The prognostic significance of preexisting diabetes in patients with surgically treated renal cell carcinoma: the ongoing debate

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Because renal cell carcinoma (RCC) patients are likely to have substantial comorbidities due to advanced age at the time of diagnosis, it is important to explore the effects of preexisting medical diseases on survival after definitive surgical treatment (1). Several epidemiological studies have detected a significant association between RCC prognosis and metabolic syndrome components, such as obesity, hypertension, diabetes mellitus (DM), and dyslipidemia (2-5). Although obesity is a well-known risk factors for RCC development, growing evidence suggests that high body mass index (BMI) is significantly associated with favorable overall survival (OS), cancer-specific survival (CSS), and recurrence-free survival (RFS) in patients with RCC, paradoxically (3). The relationship between hypertension and the risk of RCC remains still controversial, whereas evidence suggests that tyrosine kinase inhibitor-associated hypertension may be a correlative biomarker of antitumor efficacy in metastatic RCC (4,6). An adverse correlation between preexisting DM and tumor recurrence or survival has been reported for several malignancies such as liver, breast, colorectal and endometrial cancers (7-10). With regard to RCC, some studies suggest that DM is associated significantly with a poor prognosis after nephrectomy, while others show no significant association (5,11-14). This controversy might stem from study limitations such as relatively small sample sizes and short follow-up times, the absence of data about potential confounders, inclusion of heterogeneous RCC histological subtypes. Long-time interval also warrant consideration which could represent a

confounding factor for the analysis.

In a recent article by Nayan *et al.* in '*Urologic Oncology: Seminars and Original Investigations*', the authors conducted a multi-center study to determine whether preexisting DM can predict the prognosis of clinically nonmetastatic RCC using the Canadian Kidney Cancer information system database (15). The investigators used propensity score methods based on various clinical, operative, and pathological characteristics to further reduce selection bias. The authors of this interesting work conclude that diabetics have similar survival outcomes compared to nondiabetics after nephrectomy. Although this multicenter study is well designed and provides more definitive information about the prognostic impact of DM on RCC survival, aforementioned long-time interval between 1989 and 2017 is one of the major drawbacks of the study. Disease management in terms of minimal invasive and nephron sparing approaches for RCC has widely evolved within the last decades and should be taken into account. Moreover, the treatment of recurrent or metastatic RCC after initial curative surgery was revolutionized with the advent of antiangiogenic drugs, tyrosine-kinase inhibitors or immune checkpoint inhibitors during the last decade. Not all patients have access to modern treatment for recurrent or metastatic RCC, which is another confounding factor given the recruitment period of the study. Conceding to this view of the subject, the investigators performed a subgroup analysis based on cohort era and demonstrated similar results to the primary analyses. On the other hand,

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contemporary series in the literature have detected a significant association between preexisting DM and cancer survival in patients with RCC. Ha *et al.* (11) identified diabetes as an independent prognostic factor in terms of RFS, CSS, and OS using multicenter data for 2,597 Korean patients with pT1-2 localized clear cell RCC. Another study by Lee and colleagues applied similar study design and methodology with current study. The authors conducted a propensity score matching in a 1:2 ratio for patients with diabetes and those without diabetes, respectively (12). In matched cohorts, diabetes was an independent predictor of progression free survival (HR 1.766), OS (HR 1.825) and CSS (HR 2.266). Notably, high preoperative HbA1c independently associated with progression free survival (HR 2.221) among patients with diabetes (12). Recently, Chen *et al.* (5) performed a meta-analysis of literature published between 2005 and 2014, which includes eighteen cohort studies. The results demonstrated that DM is significantly associated with poor OS (HR 1.56), CSS (HR 2.03), and RFS (HR 1.73) in RCC patients. In addition, DM was significantly associated with both poor OS and CSS in subgroup with localized RCC, clear cell RCC, and RCC with surgical treatment (5). Comprehensively, the question still remains whether diabetes exerting a detrimental effect on long-term survival, or whether these negative oncologic outcomes are secondary to diabetes itself in RCC. Additional well-conducted prospective studies are inevitable to demonstrate a more convincing association between DM and RCC prognosis.

In conclusion, the findings from Nayan *et al.* attempted to address the question of whether diabetes is associated with survival in RCC. Although current interesting study provides a highly generalizable insight into the effect of diabetes on survival, the prognostic significance of preexisting DM in RCC remains to be clarified.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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.

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