P > 0.05$ ) compared to non-DI patients, although this was not statistically significant. BMI was not a significant predictor of conversion to DI, although both groups had a mean BMI  $> 29$ . Diabetes was significantly associated with worse OS. The following factors correlate with decreased OS on univariable analysis: diabetes (OR 5.84, 95% CI 1.84–18.42,  $P = 0.01$ ), CCI (OR 1.38, 95% CI 1.08–1.76,  $P = 0.01$ ), tumor size (OR 1.56, 95% CI 1.14–2.11,  $P = 0.01$ ), and tumor GRs (OR 8.24, 95% CI 1.52–44.5,  $P = 0.01$ ).

**Conclusion:** Patient-level factors – such as diabetes and eGFR – are associated with the rate of DI and OS among SRM patients. Consideration of these factors may facilitate better AS protocols and improve patient outcomes for those with SRMs.

**Keywords:** Diabetes, Chronic kidney disease, Diabetic kidney disease, Nephropathy, Glycemic control, Hemoglobin A1c

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### Introduction

Diabetes mellitus is a growing epidemic and is the most common cause of chronic kidney disease (CKD) and kidney failure. Diabetic nephropathy affects approximately 20–40 % of individuals who have diabetes, [1] making it one of the most common complications related to diabetes. Screening for diabetic nephropathy along with early intervention is fundamental to delaying its progression in conjunction with providing proper glycemic control.

The presence and severity of CKD identify individuals who are at increased risk of adverse health outcomes — including frailty, reduced quality of life, end-stage renal disease (ESRD) and progressive endorgan damage at other sites — and premature mortality. Indeed, excess mortality associated with type 1 diabetes and type 2 diabetes is largely confined to those with CKD. [2,3,4,5] Approximately half of all patients with type 2

diabetes and one-third with type 1 diabetes will develop CKD, which is clinically defined by the presence of impaired renal function or elevated urinary albumin excretion, or both. [6,7] The prevalence of CKD among people with diabetes is >25%, and it has been estimated that 40% of people with diabetes develop CKD during their lifetime. As the prevalence of diabetes has increased, the prevalence of CKD attributable to diabetes has grown proportionally. [8]

Active surveillance (AS) of suspicious renal masses <4.0 cm in size – known as small renal masses (SRMs) – has a growing body of literature supporting its practice. [9,10,11] Typically consisting of serial monitoring of tumor size through abdominal imaging, AS has been shown to have survival outcomes similar to interventions such as partial nephrectomy (PN) and radical nephrectomy (RN) and percutaneous ablation in well-selected patients. [10] Although >80% of these masses have malignant potential, [12] <2.0% of SRMs progress to metastatic disease. [13] Largely consisting of an elderly population, patients undergoing AS have an increased number of comorbidities such as diabetes mellitus (DM) and chronic kidney disease (CKD). [10,14,15] As DM and other comorbidities may be associated with the development of renal cell carcinoma (RCC), [16] understanding the clinical impact of these comorbidities on patients undergoing AS for SRMs is essential.

Hence, in this retrospective analysis of AS for patients with SRMs, we investigate the relationship between DM, CKD, and other risk factors affecting the rate of progression to delayed intervention (DI) and overall survival (OS).

### Material & Methods

The present study was conducted in the Department of Urology, ESICMCH, Bihta, Patna, Bihar, India for 24 months. Our study identified 100 patients on AS protocols for SRMs within the small kidney tumor database who met the inclusion/exclusion criteria. A waiver of consent was obtained before study start. The procedures adhered to the ethical guidelines of Declaration of Helsinki and its amendments. Patient data were collected from those on AS for small kidney tumors at Department of urology, ESICMCH, Bihta, Patna, Bihar, India for the duration of 2 years.

At our institution, patients are denoted to be on AS if they were designated AS candidates at our small kidney tumor conference if they did not receive intervention within the first 6 months of diagnosis, and if the patient agreed to regular imaging and follow-up. Patients were 18-years-old or older with a clinically localized, solid, contrast-enhancing SRM incidentally found on axial imaging (computed tomography or magnetic resonance imaging).

Patients are followed prospectively from the time of study entry until death or loss to follow-up.

### Exclusion Criteria

Included inability to undergo intervention, a prior RCC history, and/or a familial RCC syndrome.

### Methodology

All patients meeting the inclusion criteria met with their urologist and were counseled regarding AS and primary intervention (PI).

### Active Surveillance Protocol:

To be considered for AS, patients must be able to undergo surgical or percutaneous intervention if indicated. AS consisted of cross-sectional imaging every 6–12 months following initial diagnosis with subsequent annual history and physical, chest imaging, and appropriate investigations. Intervention was generally recommended for renal masses with a linear growth rate (GR) that exceeded 0.5 cm/year or if the greatest tumor diameter became larger than 4.0 cm. Patients may also choose DI at any time or continue on AS. Patients choosing DI are followed at the discretion of the attending urologist.

### Data Collection, Analysis, and Outcomes

The data were stored and managed in a secure REDCap database. The following variables were either collected directly from electronic medical records, or calculated from information provided by electronic medical records: age, gender, race, body mass index (BMI), Charlson Comorbidity Index (CCI), estimated glomerular filtration rate (eGFR), diabetes status, metastasis status, final tumor size, tumor GR, time since starting surveillance, types and dates of imaging, types, and dates of surgical interventions, and time to surgical intervention since starting surveillance. Tumor size was measured by maximal axial diameter. The tumor GR was calculated as the final maximum axial diameter minus the initial maximum axial diameter as a function of time (years). Univariable logistic regression models were fit for all independent variables to assess association with progression to DI and OS.

### Statistical Analysis

Variables that had a  $P < 0.15$  were included in a multivariable logistic regression model. A backward elimination method was utilized in which the independent variables were entered into the regression before being removed one at a time to obtain a parsimonious model. Statistical significance was defined as  $P < 0.05$ , and all analyses were completed with SAS 9.4 (Cary, NC). The primary outcome was an odds ratio (OR) determining the risk of DI and OS.

## Results

Table 1: Patient and disease characteristics

Demographics	Total, n (%)
Age (years)	
Mean (SD)	72.08 (12.48)
0–59	11 (11)
60–69	19 (19)
70–79	30 (30)
80+	40 (40)
Gender	
Male	55 (55)
Female	45 (45)
CCI	
Mean (SD)	4.76 (2.38)
Median (IQR)	5 (0–11)
BMI	
Mean (SD)	28.52 (6.61)
Median (IQR)	28.8 (17.3–52.8)
Diabetes	
Yes	35 (35)
No	65 (65)
Final tumour size (cm)	
Mean (SD)	2.46 (1.57)
Median (IQR)	2 (0–9.5)
Mean growth rate (cm/year) (SD)	0.122 (0.32)
Crossover	
Intervention	25 (25)
No intervention	75 (75)
Overall survival	
Deceased	15 (15)
Not deceased	85 (85)

Gender was closely distributed with 55 male patients (55%) and 45 (45%) female. There were 11 patients less than age 60 years who opted for AS versus initial surgical intervention. DM was present in 35 (35%) of the patients. Following placement on AS, 15 (15%) patients died.

Table 2: Factors associated with delayed intervention

Variable	No intervention	Delayed intervention	Univariable, OR (95% CI) P	Multivariable, OR (95% CI) P
Total patients, n (%)	75	25	-	-
Female, n (%)	30	15	0.99 (0.40–2.46) 0.99	-
Diabetic, n (%)	24	11	1.59 (0.62–4.02) 0.33	-
Mean age (SD)	76.6 (10.7)	69.5 (12.1)	0.946 (0.90–0.98) 0.02	0.95 (0.91–0.99) 0.02
Mean BMI (SD)	29.6 (6.40)	31.4 (7.25)	1.05 (0.97–1.11) 0.19	-
Mean CCI (SD)	4.87 (2.46)	4.38 (1.95)	0.91 (0.74–1.11) 0.36	-
Mean eGFR (SD)	63.8 (22.6)	78.3 (22.4)	1.03 (1.00–1.05) 0.02	>0.05
Mean final tumour size (SD)	2.42 (1.62)	2.58 (1.40)	1.07 (0.80–1.40) 0.66	-
Mean growth rate (SD)	0.11 (0.10)	0.44 (0.35)	6.20 (1.36–28.1) 0.02	5.49 (1.13–26.58) 0.03

In total, 25 (25%) patients crossed over to DI. On average, DI patients were significantly younger at 69.5 years old as compared to 76.6 among non crossover patients ( $P = 0.01$ ). DI patients had a faster tumor GR of 0.44 cm/year (SD 0.35) as compared to 0.11 cm/year (SD 0.10;  $P = 0.01$ ). DI patients had a higher mean eGFR at 78.3 mL/min/1.73 m<sup>2</sup> (SD 22.44) as compared to 63.8 mL/min/1.73 m<sup>2</sup> (SD

22.6) among non-DI patients ( $P = 0.01$ ). There was a trend toward larger tumors and the likelihood of intervention in cross-over patients (mean size = 2.55 cm,  $P > 0.05$ ) compared to non-DI patients, although this was not statistically significant. BMI was not a significant predictor of conversion to DI, although both groups had a mean BMI  $> 29$ .

**Table 3: Factors influencing overall survival**

Variable	Alive	Deceased	Univariable, OR (95% CI) P	Multivariable, OR (95% CI) P
Total patients, n (%)	85	15	-	-
Female, n (%)	35	10	1.21 (0.41–3.49) 0.73	-
Diabetic, n (%)	23	12	5.84 (1.84–18.42) 0.01	5.09 (1.50–17.2) 0.01
Mean age (SD)	74.6 (11.9)	78.1 (7.25)	1.03 (0.97–1.08) 0.26	-
Mean BMI (SD)	30.0 (6.97)	29.6 (3.96)	0.99 (0.91–1.07) 0.80	-
Mean CCI (SD)	4.52 (2.29)	6.25 (2.29)	1.38 (1.08–1.76) 0.01	>0.05
Mean eGFR (SD)	69.0 (21.7)	55.0 (28.55)	0.97 (0.95–0.99) 0.03	0.97 (0.95–1.00) 0.05
Mean final tumor size (SD)	2.26 (1.35)	3.61 (2.25)	1.56 (1.14–2.11) 0.01	>0.05
Mean growth rate (SD)	0.09 (0.29)	0.31 (0.40)	8.24 (1.52–44.5) 0.01	9.50 (1.42–63.3) 0.02

Diabetes was significantly associated with worse OS. The following factors correlate with decreased OS on univariable analysis: diabetes (OR 5.84, 95% CI 1.84–18.42,  $P = 0.01$ ), CCI (OR 1.38, 95% CI 1.08–1.76,  $P = 0.01$ ), tumor size (OR 1.56, 95% CI 1.14–2.11,  $P = 0.01$ ), and tumor GRs (OR 8.24, 95% CI 1.52–44.5,  $P = 0.01$ ). Higher eGFR was correlated with improved mortality (OR 0.97, 95% CI 0.95–0.99,  $P = 0.03$ ). On multivariable analysis, diabetes (OR 5.09, 95% CI 1.50–17.2,  $P = 0.01$ ) and higher GR (OR 9.50, 95% CI 1.42–63.3,  $P = 0.02$ ) were independently associated with mortality while higher eGFR was inversely associated with mortality (OR 0.97, 95% CI 0.95–1.00,  $P = 0.05$ ). Female gender and mean BMI were not significantly different among the two groups.

### Discussion

Diabetic kidney disease (DKD) is a frequent long-term complication of diabetes. Globally, DKD is the leading cause of chronic kidney disease (CKD) and end-stage kidney disease (ESKD), accounting for 50% of cases. [17] Typically, DKD is defined by the presence of chronic kidney disease (CKD) characterized by persistently (at least 3 months) elevated urinary albumin excretion (albumin-to-creatinine ratio [ACR]  $\geq 30$  mg/g) and/or low estimated glomerular filtration rate (eGFR  $< 60$  mL/min/1.73 m<sup>2</sup>) in a person with diabetes.<sup>18</sup> The risk of adverse outcomes, including death and ESKD, increases with decreasing GFR and increasing albuminuria. Individuals with a GFR below 30 mL/min/1.73 m<sup>2</sup> (i.e., CKD stage 4–5) are at especially high risk across all albuminuria categories. [18]

Gender was closely distributed with 55 male patients (55%) and 45 (45%) females. There were 11 patients less than age 60 years who opted for AS versus initial surgical intervention. DM was present in 35 (35%) of the patients. Following placement on AS, 15 (15%) patients died. In total, 25 (25%) patients crossed over to DI. On average, DI patients were significantly younger at 69.5 years old as compared to 76.6 among non-crossover patients ( $P = 0.01$ ). DI

patients had a faster tumor GR of 0.44 cm/year (SD 0.35) as compared to 0.11 cm/year (SD 0.10;  $P = 0.01$ ). DI patients had a higher mean eGFR at 78.3 mL/min/1.73 m<sup>2</sup> (SD 22.44) as compared to 63.8 mL/min/1.73 m<sup>2</sup> (SD 22.6) among non-DI patients ( $P = 0.01$ ). Prior studies analyzing diabetics in the general US population have cited an increased risk of mortality (HR 1.93, CI 1.94–2.03) among diabetics as compared to nondiabetics, with an estimated 11.5% of overall deaths in the US attributable to the disease. [19] Pstuka et al. have previously published worsened OS and cause-specific survival (CSS) among diabetic patients treated surgically for RCC – a trend that is seen across a broad range of malignancies including hepatocellular, pancreatic, ovarian, colorectal, lung, bladder, and breast cancer. [20,21] This high rate of non-RCC-related mortality suggests that OS may play a larger role than CSS when considering the clinical management of diabetic AS patients. Specifically, the high prevalence of vascular and nonvascular causes of mortality emphasizes the importance of a multi-disciplinary approach involving urology, endocrinology, cardiology, and primary care when managing diabetic AS patients.

There was a trend toward larger tumors and the likelihood of intervention in cross-over patients (mean size = 2.55 cm,  $P > 0.05$ ) compared to non-DI patients, although this was not statistically significant. BMI was not a significant predictor of conversion to DI, although both groups had a mean BMI  $> 29$ . Diabetes was significantly associated with worse OS. The following factors correlate with decreased OS on univariable analysis: diabetes (OR 5.84, 95% CI 1.84–18.42,  $P = 0.01$ ), CCI (OR 1.38, 95% CI 1.08–1.76,  $P = 0.01$ ), tumor size (OR 1.56, 95% CI 1.14–2.11,  $P = 0.01$ ), and tumor GRs (OR 8.24, 95% CI 1.52–44.5,  $P = 0.01$ ). Higher eGFR was correlated with improved mortality (OR 0.97, 95% CI 0.95–0.99,  $P = 0.03$ ). On multivariable analysis, diabetes (OR 5.09, 95% CI 1.50–17.2,  $P = 0.01$ ) and higher GR (OR 9.50, 95% CI 1.42–63.3,  $P = 0.02$ ) were independently associated with mortality while higher eGFR was inversely

associated with mortality (OR 0.97, 95% CI 0.95-1.00,  $P = 0.05$ ). Female gender and mean BMI were not significantly different among the two groups. While the rate of crossover to DI was not significantly affected by diabetes (OR 1.05, 95% CI 0.62-4.02,  $P = 0.33$ ) it was associated with CKD status, with higher eGFRs more often proceeding to DI on univariable analysis, though this was not an independent predictor of DI. The increased crossover rate among patients with higher eGFR could be reflective of surgical risk, as patients with CKD have been shown to have significantly higher rates of intra- and post-operative complications, in-hospital mortality, and longer hospital stays. [22,23] As management of these conditions often falls outside of the scope of urologic practice, it may be beneficial to incorporate a multi-disciplinary approach to AS patients. Recent studies have shown a significant mismatch between guideline recommendations regarding the multi-disciplinary management of renal cancer patients and real-life urologic practice. [24,25,26]

### Conclusion

The present study showed that comorbidities such as diabetes and CKD may be associated with worse survival among AS patients with SRMs. In addition, the presence of DM, specifically, did not affect the rate of crossover to DI. Conversely, patients with better kidney function were more likely to crossover to DI emphasizing how these patients may be good surgical candidates. This study highlights how consideration of patient-level factors, such as DM and CKD, and a multidisciplinary approach are essential for the optimal management of this unique patient population on AS.

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