Prognostic values of the clinicopathological characteristics and survival outcomes in micropapillary urothelial carcinoma of the bladder: A SEER database analysis

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Abstract
Purpose: To study prognostic values of the clinicopathological characteristics and survival outcomes in micropapillary urothelial carcinoma (MPUC) of the urinary bladder.

Method: We used the national Surveillance, Epidemiology, and End Results database (2004-2016) to compare MPUC with transitional cell carcinoma (TCC) and to investigate prognostic values of clinicopathological characteristics, as well as survival outcomes, in MPUC of the urinary bladder. A multivariable Cox proportional hazard model, subgroup analyses, and propensity score matching were used.

Results: In all, 519 patients with MPUC and 154,453 patients with TCC were enrolled. Compared with TCC, patients with MPUC had a higher rate of muscle invasive disease ($P < .001$), lymph node metastasis ($P < .001$), and distal metastasis ($P < .001$), as well as higher tumor grade ($P < .001$). According to the survival analyses, the MPUC group also had lower survival probability in both cancer-specific mortality (CSM) ($P < .0001$) and overall mortality (OM) analyses ($P < .0001$). Cox proportional hazard regression showed that the MPUC group had a higher risk of OM (hazard ratios [HR] = 1.39, 95% confidence intervals [CI] = 1.22-1.57, $P < .0001$), although the CSM (HR = 1.18, 95% CI = 1.00-1.40, $P = .0505$) in that group was fair. In the subgroup analysis, only MPUC patients without distal metastasis faced a higher risk of CSM (HR = 1.33, 95% CI = 1.101-1.61, $P < .0001$).

Conclusions: Micropapillary urothelial carcinoma prognosis is poorer than that of TCC. Micropapillary urothelial carcinoma is an independent prognostic factor for OM in patients with urinary bladder cancer.

Keywords
micropapillary urothelial carcinoma, prognosis, SEER Program, urinary bladder
1 | INTRODUCTION

Bladder cancer is one of the most common cancer types and is a significant cause of tumor-related death worldwide. The worldwide age-standardized incidence rate (per 100,000 person/year) of bladder cancer is 9.0 for men and 2.2 for women. The most common pathological type is transitional cell carcinoma (TCC), and thus, treatments for bladder cancer focus primarily on TCC. Since Amin et al. reported a micropapillary component in TCC of the urinary bladder and its poor prognosis in 1994, the incidence of micropapillary urothelial carcinoma (MPUC) is 0.7%-8.3%, according to various published articles. Micropapillary urothelial carcinoma is characterized by small, tight clusters of high-grade tumor cells that lack true fibrovascular cores and are contained within lacunar spaces; thus, it often has an aggressive clinical course. However, MPUC histology as an independent prognostic factor is still controversial. According to Sui et al.'s analysis of the National Cancer Database, MPUC has a poor prognosis regardless of treatment modality. However, the multi-institutional analysis by Mitra et al. found that even MPUC is associated with advanced disease at cystectomy, but the clinical outcomes are similar to those of pure TCC after controlling for pathologic features. Moreover, a meta-analysis supports the finding that patients with MPUC who undergo radical cystectomy (RC) have survival outcomes similar to those of patients with TCC. Thus far, given MPUC's rarity, there is no analysis based on sufficient sample size. Therefore, we used the national Surveillance, Epidemiology, and End Results (SEER) database (2004-2016) to investigate prognostic values of clinicopathological characteristics and survival outcomes in MPUC of the urinary bladder.

2 | MATERIALS AND METHODS

2.1 | Data resource and study population

Adults patients (≥18 years of age) who were registered from 2004 to 2016 in the SEER database were selected. The primary cancer site was restricted to the urinary bladder according to the International Classification of Disease for Oncology, Third Edition. Patients were included only if the histology was MPUC or TCC. The diagnosis was confirmed by positive histology and was their first or only cancer diagnosis (first positive indicator of malignancy).

2.2 | End points

The main end points were overall mortality (OM) and cancer-specific mortality (CSM) according to data in the SEER database. Overall mortality refers to deaths from any cause, while CSM is defined as death from MPUC or TCC according to the recorded cause of death. Survival time was the duration from initial diagnosis to death from any cause or to the last follow-up.

2.3 | Statistical analysis

Baseline characteristics were assessed to determine whether there were significant differences in the distribution of the study population. Two-sample t tests and Pearson's chi-square tests were performed for continuous variables and categorical variables, respectively. Continuous variables were presented as the mean ± SD. For age at diagnosis and survival (in months), medians and interquartile ranges were also reported. Categorical variables were shown as frequencies and their proportions. The OM and CSM of each histological subtype were compared using unadjusted Kaplan-Meier curves and the log-rank test.

The multivariable Cox proportional hazard model was used to calculate hazard ratios (HR) and their 95% confidence intervals (95% CI) stratified by histological types. The following covariates were adjusted: sex, age at diagnosis, primary site, treatment modality (surgery and radiation), and tumor-node-metastasis (TNM) stage. Subgroup analyses were performed by multivariate regression analysis. Sex, age at diagnosis, TNM stage, and treatment modality (surgery and radiation) were adjusted in the Cox model. Tests to determine interactions were also used in the subgroup analyses. Propensity score matching (PSM) was used to further adjust the model for potential baseline confounding factors. All analyses were performed with the statistical software packages R (http://www.R-project.org; The R Foundation) and EmpowerStats (http://www.empowerstats.com; X&Y Solutions, Inc).

3 | RESULTS

3.1 | Baseline characteristics of the study population

In all, 154,972 patients were diagnosed with TCC and MPUC in the SEER database from 2004 to 2016. This study included 154,453 patients with TCC and 519 patients with MPUC were included. Table 1 includes the patients’ baseline characteristics. At diagnosis, patients with MPUC were close in age to those with TCC (MPUC 71.16 ± 10.91 vs TCC 70.91 ± 12.06, P = .628). Most patients were males in both the MPUC (80.54%) and TCC (76.97%) groups, and there was no difference in the proportion of males and females between the two groups (P = .315). Patients in the MPUC group presented at a more advanced stage than those in the
TABLE 1  Baseline demographic and clinicopathologic characteristics of patients with MPUC compared to TCC

|                        | MPUC (n = 519) | TCC (n = 154,453) | P-value |
|------------------------|----------------|-------------------|---------|
| Mean age (y, SD)       | 71.16 ± 10.91  | 70.91 ± 12.06     | .628    |
| Median age (y, IQR)    | 71.00 (64.00-79.00) | 72.00 (63.00-80.00) | .866    |
| Sex                    |                |                   | .054    |
| Male                   | 418 (80.54%)   | 118,876 (76.97%)  |         |
| Female                 | 101 (19.46%)   | 35,577 (23.03%)   |         |
| Marital status         |                |                   | .065    |
| Married                | 322 (62.04%)   | 92,245 (59.72%)   |         |
| Single                 | 60 (11.56%)    | 15,571 (10.08%)   |         |
| Widowed/Divorced       | 108 (20.81%)   | 33,334 (21.58%)   |         |
| Unknown                | 29 (5.59%)     | 13,303 (8.61%)    |         |
| Race                   |                |                   | .164    |
| White                  | 462 (89.02%)   | 138,377 (89.59%)  |         |
| Black                  | 30 (5.78%)     | 7,584 (4.91%)     |         |
| Other                  | 25 (4.82%)     | 6,368 (4.12%)     |         |
| Unknown                | 2 (0.39%)      | 2,124 (1.38%)     |         |
| Year of diagnosis      |                |                   | <.001   |
| 2004                   | 12 (2.31%)     | 11,581 (7.50%)    |         |
| 2005                   | 11 (2.12%)     | 11,076 (7.17%)    |         |
| 2006                   | 23 (4.43%)     | 11,365 (7.36%)    |         |
| 2007                   | 23 (4.43%)     | 11,745 (7.60%)    |         |
| 2008                   | 26 (5.01%)     | 11,643 (7.54%)    |         |
| 2009                   | 44 (8.48%)     | 11,632 (7.53%)    |         |
| 2010                   | 42 (8.09%)     | 11,919 (7.72%)    |         |
| 2011                   | 36 (6.94%)     | 11,794 (7.64%)    |         |
| 2012                   | 42 (8.09%)     | 12,299 (7.96%)    |         |
| 2013                   | 48 (9.25%)     | 12,157 (7.87%)    |         |
| 2014                   | 68 (13.10%)    | 12,341 (7.99%)    |         |
| 2015                   | 67 (12.91%)    | 12,534 (8.12%)    |         |
| 2016                   | 77 (14.84%)    | 12,367 (8.01%)    |         |
| Primary site           |                |                   | <.001   |
| Trigone of bladder     | 27 (5.20%)     | 9,944 (6.44%)     |         |
| Dome of bladder        | 27 (5.20%)     | 4,541 (2.94%)     |         |
| Lateral wall of bladder| 97 (18.69%)    | 34,216 (22.15%)   |         |
| Anterior wall of bladder| 9 (1.73%)     | 2,861 (1.85%)     |         |
| Posterior wall of bladder| 44 (8.48%)   | 14,551 (9.42%)    |         |
| Bladder neck           | 11 (2.12%)     | 4,481 (2.90%)     |         |
| Ureteric orifice       | 5 (0.96%)      | 6,986 (4.52%)     |         |
| Urachus                | 1 (0.19%)      | 25 (0.02%)        |         |
| Overlapping lesion of bladder | 85 (16.38%) | 14,142 (9.16%)    |         |
| Bladder, NOS           | 213 (41.04%)   | 62,706 (40.60%)   |         |

(Continues)
|                 | MPUC (n = 519) | TCC (n = 154 453) | P-value |
|----------------|----------------|-------------------|---------|
| **T stage**    |                |                   |         |
| Ta             | 18 (3.47%)     | 99 586 (64.48%)   | <.001   |
| Tis            | 5 (0.96%)      | 2450 (1.59%)      |         |
| T1             | 164 (31.60%)   | 36 159 (23.41%)   |         |
| T2             | 195 (37.57%)   | 10 394 (6.73%)    |         |
| T3             | 75 (14.45%)    | 2014 (1.30%)      |         |
| T4             | 59 (11.37%)    | 2095 (1.36%)      |         |
| Unknown        | 3 (0.58%)      | 1755 (1.14%)      |         |
| **N stage**    |                |                   | <.001   |
| N0             | 384 (73.99%)   | 149 639 (96.88%)  |         |
| N1             | 32 (6.17%)     | 992 (0.64%)       |         |
| N2             | 86 (16.57%)    | 979 (0.63%)       |         |
| N3             | 8 (1.54%)      | 72 (0.05%)        |         |
| Unknown        | 9 (1.73%)      | 2771 (1.79%)      |         |
| **M stage**    |                |                   | <.001   |
| M0             | 459 (88.44%)   | 150 922 (97.71%)  |         |
| M1             | 56 (10.79%)    | 1810 (1.17%)      |         |
| Unknown        | 4 (0.77%)      | 1721 (1.11%)      |         |
| **Grade**      |                |                   | <.001   |
| Low            | 9 (2.51%)      | 39 365 (50.62%)   |         |
| High           | 349 (97.49%)   | 38 407 (49.38%)   |         |
| **Surgery**    |                |                   | <.001   |
| No surgery     | 17 (3.28%)     | 8192 (5.30%)      |         |
| TURBT          | 244 (47.01%)   | 111 962 (72.49%)  |         |
| Partial cystectomy | 9 (1.73%)   | 1134 (0.73%)      |         |
| Radical cystectomy | 100 (19.27%) | 4143 (2.68%)      |         |
| Pelvic exenteration | 90 (17.34%) | 2404 (1.56%)      |         |
| Other          | 58 (11.18%)    | 26 357 (17.06%)   |         |
| Unknown        | 1 (0.19%)      | 261 (0.17%)       |         |
| **Lymph nodes removed** |       |                   | <.001   |
| None           | 319 (61.46%)   | 147 899 (95.76%)  |         |
| More than one  | 200 (38.54%)   | 6554 (4.24%)      |         |
| **Radiation**  |                |                   | <.001   |
| Beam radiation | 58 (11.18%)    | 3094 (2.00%)      |         |
| Radioactive implants | 0 (0.00%)   | 12 (0.01%)        |         |
| Combination of beam and implants | 0 (0.00%) | 2 (0.00%)        |         |
| Radioisotopes | 0 (0.00%)      | 11 (0.01%)        |         |
| Radiation unknown | 0 (0.00%)    | 68 (0.04%)        |         |
| Performance unknown | 461 (88.82%) | 151 266 (97.94%)  |         |
| **Cancer-specific mortality** |       |                   | <.001   |
| Alive          | 373 (71.87%)   | 141 802 (91.81%)  |         |
| Dead           | 146 (28.13%)   | 12 651 (8.19%)    |         |
TCC group, as shown by a higher rate of muscle invasive disease (63.39% vs 9.39%, \( P < .001 \)), lymph node metastasis (24.28% vs 1.32%, \( P < .001 \)), and distal metastasis (10.79% vs 1.17%, \( P < .001 \)). Higher-grade disease was also more common in the MPUC group (97.49% vs 49.38%, \( P < .001 \)). The surgery constituent ratio was significantly different between the two groups (\( P < .001 \)), and patients in the MPUC group were more likely to undergo RC (19.27% vs 2.68%) and pelvic exenteration (17.34% vs 1.56%). Moreover, lymph nodes were more likely to be removed from patients in the MPUC group than from patients in the TCC group (38.54% vs 4.24%, \( P < .001 \)).

### 3.2 Survival analyses

In survival analyses, the overall survival probability of patients in the MPUC group declined significantly faster than that of patients in the TCC group (\( P < .0001 \); Figure 1). When the landmark was set at 5 years (60 months), the survival probability of the MPUC group also declined faster in the OM analyses (Figure S1). The MPUC group also had a lower survival probability in the CSM analyses (\( P < .0001 \); Figure 1).

Table 2 presents multivariable Cox proportional hazard models. After adjustments for age, sex, TNM stage, tumor site, and treatment method, the adjusted model II showed that the MPUC group had a significantly higher risk of OM compared with the TCC group (HR = 1.39, 95% CI = 1.22-1.57,

### Table 1 (Continued)

|          | MPUC (n = 519) | TCC (n = 154 453) | \( P \)-value |
|----------|----------------|-------------------|---------------|
| Overall mortality |                 |                   |               |
| Alive    | 268 (51.64%)   | 54 682 (35.40%)   | < .001        |
| Dead     | 251 (48.36%)   | 99 771 (64.60%)   |               |
| Survival time (y, SD) | 31.76 (33.08) | 54.94 (42.02)     | < .001        |
| Survival time (y, IQR) | 19.00 (8.00-44.00) | 46.00 (19.00-85.00) | < .001       |

Abbreviations: IQR, interquartile range; MPUC, micropapillary urothelial carcinoma; NOS, not otherwise specified; TCC, transitional cell carcinoma; TURBT, transurethral resection of bladder tumor.

**FIGURE 1** Cancer-specific mortality and overall mortality of patients with micropapillary urothelial carcinoma (MPUC) and transitional cell carcinoma (TCC) respectively.
However, in the OM analysis, the $P$-value for baseline factors was .0505. To minimize selection bias, PSM was performed after further adjustment for $T$ stage and grade. A multi-institutional analysis based on 151 MPUC patients demonstrated that MPUC was not independently associated with the risks of recurrence or OM. Although Abufaraj et al included 15 studies in their meta-analysis, their results focused on patients undergoing RC or neoadjuvant chemotherapy. Compared with the above studies, the present study analyzed a sufficient number of patients and adjusted covariates to consider overall survival. Briefly, this study indicated that MPUC is an independent prognostic factor for OM at the population level. Interestingly, in the subgroup analysis of this study, MPUC patients without distal metastasis faced a higher risk of CSM ($HR = 1.33, 95% CI = 1.10-1.61, P < .0001$), even though CSM, as an independent prognostic factor, remains controversial. This finding indicated that M0 MPUC patients may require aggressive treatments to improve CSM.

Most MPUC cases in this study were diagnosed with muscle invasive bladder cancer (MIBC) compared with

### Discussion

In this study, we aimed to investigate prognostic values of clinicopathological characteristics and survival outcomes in MPUC of the urinary bladder. Given that TCC accounts for approximately 95% of bladder cancers, MPUC, and TCC were compared using records from the SEER database according to specified inclusion criteria. Micropapillary urothelial carcinoma and TCC had different effects on patients' OM, especially the 5-year survival status ($P < .0001$). Moreover, patients with MPUC were at a higher risk of OM ($HR = 1.39, 95% CI = 1.22-1.57, P < .0001$), but their CSM ($HR = 1.18, 95% CI = 1.00-1.40, P = .0505$) was fair. This indicated that MPUC could be an independent prognostic factor for OM in patients with urinary bladder cancer. Furthermore, in the subgroup analysis, only MPUC patients without distal metastasis faced a higher risk of CSM ($HR = 1.33, 95% CI = 1.10-1.61, P < .0001$).

Table 2

| Outcome               | MPUC HR (95% CI) | $P$-value |
|-----------------------|------------------|-----------|
| **Overall mortality** |                  |           |
| Non-adjusted         | 1.50 (1.33, 1.70) | .0001     |
| Adjusted I           | 1.40 (1.24, 1.59) | .0001     |
| Adjusted II          | 1.39 (1.22, 1.57) | <.0001    |
| PSM non-adjusted     | 1.48 (1.29, 1.71) | <.0001    |
| PSM adjusted         | 1.10 (0.93, 1.31) | .2688     |

| **Cancer-specific mortality** |                 |           |
| Non-adjusted              | 5.20 (4.42, 6.12) | <.0001   |
| Adjusted I                | 1.06 (0.90, 1.25) | .5044    |
| Adjusted II               | 1.18 (1.00, 1.40) | .0505    |
| PSM non-adjusted          | 1.35 (1.12, 1.62) | .0016    |
| PSM adjusted              | 1.30 (1.00, 1.67) | .0469    |

Note: Adjusted I model adjust for: T stage; N stage; M stage; surgery; radiation.

Adjusted II model adjust for: Sex; Age; Primary Site; T stage; N stage; M stage; surgery; radiation; lymph nodes removed.

PSM non-adjusted model adjust for none.

PSM adjusted model adjust for: T stage; N stage; M stage; surgery; radiation; lymph nodes removed.

Abbreviations: HR, hazard ratio; MPUC, micropapillary urothelial carcinoma; PSM, propensity score matching.

$P < .0001$), while no difference in CSM was observed between the two groups ($HR = 1.18, 95% CI = 1.00-1.40, P = .0505$). To minimize selection bias, PSM was performed for baseline factors and treatments (Table 3). However, there were still differences in N stage, M stage, surgery, and CSM, as an independent prognostic factor, remains controversial. This finding indicated that M0 MPUC patients may require aggressive treatments to improve CSM.

3.3 | Subgroup analyses

The subgroup analytical results are shown in Figure 2. After adjusting for potential covariates, the tests for interaction were not statistically significant for sex, age, T stage, and N stage in terms of both OM and CSM. This indicated that MPUC had a worse prognosis in all groups except for distal metastasis. Only MPUC patients without distal metastasis faced a higher risk of CSM ($HR = 1.33, 95% CI = 1.10-1.61, P < .0001$). However, in the OM analysis, the $P$-value of N stage in the test for interaction was .0521 and near .05. This might have resulted from a relatively insufficient sample size or lymph node metastasis might interact with MPUC histology.
TABLE 3  Propensity score matching for baseline factors

|                          | MPUC (n = 519) | TCC (n = 1996) | Standardized difference | P-value  |
|--------------------------|----------------|----------------|--------------------------|----------|
| Mean Age (y, SD)         | 71.06 ± 10.90  | 71.01 ± 11.40  | 0.0046                   | .9280    |
| Sex                      |                |                |                          |          |
| Male                     | 401 (80.4)     | 1604 (80.4)    |                          | 1.0000   |
| Female                   | 98 (19.6)      | 392 (19.6)     |                          |          |
| Marital status           |                |                |                          | .2326    |
| Married                  | 312 (62.5)     | 1149 (57.6)    | 0.1014                   |          |
| Single                   | 58 (11.6)      | 247 (12.4)     | 0.0231                   |          |
| Widowed/Divorced         | 101 (20.2)     | 470 (23.5)     | 0.0800                   |          |
| Unknown                  | 28 (5.6)       | 130 (6.5)      | 0.0378                   |          |
| Race                     |                |                |                          | .8007    |
| White                    | 442 (88.6)     | 1776 (89)      | 0.0127                   |          |
| Black                    | 30 (6)         | 125 (6.3)      | 0.0104                   |          |
| Other                    | 25 (5)         | 83 (4.2)       | 0.0407                   |          |
| Unknown                  | 2 (0.4)        | 12 (0.6)       | 0.0284                   |          |
| Primary site             |                |                |                          | .1086    |
| Trigone of bladder       | 26 (5.2)       | 89 (4.5)       | 0.0350                   |          |
| Dome of bladder          | 26 (5.2)       | 73 (3.7)       | 0.0755                   |          |
| Lateral wall of bladder  | 96 (19.2)      | 347 (17.4)     | 0.0479                   |          |
| Anterior wall of bladder | 9 (1.8)        | 55 (2.8)       | 0.0638                   |          |
| Posterior wall of bladder| 42 (8.4)       | 153 (7.7)      | 0.0276                   |          |
| Bladder neck             | 11 (2.2)       | 63 (3.2)       | 0.059                    |          |
| Ureteric orifice         | 5 (1)          | 51 (2.6)       | 0.1177                   |          |
| Urachus                  | 1 (0.2)        | 1 (0.1)        | 0.0425                   |          |
| Overlapping lesion of bladder | 81 (16.2)   | 283 (14.2)     | 0.0572                   |          |
| Bladder, NOS             | 202 (40.5)     | 881 (44.1)     | 0.0741                   |          |
| T stage                  |                |                |                          | .0931    |
| Ta                       | 18 (3.6)       | 72 (3.6)       | 0                        |          |
| Tis                      | 4 (0.8)        | 16 (0.8)       | 0                        |          |
| T1                       | 156 (31.3)     | 648 (32.5)     | 0.0258                   |          |
| T2                       | 193 (38.7)     | 771 (38.6)     | 0.0010                   |          |
| T3                       | 71 (14.2)      | 244 (12.2)     | 0.0592                   |          |
| T4                       | 55 (11)        | 194 (9.7)      | 0.0427                   |          |
| Unknown                  | 2 (0.4)        | 51 (2.6)       | 0.1792                   |          |
| N stage                  |                |                |                          | <.0001   |
| N0                       | 372 (74.5)     | 1535 (76.9)    | 0.0549                   |          |
| N1                       | 29 (5.8)       | 116 (5.8)      | 0                        |          |
| N2                       | 81 (16.2)      | 215 (10.8)     | 0.1603                   |          |
| N3                       | 8 (1.6)        | 13 (0.7)       | 0.0903                   |          |
| Unknown                  | 9 (1.8)        | 117 (5.9)      | 0.2126                   |          |
| M stage                  |                |                |                          | .0269    |
| M0                       | 444 (89)       | 1788 (89.6)    | 0.0194                   |          |
| M1                       | 51 (10.2)      | 160 (8)        | 0.0766                   |          |
| Unknown                  | 4 (0.8)        | 48 (2.4)       | 0.1279                   |          |

(Continues)
TCC cases (63.39% vs 9.39%, $P < .001$), and MPUC patients had higher rates of lymph node metastasis (24.28% vs 1.32%, $P < .001$) and distal metastasis (10.79% vs 1.17%, $P < .001$). Higher-grade disease was also more common in the MPUC group (97.49% vs 49.38%, $P < .001$). These aggressive pathologic features have also been noted in other studies.8,9,12 According to another study, even if MPUC constituted less than 10% of a UC, the patients had worse outcomes.

| Grade          | MPUC (n = 519) | TCC (n = 1996) | Standardized difference | $P$-value |
|----------------|----------------|----------------|-------------------------|-----------|
| Low            | 6 (1.7)        | 112 (11)       | 0.3848                  | <.0001    |
| High           | 337 (98.3)     | 909 (89)       |                         |           |

| Surgery        | MPUC (n = 519) | TCC (n = 1996) | Standardized difference | $P$-value |
|----------------|----------------|----------------|-------------------------|-----------|
| No surgery     | 16 (3.2)       | 92 (4.6)       | 0.0724                  |           |
| TURBT          | 233 (46.7)     | 1115 (55.9)    | 0.1842                  |           |
| Partial cystectomy | 9 (1.8) | 30 (1.5)       | 0.0236                  |           |
| Radical cystectomy | 97 (19.4) | 336 (16.8)     | 0.0677                  |           |
| Pelvic exenteration | 86 (17.2) | 201 (10.1)     | 0.2098                  |           |
| Other          | 57 (11.4)      | 218 (10.9)     | 0.0159                  |           |
| Unknown procedure | 1 (0.2)   | 4 (0.2)        |                         |           |

| Lymph nodes removed | MPUC (n = 519) | TCC (n = 1996) | Standardized difference | $P$-value |
|---------------------|----------------|----------------|-------------------------|-----------|
| None                | 306 (61.3)     | 1469 (73.6)    | 0.2643                  | <.0001    |
| More than one       | 193 (38.7)     | 527 (26.4)     |                         |           |

| Radiation          | MPUC (n = 519) | TCC (n = 1996) | Standardized difference | $P$-value |
|--------------------|----------------|----------------|-------------------------|-----------|
| Beam radiation     | 58 (11.6)      | 183 (9.2)      | 0.0805                  |           |
| Radiation unknown  | 0 (0)          | 3 (0.2)        | 0.0549                  |           |
| Performance unknown| 441 (88.4)     | 1810 (90.7)    | 0.0753                  |           |

| Cancer-specific mortality | MPUC (n = 519) | TCC (n = 1996) | Standardized difference | $P$-value |
|---------------------------|----------------|----------------|-------------------------|-----------|
| Alive                     | 353 (70.7)     | 1496 (74.9)    | 0.0947                  |           |
| Dead                      | 146 (29.3)     | 500 (25.1)     |                         |           |

| Overall mortality        | MPUC (n = 519) | TCC (n = 1996) | Standardized difference | $P$-value |
|--------------------------|----------------|----------------|-------------------------|-----------|
| Alive                    | 256 (51.3)     | 1065 (53.4)    | 0.0411                  | .4400     |
| Dead                     | 243 (48.7)     | 931 (46.6)     |                         |           |

Abbreviations: MPUC, micropapillary urothelial carcinoma; NOS, not otherwise specified; TCC, transitional cell carcinoma; TURBT, transurethral resection of bladder tumor.

**TABLE 3** (Continued)

**FIGURE 2** Subgroup analysis for interaction between micropapillary urothelial carcinoma and potential covariates in both overall mortality and cancer-specific mortality.
participate in MPUC polarity reversal.16 These molecular mechanisms might be helpful for early diagnosis and further treatment of this cancer.

In this study, the most common surgery type in the MPUC group was TURBT (47.01%, 244/519), followed by RC (19.27%, 100/519) and pelvic exenteration (17.34%, 90/519). In addition, MPUC patients had more lymph nodes removed (38.54% vs 4.24%, \( P < .001 \)) and were more likely to be treated with beam radiation (11.18% vs 2.00%, \( P < .001 \)) than patients in the TCC group. Given that 63.39% of MPUC patients have MIBC, the treatment is relatively conservative and may be responsible for worse prognoses. Although RC was recommended in MIBC guidelines, early RC in non-MIBC patients is still controversial.10 A population-based study showed no difference between RC and bladder preservation surgery for cT1 MPUC,8 while Willis et al reported a better prognosis after early RC.17 Cisplatin-based neoadjuvant therapy was commonly given to improve MIBC prognoses, but it is unclear whether it actually does. Sui et al found no survival benefit from MPUC after neoadjuvant chemotherapy.8 Although other studies reported pathological downstaging, this does not translate into better survival outcomes.18 In this study, MPUC was found to be an independent prognostic factor for OM and for CSM in the M0 subgroup. We suggest that, once MPUC components are found by biopsy, an advanced combined treatment should be considered. However, multicenter clinical trials are needed to establish a better therapeutic protocol for this rare, but aggressive, cancer.

This study had several strengths. First, we enrolled 519 patients with MPUC of the urinary bladder from 2004 to 2016; thus, we had a sufficient sample size to perform an exact and multiform analysis. Subgroup analyses and PSM were used to analyze potential confounding factors. Second, we updated clinicopathological characteristics and survival outcomes of MPUC, based on recent data. However, our study also had some limitations. First, this study had strict limitations due to its retrospective nature. Selection bias may exist, which is inevitable for clinical observational studies, even those using PSM. Second, the SEER database lacked some essential variables; for example, treatment regimens were classified into two major categories as either surgery or radiotherapy, but chemotherapy and new therapies such as checkpoint-inhibitor drugs were absent; including these treatment modalities might have led to different outcomes.

### 5 CONCLUSIONS

The prognosis of MPUC is poorer than that of TCC. Micropapillary urothelial carcinoma is an independent prognostic factor for OM in patients with urinary bladder cancer. In the subgroup analysis, only MPUC patients without distal metastasis faced a higher risk of CSM.

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### CONFLICT OF INTEREST

Nonfinancial associations that may be relevant to the submitted manuscript.

### AUTHORS’ CONTRIBUTION

The first three authors contributed equally as first authors of this manuscript. All authors contributed to the design of the project, data collection and analysis, and contributed to the final manuscript. All authors have read and approved the final submitted manuscript.

### DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://seer.cancer.gov/data/.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.