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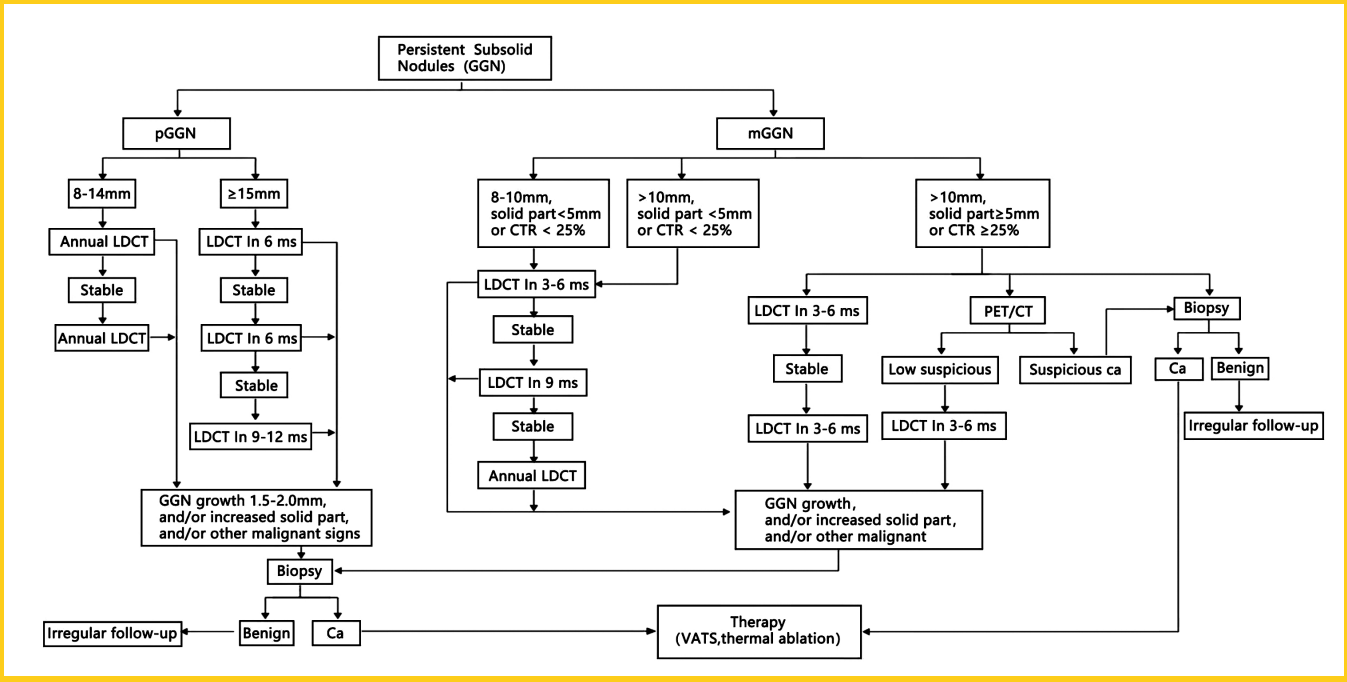

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Original Article

The impact of patient sex on characteristic-adjusted bladder cancer prognosis

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ABSTRACT

Context: Bladder cancer is one of the most common malignancies worldwide. Some studies noted sex differences in the prognosis of bladder cancer, but results are inconsistent.

Subjects and Methods: In this study, we assessed whether women with bladder cancer exhibit a worse prognosis, after adjustment for disease stage, age, and body mass index (BMI), using clinical data from The Cancer Genome Atlas. We used a Student's *t*-test to compare age and BMI in groups with different sexes.

Statistical Analysis Used: The Kaplan–Meier method with log-rank test was used to determine clinical prognosis.

Results: The BMI (30.15 vs. 26.68, $P = 0.0035$) and age (67.54 years vs. 66.01 years, $P = 0.045$) of female patients with muscle-invasive bladder cancer (MIBC) were higher than those of male patients. The overall survival (OS) prognosis of female patients was worse than that of male patients. After grouping by disease characteristics, the disease-free survival (DFS) and OS prognoses of female patients under 60 years of age were worse than those of male patients. In the group with BMI >24, the OS prognosis of female patients was worse than that of male patients, but no difference was found in DFS prognosis. In the group with BMI ≤24, the DFS prognosis of female patients was worse than that of male patients, but no difference was found in OS prognosis. Compared to males, female patients with Stage III disease demonstrated a worse DFS prognosis and poorer OS prognosis, women with stage T3 demonstrated a worse DFS prognosis, and women with stage N0 demonstrated a poorer OS prognosis. No difference was found in prognosis between male and female patients in all other groups.

Conclusions: In patients with MIBC, women tended to exhibit a worse prognosis than men. More specifically, we found a correlation between prognosis and sex after grouping patients by BMI.

KEY WORDS: Bladder cancer, body mass index, disease stage, prognosis, sex, the Cancer Genome Atlas

INTRODUCTION

Bladder cancer is one of the most common malignancies worldwide, causing almost 150,000 deaths each year.[1] Bladder cancer is prone to recurrence and is strongly invasive. It develops into muscle-invasive bladder cancer (MIBC) or metastatic disease, which has a worse prognosis, either as an initial diagnosis or during treatment in approximately 25% of patients. Many factors are associated with the development and prognosis of bladder cancer,[2,3] among which a history of smoking is the most common risk factor.[4] In addition, patient sex has always been considered to be an important factor affecting the prognosis of bladder cancer;[5] however, the influence of body mass index (BMI) combined with sex remains unclear. The discovery of new prognostic factors can allow for a better understanding of bladder cancer while providing a basis for disease guidance and prognosis evaluation.

To date, many studies explored the relationship between sex and bladder cancer prognosis, but they produced inconsistent conclusions. Previous studies showed that the prevalence of male patients with MIBC is about three times that of female patients. However, compared with male patients, female patients with bladder cancer exhibit a higher risk of cancer-specific mortality (CSM)[6,7] and

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the 5-year survival rate of women in every disease stage is poorer.[8] Moreover, being a female is an independent predictor and risk factor of CSM for bladder cancer as well as requiring a radical cystectomy (RC).[9,10]

Nevertheless, the relationship between sex and prognosis post-RC remains unclear. After matching female and male patients with respect to demographic characteristics, tumor characteristics, and therapy, one study noted no difference in the disease-free survival (DFS) prognosis and overall survival (OS) prognosis of males and females.[11] In another study, no association was found between sex and postoperative survival after stratifying patients according to a number of variables, including tumor stage.[12,13] Several other large-scale studies found that, among patients with stage T4 bladder cancer, women exhibited a notably worse prognosis, and they were at a higher risk of CSM and disease recurrence.[14,15] However, an additional study of 128 patients with T4 bladder cancer tumors did not find any association between sex and survival.[5,16]

Controversy Inconsistencies have also been found in the relationship between sex and non-MIBC (NMIBC) prognosis. Some studies found that, among patients with T1G3 bladder cancer who received *Bacillus* Calmette–Guerin (BCG) treatment, recurrence, progression, and death from bladder cancer were more likely in females;[17,18] however, since the patients in this study were not treated with secondary electrotomy, the application of these results is limited. Other studies found that females with NMIBC exhibit a higher CSM than male patients,[19,20] and among patients with carcinoma *in situ*, women exhibited a high risk of CSM.[21,22] Nonetheless, other research studies suggested that no association exists between sex and disease progression or mortality risk.[18,23] For instance, in patients with NMIBC treated with BCG, no correlation is found between patient sex and recurrence or progression.[24] A meta-analysis of 15,215 patients with high-grade T1 bladder cancer found that being a woman was associated with a risk of disease progression but demonstrated no relevance to the risk of tumor recurrence or cancer-specific survival.[25,26]

Since the relationship between sex and bladder cancer prognosis remains unclear, in this study, we aimed to analyze the relationship between patient sex and prognosis in patients with bladder cancer using recent clinical data for patients with MIBC and NMIBC in The Cancer Genome Atlas (TCGA) database. In addition, we aimed to evaluate the relationship between sex and bladder cancer prognosis from new perspectives, such as including BMI, while verifying the results of previous studies, thus providing a basis for disease prevention and treatment.

SUBJECTS AND METHODS

The authors state that they have been approved by the Ethics Committee of Nanjing Medical University and have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations.

Clinical information for patients with MIBC was downloaded directly from TCGA (https://portal.gdc.cancer.gov/) and cBioPortal for Cancer Genomics (http://www.cbioportal.org/index.do) websites.[27] Clinical data for 413 eligible patients were downloaded. Inclusion criteria included being chemotherapy naive and presenting with invasive, high-grade MIBC. In addition, only patients with complete clinical data, including sex, age, BMI, tumor stage, tumor-node-metastasis (TNM) stage, tumor grade, OS prognosis, and DFS prognosis, were selected for follow-up analysis. All informed signed consent had been obtained from all subjects during the original research.

After screening, a total of 233 patients were selected for inclusion in the analysis, including 177 males (76%) and 56 females (24%). The clinical information for all patients is summarized in Table 1. In addition, to evaluate the effects of sex in patients with NMIBC, we also downloaded the clinical information of 105 eligible patients with NMIBC from the same websites; this information is summarized in Table 2.

Table 1: Clinical characteristics of patients with muscle-invasive bladder cancer

Characteristic	Sex		*P*
	Male	Female	
Age (years)	66.01	67.54	
Range	47-90	37-89	
Tumor stage			
T0	1	0	0.8447
T1	2	0	
T2	22	7	
T2a	20	3	
T2b	23	8	
T3	20	8	
T3a	32	8	
T3b	37	15	
T4	2	0	
T4a	16	7	
T4b	2	0	
Metastasis stage			
M0	75	25	0.2512
M1	4	0	
MX	98	31	
Lymphnode stage			
N0	114	34	0.5755
N1	24	6	
N2	23	12	
N3	2	1	
NX	14	3	
Disease stage			
Stage I	2	0	0.7669
Stage II	56	16	
Stage III	68	21	
Stage IV	51	19	
Histologic grade			
High grade	159	55	0.0457
Low grade	18	1	
Tumor histologic subtype			
Nonpapillary	114	38	0.6365
Papillary	63	18	

P<0.05 was considered statistically significant, using Chi-square test

Patient demographic characteristics, including age (≤60 and >60 years old), BMI (≤24 and >24), and clinicopathological characteristics, including grade and TNM stage, were collected. TNM stages of bladder cancer were determined according to the American Joint Committee on Cancer (AJCC) staging system using available clinical and pathological data on tumor invasion, lymphnode status, and distant metastasis, respectively.

In terms of survival outcome, OS was defined as the time between the date of surgery and the date of death or last follow-up. DFS was defined as the time from the date of surgery to the date of bladder cancer recurrence. Cause of death was obtained from death certificates. All patients with MIBC exhibited a median follow-up period of 19.02 months (range: 0.43–165.9 months) for OS and 15.9 months (range: 0.43–142.7 months) for DFS.

All statistical analyses were performed using GraphPad Prism® 8.0.2 (GraphPad Software, La Jolla, CA, USA). The Kaplan–Meier method was used to calculate outcome functions, and differences were assessed using the log-rank statistic. A two-tailed Chi-square test was used to examine differences between categorical variables. All reported *P* values are two sided, and a $P < 0.05$ was considered statistically significant.

RESULTS

A total of 233 eligible patients with MIBC were included in this study. They consisted of 177 male patients (76%) and 56 female patients (24%). The median follow-up period was 19.02 months (range: 0.43–165.9) for OS and 15.9 months (range: 0.43–142.7) for DFS. Among patients with NMIBC, there were 80 male patients (76.2%) and 25 female patients (23.8%) in all. The association between sex and the demographic and clinicopathological characteristics of patients with MIBC is presented in Table 1, whereas those for patients with NMIBC are presented in Table 2. The clinical data for patients with NMIBC did not contain prognostic information, so for this group, we could only compare the relationship between disease characteristics and sex. Female patients with both MIBC and NMIBC demonstrated a lower risk of exhibiting a high histologic grade tumor than male patients ($P = 0.0457$ and $P = 0.05$, respectively). Moreover, in patients with MIBC, BMI (30.15 vs. 26.68, $P = 0.0035$) and age (67.54 years vs. 66.01 years, $P = 0.045$) were higher in female patients than in male patients [Figure 1a and b].

A total of 63 (27.04%) patients with MIBC died during this study. In the Kaplan–Meier analyses, female patients demonstrated a significantly lower OS than male patients ($P = 0.0429$), but no difference was found between sexes in terms of DFS [Figure 1c and d].

To further analyze the relationship between patient sex and prognosis, we divided all patients into groups, and then, we compared the prognostic differences to the sex differences within each group, in an attempt to uncover a new relationship between sex and prognosis. First, we divided all patients into one of two groups based on age (over 60 and under 60 years old) and then analyzed OS and DFS. In the ≤60-year-old patient group, female patients exhibited a shorter DFS and poorer OS [$P = 0.0011$ and $P = 0.0272$, respectively; Figure 2a and c]. In the >60-year-old patient group, no association was found between sex and prognosis [Figure 2b and d]. In summary, among younger patients (≤60 years old), females exhibited a worse prognosis than males, but among older

Table 2: Clinical characteristics of patients with nonmuscle-invasive bladder cancer

Clinical characteristic	Sex		*P*
	Male	Female	
Age (years)	67.43	65.2	
Range	36-87	25-87	
Concomitant carcinoma *in situ*			
Yes	33	6	0.1192
No	47	19	
Number of tumors			
Multiple 2+	31	11	0.6478
Single 1	49	14	
Recurrence			
Yes	33	11	0.5178
No	42	14	
NA	4	0	
Grade			
LGTa	13	10	0.05
HGTa	24	8	
HGT1	33	5	
Tis	10	2	
Tumor size (cm)			
>3	34	9	0.564
<3	46	16	

P<0.05 was considered statistically significant using Chi-square test.
LGT=Low Grade Tumor, HGT=High Grade Tumor

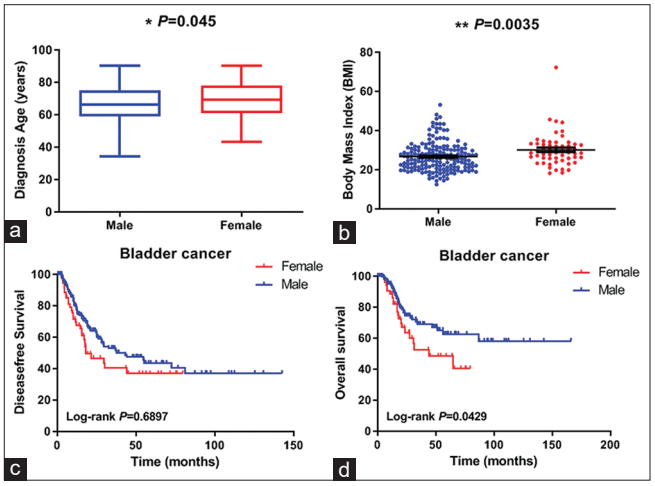

Figure 1: Characteristics of patients with MIBC according to patient sex. (a) correlation between age and sex in MIBC, (b) correlation between BMI and sex in MIBC, (c) Kaplan–Meier disease recurrence curves for patients with MIBC, stratified by sex, (d) Kaplan–Meier survival curves for patients with bladder cancer, stratified by sex. MIBC = Muscle-invasive bladder cancer, BMI = Body mass index

patients (>60 years old), no notable difference was found in prognosis across sex.

Then, we divided the patients into an overweight group and a healthy-weight group, using a BMI of 24 as the cutoff. In the group of patients with BMI >24, no differences were found in DFS across sex [Figure 3a], but OS was lower in women than men [$P = 0.0431$, Figure 3c]. In patients with BMI ≤24, DFS was shorter in women than men [$P = 0.0205$, Figure 3b], but no difference was found in OS across the two sexes [Figure 3d]. In summary, overweight women (BMI >24) demonstrated a worse survival rate than men, but healthy normal weight women (BMI ≤24) were more likely than men to exhibit disease recurrence.

Next, we divided the patients into groups according to disease stage, according to the AJCC. We found that, among patients with stage III disease, female patients exhibited shorter DFS and worse OS than male patients [$P = 0.0427$, $P = 0.0078$, Figure 4b and e].

No association was found between sex and prognosis among Stage II and IV patients [Figure 4]. Thus, women with Stage III disease exhibited a worse prognosis; however, no difference was found in the prognosis of male and female patients in other stages of disease. This result is consistent with those of previous studies.

Finally, in terms of the effect of the patient's TNM stage, we found that among patients in stage T3, the DFS of female patients was notably shorter than that of male patients [$P = 0.0212$, Figure 5b]. Among patients with stage N0 disease, female patients also exhibited worse OS than male patients [$P = 0.0289$, Figure 6c]. For patients in the other T and N stages, sex resulted in no effect on prognosis [Figures 5 and 6]. The 5-year survival rates for all groups are summarized in Table 3.

DISCUSSION

Bladder cancer remains one of the most common malignancies worldwide.[1,28] The characteristics of bladder tumors ensure that it is more prone to recurrence, invasion, and metastasis. Therefore, further analyses of the factors related to the progression, recurrence, and prognosis of bladder cancer improve our understanding of the disease, and they can provide a basis for disease guidance and prognosis evaluated the effect of sex on the prognosis of bladder cancer (mainly MIBC). Moreover, we divided patients into groups according to different patient and tumor characteristics, then analyzed

Table 3: Overall survival estimates according to clinicopathological characteristics and patient sex

Characteristics	Five-year survival probability	
	Male	Female
Age (years)		
≤60	58.19	58.49
>60	54.81	60.28
BMI		
≤24	51.06	42.19
>24	69.27	53.07
Disease stage		
Stage II	75.03	88.21
Stage III	76.75	45.77
Stage IV	32.92	32.57
Tumor stage		
T2	71.85	84.85
T3	54.2	49.14
T4	36.62	0
Lymph node stage		
N0	78.89	70.14
N1-N3	32.9	32.57

BMI=Body mass index

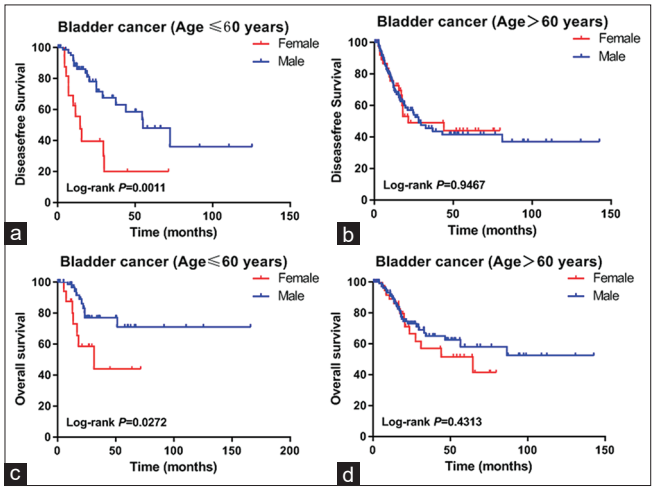

Figure 2: Kaplan–Meier analyses for DFS and OS within each age group of patients with MIBC, stratified by sex. (a and b) Kaplan–Meier analyses of DFS within each age group. (c and d) Kaplan–Meier analyses of OS within each age group. DFS = Disease-free survival, OS = Overall survival, MIBC = Muscle-invasive bladder cancer

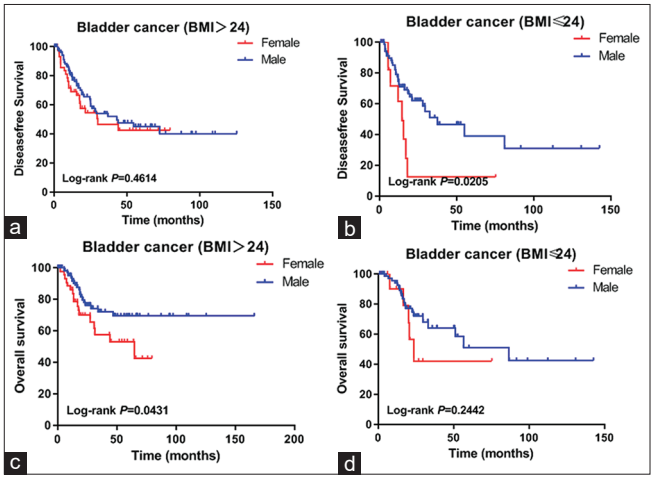

Figure 3: Kaplan–Meier analyses of DFS and OS within each BMI group of patients with MIBC, stratified by sex. (a and b) Kaplan–Meier analyses of DFS within each BMI group, (c and d) Kaplan–Meier analyses of OS within each BMI group. DFS = Disease-free survival, OS = Overall survival, MIBC = Muscle-invasive bladder cancer, BMI = Body mass index

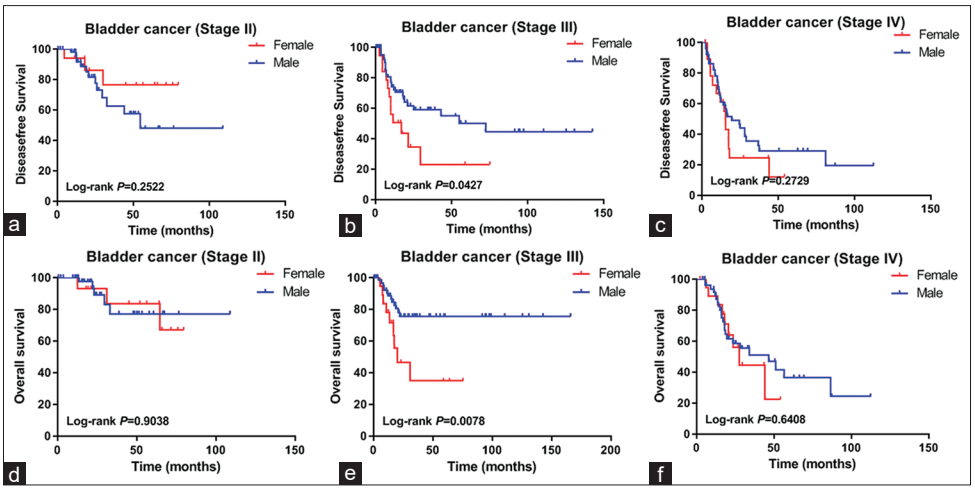

Figure 4: Kaplan–Meier analyses of DFS and OS within each stage group of patients with MIBC, stratified by sex. (a-c) Kaplan–Meier analyses of DFS within each stage group, (d-f) Kaplan–Meier analyses of OS within each stage group. DFS = Disease-free survival, OS = Overall survival, MIBC = Muscle-invasive bladder cancer

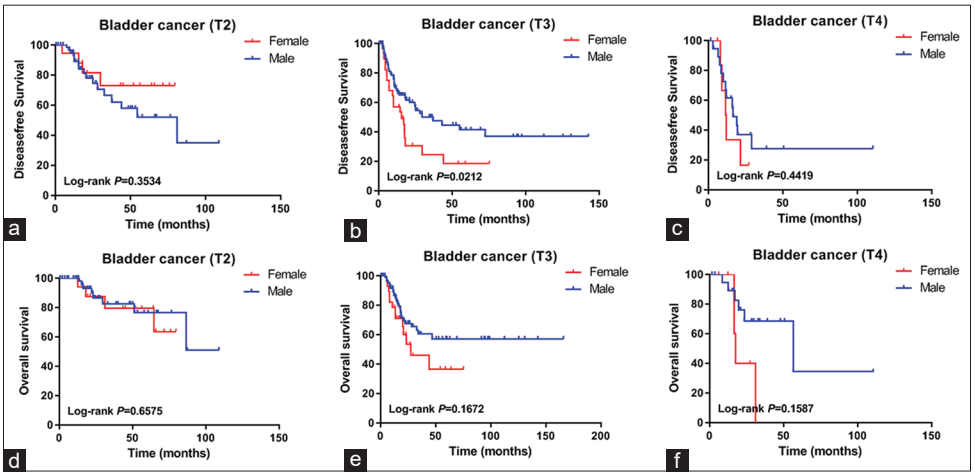

Figure 5: Kaplan–Meier analyses of DFS and OS within each T-stage group in patients with MIBC, stratified by sex. (a-c) Kaplan–Meier analyses of DFS within each T-stage group. (d-f) Kaplan–Meier analyses of OS within each T-stage group. DFS = Disease-free survival, OS = Overall survival, MIBC = Muscle-invasive bladder cancer

the effect sex on different prognosis characteristics. On the one hand, we obtained partial results that were consistent with those from previous studies. On the other hand, we also found a new association between sex and prognosis in different BMI groups.

With regard to the relationship between sex and bladder cancer prognosis, previous studies found that, upon stratification by patient stage, women with bladder cancer exhibited a worse prognosis than men. Our research revealed that, compared to men, women with Stage III exhibited shorter DFS and worse OS, women with Stage T3 exhibited shorter DFS, and women with Stage N0 exhibited worse OS; this reconfirmed the results from previous studies. Conversely, no difference was found in prognosis across the sexes in Stages II and IV, as well as in other T and N stages. These results indicate that the prognosis of female patients with bladder cancer was worse than that of male patients and that patients with specific stages should be paid particular attention since early intervention and active treatment may improve their prognosis.

As for the causes of poor prognosis in women, some research attributed this effect to hormones, whereas other research suggested an association with metabolism.[22] In this study, we compared the tumor characteristics of patients with NMIBC and MIBC, noting that the number of patients with higher-grade tumors was lower in women with NMIBC, but among those with MIBC, the proportion of female patients with high-level tumors was significantly higher. As for the reason for poorer prognosis in some women, the average diagnostic age and BMI were higher in female patients than in male patients.

In this study, we introduced BMI stratification for the first time; previous studies have not examined the relationship between sex and BMI in terms of bladder cancer prognosis. Our study found that, among patients with bladder cancer,

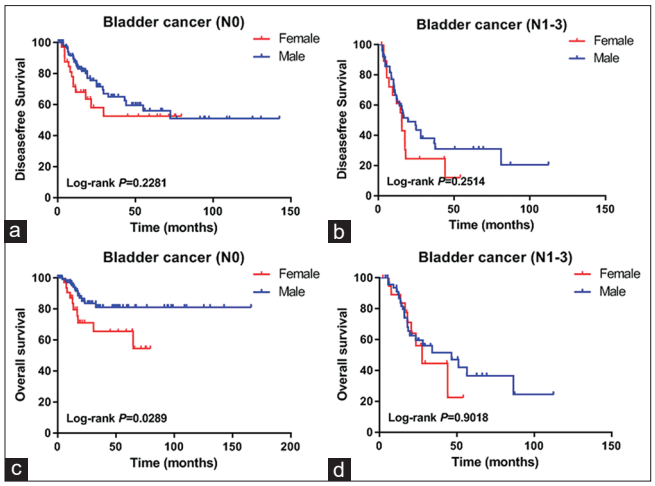

Figure 6: Kaplan–Meier analyses of DFS and OS within each N-stage group in patients with MIBC, stratified by sex. (a,b) Kaplan–Meier analyses of DFS within each N-stage group, (c,d) Kaplan–Meier analyses of OS within each N-stage group. DFS = Disease-free survival, OS = Overall survival, MIBC = Muscle-invasive bladder cancer

female patients exhibited a higher BMI than male patients, and after stratification by BMI, these patients exhibited different DFS and OS; In the group of patients with BMI >24, female patients exhibited worse OS than male patients, whereas in the group with BMI ≤24, female patients exhibited shorter DFS than male patients. These results suggest that overweight women (BMI >24) exhibited a worse survival rate than men, but healthy-weight women (BMI ≤24) were more likely to relapse than men. These results suggest a role of metabolism and obesity in the disease process. Female patients with different BMIs should be offered different clinical treatment and follow-up strategies to increase their clinical benefits.

Conversely, some of our results differed from those of previous studies. For example, in the Stage II patient group, although no difference was found in prognosis across sex, the prognosis and 5-year survival rate of female patients tended to better than that of male patients, unlike in previous studies. Upon the addition of new clinical data, future studies may find statistically significant differences across sex; this is worthy of further study.

This study demonstrated some limitations. Although the latest TCGA clinical data was used, the clinical sample that met the study requirements was small, the clinical data were limited, and the data for patients with NMIBC did not contain prognostic information. In future studies, we aim to further study the relationship between sex and bladder cancer prognosis using a larger clinical sample and more complete clinical data, in addition to seeking its molecular mechanism through basic research.

CONCLUSION

This study found that, compared to male patients, female patients with bladder cancer exhibited a worse prognosis when in specific stages, obese women with a high BMI exhibited a worse survival rate, and women with a healthy weight (BMI <24) were more likely to relapse. Uncovering new factors related to bladder cancer prognosis can provide a basis for disease guidance and patient prognosis evaluation.

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Conflicts of interest

There are no conflicts of interest.

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