Original Article

Prognostic factors and nomogram development for survival in renal cell carcinoma patients with multiple primary cancers: a retrospective study

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Background: Patients with renal cell cancer have an increased risk of developing multiple primary cancers (MPCs) due to improved survival rates. The purpose of this study was to evaluate the clinicopathological features of MPCs and to generate a useful tool for predicting cancer-specific survival (CSS) in these patients.

Methods: A retrospective analysis was conducted on data from renal cell carcinoma (RCC) who were diagnosed with MPCs between 2001 and 2021 from the Surveillance, Epidemiology, and End Results (SEER) database. Patients with RCC meeting the criteria were selected for Kaplan-Meier (KM) survival analysis. The main outcome of this study was CSS, defined as the time from the initial diagnosis to either death due to cancer or the last follow-up. The Cox regression model was used to analyze the CSS factors of MPCs, the results of the multivariate analysis were displayed in a forest map, and the significant variables identified in the multivariate Cox analysis were used to construct the nomogram. Area under the curve (AUC) and calibration plots were used to evaluate the predictive performance of the nomogram.

Results: A total of 2,078 cases of renal cancer with MPCs diagnosed between 2001 and 2021 were included. Age and grade were determined through both univariate and multivariate analyses to be independent prognostic factors affecting CSS. Based on clinical practice, the final nomogram was constructed using the variables: sex, age, grade, summary stage, tumor-node-metastasis (TNM) stage and tumor size to predict CSS at 60, 120, and 180 months. The concordance index (C-index) for the CSS nomogram was 0.670 [95% confidence interval (CI): 0.642–0.698]. The model demonstrated a good predictive performance. To assess the consistency between observed and predicted values, a calibration curve was developed.

Conclusions: This study identified risk factors for CSS in patients with clear cell RCC (ccRCC) with MPCs and developed a nomogram to predict CSS in these patients. The model demonstrates strong clinical applicability and can serve as a valuable clinical decision-making tool for physicians and patients.

Keywords: Renal cell carcinoma (RCC); multiple primary cancers (MPCs); cancer-specific survival (CSS); risk factors; Surveillance, Epidemiology, and End Results database (SEER database)

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Introduction

Among genitourinary malignancies, prostate cancer is the most common cancer in men, accounting for 15% of all male cancers. Prostate cancer cases in 2040 have been projected based on data from global population changes and increased life expectancy. The findings suggest that the annual number of new cases will increase from 1–4 million in 2020 to 2–9 million in 2040 (1). The incidence of renal cell carcinoma (RCC) accounts for 3–5% of all malignant tumors in adults, and it is second only to prostate cancer and bladder cancer in male genitourinary malignancies (2). RCC is a malignant tumor originating in the epithelial system of the urinary tubules of the renal parenchyma. It is typically classified into two primary histological subtypes: clear cell RCC (ccRCC) and non-clear cell RCC (nccRCC). Various subtypes comprise ccRCC, with each characterized by distinct histological features and molecular biological profiles, including papillary RCC (PRCC), chromophobe RCC (CRCC), collecting duct carcinoma (CDC), renal medullary carcinoma (RMC), Xp11.2 translocation-associated RCC (XARM), and sarcomatoid differentiation-associated RCC (SDARCC) (3). It is known for its higher degree of malignancy, with a 5-year survival rate of 50–69% at the time of diagnosis. However, if the tumor measures over 7 cm or has metastasized at the time of diagnosis, the 5-year survival rate drops to 10% (4,5). With the development of artificial intelligence, high-throughput technology, molecular biology, and other fields, the development of new anti-tumor targets and innovative drugs is increasing, and the drug treatment of RCC has shifted from non-specific immunotherapy to molecular-targeted therapy, which is now transitioning to immune checkpoint inhibitor therapy. These therapies have contributed to positive trends in the survival rates for RCC (3,6-8). Improved survival means that the likelihood of secondary cancer is increasing. Based on the interval between the occurrences of primary tumors, those diagnosed within 6 months are referred to as synchronous multiple primary cancers (MPCs), whereas those diagnosed after more than 6 months are classified as metachronous MPCs. There is currently a scarcity of clinical research on RCC with MPCs. Consequently, due to a lack of sufficient clinical treatment experience, clinicians often find it challenging to determine the optimal treatment strategy. Therefore, utilizing data from the Surveillance, Epidemiology, and End Results (SEER) database, we conducted a multicenter retrospective clinical study. To gain a better understanding of the prognosis for patients with MPCs with ccRCC as the first primary cancer, this study explored prognostic factors. We present this article in accordance with the TRIPOD reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-24-509/rc).

Highlight box

Key findings

- Our research uncovered that roughly 14.43% of postoperative renal cell cancer patients developed multiple primary cancers (MPCs), predominantly of the lung, prostate, and breast.

What is known and what is new?

- Patients with renal cell carcinoma (RCC) have an increased risk of developing MPC, primarily due to improved survival rates.
- This study provides a comprehensive analysis of the incidence and patterns of subsequent cancers in RCC patients, identifies specific prognostic factors for cancer-specific survival, and develops a predictive nomogram, addressing gaps in previous research.

What is the implication, and what should change now?

- Given the higher incidence of metachronous tumors found in our cohort compared to other cancer populations, there is a clear need for revised clinical guidelines focusing on targeted, gender-specific surveillance.

Methods

Data sources

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Since the original data came from the SEER database, the study did not need to be approved by the institutional ethics board and the participants did not need to give informed consent before taking part. Data were obtained from the SEER Research Data 8 Registries database, April 2024 release. At present, the SEER database contains comprehensive cancer incidence and survival statistics that encompass 28% of the American population. The International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) guidelines were used in classifying cancer sites and histology.

The SEER variable 'First Malignant Primary Indicator' was used to detect individuals with ccRCC as their first primary cancer. The presence of additional primary tumors was determined by analyzing the data from the field labeled "Total Number of In Situ/Malignant Tumors" for the patient. Individuals with 2 or more cancerous primary growths were categorized as having multiple tumors.

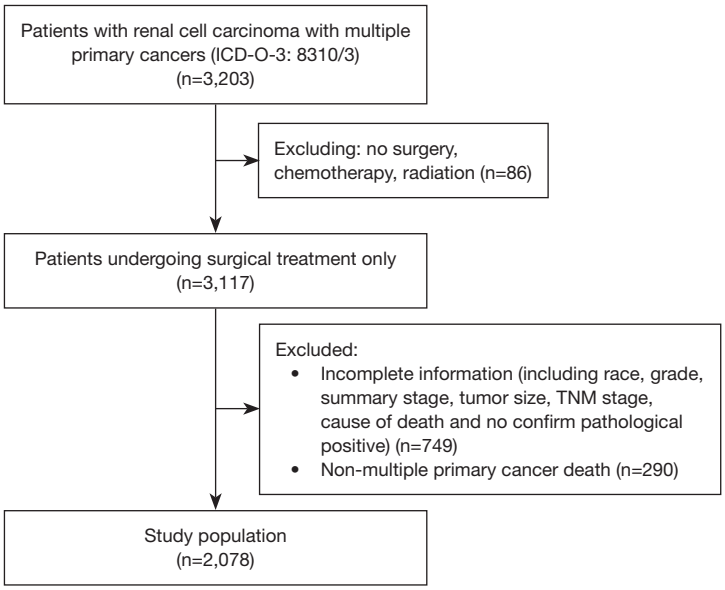

Figure 1 Selection flow chart. ICD-O-3, International Classification of Diseases for Oncology, 3rd edition; TNM stage, tumor-node-metastasis staging system.

Study population

Patients with ccRCC diagnosed between 2001 and 2021, who underwent surgical resection, were included in our study based on the ICD-O-3, with site code C64.9 and histology code 8310/3. Patients were not included if there was missing data on cause of death or follow-up duration. In order to concentrate on metachronous secondary malignancies, we eliminated patients who were diagnosed with a second cancer within 6 months of their initial diagnosis of RCC. A flow chart detailing the selection process is displayed in *Figure 1*.

Cancer-specific survival (CSS) was used as the survival endpoint for prognosis analyses to distinguish mortality from ccRCC and other non-cancer causes. CSS was defined as the period from the initial diagnosis of the primary renal cell cancer to the date of death specifically attributable to cancer. Patients with multiple primary tumors were assessed for the time between the initial diagnosis of RCC and the detection of additional primary malignancies.

Statistical analysis

The data was processed using SPSS 26.0 (IBM Corp., Armonk, NY, USA). Categorical data were presented as frequency (n) and percentage (%). Kaplan-Meier survival curves were constructed to evaluate CSS rates for patients with different characteristics, including sex, age, race, grade, summary stage, tumor-node-metastasis (TNM) stage, lymph node dissection, tumor size, and tumor number. Log-rank regression analysis was performed to assess differences in CSS rates among these groups. Cox proportional hazards models were used for univariate and multivariate survival analyses, with results displayed in a forest plot to evaluate the impact of each parameter on CSS. Analyzing multivariate Cox regression results, a nomogram was constructed using R (R Foundation for Statistical Computing, Vienna, Austria), with a concordance index (C-index) calculated for model validation. Receiver operating characteristic (ROC) curves and calibration plots were also generated to assess the model's predictive accuracy. Statistical significance was determined by a P value of less than 0.05.

Results

Baseline characteristics of the study population

Based on our inclusion and exclusion criteria, 2,078 patients with ccRCC in the SEER database, meeting the criteria of our study, were included. The clinical characteristics of the patients included sex, age, race, grade, summary stage, TNM stage, lymph node dissection, tumor size, and tumor number. Among these patients, 1,375 were male (66.2%),

Table 1 Patient demographics and baseline characteristics

Characteristic	Value (n=2,078)
Sex	
Male	1,375 (66.2)
Female	703 (33.8)
Age (years)	
≤49	246 (11.8)
50–69	1,309 (63.0)
>69	523 (25.2)
Race	
White	1,770 (85.2)
Black	101 (4.9)
Other	207 (10.0)
Grade	
Grade I	287 (13.8)
Grade II	1,178 (56.7)
Grade III	520 (25.0)
Grade IV	93 (4.5)
Summary stage	
Regional	416 (20.0)
Localized	1,641 (79.0)
Distant	21 (1.0)
TNM stage	
I	1,470 (70.7)
II	171 (8.2)
III	411 (19.8)
IV	26 (1.3)
Lymph node dissection	
None	1,888 (90.9)
Yes	190 (9.1)
Tumor size (mm)	
≤70	1,701 (81.9)
71–100	250 (12.0)
>100	127 (6.1)
Tumor number	
≤2	1,730 (83.3)
>2	348 (16.7)
Survival months	106±53
Vital status	
Alive	1,435 (69.1)
Dead	643 (30.9)

Data are presented as mean ± standard deviation or n (%). TNM stage, tumor-node-metastasis staging system.

and 1,309 were between the ages of 50 and 69 years (63.0%). The racial distribution showed that 1,770 patients were White (85.2%). There were 1,178 patients with a Grade II tumor (56.7%), whereas 1,641 patients were in the localized stage (79.0%). As for TNM stage, 1,470 patients were in Stage I (70.7%). A total of 1,888 patients had not undergone lymph node dissection (90.9%), 1,701 had tumor sizes less than 70 mm (81.9%), and 348 had more than 2 MPCs (16.7%). The median CSS was 106 months (*Table 1*).

Analysis of CSS outcomes

Survival results

The CSS rate curves for patients with RCC and MPCs are shown in *Figure 2*. Log-rank regression analysis revealed that patients aged ≤49 years and female patients had higher CSS rates compared to those aged >69 years (P<0.001) and male patients (P=0.02). Additionally, patients with Grade I + II tumors exhibited higher survival rates than those with Grade III + IV tumors (P<0.001). Statistically significant differences in CSS rates were observed among patients stratified by age, sex, grade, summary stage (P<0.001), TNM stage (P<0.001), and tumor size (P=0.001).

Prognostic factor analysis

Univariate Cox proportional hazards regression analysis of CSS rates identified gender, age at diagnosis, summary stage, TNM stage, and tumor size as prognostic factors for patients with MPCs. However, there was no significant difference in CSS rates between patients who underwent lymph node dissection (P=0.15) and those who did not, as well as among patients with different numbers of primary cancers (P=0.71) (*Figure 3*). Incorporating all significant factors from the univariate analysis into a multivariate Cox proportional hazards regression model revealed that age and tumor grade were independent prognostic factors (P<0.001) (*Figure 4*).

Development and validation of the predictive model nomogram

Based on the analysis results, a nomogram was developed in which each variable was assigned a corresponding score. For each patient with MPCs, the scores for each variable were added together to obtain a total score. By drawing a vertical line from the total score to the survival probability axis, one can estimate the CSS rates at 60, 120, and 180 months (*Figure 5*). The nomogram's performance was

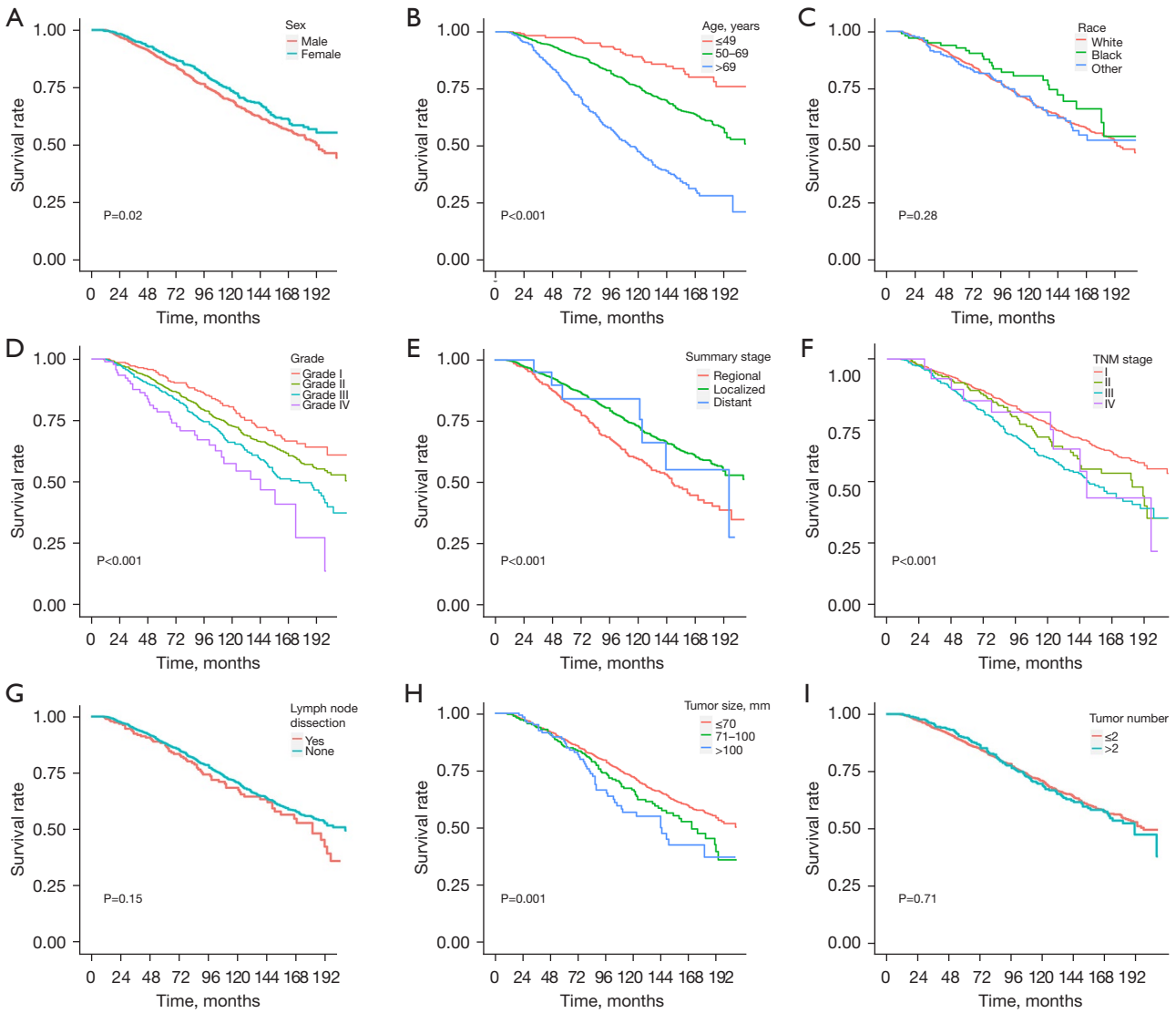

Figure 2 Kaplan-Meier survival curves of CSS based on (A) sex, (B) age, (C) race, (D) grade, (E) summary stage, (F) TNM stage, (G) lymph node dissection, (H) tumor size and (I) tumor number. TNM stage, tumor-node-metastasis staging system; CSS, cancer-specific survival.

internally validated through discrimination and calibration techniques (C-index 0.672). The calibration curves for 60, 120, and 180 months showed a strong agreement between the predicted and observed survival probabilities, and the curves closely followed the diagonal line. This indicates that the nomogram is well-calibrated and provides reliable predictions of CSS at these time points (*Figure 6*). The decision curve analysis (DCA) curves for 60, 120, and 180 months showed that the nomogram provides a higher net benefit compared to the "Treat All" and "Treat None" strategies across a wide range of threshold probabilities (*Figure 7*). This indicates that the nomogram is clinically useful, as it helps identify patients who are more likely to benefit from treatment, thereby avoiding unnecessary interventions for those with low predicted survival probabilities.

Discussion

Improvements in early detection and treatment contribute to positive trends in the survival rates for RCC with MPCs. As cancer survivors live longer, the incidence of second primary malignancies increases. Studies have shown that cancer patients have a higher risk of developing subsequent

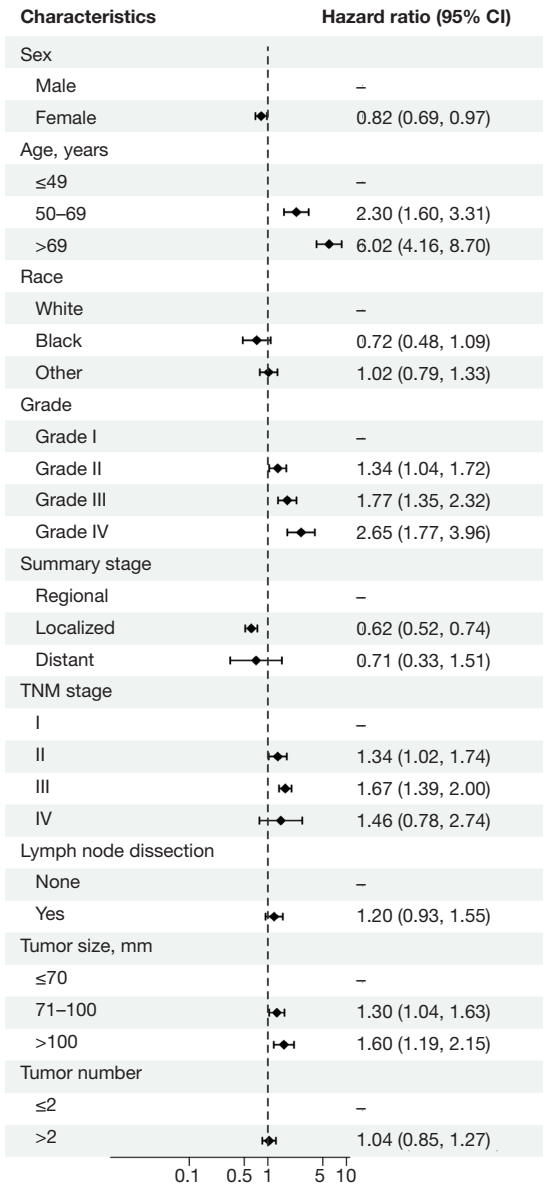

Figure 3 Univariate survival analysis of MPC patients with ccRCC as the first primary malignancy. CI, confidence interval; ccRCC, clear cell renal cell carcinoma; MPC, multiple primary cancer; TNM stage, tumor-node-metastasis staging system.

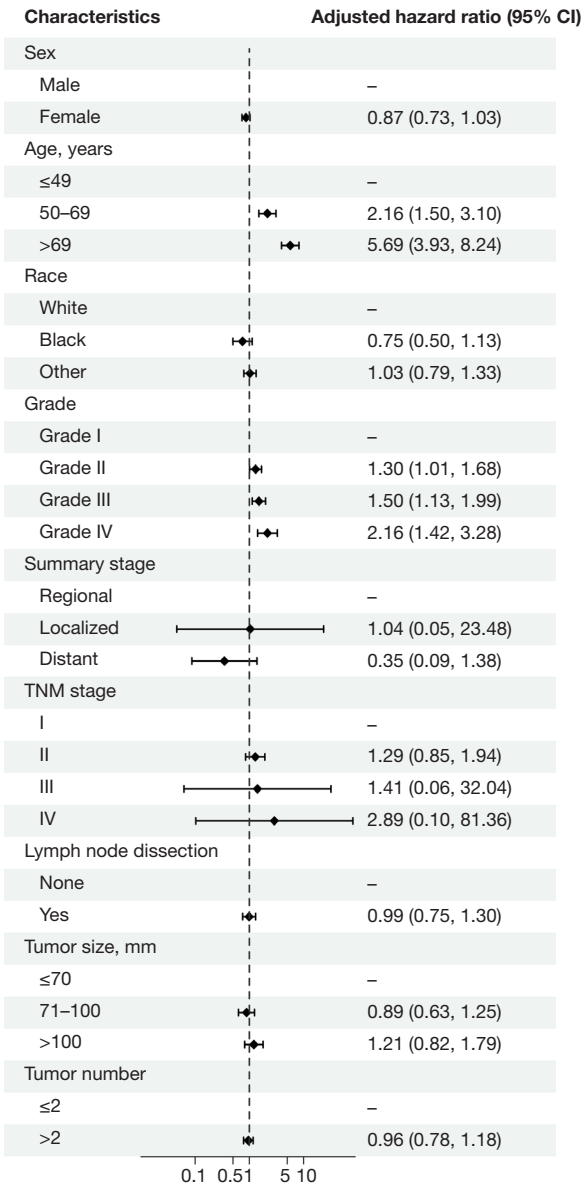

Figure 4 Multivariate survival analysis of MPC patients with ccRCC as the first primary malignancy. CI, confidence interval; ccRCC, clear cell renal cell carcinoma; MPC, multiple primary cancer; TNM stage, tumor-node-metastasis staging system.

cancers compared to the general population (9-11). The management principles for MPCs differ from those for common metastatic and recurrent cancers, typically requiring comprehensive consideration from multiple aspects. Therefore, the prognosis and treatment choices for patients with MPCs pose a new challenge for clinicians. Survivors of ccRCC are at a heightened risk of developing MPCs, such as bladder cancer, prostate cancer, lung cancer, colorectal cancer, melanoma, and non-Hodgkin lymphoma (NHL) (12). Previous studies have primarily focused on analyzing the incidence and survival rates of RCC (9,13-15). Due to the limited sample size of RCC combined with MPCs, and the lack of large-scale studies on these patients, further investigation into the clinicopathological characteristics and prognosis of RCC combined with MPCs can help in understanding this subset of patients. This will

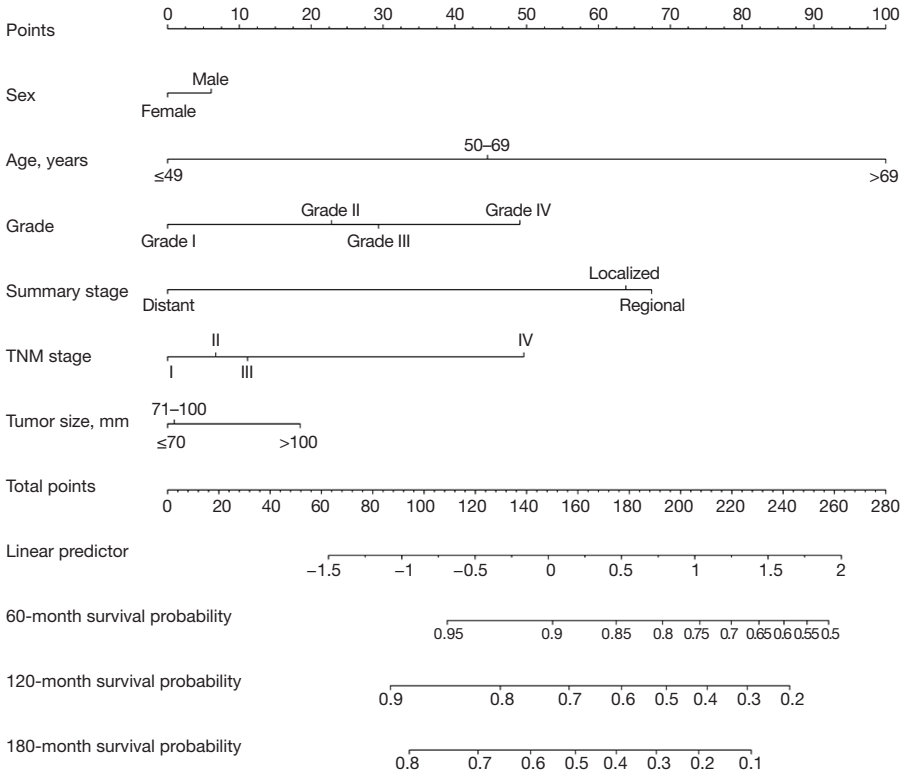

Figure 5 Nomogram for predicting the 60-, 120-, and 180-month CSS rates of MPC patients with ccRCC as the first primary malignancy. ccRCC, clear cell renal cell carcinoma; CSS, cancer-specific survival; MPC, multiple primary cancer; TNM stage, tumor-node-metastasis staging system.

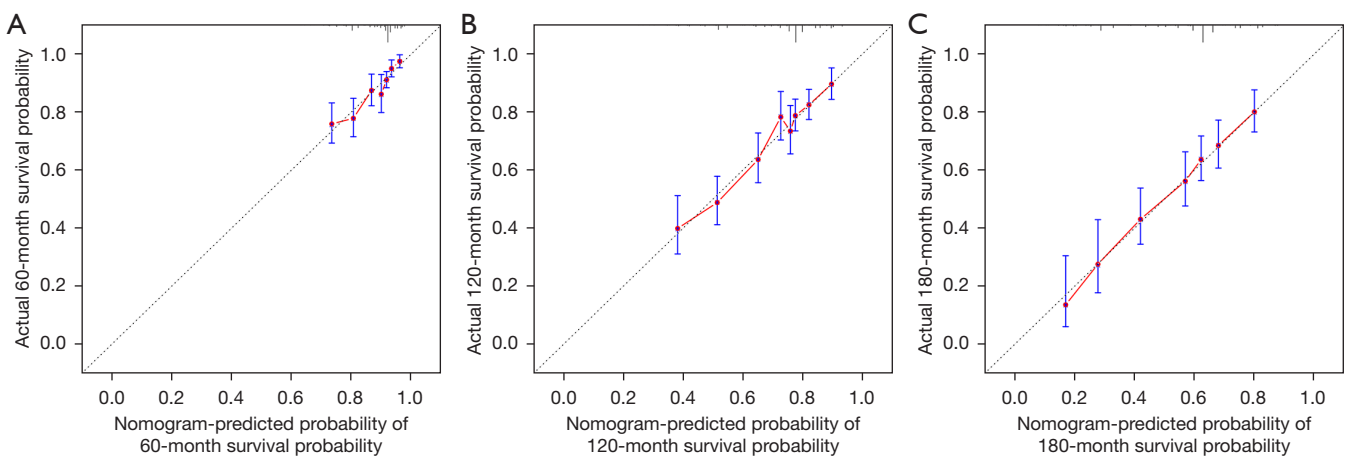

Figure 6 Calibration plots for the (A) 60-, (B) 120-, and (C) 180-month CSS. CSS, cancer-specific survival.

help improve our understanding of this type of patient. By evaluating SEER data (updated: April 2024), our study begins to fill this knowledge gap, investigating the risk of MPCs in patients with RCC. Further, we also sought to examine the effect of MPCs on the survival of RCC patients.

In this study, age was identified as an independent factor affecting the survival prognosis of renal cancer

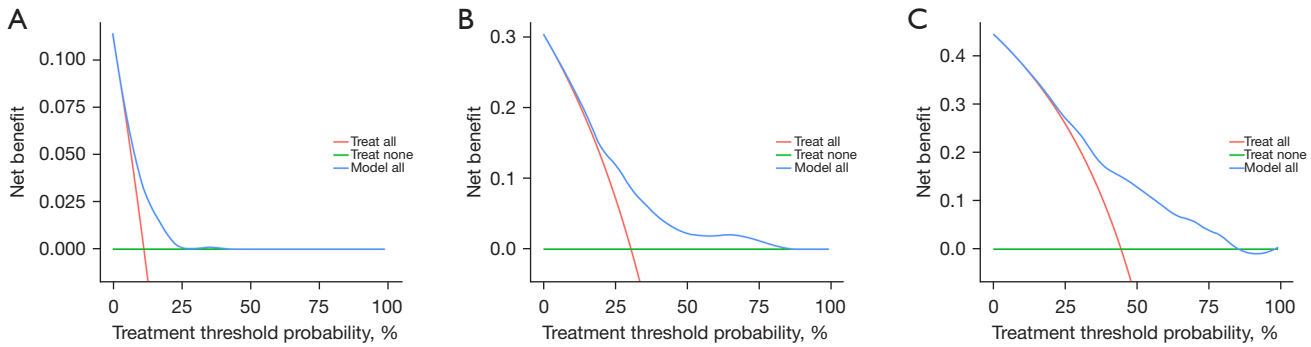

Figure 7 The DCA curves for the (A) 60-, (B) 120-, and (C) 180-month CSS. DCA, decision curve analysis; CSS, cancer-specific survival.

with MPCs, which is consistent with previous research findings (16,17). Multiple studies have indicated that male patients with RCC combined with MPCs have a poorer CSS compared to female patients (18,19). In one study, after adjusting for age, the incidence and relative survival rates were calculated for different gender groups, revealing that the incidence rate in males was twice that of females, whereas the relative survival rate was lower than that of females (17). This disparity may be attributed to factors such as male habits of alcohol consumption, smoking, and a lack of emphasis on regular health check-ups (20,21). The prognostic advantage in women could be attributed to the effects of intrinsic hormones, a lower degree of tumor progression, and variations in the expression of specific genes that are relevant to these factors (22,23). Some studies have examined the differences in treatment and survival outcomes between White and Black patients with RCC. Results indicate that, after adjusting for demographic information and other cancer prognostic factors, White patients tend to have a higher overall survival rate than Black patients. This disparity may be attributed to a lower proportion of Black patients receiving surgical treatment and a higher prevalence of other chronic diseases among them (24-26). This study also confirmed this observation, but the difference between the 2 groups was not statistically significant. This could be due to insufficient sample size and potential inaccuracies in the racial information recorded in the database, leading to biased results. The TNM staging system is a common method for clinically evaluating various malignant tumors. However, some studies suggest that relying solely on tumor size or depth of invasion, lymph node involvement, and distant metastasis for assessing patient prognosis might overlook other factors in clinical practice that could also have an impact on outcomes, including genetic differences (such as polymorphisms) and environmental changes (for example, eating habits, exposure to environmental carcinogens, and lifestyle), which could affect the risk of survival positively or negatively (27,28). Our univariate Cox regression analysis showed that gender, age at diagnosis, summary stage, TNM stage, grade, and tumor size were prognostic factors for patients with MPCs. However, in the multivariate Cox proportional hazards regression model, only age at diagnosis and grade were identified as independent prognostic factors. It is essential to emphasize that these factors are often identified as equally significant prognostic indicators as those for RCC in general; however, in the context of MPCs, the relevance and impact of these factors may vary or be affected by the presence of concurrent tumors. Although age was widely recognized as a prognostic factor, our study revealed that it significantly influences CSS among patients with MPCs. This finding may be attributed to the tendency of such patients to be older and to present with a higher burden of comorbidities. Furthermore, the prognostic importance of tumor grade in RCC is well-documented. In our investigation, tumor grade was similarly identified as an independent prognostic factor affecting CSS. Nonetheless, within the framework of MPCs, the significance of tumor grade may be modulated by various factors, including tumor interactions, the complexity of treatment regimens, and the overall health status of the patient.

The site and histological type of MPCs are important factors that may influence the prognosis of patients with RCC as their first primary cancer. Previous studies have suggested that the site of the second primary cancer can significantly impact survival outcomes (29-31). For example, patients with lung or liver as the site of the second primary cancer often have a worse prognosis due to the aggressive nature of cancers in these organs. In contrast, cancers in sites such as the prostate or breast may

have a relatively better prognosis, especially if detected at an early stage. Similarly, the histological type of the second primary cancer plays a crucial role. Patients with a second primary cancer of a more aggressive histological subtype (e.g., small cell carcinoma or poorly differentiated adenocarcinoma) may experience shorter CSS compared to those with less aggressive subtypes (e.g., well-differentiated adenocarcinoma or low-grade tumors). In our cohort, we observed that the most common sites for second primary cancers were the lung, prostate, and breast, which aligns with findings from other studies. However, due to the limited sample size for each specific site and histological type in our dataset, we were unable to perform a detailed subgroup analysis. This limitation is particularly relevant for rare cancer sites or histological types, which may have unique prognostic implications but were underrepresented in our study. Future studies with larger cohorts should aim to explore the impact of the site and histological type of MPCs on prognosis in greater detail. This could help identify high-risk patient subgroups and inform more personalized surveillance and treatment strategies.

Although some variables may not be significant in multivariate analysis, considering clinical relevance, controlling for confounding factors, enhancing predictive power, and meeting clinical practice needs, the nomogram predictive model can help identify and incorporate additional meaningful factors. When combined with the TNM staging system, this approach offers a more comprehensive advantage in prognosis prediction. This approach can assist in constructing a more comprehensive and accurate predictive model, providing clinicians with more valuable information to enhance patient management and treatment outcomes.

Conclusions

In summary, we conducted the first comprehensive analysis of MPCs with RCC as the primary malignant cancer using data from the SEER database. We investigated the prognostic significance of factors influencing CSS in patients with RCC with MPC. There are several limitations associated with this study, including its retrospective nature and the inherent limitations of publicly available registry databases. The constraints of the study may encompass inadequate reporting of specific variables, such as the type of surgical treatment. Furthermore, there was a deficiency in data regarding variables such as the dosage of radiation therapy and a description of the types of systemic therapy utilized for metastatic renal cell cancer. Additionally, the study did not collect specific data on environmental lifestyle factors and comorbidities beyond cancer. It is also possible that there are unmeasured confounding variables that were not accounted for in the analysis. External validation in a variety of populations will be essential to validate the applicability of our results.

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None.

Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-24-509/rc

Peer Review File: Available at https://tau.amegroups.com/article/view/10.21037/tau-24-509/prf

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-24-509/coif). 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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