Original Article

Impact of diabetes mellitus and hypertension on renal function during first-line targeted therapy for metastatic renal cell carcinoma: a retrospective multicenter study

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Background: Renal function deterioration during systemic therapy in patients with metastatic renal cell carcinoma (mRCC) is a long-term concern in treatment planning. Although hypertension (HTN) and diabetes mellitus (DM) are the most common factors that affect chronic kidney disease (CKD) development and progression, their impact on renal function during targeted therapy is unclear. This study investigated whether DM and HTN were associated with a decline in renal function during first-line targeted therapy for mRCC.

Methods: This retrospective multicenter study analyzed patients receiving first-line targeted therapy for mRCC. They were classified as follows: group 1: HTN–, DM–; group 2: HTN+, DM–; group 3: HTN–, DM+; and group 4: HTN+, DM+. Changes in renal function and factors affecting progression to stage 4 CKD after targeted therapy were analyzed.

Results: Among the 424 enrolled patients, 303 (71.5%) and 121 (28.5%) were treated with sunitinib and pazopanib, respectively [median duration: 10.3 months, interquartile range (IQR), 3.1–37.0 months]. Although all groups showed a decreased mean estimated glomerular filtration rate (eGFR) after treatment (P<0.001 for group 1, group 2, and group 4, P=0.02 for group 3, respectively), there were no significant differences in changes in eGFR (ΔeGFR) between groups (P=0.10). However, actual renal function change calculated using percent ΔeGFR (%ΔeGFR) showed differences between groups (P=0.02); the %ΔeGFR of group 4 was significantly lower compared with group 1 (P=0.008). The mean progression time to stage 4 CKD in group 4 (38.6 months) was significantly shorter compared to the other groups (P<0.001). Multivariate analysis identified increased age (P=0.008), increased number of metastatic sites (P=0.047), and DM and HTN coexistence (P<0.001) as predictors of progression to stage 4 CKD.

Conclusions: Patients with DM and HTN experienced further decline in renal function and had a higher risk of progression to stage 4 CKD after targeted therapy compared to patients without these risk

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factors. Recognition and proactive management of DM and HTN are necessary to facilitate the proper administration of life-prolonging oncological treatments.

Keywords: Targeted therapy; renal function; chronic kidney disease (CKD); diabetes mellitus (DM); hypertension (HTN)

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Introduction

Renal cell carcinoma (RCC) accounts for 3% of all new malignancies worldwide (1,2). Approximately, one-third of patients have metastatic disease at initial diagnosis and 20–30% of cases of surgically resected localized disease subsequently develop local recurrence or distant metastasis (3,4). Significant improvement in the prognosis of recurrent or metastatic RCC (mRCC) has been achieved with the introduction of molecular targeted agents, such as vascular endothelial growth factor (VEGF)-targeting tyrosine kinase inhibitors (TKIs) and mammalian target of rapamycin inhibitors (mTORi) (5). Among the various targeted therapies, TKI-based sequential therapy has been widely used for the treatment of mRCC for several decades. More recently, TKIs were combined with immune checkpoint inhibitors (ICIs) for the treatment of all International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk groups (6,7). Specifically, compared to the ICI + ICI combination, patients who received ICI + TKI combinations showed longer progression-free survival (PFS) and overall survival (OS) in the IMDC intermediate risk group, while similar oncologic outcomes were observed in the IMDC poor risk patients (8). As a result, ICI+TKI combinations have become the current standard of care for advanced mRCC. Furthermore, TKIs are recommended as an alternative treatment for mRCC patients who experienced severe adverse events (AEs) during ICI-based treatment or progressed disease after ICI treatment (6,7). In this context, TKIs continue to play an important role in the management of advanced RCC or mRCC.

Despite an improved prognosis, renal function deterioration during systemic therapy in patients with mRCC or advanced RCC is a long-term concern for treatment planning. However, whether TKIs directly cause renal function deterioration or whether the glomerular filtration rate (GFR) declines significantly after TKI therapy remains controversial (9-11). In particular, in patients with chronic kidney disease (CKD), whether TKIs exacerbate the decline in renal function is a focus of interest and debate.

Hypertension (HTN) and diabetes mellitus (DM) are the most common and important factors that affect CKD development and progression (12,13). In real-world clinical practice, patients with DM and HTN are common among those with surgical CKD resulting from nephrectomy or medical CKD caused by aging and the presence of comorbidities. However, the impact of DM and HTN on renal function in patients with mRCC receiving TKI treatment remains unclear. Thus, this study aimed to determine the impact of DM and HTN on renal function during first-line targeted therapy for patients with mRCC. We present this article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/

Highlight box

Key findings

- Patients with diabetes mellitus (DM) and hypertension (HTN) experienced further decline in renal function and had a higher risk of progression to stage 4 chronic kidney disease (CKD) after targeted therapy compared to patients without these comorbidities.

What is known and what is new?

- Although HTN and DM are the most common factors influencing the development and progression of CKD, their impact on renal function during targeted therapy is unclear.
- Patients with DM and HTN had further reduced renal function and were more likely to progress to stage 4 CKD than patients without these risk factors. The coexistence of DM and HTN was a significant predictor of progression to stage 4 CKD after targeted therapy.

What is the implication, and what should change now?

- Recognition and proactive management of DM and HTN are necessary to facilitate the proper administration of life-prolonging oncologic treatments.

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Methods

Study approval and patient selection

This was a multicenter, retrospective study. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the institutional ethics review board of Inje University Busan Paik Hospital (BPIRB 2023-12-037). The informed consent for this retrospective and observational study was waived according to the provisions of the ethics committee and the ethics guideline in South Korea. A total of 527 patients with mRCC treated with either sunitinib or pazopanib as first-line therapy from February 2007 to February 2019 were retrospectively recruited from four tertiary medical centers in South Korea. Patients who had no follow-up data on renal function and the oncologic outcome of first-line systemic therapy, had stage 4 or 5 CKD, were undergoing hemodialysis at the start of targeted therapy, or had a history of other targeted therapies were excluded (n=103), and the final study cohort comprised 424 patients. Demographic, clinical, and laboratory variables at the time of metastasis diagnosis were collected, including age, gender, prior nephrectomy status, DM and HTN status, and IMDC risk score. Patients with HTN were defined as those whose blood pressure was >140/90 mmHg or who were receiving antihypertensive agents. Patients with DM were defined as those who were receiving hypoglycemic agents and/or insulin injections. The patients were classified into four groups according to their DM and HTN status as follows: group 1, HTN–, DM–; group 2, HTN+, DM–; group 3, HTN–, DM+; and group 4, HTN+, DM+.

Treatment with targeted agents

The targeted agents administered included sunitinib (50 mg orally, once daily in repeated 6-week cycles consisting of 4 weeks on followed by 2 weeks off or 2 weeks on followed by 1 week off) or pazopanib (800 mg orally, once daily). The targeted agents were administered until disease progression or the development of intolerable AEs. The dose was reduced or interrupted based on the guidelines for each agent and the patient's general condition. AEs were graded using Common Terminology Criteria for Adverse Events v4.0. Progression was defined as clinical progression or fulfillment of radiographic criteria using Response Evaluation Criteria in Solid Tumors v1.1 (14).

Renal function evaluation

Renal function was determined at the initiation and end of targeted therapy based on the estimated GFR (eGFR) using the modification of diet in renal disease formula: eGFR (mL/min/1.73 m^2) = 186 × (serum creatinine)$^{-1.154}$ × (age)$^{-0.203}$ × (0.742 if female) (15). The change in eGFR (ΔeGFR) was defined as the difference between eGFR at the initiation and termination of first-line targeted therapy. For the detection of actual renal function changes, we calculated the percent ΔeGFR [%ΔeGFR = (ΔeGFR/pretreatment eGFR) ×100] (16,17). The eGFR value at the start and end of targeted therapy was used to define the CKD stage of each patient as follows: stage 1 (>90 mL/min/1.73 m^2), stage 2 (60–89.9 mL/min/1.73 m^2), stage 3a (45–59.9 mL/min/1.73 m^2), stage 3b (30–44.9 mL/min/1.73 m^2), and stage 4 (15–29.9 mL/min/1.73 m^2) (18).

Statistical analysis

Continuous variables were presented as means with standard deviations or medians with interquartile ranges (IQRs). Categorical variables were presented as frequencies with percentages. Differences in variable distribution among groups were evaluated using Pearson Chi-squared test and linear-by-linear association for categorical variables and Student's *t*-test and one-way analysis of variance for continuous variables. The eGFR values before and after first-line targeted therapy were compared using a paired *t*-test. Progression to stage 4 CKD after first-line targeted therapy was estimated using the Kaplan-Meier method and compared using the log-rank test. Univariate logistic regression was used to identify clinicopathological factors that might have affected the progression to stage 4 CKD after treatment. Finally, a multivariate logistic regression model, which was used in conjunction with the standard entry method, was applied to potential covariates. The odd ratios (ORs) and 95% confidence intervals (CIs) were determined using the reference group. Statistical analysis was performed using SPSS v27.0 (IBM Corp., Armonk, NY, USA) and MedCalc v22.0 (MedCalc Software, Ostend, Belgium). A two-sided P value <0.05 was considered statistically significant for all tests.

Results

The median patient age at the start of first-line targeted

therapy was 60.0 years (IQR, 43–85 years). Of the 424 patients with mRCC, 303 (71.5%) and 121 (28.5%) were treated with sunitinib or pazopanib, respectively, as first-line treatment. The median duration of first-line targeted therapy was 10.3 months (IQR, 3.1–37.0 months). Overall, 316 (74.5%) patients died after the initiation of first-line targeted therapy, with a median follow-up of 30.4 months (IQR, 4.6–92.5 months).

Patients were allocated to four groups according to their DM and HTN status, and their clinicopathological characteristics are summarized in *Table 1*. There were no intergroup differences in baseline characteristics, including the CKD stage before targeted therapy and treatment duration.

There were no intergroup differences in mean eGFR before targeted therapy (*Table 2*). The pretreatment mean eGFR was 70.0±21.4 mL/min/1.73 m^2, and it decreased significantly to 60.8±22.3 mL/min/1.73 m^2 after treatment (P<0.001) (*Figure 1A*). In patients with stage 1 and 2 CKD, the post-treatment mean eGFR was significantly lower than the pretreatment mean eGFR (82.5±27.4 and 61.6±19.0 mL/min/1.73 m^2 *vs.* 107.6±16.4 and 72.3±8.5 mL/min/1.73 m^2, respectively; all, P<0.001) (*Figure 1B*). Although the mean eGFR decreased after treatment in all groups (P<0.001 for group 1, group 2, and group 4, P=0.02 for group 3, respectively) (*Figure 1C*), there were no significant differences in ΔeGFR between groups (P=0.10) (*Table 2*). However, the actual change in renal function as determined by %ΔeGFR showed differences in renal function change between groups (P=0.02) (*Table 2*), and the %ΔeGFR of group 4 was significantly lower compared with group 1 (P=0.008) (*Figure 1D*).

After first-line therapy, 22 (5.2%) patients progressed to stage 4 CKD, and the estimated probability of such progression increased with worsening baseline CKD grade (log-rank test, P=0.003) (*Figure 2A*). The mean time for progression to stage 4 CKD in group 4 was 38.6 months (95% CI: 33.9–43.4), which was significantly shorter compared with groups 1, 2, and 3 [85.6 months (95% CI: 82.0–89.2), 63.9 months (95%: CI: 61.3–66.6), and 40.7 months (95% CI: 36.1–45.3), respectively; P<0.001] (*Figure 2B*). Multivariate analysis revealed increased age (OR: 1.07, 95% CI: 1.01–1.13; P=0.008), increased number of metastatic sites (OR: 1.48, 95% CI: 1.01–2.20; P=0.047), and DM and HTN coexistence (OR: 10.13, 95% CI: 3.06–33.55; P<0.001) as predictors of progression to stage 4 CKD (*Table 3*). There was no difference between the groups in the incidence of AEs ≥ grade 3 during first-line targeted therapy. However, compared with other patients, those with DM and those with coexisting DM and HTN more frequently experienced ≥50% dose reduction of targeted therapy than patients without DM and HTN (40.6% *vs.* 37.1% *vs.* 17.5%; P<0.001) (*Table 4*).

Discussion

Following the introduction of TKI-based targeted therapies, there has been a steady stream of retrospective studies addressing concerns about the potential for drug-induced renal function deterioration (9-11). To date, no definitive conclusions regarding the association between decline of renal function and use of TKI have been reported, and this remains controversial. Population pharmacokinetic analyses did not reveal any correlation between TKI exposure and renal function in subjects with mild, moderate, or severe renal impairment who were not on dialysis (11). However, similar to our study, several investigations have indicated that extended TKI treatment might result in renal function decline (9,10,19). The most important cause of overall renal function decline in patients undergoing TKI treatment is the aggravation of preexisting renal impairment (20). The discrepancies among previous studies are due to differences in the main parameters used to describe changes in renal function. Studies reporting no effect of TKIs on renal function used simple, traditional parameters of renal function change, such as eGFR reduction or changes in the CKD stage after TKI treatment. However, these parameters have limitations in reflecting actual changes in renal function and progression to renal failure in patients with different levels of baseline renal function. For example, as shown in our study, although patients with stage 1 or 2 CKD showed a greater decline in eGFR following TKI treatment than patients with stage 3 CKD, progression to stage 4 CKD was rarely observed in patients with stage 1 or 2 CKD. Therefore, to compensate for these shortcomings and examine the actual changes in renal function more closely, we used more detailed approaches, such as post-treatment changes in eGFR (ΔeGFR), %ΔeGFR, and changes in CKD stage (16,17), which resulted in the demonstration of declined renal function after TKI treatment and revealed its association with HTN and DM.

To the best of our knowledge, this is the first study to demonstrate DM and HTN as major contributors to renal deterioration in patients with mRCC receiving TKIs. Both HTN and DM are generally recognized as the most

Table 1 Patients' characteristics according to their DM and HTN status

Characteristics	Hypertension and diabetes mellitus status				P value
	Group 1 (HTN–, DM–) (n=194)	Group 2 (HTN+, DM–) (n=136)	Group 3 (HTN–, DM+) (n=32)	Group 4 (HTN+, DM+) (n=62)	
Age (years)	58 [45–83]	61 [43–84]	62 [46–79]	61 [45–79]	0.07
Sex					
Male	149 (76.8)	106 (77.9)	28 (87.5)	52 (83.9)	0.14
Female	45 (23.2)	30 (22.1)	4 (12.5)	10 (16.1)	
No. of metastatic organ					
Single	95 (49.0)	72 (52.9)	8 (25.0)	30 (48.4)	0.13
Two	61 (31.4)	44 (32.4)	13 (40.6)	18 (29.0)	
Three	34 (17.5)	11 (8.1)	9 (28.1)	8 (12.9)	
≥ Four	4 (2.1)	9 (6.6)	2 (6.3)	6 (9.7)	
Timing of metastasis					
Synchronous	111 (57.2)	83 (61.0)	14 (43.8)	32 (51.6)	0.29
Metachronous	83 (42.8)	53 (39.0)	18 (56.2)	30 (48.4)	
IMDC risk groups					
Favorable	44 (22.7)	36 (26.5)	5 (15.6)	9 (14.5)	0.15
Intermediate	127 (65.5)	90 (66.2)	21 (65.6)	44 (71.0)	
Poor	23 (11.9)	10 (7.3)	6 (18.8)	9 (14.5)	
Nephrectomy					
No	39 (20.1)	25 (18.4)	3 (9.4)	12 (19.4)	0.56
Yes	155 (79.9)	111 (81.6)	29 (90.6)	50 (80.6)	
Stage of CKD before targeted therapy					
CKD 1	37 (19.1)	19 (13.9)	2 (6.3)	7 (11.3)	0.16
CKD 2	93 (47.9)	70 (51.5)	21 (65.6)	31 (50.0)	
CKD 3a	49 (25.3)	36 (26.5)	7 (21.9)	17 (27.4)	
CKD 3b	15 (7.7)	11 (8.1)	2 (6.3)	7 (11.3)	
First-line targeted agent					
Sunitinib	142 (73.2)	93 (68.4)	23 (71.9)	45 (72.6)	0.85
Pazopanib	52 (26.8)	43 (31.6)	9 (28.1)	17 (27.4)	
Duration of treatment (months)	10.5 [3.0–36.7]	9.7 [3.1–31.6]	10.6 [4.2–44.1]	10.5 [3.2–37.8]	0.78

Data are presented as median [IQR] and n (%). DM, diabetes mellitus; HTN, hypertension; IMDC, international mRCC database consortium; CKD, chronic kidney disease; IQR, interquartile range; mRCC, metastatic renal cell carcinoma.

important factors influencing CKD progression (12,13). This study showed that renal function in patients with DM and HTN was further reduced after TKI treatment compared with patients without these risk factors. Specifically, patients with DM and HTN had a higher rate of progression to stage 4 CKD and a shorter time to progression to stage 4 CKD than patients without these risk factors.

Considering the mechanism of action of TKIs, it is not

Table 2 Pretreatment and post-treatment renal function data stratified by DM and HTN status

Characteristics	Group 1 (HTN–, DM–)	Group 2 (HTN+, DM–)	Group 3 (HTN–, DM+)	Group 4 (HTN+, DM+)	P value
Pre-treatment: mean eGFR (mL/min/1.73 m^2)	71.6±20.9	70.1±23.5	67.1±17.3	66.2±19.8	0.30
Post-treatment: mean eGFR (mL/min/1.73 m^2)	64.8±22.1	59.5±19.7	57.8±23.2	52.4±25.1	0.001
ΔeGFR (mL/min/1.73 m^2)	−6.7±18.6	−10.6±22.8	−9.1±21.7	−13.8±22.6	0.10
%ΔeGFR (%)	−7.2±24.4	−11.6±30.3	−11.7±30.3	−19.9±33.9	0.02

Data are presented as mean ± SD. DM, diabetes mellitus; HTN, hypertension; eGRF, estimated glomerular filtration rate; SD, standard deviation.

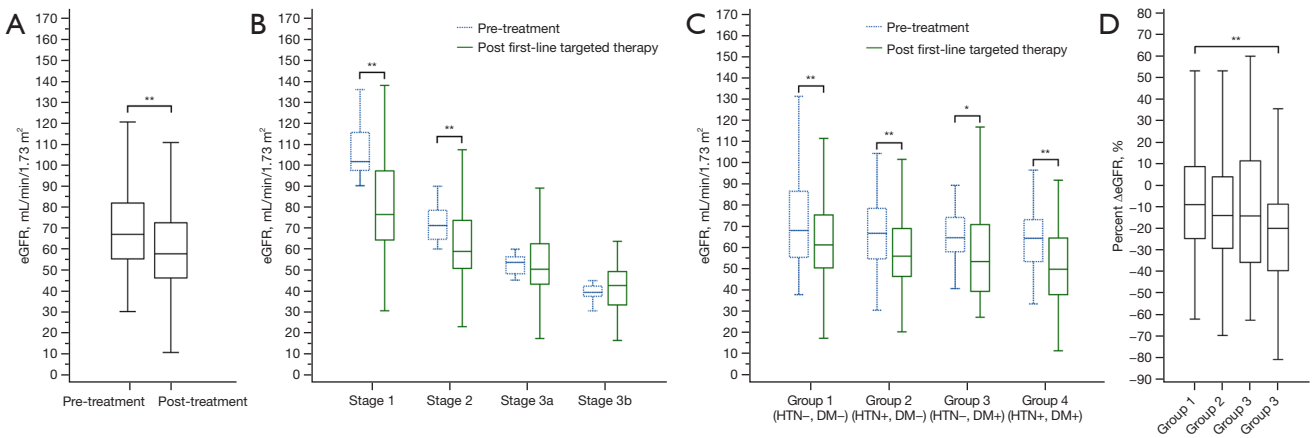

Figure 1 Renal function changes after first-line targeted therapy. (A) Pre-treatment and post-treatment mean eGFR of the entire cohort (70.0±21.4 and 60.8±22.3 mL/min/1.73 m^2, respectively; P<0.001). (B) Pre-treatment and post-treatment mean eGFR stratified by CKD stage. (C) Pre-treatment and post-treatment mean eGFR stratified by DM and HTN status. (D) %ΔeGFR stratified by DM and HTN status. *, P<0.05; **, P<0.01. eGRF, estimated glomerular filtration rate; CKD, chronic kidney disease; HTN, hypertension; DM, diabetes mellitus; ΔeGFR, changes in eGFR.

unexpected that the most common adverse effect of TKI treatment is HTN (21) and that the incidence of HTN is dose related (22). The proposed mechanism of TKI-induced HTN involves reduced formation of nitric oxide by endothelial cells, increased production of vasoconstrictive factors, and reduced microvascular density (rarefaction) (21,23). This process induces endothelial injury and further accelerates glomerular thrombotic microangiopathy (TMA). Therefore, the cause of further decline in renal function in patients with HTN in our study was the addition of TKI-induced HTN to the HTN preexisting before TKI treatment, which further aggravated the decline in renal function. The decreased renal function after treatment in patients with DM is related to the mechanism of diabetic nephropathy. Under physiological conditions, VEGF is a paracrine-secreted product of podocytes that is involved in endothelial cell homeostasis (24). In early-stage diabetic nephropathy, excessive VEGF production by podocytes induces abnormal renal pathology. However, as the disease progresses, podocyte necrosis and glomerulosclerosis prevent VEGF production (25). This leads to the development of renal TMA, causing further endothelial cell damage and end-stage renal disease. Additionally, the use of TKIs for mRCC treatment may accelerate and worsen TMA because TKIs, including sunitinib and pazopanib, are associated with drug-induced TMA (26). Cases of diabetic nephropathy complicated with renal TMA lesions deteriorate more rapidly than uncomplicated cases of diabetic neuropathy, and decreased VEGF expression in the glomeruli is correlated with decreased eGFR (27,28). Given these mechanisms, it is unsurprising that TKI use and the presence of DM and HTN in patients with mRCC may

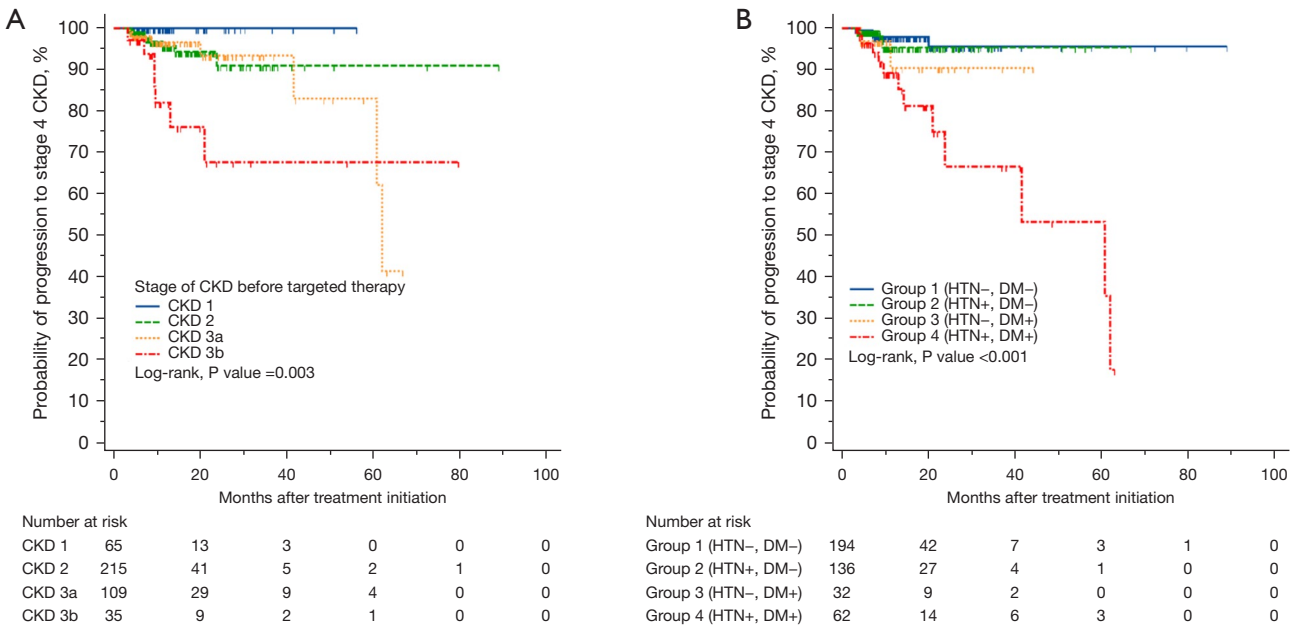

Figure 2 Stage 4 CKD progression-free survival after first-line targeted therapy for patients with mRCC according to (A) CKD stage before treatment and (B) DM and HTN status. CKD, chronic kidney disease; HTN, hypertension; DM, diabetes mellitus; mRCC, metastatic renal cell carcinoma.

Table 3 Univariate and multivariate logistic regression analysis of factors influencing progression to stage four CKD after first-line targeted therapy

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
Age (years)	1.06	1.01–1.12	0.009	1.07	1.01–1.13	0.008
Sex (male *vs.* female)	1.11	0.39–3.11	0.84			
HTN and DM status						
Group 1 (HTN–, DM–)	1	–		1	–	
Group 2 (HTN+, DM–)	1.44	0.35–5.86	0.61	1.17	0.28–4.86	0.83
Group 3 (HTN–, DM+)	3.17	0.56–18.05	0.19	2.35	0.39–13.86	0.34
Group 4 (HTN+, DM+)	11.40	3.52–36.86	<0.001	10.13	3.06–33.55	<0.001
Nephrectomy status (no *vs.* yes)	1.48	0.43–5.12	0.54			
Timing of metastasis (synchronous *vs.* metachronous)	1.32	0.56–3.12	0.52			
IMDC risk groups						
Favorable	1	–				
Intermediate	2.58	0.58–11.51	0.21			
Poor	5.35	0.99–28.68	0.051			
No. of metastatic sites (every 1 site increase)	1.54	1.05–2.25	0.03	1.48	1.01–2.20	0.047

CKD, chronic kidney disease; HTN, hypertension; DM, diabetes mellitus; IMDC, international mRCC database consort; OR, odds ratio; CI, confidence interval; mRCC, metastatic renal cell carcinoma.

Table 4 Adverse event, dose reduction, and treatment discontinuation during first line targeted therapy

Variables	Group 1 (HTN–, DM–) (n=194)	Group 2 (HTN+, DM–) (n=136)	Group 3 (HTN–, DM+) (n=32)	Group 4 (HTN+, DM+) (n=62)	P value
Grade 3 AEs	48 (24.7)	26 (19.1)	11 (34.4)	20 (32.3)	0.19
Grade 4 AEs	1 (0.5)	1 (0.7)	1 (3.1)	2 (3.2)	0.08
Dose reduction of targeted therapy	120 (61.9)	86 (63.2)	17 (53.1)	45 (72.6)	0.29
≥50% dose reduction of targeted therapy	34 (17.5)	30 (22.1)	13 (40.6)	23 (37.1)	<0.001
Discontinuation of targeted therapy	21 (10.8)	20 (14.7)	5 (15.6)	10 (16.1)	0.22
Discontinuation of targeted therapy for more than 3 weeks	14 (7.2)	17 (12.5)	2 (6.3)	7 (11.3)	0.38

Data are presented as n (%). AEs, adverse events; HTN, hypertension; DM, diabetes mellitus.

accelerate the decline in renal function due to the adverse effects of these three factors on each other.

Compared with patients with normal renal function, patients with mRCC and impaired renal function treated with anti-VEGF drugs did not differ in response rate, time to treatment failure, and OS (29). However, Khan *et al.* reported that kidney injury development during treatment was a risk factor for progressive decline in renal function and increased the risk of dose reduction due to renal insufficiency (9). This phenomenon was also observed in our study. Compared with patients without DM and HTN, patients with both DM and HTN had a greater likelihood of >50% dose reduction of targeted therapy. It is important to recognize that our study provides evidence for close monitoring and management of blood pressure and diabetes control in patients with DM and HTN receiving TKI treatment. Our findings demonstrate that DM and HTN at the time of TKI initiation could lead to treatment interruptions and increase the risk of CKD progression. However, there are still gaps in our knowledge regarding the coexistence of DM and HTN at the time of TKI initiation and the optimal management of these comorbidities. The management of DM and HTN in patients receiving TKI or other anticancer therapy is largely empirical, with no current guidelines or recommendations supporting specific agents or treatment goals in this unique population. Therefore, future research should focus on investigating the impact of DM and HTN on disease progression, renal function, and treatment outcomes in patients with mRCC who receive systemic therapy. The research should address epidemiological aspects related to common risk factors and mechanisms of renal deterioration, as well as explore strategies for managing DM and HTN during and after systemic therapy.

Although this was a multicenter study, our findings were limited by its retrospective and observational design. First, unmeasured or immeasurable confounders of renal function and treatment interruption due to other side effects during TKI treatment may have affected our results. Second, although we investigated the association between the prevalence of DM, HTN, and reduced renal function, we did not analyze whether active control of this comorbidity was achieved or the effect of comorbidity control on renal function. In addition, the impact of DM exacerbated by antineoplastic treatment and new-onset HTN secondary to TKI treatment on renal function and treatment interruption should be investigated in future studies. Third, data on the presence of proteinuria, which is considered an indicator of renal impairment when using TKIs, and the urinary albumin-to-creatinine ratio, which is a more reliable proteinuria assessment parameter, were unavailable due to our study's retrospective design. Fourth, our study did not include patients who received ICI-based systemic treatment, which was recently proposed as the standard of care for mRCC. Although ICI-based systemic therapy is the standard of care, long-term follow-up data on ICI-based first-line treatment of mRCC in clinical practice are lacking. Therefore, there is a need for further studies to fill in the gaps and limitations of the present study.

Conclusions

Long-term first-line TKI treatment in patients with mRCC was associated with declined renal function. Additionally, preexisting comorbidities, such as DM and HTN, may accelerate the decline in renal function. Because treatment

discontinuation or modification due to comorbidities may pose difficulties in achieving long-term disease control, recognition and proactive management of DM and HTN are necessary to facilitate the proper administration of life-prolonging oncological treatments.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-24-231/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the institutional ethics review board of Inje University Busan Paik Hospital (BPIRB 2023-12-037). The informed consent for this retrospective and observational study was waived according to the provisions of the ethics committee and the ethics guideline in South Korea.

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