

Original Article

Cause of death of patients with non-muscular invasive, non-metastatic muscular invasive and metastatic bladder cancer after diagnosis

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Abstract: Background: The purpose of this study was to evaluate the various causes of death among patients with non-muscular invasive bladder cancer (NMIBC), non-metastatic muscle invasive bladder cancer (non-MMIBC) and metastatic bladder cancer (MBC) after diagnosis. Methods: With the Surveillance, Epidemiology, and Final Results database, patients diagnosed with bladder cancer from 2004 to 2015 were identified. All causes of death and the standardization mortality ratio (SMR) were analyzed. Results: A total of 111,784 NMIBC, 26,546 non-MIBC and 4,678 MBC patients were identified. For NMIBC patients, 44,638 patients died during the follow-up, including 20.57% of bladder cancer, 18% of other tumors and 61.36% of non-tumor diseases. Main causes of other tumors death were cancers from lung and bronchus [n=2,860, SMR: 1.56 (1.51-1.62)], pancreas [n=506, SMR: 1.15 (1.05-1.26)], and prostate [n=442, SMR: 0.62 (0.56-0.68)]. Main causes of non-tumor deaths were diseases of heart [n=10,007, SMR: 1.15 (1.13-1.17)], chronic obstructive pulmonary disease (COPD) [n=3,153, SMR: 1.54 (1.49-1.59)], cerebrovascular diseases [n=1,704, SMR: 0.96 (0.91-1)], alzheimers [n=1,211, SMR: 0.87 (0.82-0.92)] and diabetes mellitus [n=1,047, SMR: 1.19 (1.12-1.27)]. Among the 18829 deaths in non-MMIBC patients, 62.65% patients died of bladder cancer, 11.08% of other tumors and 26.39% of non-tumor causes. Main deaths of other cancers were tumors from lung and bronchus [n=435, SMR: 1.83 (1.66-2.01)], prostate [n=192, SMR: 2.21 (1.91-2.54)]. Main causes of non-tumor death were diseases of heart [n=1717, SMR: 1.56 (1.49-1.64)], COPD [n=561, SMR: 2.18 (2.01-2.37)], and cerebrovascular diseases [n=290, SMR: 1.28 (1.14-1.44)]. Among the 4,392 deaths of MBC patients, 3,486 (79.37%) died of bladder cancer. Main cause of other deaths included diseases of heart (n=128) and prostate cancer (n=57). Conclusion: For NMIBC patients, leading causes of death were diseases of heart, COPD, lung and bronchus cancer, cerebrovascular diseases, Alzheimer's, and diabetes mellitus. Leading causes of deaths for non-MMIBE patients were bladder cancer, diseases of heart, COPD, lung and bronchus cancer, cerebrovascular diseases and prostate cancer. Main causes of death for MBC patients were bladder cancer itself. Our results of all causes of death and mortality risks provided useful information for bladder cancer patients.

Keywords: Bladder cancer, causes of death, SMR, SEER

Introduction

Bladder cancer ranks ninth among the most common cancers in the world, and the incidence of bladder cancer is the highest in countries in Southern Europe, Western Europe, North America, North Africa, and West Asia [1]. According to recent statistics, the number of new cases of bladder cancer in the United States in 2021 was 83,730, and the death in these cases was 17,200 [2]. Thus, it seriously

threatens the life and health of patients and has also brought huge economic and social burdens.

Tumors isolated on the urothelium (Ta stage) and lamina propria (T1 stage) are considered to be non-muscle invasive bladder cancer (NMIBC). Their treatment is different from tumors of T2-4 stages which are called muscle-invasive bladder cancer (MIBC) [3]. NMIBC represents approximately 70% of organ-confined

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bladder cancer. The standard treatment for NMIBC is transurethral resection of bladder tumor (TURBT) with risk-based recommendations regarding intravesical therapy [4]. Kong et al pointed out that even 20 years after the diagnosis of primary bladder cancer, the probability of death from primary bladder cancer was still observed as an important cause of death (the cancer itself was still observed as an important cause of death), but the heart and non-malignant lung causes accounted for a large proportion of deaths among long-term bladder cancer survivors [5]. Muscle-invasive bladder cancer represents the remaining 30% of local bladder disease [6]. The standard therapy for MIBC (T2-T4) is radical cystectomy (RC) with bilateral pelvic lymph node dissection (PLND) [7]. Although bladder cancer-specific deaths accounted for a relatively high proportion of MIBC, there are still a large proportion of non-bladder cancer-specific deaths [8].

Although lots of studies have evaluated the prognosis of patients with bladder cancer, most of them focused on the tumor itself and the deaths it caused. Few studies assessed other deaths during the survivorship. As other causes of death including other tumors and non-tumor causes accounted for a considerable proportion of all deaths, it's worthy of attention. To our knowledge, there is not a study that evaluated the other causes of deaths among NMIBC, non-MIBC and MBC patients. The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) 18 registries collected cancer data that covers approximately 28% of the United States population from 2004 to 2015 [9]. This demonstrated that the regional data reported by SEER can represent the US population and can be generalized. The general population data could be obtained from the United States Centers for Disease Control and Prevention (CDC). Therefore, we evaluated all causes of death including bladder cancer, other tumors and non-tumor causes, and calculated mortality risk of each cause comparing with the general population.

Materials and methods

Data source

Data for bladder cancer patients came from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) 18 regis-

tries. The SEER*Stat software version 8.3.9 (National Cancer Institute, USA) was utilized to access the data from the SEER database. Meanwhile, the data for the general population came from the United States CDC. Our data was de-identified and not considered as human subject research. Therefore, approval by the institutional review board was not required.

Patients

Patients who were histologically diagnosed with bladder cancer as the first primary tumor and had clear TNM stages and follow-up time were identified. The living status (alive or died), the alive time after diagnosis and detailed causes of death in these patients were clearly known. The last follow-up time was December 31, 2015. According to the definition of the National Cancer Institute, survival included any patients undergoing treatment and those after treatment [14]. We divided these patients into NMIBC, non-MMIBC and MBC according to the depth of tumor invasion and aggressiveness and classified and analyzed their causes of death.

Study variables

The following variables were collected, including age (15-44 years, 45-54 years, 55-64 years, 65-74 years and >75 years), sex (male and female), race (white, black, American Indian/Alaska Native and Asian or Pacific Islander), differentiation (grade I, II, III, and IV), pathology, surgical treatments (local tumor excision, partial cystectomy, radical cystectomy, other surgery, and no surgical treatments), chemotherapy (yes, no/unknown), and radiation (yes, no/unknown). The causes of deaths during the whole follow-up and different periods (<1 year, 1-5 years, 5-10 years, and >10 years after diagnosis) and related SMRs were regarded as the main outcomes.

Statistical analyses

For the baseline characteristics of patients with different stages of bladder cancer, we calculated the number of all causes of deaths stratified by age, sex, race, differentiation, pathology, treatments. The causes of death including bladder cancer, other tumors, and non-tumor were analyzed and the number of cases was calculated among patients with NMIBC, non-

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MMIBC and MBC. The SMR of different reasons for death were also calculated by comparing the observed number of deaths to the expected number. The expected number of deaths was based on the total number of patient-years and the incidence of the general population. The statistical significance of SMR was based on the *P*-value generated by the two-sided test. All these analyses were performed using SEER*Stat version 8.3.9. Pie charts of the proportion of different causes of death were drawn with Microsoft Excel 2016.

Results

Baseline characteristics

A total of 143,008 patients diagnosed with bladder cancer were extracted from the SEER database. 78.17% of all patients were with NMIBC, 18.56% with non-MMIBC, and 3.27% with MBC. 67,859 (47.45%) died during follow-up, the number of male patients exceeded that of females (75.96%), most patients were white (89.99%), transitional cell carcinoma was the main pathological type group (76.71%), but squamous cell carcinoma had the highest risk of death. 94.04% of people received surgery, 21.16% received chemotherapy, and 81.64% received radiotherapy. Among all included patients, a total of 67,859 patients (47.45%) died during the follow-up period. NMIBC deaths most occurred at 5-10 years after diagnosis (31.62%). Most deaths from non-MMIBC (38.82%) and MBC (41.55%) occurred within 1 year after diagnosis. NMIBC and non-MMIBC total number and death toll baseline information is reported in **Table 1** and the information about MBC is reported in **Table 2**.

Cause of death in patients with NMIBC

During the follow-up period, 44,638 patients died after being diagnosed with NMIBC, 9,183 (20.57%) died of bladder cancer, 8,066 (18.07%) died of other cancers (non-bladder cancer), and 27,7389 died of neoplastic disease (61.36%). The risk of dying from bladder cancer was higher than that of ordinary Americans [SMR: 31.52, 95% CI (30.88-32.17)]. The SMR of dying from bladder cancer gradually decreased over time. The risk of dying from lung and bronchial cancer was also higher than that of ordinary Americans [SMR: 1.56, 95% CI (1.51-1.62)], but on the contrary, the SMR value

gradually increased with time. The risk of death of pancreas cancer [SMR: 1.15, 95% CI (1.05-1.26)], kidney and renal pelvis cancer [SMR: 1.86, 95% CI (1.66-2.07)], liver and intrahepatic bile duct cancer [SMR: 1.26, 95% CI (1.13-1.41)] was significantly higher than that of the general population in the United States. The most common cause of non-cancerous death was the diseases of the heart (10007 cases, 22.42%), followed by chronic obstructive pulmonary disease and allied cond (3153 cases, 7.06%), and both were higher than the expected number of deaths, the SMR is 1.15, 95% CI (1.13-1.17) and 1.54, 95% CI (1.49-1.59). Diabetes mellitus and nephritis, nephrotic syndrome, and nephrosis were also higher than expected deaths [SMR: 1.19, 95% CI (1.12-1.27)] and [SMR: 1.18, 95% CI (1.1-1.26)]. It was worth noting that although deaths from septicemia and other infectious and parasitic diseases including HIV were higher than the general population [SMR: 1.15, 95% CI (1.05-1.25)] and [SMR: 1.21, 95% CI (1.07-1.36)], the highest risk of death was within one year after NMIBC diagnosis [SMR: 1.26, 95% CI (0.97-1.62)] and [SMR: 1.56, 95% CI (1.12-2.1)]. The risk of death from Alzheimer's was reduced [SMR: 0.87, 95% CI (0.82-0.92)]. Cerebrovascular diseases [SMR: 0.96, 95% CI (0.91-1)], pneumonia and influenza [SMR: 0.97, 95% CI (0.91-1.05)] etc. were not statistically significant. The data of various causes of death of NMIBC patients are shown in **Table 3**, and their respective proportions are shown in **Figure 1A**.

Cause of death in patients with non-MMIBC

Statistics showed that 18,829 patients died after the diagnosis of non-MMIBC, 11,797 (62.65%) died of bladder cancer, 2063 (10.96%) died of other cancers (non-bladder cancer), and 4969 died of non-neoplastic diseases (26.39%). Among tumorous diseases other than bladder cancer, the risk of dying of lung and bronchus [SMR: 1.83, 95% CI (1.66-2.01)] and pancreas [SMR: 1.45, 95% CI (1.15-1.8)] were higher than the general population. Unlike NMIBC, non-MMIBC has a significantly increased risk of dying from prostate cancer [SMR: 2.21, 95% CI (1.91-2.54)], and the risk of dying from kidney and renal pelvis cancer was 4 times than that of the general population [SMR: 4.28, 95% CI (3.46-5.23)], the risk of dying from ureteral cancer was 26 times than

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Table 1. Baseline characteristics of patients with non-muscular invasive bladder cancer (NMIBC) and non-metastatic muscle invasive bladder cancer (non-MMIBC)

Variables	Total			<1 year			1-3 years			3-5 years			5-10 years			>10 year		
	Patients	Deaths	SMR (95% CI)	Patients	Deaths	SMR (95% CI)	Patients	Deaths	SMR (95% CI)	Patients	Deaths	SMR (95% CI)	Patients	Deaths	SMR (95% CI)	Patients	Deaths	SMR (95% CI)
NMIBC																		
Total	111784	44638	1.40* (1.38/1.41)	111784	5230	1.45* (1.41/1.49)	106181	11700	1.43* (1.4/1.45)	93500	9802	1.40* (1.38/1.43)	68316	14117	1.36* (1.34-1.38)	24255	3789	1.36* (1.31-1.4)
Age																		
15-54 years	12617	1394	2.03* (1.93-2.14)	12617	110	2.36* (1.94-2.85)	12431	314	2.54* (2.27-2.84)	11931	269	2.14* (1.9-2.42)	9850	502	1.85* (1.69-2.02)	4804	199	1.67* (1.45-1.92)
55-64 years	24077	4840	1.73* (1.68-1.78)	24077	387	1.80* (1.63-1.99)	23590	1079	1.94* (1.83-2.06)	22251	1023	1.88* (1.77-2)	17429	1764	1.66* (1.58-1.74)	7372	587	1.40* (1.29-1.51)
65-74 years	33685	11588	1.50* (1.47-1.53)	33685	957	1.50* (1.4-1.59)	32644	2645	1.62* (1.56-1.69)	29747	2511	1.62* (1.55-1.68)	21895	4101	1.45* (1.4-1.49)	7561	1374	1.28* (1.21-1.35)
75-84 years	29770	17497	1.20* (1.18-1.21)	29770	1969	1.40* (1.33-1.46)	27718	4514	1.27* (1.23-1.31)	22996	3849	1.14* (1.11-1.18)	15699	5740	1.11* (1.08-1.14)	4137	1425	1.29* (1.22-1.36)
85+ years	11621	9319	1.52* (1.49-1.55)	11621	1807	1.40* (1.34-1.47)	9784	3148	1.35* (1.3-1.4)	6562	2150	1.55* (1.49-1.62)	3431	2010	1.93* (1.84-2.01)	376	204	2.97* (2.58-3.41)
Sex																		
Male	86021	34976	1.39* (1.38-1.4)	86021	3855	1.34* (1.3-1.39)	81904	9224	1.41* (1.39-1.44)	71967	7894	1.43* (1.4-1.46)	52204	11098	1.37* (1.34-1.4)	18341	2905	1.34* (1.29-1.39)
Female	25763	9662	1.42* (1.39-1.45)	25763	1375	1.87* (1.77-1.97)	24277	2476	1.48* (1.42-1.54)	21533	1908	1.30* (1.24-1.36)	16112	3019	1.33* (1.28-1.37)	5914	884	1.41* (1.32-1.5)
Race																		
White	101420	40699	1.37* (1.36-1.38)	101420	4644	1.39* (1.35-1.43)	96470	10617	1.40* (1.37-1.42)	85023	8953	1.38* (1.35-1.41)	62291	12998	1.34* (1.32-1.37)	22171	3487	1.34* (1.3-1.39)
Black	5440	2320	1.72* (1.65-1.79)	5440	373	2.27* (2.04-2.51)	5042	654	1.82* (1.68-1.96)	4339	497	1.70* (1.56-1.86)	3078	624	1.48* (1.37-1.61)	1052	172	1.54* (1.32-1.79)
	274	111	3.60* (2.96-4.33)	274	18	4.71* (2.79-7.44)	255	25	2.93* (1.9-4.32)	223	26	4.22* (2.76-6.19)	148	30	3.12* (2.11-4.46)	53	12	4.40* (2.27-7.68)
Asian or Pacific Islander	4650	1508	1.72* (1.63-1.81)	4650	195	1.97* (1.7-2.26)	4414	404	1.79* (1.62-1.97)	3915	326	1.69* (1.51-1.89)	2799	465	1.66* (1.51-1.81)	979	118	1.50* (1.24-1.79)
Differentiation																		
Grade I	17233	6102	1.20* (1.17-1.24)	17233	505	1.02 (0.93-1.11)	16657	1367	1.16* (1.1-1.23)	15161	1315	1.21* (1.15-1.28)	12187	2182	1.25* (1.2-1.3)	4981	733	1.31* (1.21-1.41)
Grade II	33904	12445	1.22* (1.2-1.25)	33904	1069	1.06 (1-1.13)	32737	2721	1.14* (1.1-1.18)	29730	2625	1.25* (1.21-1.3)	21816	4527	1.27* (1.24-1.31)	9767	1503	1.34* (1.28-1.41)
Grade III	14851	7448	1.60* (1.56-1.64)	14851	1044	1.96* (1.84-2.08)	13757	1989	1.71* (1.63-1.78)	11682	1492	1.49* (1.42-1.57)	9074	2280	1.51* (1.44-1.57)	3553	643	1.45* (1.34-1.56)
Grade IV	23627	10430	1.67* (1.64-1.71)	23627	1525	1.82* (1.73-1.91)	22013	3318	1.82* (1.76-1.88)	18446	2378	1.71* (1.64-1.78)	11443	2666	1.48* (1.43-1.54)	3359	543	1.41* (1.29-1.53)
T stage																		
Ta	71504	25213	1.21* (1.19-1.22)	71504	2154	0.97 (0.93-1.01)	69140	6022	1.15* (1.12-1.18)	62475	5701	1.24* (1.21-1.27)	46328	8868	1.27* (1.25-1.3)	16766	2468	1.30* (1.25-1.35)

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Tis	7385	3205	1.37# (1.33-1.42)	7385	315	1.26# (1.13-1.41)	7046	780	1.36# (1.26-1.45)	6215	706	1.42# (1.32-1.53)	4634	1107	1.41# (1.33-1.49)	1753	297	1.31# (1.16-1.46)
T1	31804	15561	1.84# (1.81-1.86)	31804	2524	2.31# (2.22-2.4)	29146	4707	2.03# (1.97-2.09)	24159	3289	1.78# (1.72-1.85)	16920	4043	1.57# (1.53-1.62)	5608	998	1.53# (1.43-1.62)
Pathology																		
Papillary transitional cell carcinoma	92360	35229	1.32# (1.3-1.33)	92360	3451	1.17# (1.13-1.21)	88603	8967	1.32# (1.29-1.34)	78818	7911	1.35# (1.32-1.38)	57931	11690	1.33# (1.31-1.36)	20886	3210	1.35# (1.3-1.39)
Transitional cell carcinoma	16766	7949	1.76# (1.72-1.79)	16766	1307	2.29# (2.17-2.42)	15409	2352	1.93# (1.85-2.01)	12913	1681	1.70# (1.62-1.78)	9081	2110	1.51# (1.44-1.57)	2881	499	1.43# (1.31-1.56)
Papillary carcinoma	527	234	1.40# (1.22-1.59)	527	24	1.46 (0.93-2.17)	502	57	1.53# (1.16-1.98)	443	38	1.19 (0.84-1.64)	354	82	1.37# (1.09-1.7)	181	33	1.50# (1.03-2.1)
Squamous cell carcinoma	185	146	5.04# (4.26-5.93)	185	76	14.33# (11.29-17.94)	107	36	4.52# (3.17-6.26)	69	14	2.52# (1.38-4.23)	46	16	2.17# (1.24-3.52)	14	4	1.46 (0.4-3.75)
Adenocarcinoma	183	95	2.48# (2-3.03)	183	26	4.77# (3.12-6.99)	155	23	2.24# (1.42-3.37)	132	25	3.33# (2.16-4.92)	92	17	1.44 (0.84-2.31)	26	4	1.18 (0.32-3.01)
Surgery																		
Local tumor excision	102721	40681	1.37# (1.36-1.39)	102721	4424	1.33# (1.29-1.37)	97966	10690	1.41# (1.38-1.43)	86393	8986	1.39# (1.36-1.42)	63073	13046	1.36# (1.33-1.38)	22486	3535	1.36# (1.32-1.41)
Cystectomy	2428	947	1.72# (1.62-1.84)	2428	127	2.26# (1.88-2.69)	2286	232	1.78# (1.56-2.02)	2027	207	1.74# (1.51-1.99)	1502	312	1.64# (1.46-1.83)	508	69	1.30# (1.01-1.65)
other	6635	3010	1.66# (1.6-1.72)	6635	679	3.02# (2.8-3.26)	5929	778	1.65# (1.53-1.77)	5080	609	1.55# (1.43-1.68)	3741	759	1.30# (1.21-1.4)	1261	185	1.32# (1.14-1.52)
Chemotherapy																		
Yes	16762	5397	1.38# (1.34-1.41)	16762	556	1.13# (1.04-1.22)	16145	1650	1.42# (1.36-1.49)	14317	1335	1.40# (1.33-1.48)	9154	1579	1.40# (1.34-1.47)	2120	277	1.43# (1.26-1.6)
No/Unknown	95022	39241	1.40# (1.39-1.41)	95022	4674	1.50# (1.46-1.55)	90036	10050	1.43# (1.4-1.46)	79183	8467	1.40# (1.37-1.43)	59162	12538	1.35# (1.33-1.38)	22135	3512	1.35# (1.31-1.4)
Radiation																		
yes	111006	43999	1.38# (1.37-1.4)	111006	5037	1.41# (1.37-1.45)	105599	11465	1.41# (1.38-1.43)	93155	9698	1.40# (1.37-1.42)	68114	14026	1.36# (1.33-1.38)	24200	3773	1.36# (1.31-1.4)
No/Unknown non-MMIBC	778	639	3.68# (3.4-3.98)	778	193	5.23# (4.52-6.02)	582	235	4.10# (3.59-4.66)	345	104	3.04# (2.48-3.68)	202	91	2.38# (1.92-2.92)	55	16	2.34# (1.34-3.8)
Total	26546	18829	4.67# (4.6-4.73)	26546	7309	9.62# (9.4-9.84)	19096	6948	6.07# (5.93-6.21)	11935	2159	2.72# (2.61-2.84)	7808	1970	1.85# (1.77-1.93)	2511	443	1.64# (1.49-1.8)
Age																		
15-54 years	2535	1331	15.54# (14.72-16.4)	2535	410	44.62# (40.4-49.15)	2116	593	32.27# (29.73-34.98)	1485	170	10.96# (9.38-12.74)	1086	126	4.20# (3.5-5)	491	32	2.54# (1.74-3.59)
55-64 years	5496	3166	8.56# (8.26-8.86)	5496	975	21.73# (20.38-23.13)	4482	1379	16.01# (15.17-16.88)	3046	379	5.35# (4.82-5.91)	2175	342	2.75# (2.46-3.05)	811	91	2.09# (1.68-2.57)
65-74 years	7542	4984	5.21# (5.06-5.35)	7542	1652	13.00# (12.38-13.65)	5849	1924	8.13# (7.77-8.5)	3870	631	3.37# (3.11-3.65)	2510	621	2.05# (1.89-2.22)	777	156	1.50# (1.28-1.76)

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75-84 years	7463	6078	3.43 [#] (3.34-3.51)	7463	2539	8.78 [#] (8.44-9.13)	4889	2041	4.17 [#] (3.99-4.35)	2802	678	1.79 [#] (1.66-1.93)	1713	682	1.33 [#] (1.23-1.43)	391	138	1.33 [#] (1.12-1.58)
85+ years	3510	3270	3.85 [#] (3.72-3.99)	3510	1733	5.98 [#] (5.7-6.27)	1760	1011	3.22 [#] (3.02-3.42)	732	301	2.12 [#] (1.89-2.37)	324	199	2.07 [#] (1.79-2.38)	41	26	3.79 [#] (2.48-5.55)
Sex																		
Male	19317	13457	4.36 [#] (4.29-4.44)	19317	4872	8.57 [#] (8.33-8.81)	14353	5123	5.82 [#] (5.67-5.99)	9068	1619	2.65 [#] (2.53-2.79)	5958	1504	1.84 [#] (1.75-1.93)	1918	339	1.63 [#] (1.46-1.81)
Female	7229	5372	5.65 [#] (5.5-5.81)	7229	2437	12.74 [#] (12.24-13.26)	4743	1825	6.87 [#] (6.56-7.2)	2867	540	2.94 [#] (2.7-3.2)	1850	466	1.88 [#] (1.71-2.06)	593	104	1.67 [#] (1.37-2.03)
Race																		
White	23280	16527	4.50 [#] (4.43-4.57)	23280	6381	9.27 [#] (9.05-9.5)	16805	6047	5.81 [#] (5.67-5.96)	10581	1921	2.66 [#] (2.54-2.78)	6924	1783	1.83 [#] (1.74-1.91)	2220	395	1.60 [#] (1.45-1.77)
Black	1961	1503	6.63 [#] (6.3-6.98)	1961	629	13.42 [#] (12.39-14.51)	1319	585	8.63 [#] (7.94-9.36)	723	141	3.16 [#] (2.66-3.73)	465	120	2.25 [#] (1.86-2.69)	135	28	2.02 [#] (1.34-2.92)
American Indian-Alaska Native	106	76	15.66 [#] (12.34-19.6)	106	35	26.84 [#] (18.69-37.32)	70	29	17.21 [#] (11.52-24.71)	40	6	7.25 [#] (2.66-15.77)	24	6	6.34 [#] (2.33-13.79)	9	0	0 (0-41.37)
Asian or Pacific Islander	1199	723	5.55 [#] (5.16-5.97)	1199	264	11.19 [#] (9.88-12.63)	902	287	8.20 [#] (7.28-9.21)	591	91	3.59 [#] (2.89-4.41)	395	61	1.66 [#] (1.27-2.14)	147	20	2.09 [#] (1.27-3.22)
Differentiation																		
Grade I	316	196	3.05 [#] (2.64-3.51)	316	66	8.11 [#] (6.27-10.32)	247	58	3.86 [#] (2.93-4.99)	187	20	1.5 (0.92-2.32)	146	41	1.89 [#] (1.35-2.56)	50	11	1.83 (0.91-3.27)
Grade II	1473	1007	4.09 [#] (3.84-4.35)	1473	362	9.44 [#] (8.5-10.47)	1102	313	4.84 [#] (4.32-5.41)	775	145	2.99 [#] (2.52-3.52)	546	152	2.13 [#] (1.8-2.49)	197	35	1.51 [#] (1.05-2.1)
Grade III	8222	6220	4.71 [#] (4.59-4.83)	8222	2410	10.06 [#] (9.66-10.47)	5768	2252	6.46 [#] (6.19-6.73)	3456	663	2.66 [#] (2.46-2.87)	2486	706	1.87 [#] (1.74-2.02)	977	189	1.77 [#] (1.53-2.04)
Grade IV	14765	10146	4.67 [#] (4.58-4.76)	14765	3886	9.21 [#] (8.92-9.5)	10809	3889	6.05 [#] (5.86-6.24)	6802	1199	2.76 [#] (2.61-2.92)	4188	982	1.80 [#] (1.69-1.91)	1199	190	1.51 [#] (1.3-1.74)
T																		
T2a	4651	2918	3.57 [#] (3.44-3.7)	4651	962	6.52 [#] (6.11-6.94)	3673	1067	4.36 [#] (4.1-4.63)	2562	411	2.38 [#] (2.15-2.62)	1685	386	1.86 [#] (1.68-2.06)	444	92	2.01 [#] (1.62-2.47)
T2b	3899	2622	4.08 [#] (3.93-4.24)	3899	960	8.49 [#] (7.96-9.05)	2911	959	5.67 [#] (5.31-6.04)	1908	312	2.51 [#] (2.24-2.81)	1325	304	1.67 [#] (1.49-1.87)	486	87	1.62 [#] (1.3-2)
T3a	3016	2116	5.01 [#] (4.8-5.23)	3016	666	9.65 [#] (8.93-10.41)	2340	894	7.90 [#] (7.39-8.44)	1426	257	2.98 [#] (2.63-3.37)	939	249	2.01 [#] (1.77-2.28)	288	50	1.63 [#] (1.21-2.15)
T3b	1552	1163	6.48 [#] (6.12-6.87)	1552	463	13.38 [#] (12.19-14.66)	1084	494	10.17 [#] (9.29-11.11)	581	90	2.63 [#] (2.11-3.23)	371	97	1.92 [#] (1.55-2.34)	102	19	1.68 [#] (1.01-2.62)
T4a	3076	2514	7.19 [#] (6.92-7.48)	3076	1106	14.83 [#] (13.97-15.73)	1950	931	9.28 [#] (8.69-9.89)	1002	258	3.92 [#] (3.46-4.43)	615	188	2.16 [#] (1.87-2.5)	216	31	1.42 (0.96-2.01)

Cause of death with bladder cancer

T4b	655	599	24.19# (22.29-26.21)	655	396	42.31# (38.24-46.69)	252	167	23.93# (20.43-27.84)	81	22	6.85# (4.29-10.36)	50	13	3.23# (1.72-5.53)	19	1	0.84 (0.02-4.71)
N																		
N0	22110	15233	4.17# (4.1-4.23)	22110	5827	8.69# (8.47-8.92)	16166	5371	5.19# (5.05-5.33)	10613	1844	2.54# (2.43-2.66)	7033	1782	1.82# (1.74-1.91)	2248	409	1.66# (1.5-1.83)
N1	2066	1605	8.52# (8.11-8.95)	2066	608	15.56# (14.35-16.85)	1450	715	13.52# (12.55-14.55)	720	164	4.80# (4.09-5.59)	440	101	2.09# (1.71-2.55)	160	17	1.21 (0.71-1.94)
N2	1823	1527	12.51# (11.89-13.15)	1823	645	19.95# (18.44-21.55)	1168	704	20.00# (18.55-21.53)	449	114	5.37# (4.43-6.45)	245	56	2.07# (1.57-2.69)	70	8	1.27 (0.55-2.5)
N3	69	62	14.70# (11.27-18.85)	69	29	22.08# (14.79-31.71)	40	26	17.87# (11.67-26.18)	14	5	6.39# (2.07-14.91)	3	2	3 (0.36-10.85)	0	0	0 (0-0)
Pathology																		
Transitional cell carcinoma	14794	10692	5.02# (4.93-5.12)	14794	4321	10.29# (9.99-10.6)	10400	4026	6.68# (6.48-6.89)	6252	1114	2.70# (2.54-2.86)	4089	1006	1.82# (1.71-1.94)	1305	225	1.58# (1.38-1.81)
Papillary transitional cell carcinoma	8540	5761	3.69# (3.6-3.79)	8540	1821	6.69# (6.39-7)	6671	2166	4.82# (4.62-5.03)	4435	814	2.59# (2.42-2.78)	2921	778	1.86# (1.73-1.99)	961	182	1.72# (1.48-1.99)
Squamous cell carcinoma	765	615	7.66# (7.07-8.29)	765	374	23.87# (21.51-26.41)	385	147	7.92# (6.69-9.31)	237	36	2.31# (1.62-3.2)	173	51	2.12# (1.58-2.79)	52	7	1.09 (0.44-2.24)
Small cell carcinoma	421	317	6.44# (5.75-7.19)	421	144	13.90# (11.72-16.37)	276	119	8.74# (7.24-10.46)	152	29	3.16# (2.11-4.53)	95	22	1.64# (1.03-2.49)	27	3	1.13 (0.23-3.3)
Transitional cell carcinoma, spindle cell	263	194	7.43# (6.42-8.55)	263	114	21.65# (17.86-26.01)	147	55	7.32# (5.52-9.53)	90	12	2.22# (1.15-3.89)	65	11	1.72 (0.86-3.07)	15	2	1.29 (0.16-4.65)
Surgery																		
Partial cystectomy	1179	713	3.15# (2.92-3.39)	1179	186	5.38# (4.64-6.21)	991	279	4.52# (4-5.08)	699	116	2.35# (1.94-2.81)	477	107	1.66# (1.36-2)	145	25	1.56# (1.01-2.3)
Radical cystectomy	7360	4668	3.89# (3.78-4.01)	7360	1335	8.81# (8.34-9.29)	5992	1830	6.60# (6.3-6.91)	4107	596	2.53# (2.33-2.74)	3063	714	1.74# (1.61-1.87)	1195	193	1.56# (1.35-1.8)
Other therapy	14166	11294	5.20# (5.11-5.3)	14166	5101	10.13# (9.85-10.41)	8983	3881	5.75# (5.58-5.94)	4998	1170	2.86# (2.7-3.03)	3028	957	2.00# (1.87-2.13)	897	185	1.77# (1.52-2.04)
Chemotherapy																		
Yes	10905	7181	5.11# (4.99-5.23)	10905	2124	8.11# (7.77-8.46)	8740	3320	7.71# (7.45-7.98)	5322	900	3.08# (2.88-3.28)	3165	727	2.09# (1.94-2.25)	783	110	1.54# (1.26-1.85)
No/Unknown	15641	11648	4.43# (4.35-4.51)	15641	5185	10.41# (10.13-10.7)	10356	3628	5.08# (4.91-5.25)	6613	1259	2.51# (2.38-2.66)	4643	1243	1.73# (1.63-1.83)	1728	333	1.68# (1.5-1.87)
Radiation																		
Yes	4693	3858	5.02# (4.86-5.18)	4693	1428	7.50# (7.12-7.9)	3245	1587	6.15# (5.85-6.46)	1628	448	3.02# (2.75-3.31)	887	351	2.34# (2.1-2.6)	182	44	1.95# (1.42-2.62)

Cause of death with bladder cancer

No/ Unknown	21853	14971	4.58* (4.51-4.66)	21853	5881	10.33* (10.06-10.59)	15851	5361	6.04* (5.88-6.21)	10307	1711	2.65* (2.53-2.78)	6921	1619	1.77* (1.68-1.85)	2329	399	1.61* (1.46-1.78)
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NMIBC: Non-muscular invasive bladder cancer; non-MMIBC: non-metastatic muscle invasive bladder cancer; SMR: Standard Mortality Ratio; #: significant difference.

Table 2. Baseline characteristics of patients with metastatic bladder cancer

Variables	Total			<6 m			6 m-1 year			1-3 years			years			>5 years		
	Patients	Deaths	SMR	Patients	Deaths	SMR	Patients	Deaths	SMR	Patients	Deaths	SMR	Patients	Deaths	SMR	Patients	Deaths	SMR
MBC	4678	4392	27.13* (26.33-27.94)	4678	1825	47.67* (45.51-49.91)	2823	1193	37.71* (35.6-39.91)	1616	1159	24.63* (23.24-26.09)	426	153	7.67* (6.5-8.98)	177	62	2.48* (1.9-3.18)
Age																		
15-54 years	593	538	120.08* (110.14-130.67)	593	167	231.13* (197.4-268.96)	420	155	207.00* (175.69-242.27)	261	187	152.63* (131.54-176.14)	68	19	32.74* (19.71-51.13)	33	10	8.31* (3.98-15.28)
55-64 years	1133	1046	59.56* (56-63.28)	1133	364	115.78* (104.19-128.3)	766	310	100.25* (89.4-112.05)	452	328	66.35* (59.36-73.93)	117	37	16.78* (11.82-23.14)	53	7	1.68 (0.67-3.45)
65-74 years	1327	1248	33.67* (31.82-35.59)	1327	494	66.91* (61.14-73.08)	825	345	50.55* (45.36-56.18)	476	336	29.40* (26.34-32.71)	133	55	11.72* (8.83-15.25)	46	18	2.67* (1.58-4.22)
75-84 years	1156	1105	17.02* (16.03-18.05)	1156	518	35.69* (32.69-38.9)	631	286	22.36* (19.84-25.11)	345	249	12.66* (11.14-14.33)	89	34	3.95* (2.73-5.51)	34	18	1.93* (1.14-3.04)
85+ years	469	455	12.02* (10.94-13.18)	469	282	22.52* (19.97-25.31)	181	97	11.85* (9.61-14.46)	82	59	6.03* (4.59-7.78)	19	8	2.07 (0.89-4.08)	11	9	2.57* (1.17-4.87)
Sex																		
Male	3294	3074	25.90* (25-26.84)	3294	1223	43.42* (41.02-45.92)	2050	859	36.32* (33.93-38.83)	1180	841	24.54* (22.91-26.26)	316	110	7.88* (6.47-9.49)	136	41	2.20* (1.58-2.99)
Female	1384	1318	30.49* (28.87-32.18)	1384	602	59.50* (54.84-64.45)	773	334	41.82* (37.46-46.56)	436	318	24.89* (22.23-27.78)	110	43	7.18* (5.19-9.67)	41	21	3.31* (2.05-5.05)
Race																		
White	3988	3753	26.28* (25.44-27.13)	3988	1535	46.08* (43.8-48.44)	2428	1020	36.58* (34.37-38.9)	1398	1010	24.25* (22.78-25.8)	361	133	7.58* (6.34-8.98)	147	55	2.45* (1.85-3.19)
Black	479	454	34.79* (31.66-38.14)	479	214	58.81* (51.19-67.24)	263	118	43.39* (35.91-51.96)	143	103	27.75* (22.65-33.65)	40	15	12.62* (7.06-20.81)	17	4	2.23 (0.61-5.72)
American Indian-Alaska Native	17	16	24.10* (13.78-39.14)	17	7	145.38* (58.45-299.54)	10	6	113.06* (41.49-246.08)	4	2	11.11* (1.35-40.14)	2	0	0 (0-18.45)	1	1	5.47 (0.14-30.5)

Cause of death with bladder cancer

Asian or Pacific Islander	194	169	31.57# (26.99-36.7)	194	69	53.68# (41.76-67.93)	122	49	49.84# (36.87-65.9)	71	44	29.03# (21.1-38.98)	23	5	4.94# (1.6-11.52)	12	2	3.6 (0.44-12.99)
Differentiation																		
Grade I	40	39	14.12# (10.04-19.3)	40	17	34.78# (20.26-55.68)	23	11	32.39# (16.17-57.96)	12	9	16.95# (7.75-32.18)	3	1	2.38 (0.06-13.28)	2	1	1.02 (0.03-5.66)
Grade II	187	169	17.39# (14.87-20.22)	187	68	42.41# (32.93-53.77)	115	37	27.05# (19.05-37.29)	76	51	16.99# (12.65-22.34)	23	5	2.94 (0.95-6.86)	14	8	3.92# (1.69-7.72)
Grade III	1387	1315	29.66# (28.07-31.3)	1387	571	52.85# (48.6-57.36)	809	349	39.77# (35.71-44.17)	455	337	28.10# (25.18-31.26)	113	44	9.36# (6.8-12.56)	52	14	1.74 (0.95-2.91)
Grade IV	2163	2021	25.77# (24.66-26.92)	2163	763	42.53# (39.57-45.66)	1389	582	38.13# (35.09-41.36)	803	567	24.31# (22.35-26.39)	222	79	7.60# (6.02-9.47)	85	30	2.61# (1.76-3.73)
T																		
T0	27	26	31.92# (20.85-46.77)	27	15	134.70# (75.39-222.17)	12	5	47.23# (15.33-110.21)	7	3	9.97# (2.06-29.12)	4	3	23.25# (4.79-67.94)	1	0	0 (0-22.07)
T1	613	572	20.79# (19.12-22.56)	613	229	43.25# (37.83-49.23)	377	148	31.41# (26.55-36.89)	228	152	17.67# (14.97-20.71)	73	33	8.98# (6.18-12.61)	28	10	1.91 (0.92-3.52)
T2a	318	289	22.52# (20-25.28)	318	121	41.46# (34.4-49.54)	195	79	34.36# (27.2-42.82)	114	79	21.28# (16.85-26.53)	35	8	3.82# (1.65-7.53)	17	2	1.11 (0.13-4)
T2b	432	405	21.84# (19.77-24.08)	432	138	34.96# (29.37-41.3)	293	136	42.62# (35.75-50.41)	153	105	23.67# (19.36-28.66)	44	16	7.49# (4.28-12.17)	24	10	2.07 (0.99-3.8)
T3a	204	180	16.62# (14.28-19.23)	204	57	37.16# (28.14-48.14)	147	38	25.09# (17.75-34.43)	109	68	23.79# (18.47-30.16)	36	14	8.28# (4.53-13.9)	15	3	0.93 (0.19-2.71)
T3b	201	181	19.03# (16.36-22.01)	201	60	42.82# (32.68-55.12)	140	46	33.46# (24.49-44.63)	93	64	23.78# (18.31-30.37)	28	5	3.10# (1.01-7.22)	16	6	2.47 (0.91-5.38)
T4a	733	697	38.11# (35.33-41.04)	733	283	54.00# (47.89-60.67)	445	191	43.25# (37.33-49.84)	252	201	34.95# (30.28-40.13)	48	14	7.63# (4.17-12.8)	20	8	7.64# (3.3-15.05)
T4b	325	313	41.62# (37.14-46.5)	325	155	78.63# (66.74-92.03)	168	85	62.27# (49.74-77)	83	65	47.05# (36.31-59.96)	15	4	7.39# (2.01-18.91)	9	4	1.77 (0.48-4.53)
N																		
N0	2352	2205	23.71# (22.73-24.72)	2352	914	43.43# (40.66-46.34)	1420	587	33.30# (30.66-36.11)	827	580	21.19# (19.5-22.99)	236	88	7.30# (5.85-8.99)	97	36	2.42# (1.69-3.34)
N1	661	623	30.59# (28.24-33.09)	661	228	47.72# (41.72-54.33)	432	187	47.54# (40.97-54.87)	242	177	36.51# (31.33-42.3)	58	20	8.65# (5.28-13.36)	29	11	2.45# (1.22-4.38)

Cause of death with bladder cancer

N2	879	802	31.25# (29.12-33.49)	879	293	49.08# (43.62-55.03)	579	241	46.48# (40.8-52.73)	334	243	33.87# (29.75-38.41)	84	20	6.58# (4.02-10.17)	32	5	1.16 (0.38-2.71)
N3	36	36	72.96# (51.1-101)	36	14	45.99# (25.14-77.16)	22	13	103.46# (55.09-176.92)	9	9	142.08# (64.97-269.72)	0	0	0 (0-0)	0	0	0 (0-0)
Pathology																		
Transitional cell carcinoma	2541	2404	28.49# (27.36-29.65)	2541	1025	50.65# (47.59-53.84)	1502	656	40.68# (37.62-43.91)	841	604	24.67# (22.74-26.72)	219	84	7.99# (6.37-9.89)	86	35	2.69# (1.87-3.73)
Papillary transitional cell carcinoma	1098	1000	19.84# (18.62-21.1)	1098	350	34.26# (30.76-38.04)	740	270	28.73# (25.4-32.37)	465	322	21.84# (19.52-24.36)	138	42	6.49# (4.68-8.77)	61	16	1.67 (0.95-2.71)
Squamous cell carcinoma	146	144	65.00# (54.82-76.53)	146	89	124.16# (99.71-152.79)	57	36	117.29# (82.15-162.38)	20	15	24.67# (13.81-40.69)	5	2	4.72 (0.57-17.06)	3	2	12.51# (1.51-45.18)
Small cell carcinoma	148	139	31.44# (26.43-37.12)	148	44	28.72# (20.87-38.56)	102	51	43.98# (32.75-57.83)	50	41	34.72# (24.92-47.11)	8	1	3.77 (0.1-21.02)	4	2	7.03 (0.85-25.4)
Adenocarcinoma	111	103	36.19# (29.54-43.89)	111	44	61.52# (44.7-82.59)	65	24	45.47# (29.13-67.65)	41	24	21.85# (14-32.51)	14	9	21.33# (9.75-40.49)	4	2	24.22# (2.93-87.48)
Chemotherapy																		
Yes	2598	2401	24.38# (23.41-25.37)	2598	1351	34.38# (32.57-36.26)	1228	895	28.78# (26.92-30.72)	317	115	8.66# (7.15-10.39)	116	33	2.76# (1.9-3.87)	30	7	2.46 (0.99-5.07)
No-Unknown	2080	1991	31.40# (30.04-32.81)	2080	1667	54.43# (51.85-57.11)	388	264	16.55# (14.62-18.68)	109	38	5.70# (4.03-7.82)	61	20	2.68# (1.64-4.15)	24	2	0.74 (0.09-2.66)
Radiation																		
Yes	1057	1019	33.37# (31.36-35.49)	1057	721	45.10# (41.86-48.51)	329	256	29.42# (25.93-33.25)	68	29	10.04# (6.72-14.42)	25	11	4.53# (2.26-8.11)	5	2	3.79 (0.46-13.7)
No/Unknown	3621	3373	25.68# (24.82-26.56)	3621	2297	42.59# (40.86-44.37)	1287	903	23.55# (22.04-25.13)	358	124	7.27# (6.04-8.66)	152	42	2.47# (1.78-3.34)	49	7	1.39 (0.56-2.87)

MBC: metastatic bladder cancer; SMR: Standard Mortality Ratio; #: significant difference.

Cause of death with bladder cancer

Table 3. Main cause of deaths for patients with non-muscular invasive bladder cancer

Causes of deaths	Total			<1 year			1-3 years			3-5 years			5-10 years			>10 years		
	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)
All Causes of Death	44,638	31,956.54	1.40* (1.38-1.41)	5,230	3,603.88	1.45* (1.41-1.49)	11,700	8,200.54	1.43* (1.4-1.45)	9,802	6,982.32	1.40* (1.38-1.43)	14,117	10,379.21	1.36* (1.34-1.38)	3,789	2,790.58	1.36* (1.31-1.4)
All Malignant Cancers	17,249	6,850.14	2.52* (2.48-2.56)	2,294	817.43	2.81* (2.69-2.92)	5,256	1,823.14	2.88* (2.81-2.96)	3,855	1,508.32	2.56* (2.48-2.64)	4,743	2,153.71	2.20* (2.14-2.27)	1,101	547.54	2.01* (1.89-2.13)
Urinary Bladder	9,183	291.34	31.52* (30.88-32.17)	1,628	32.18	50.59* (48.16-53.11)	3,215	74.21	43.33* (41.84-44.85)	1,989	63.69	31.23* (29.87-32.64)	1,969	95.46	20.63* (19.73-21.56)	382	25.81	14.80* (13.35-16.36)
Lung and Bronchus	2,860	1,831.09	1.56* (1.51-1.62)	192	230.7	0.83* (0.72-0.96)	744	503.37	1.48* (1.37-1.59)	697	405.41	1.72* (1.59-1.85)	980	557.99	1.76* (1.65-1.87)	247	133.6	1.85* (1.63-2.09)
Pancreas	506	438.9	1.15* (1.05-1.26)	41	50.16	0.82 (0.59-1.11)	135	114.36	1.18 (0.99-1.4)	114	96.52	1.18 (0.97-1.42)	177	141.02	1.26* (1.08-1.45)	39	36.84	1.06 (0.75-1.45)
Prostate	442	712.17	0.62* (0.56-0.68)	34	83.05	0.41* (0.28-0.57)	109	186.62	0.58* (0.48-0.7)	106	155.89	0.68* (0.56-0.82)	153	226.25	0.68* (0.57-0.79)	40	60.36	0.66* (0.47-0.9)
Colon and Rectum	440	591.94	0.74* (0.68-0.82)	33	72.94	0.45* (0.31-0.64)	94	159.97	0.59* (0.47-0.72)	97	130.46	0.74* (0.6-0.91)	172	182.9	0.94 (0.81-1.09)	44	45.67	0.96 (0.7-1.29)
Kidney and Renal Pelvis	323	173.7	1.86* (1.66-2.07)	52	20.44	2.54* (1.9-3.34)	91	45.97	1.98* (1.59-2.43)	58	38.27	1.52* (1.15-1.96)	93	54.98	1.69* (1.37-2.07)	29	14.03	2.07* (1.38-2.97)
Liver and Intrahepatic Bile Duct	314	248.33	1.26* (1.13-1.41)	20	27.74	0.72 (0.44-1.11)	74	64.23	1.15 (0.9-1.45)	86	54.75	1.57* (1.26-1.94)	103	80.49	1.28* (1.04-1.55)	31	21.12	1.47 (1-2.08)
Leukemia	273	314.43	0.87* (0.77-0.98)	15	36.43	0.41* (0.23-0.68)	65	82.27	0.79 (0.61-1.01)	57	69.13	0.82 (0.62-1.07)	110	100.69	1.09 (0.9-1.32)	26	25.91	1 (0.66-1.47)
Lymphoma	218	288.31	0.76* (0.66-0.86)	14	33.98	0.41* (0.23-0.69)	49	76.03	0.64* (0.48-0.85)	48	63.34	0.76 (0.56-1)	85	91.37	0.93 (0.74-1.15)	22	23.59	0.93 (0.58-1.41)
Non-Hodgkin Lymphoma	209	277.4	0.75* (0.65-0.86)	14	32.67	0.43* (0.23-0.72)	48	73.11	0.66* (0.48-0.87)	45	60.94	0.74* (0.54-0.99)	81	87.95	0.92 (0.73-1.14)	21	22.72	0.92 (0.57-1.41)
Esophagus	203	201.48	1.01 (0.87-1.16)	10	24.18	0.41* (0.2-0.76)	47	54.12	0.87 (0.64-1.15)	49	44.55	1.1 (0.81-1.45)	74	62.9	1.18 (0.92-1.48)	23	15.73	1.46 (0.93-2.19)
Myeloid and Monocytic Leukemia	154	150.6	1.02 (0.87-1.2)	7	17.03	0.41* (0.17-0.85)	39	38.94	1 (0.71-1.37)	36	33.05	1.09 (0.76-1.51)	56	48.69	1.15 (0.87-1.49)	16	12.9	1.24 (0.71-2.01)

Cause of death with bladder cancer

Stomach	144	129.61	1.11 (0.94-1.31)	10	16.18	0.62 (0.3-1.14)	31	35.31	0.88 (0.6-1.25)	36	28.62	1.26 (0.88-1.74)	52	39.73	1.31 (0.98-1.72)	15	9.77	1.54 (0.86-2.53)
Brain and Other Nervous System	142	133.18	1.07 (0.9-1.26)	11	15.56	0.71 (0.35-1.26)	36	35.21	1.02 (0.72-1.42)	33	29.37	1.12 (0.77-1.58)	57	42.2	1.35# (1.02-1.75)	5	10.85	0.46 (0.15-1.08)
Acute Myeloid Leukemia	134	121.68	1.1 (0.92-1.3)	7	13.85	0.51 (0.2-1.04)	36	31.63	1.14 (0.8-1.58)	33	26.75	1.23 (0.85-1.73)	48	39.2	1.22 (0.9-1.62)	10	10.25	0.98 (0.47-1.79)
Myeloma	125	149.9	0.83# (0.69-0.99)	13	17.28	0.75 (0.4-1.29)	24	39.08	0.61# (0.39-0.91)	29	32.9	0.88 (0.59-1.27)	48	48.09	1 (0.74-1.32)	11	12.55	0.88 (0.44-1.57)
Skin excluding Basal and Squamous	119	176.21	0.68# (0.56-0.81)	4	19.99	0.20# (0.05-0.51)	30	45.69	0.66# (0.44-0.94)	28	38.73	0.72 (0.48-1.04)	47	57.02	0.82 (0.61-1.1)	10	14.78	0.68 (0.32-1.24)
Intrahepatic Bile Duct	84	58.93	1.43# (1.14-1.76)	5	6.32	0.79 (0.26-1.85)	26	14.88	1.75# (1.14-2.56)	19	12.94	1.47 (0.88-2.29)	25	19.49	1.28 (0.83-1.89)	9	5.3	1.7 (0.78-3.22)
Breast	83	161.09	0.52# (0.41-0.64)	4	18.9	0.21# (0.06-0.54)	14	41.95	0.33# (0.18-0.56)	13	35.22	0.37# (0.2-0.63)	36	51.62	0.70# (0.49-0.97)	16	13.41	1.19 (0.68-1.94)
Oral Cavity and Pharynx	81	103.27	0.78# (0.62-0.97)	6	11.88	0.51 (0.19-1.1)	14	27.01	0.52# (0.28-0.87)	11	22.71	0.48# (0.24-0.87)	39	33.01	1.18 (0.84-1.62)	11	8.66	1.27 (0.63-2.27)
Non-malignant cancer																		
Diseases of Heart	10,007	8,709.92	1.15# (1.13-1.17)	1,141	1,000.64	1.14# (1.08-1.21)	2,417	2,251.26	1.07# (1.03-1.12)	2,152	1,901.96	1.13# (1.08-1.18)	3,382	2,802.12	1.21# (1.17-1.25)	915	753.94	1.21# (1.14-1.29)
Chronic Obstructive Pulmonary Disease and Allied Cond	3,153	2,048.61	1.54# (1.49-1.59)	330	232.4	1.42# (1.27-1.58)	735	528.87	1.39# (1.29-1.49)	724	448.89	1.61# (1.5-1.73)	1,093	663.07	1.65# (1.55-1.75)	271	175.37	1.55# (1.37-1.74)
Cerebrovascular Diseases	1,704	1,781.77	0.96 (0.91-1)	206	201.95	1.02 (0.89-1.17)	413	454.91	0.91# (0.82-1)	348	387.19	0.90# (0.81-1)	567	577.52	0.98 (0.9-1.07)	170	160.2	1.06 (0.91-1.23)
Alzheimers	1,211	1,395.89	0.87# (0.82-0.92)	75	134.01	0.56# (0.44-0.7)	225	326.14	0.69# (0.6-0.79)	247	297.87	0.83# (0.73-0.94)	471	486.9	0.97 (0.88-1.06)	193	150.98	1.28# (1.1-1.47)
Diabetes Mellitus	1,047	878.31	1.19# (1.12-1.27)	122	101.74	1.2 (1-1.43)	250	229.57	1.09 (0.96-1.23)	222	192.66	1.15# (1.01-1.31)	365	280.43	1.30# (1.17-1.44)	88	73.92	1.19 (0.95-1.47)
Accidents and Adverse Effects	835	901.76	0.93# (0.86-0.99)	81	97.87	0.83 (0.66-1.03)	185	227.53	0.81# (0.7-0.94)	202	196.53	1.03 (0.89-1.18)	275	297.54	0.92 (0.82-1.04)	92	82.29	1.12 (0.9-1.37)
Nephritis, Nephrotic Syndrome and Nephrosis	798	677.88	1.18# (1.1-1.26)	83	76.8	1.08 (0.86-1.34)	188	174.98	1.07 (0.93-1.24)	177	148.44	1.19# (1.02-1.38)	277	219.44	1.26# (1.12-1.42)	73	58.22	1.25 (0.98-1.58)

Cause of death with bladder cancer

Pneumonia and Influenza	789	809.41	0.97 (0.91-1.05)	81	93.85	0.86 (0.69-1.07)	192	210.04	0.91 (0.79-1.05)	171	177.04	0.97 (0.83-1.12)	269	259.33	1.04 (0.92-1.17)	76	69.15	1.1 (0.87-1.38)
Septicemia	516	450.5	1.15# (1.05-1.25)	64	50.6	1.26 (0.97-1.62)	119	115.53	1.03 (0.85-1.23)	111	98.4	1.13 (0.93-1.36)	169	146.34	1.15 (0.99-1.34)	53	39.63	1.34# (1-1.75)
Hypertension without Heart Disease	449	370.46	1.21# (1.1-1.33)	52	38.48	1.35# (1.01-1.77)	72	90.84	0.79# (0.62-1)	106	80.32	1.32# (1.08-1.6)	163	125.25	1.30# (1.11-1.52)	56	35.57	1.57# (1.19-2.04)
Symptoms, Signs and Ill-Defined Conditions	340	371.94	0.91 (0.82-1.02)	43	41.96	1.02 (0.74-1.38)	87	95.76	0.91 (0.73-1.12)	77	82.39	0.93 (0.74-1.17)	110	122.67	0.9 (0.74-1.08)	23	29.17	0.79 (0.5-1.18)
Other Infectious and Parasitic Diseases including HIV	274	226.37	1.21# (1.07-1.36)	42	27	1.56# (1.12-2.1)	76	60.63	1.25 (0.99-1.57)	63	50.06	1.26 (0.97-1.61)	79	71.21	1.11 (0.88-1.38)	14	17.46	0.8 (0.44-1.35)
Chronic Liver Disease and Cirrhosis	258	244.6	1.05 (0.93-1.19)	34	29.02	1.17 (0.81-1.64)	74	65.44	1.13 (0.89-1.42)	58	54.1	1.07 (0.81-1.39)	72	76.61	0.94 (0.74-1.18)	20	19.42	1.03 (0.63-1.59)

Abbreviations: SMR, standardized mortality ratio; CI, confidence interval; #: significant difference.

Cause of death with bladder cancer

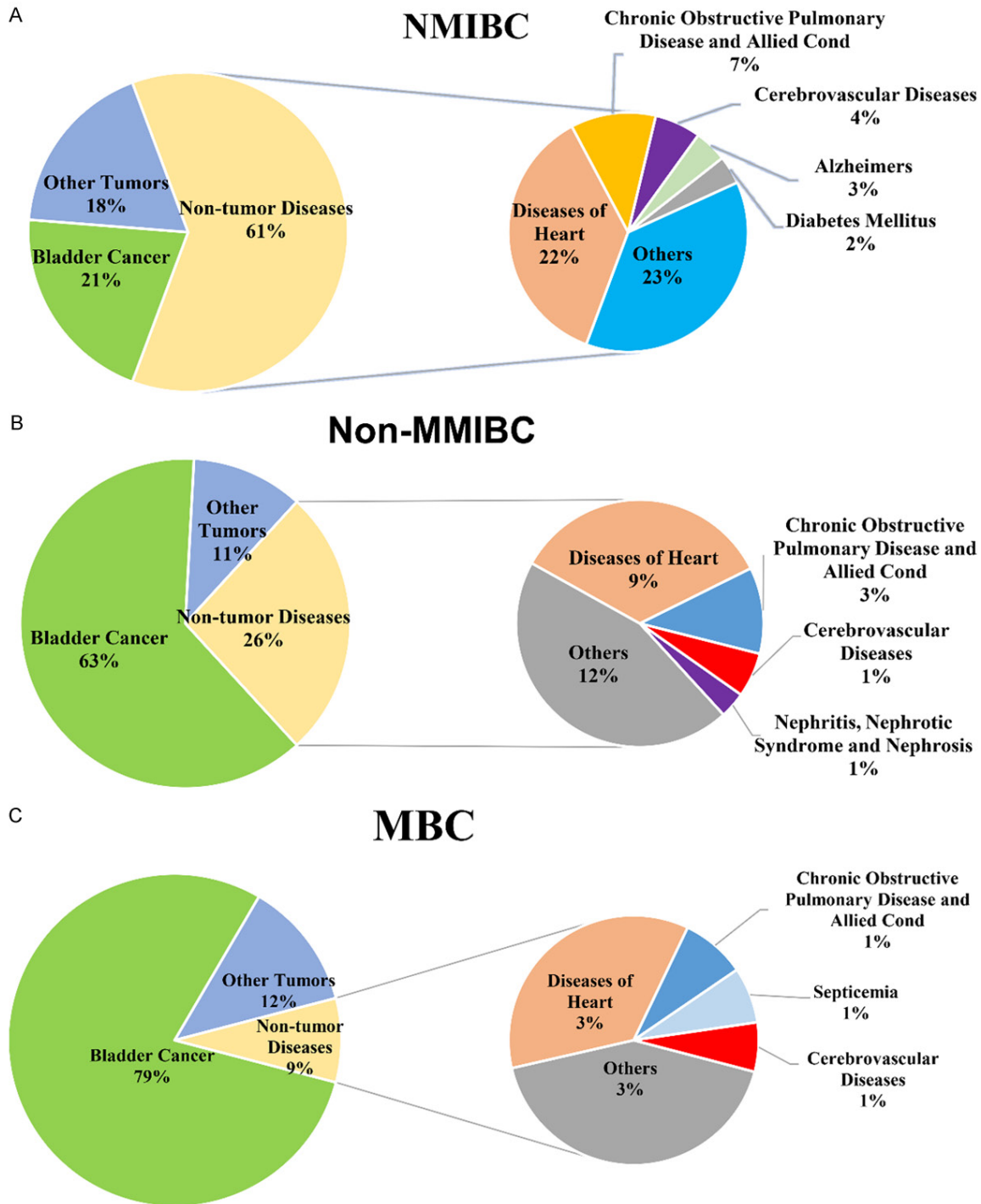


Figure 1. The percentage of death reasons for patients with non-muscular invasive, non-metastatic muscular invasive and metastatic bladder cancer. A. Cause of death among patients with non-muscular invasive bladder cancer. B. Cause of death among patients with non-metastatic muscular invasive bladder cancer. C. Cause of death among patients with metastatic bladder cancer.

that of the general population [SMR: 26.89, 95% CI (16.64-41.1)]. Death from esophagus [SMR: 1.47, 95% CI (1.04-2.01)] and stomach

[SMR: 2.00, 95% CI (1.38-2.79)] related cancer was higher than that of ordinary people, while lymphoma [SMR: 0.55, 95% CI (0.33-0.85)]

Cause of death with bladder cancer

and non-Hodgkin lymphoma [SMR: 0.57, 95% CI (0.35-0.88)] were much lower than ordinary people. The dominant non-neoplastic diseases were still diseases of the heart (1,717 cases, 9.12%) and chronic obstructive pulmonary disease and allied cond (561 cases, 2.98%). The risk of death of cerebrovascular diseases [SMR: 1.28, 95% CI (1.14-1.44)], nephritis, nephrotic syndrome and nephrosis [SMR: 1.99, 95% CI (1.7-2.31)], diabetes mellitus [SMR: 1.35, 95% CI (1.14-1.58)], hypertension without heart disease [SMR: 1.89, 95% CI (1.52-2.33)] and other diseases, were higher than that of the general population. Infection-related diseases such as septicemia [SMR: 2.88, 95% CI (2.45-3.35)], pneumonia and influenza [SMR: 1.60, 95% CI (1.37-1.87)], other infectious and parasitic diseases including HIV [SMR: 2.64, 95% CI (2.09-3.3)], which the risk of death was much higher than that of the general population. It cannot be ignored that the risk of dying from suicide and self-inflicted injury was more than twice that of ordinary people [SMR: 2.73, 95% CI (2.11-3.46)]. The data of cause of death after non-MMIBC are shown in **Table 4**, and their respective proportions are shown in **Figure 1B**.

Cause of death in patients with MBC

A total of 4,392 patients died after the diagnosis of MBC, 3,486 deaths (79.37%) from bladder cancer, 548 deaths (12.48%) from other cancers (non-bladder cancer), and 358 deaths from non-neoplastic diseases (8.15%). Malignant tumors were the main cause of death of MBC (91.85%). Compared with non-MMIBC, the risk of dying from prostate, kidney, and renal pelvis, and ureter-related tumors was greatly increased. The SMR were 17.38, 95% CI (13.17-22.52), 31.93, 95% CI (21.54-45.58), 328.79, 95% CI (157.67-604.65). Tumors in other sites such as lung and bronchus, colon and rectum and liver were all five times higher than expected. SMR was 5.17, 95% CI (3.89-6.75), 6.08, 95% CI (3.72-9.39), 9.70, 95% CI (4.84-17.35). The spectrum of death causes of non-neoplastic diseases was like that of non-MMIBC. The risk of dying from diseases of heart, chronic obstructive pulmonary disease and allied cond, cerebrovascular diseases, and other diseases was twice that of ordinary people. The SMR is 2.96, 95% CI (2.47-3.52), 2.92, 95% CI (1.97-4.17), 2.56, 95% CI (1.63-3.85), the most prominent change was that the risk of dying

from septicemia, other infectious and parasitic diseases including HIV was 11 times higher than that of ordinary people, SMR is 11.11, 95% CI (7.26-16.28), 11.15, 95% CI (6.24-18.38). The related causes of death after MBC diagnosis are shown in **Table 5**, and their respective proportions are shown in **Figure 1C**.

Discussion

There are more than 80,000 new cases and 17,000 deaths each year in the United States alone [10, 11]. We need to find out the important factors that cause bladder cancer and its death, and then optimize our health care system. There are many pathogenic factors of bladder cancer. The identified risk factors include smoking, being male, advanced age, white skinned, occupational exposure to certain chemicals, pelvic radiation, use of drugs such as cyclophosphamide, chronic bladder infection/irritation, schistosomiasis [12]. The main risk factor for bladder cancer is smoking. It is believed that the risk of bladder cancer for people who smoke regularly is 2.5 times that of people who do not smoke [13-15]. Advanced age is also a high-risk factor for bladder cancer. The average age at diagnosis is between 70 and 84. This is due to exposure to carcinogens, such as tobacco smoke, and the less common benzene chemicals and aromatic amines, plus age-related DNA repair ability decline [3]. Some research also showed that other related factors include diabetes, obesity, and human papillomavirus [16-18].

Our research data showed that the mortality and risk of death of female patients with bladder cancer were higher than that of males. The same research showed that although the incidence of bladder cancer was three times higher in men, women's outcomes consistently appeared to be worse [19, 20]. The most common clinical manifestation of bladder cancer was hematuria, but hematuria in women was usually attributed to infection, leading to delays in the diagnosis of bladder cancer, resulting in women's cancer specificity and worse overall survival rates [21]. Recent studies have shown that, compared with men, the effects of hormone receptor and genome differences in certain bladder cancers on women may also be part of the reasons [22]. Regarding race, although the number of white patients was the

Cause of death with bladder cancer

Table 4. Main cause of deaths for patients with non-metastatic muscle invasive bladder cancer

Causes of deaths	Total			<1 year			1-3 years			3-5 years			5-10 years			>10 years		
	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)	Observed	Expected	SMR (95% CI)
All Causes of Death	18,829	4,035.71	4.67* (4.6-4.73)	7,309	759.89	9.62* (9.4-9.84)	6,948	1,145.04	6.07* (5.93-6.21)	2,159	793.72	2.72* (2.61-2.84)	1,970	1,066.89	1.85* (1.77-1.93)	443	270.17	1.64* (1.49-1.8)
All Malignant Cancers	13,860	878.05	15.78* (15.52-16.05)	5,754	168.26	34.20* (33.32-35.09)	5,629	256.85	21.92* (21.35-22.5)	1,383	174.2	7.94* (7.53-8.37)	942	225.2	4.18* (3.92-4.46)	152	53.53	2.84* (2.41-3.33)
Urinary Bladder	11,797	35.78	329.74* (323.82-335.75)	5,232	6.5	805.31* (783.63-827.43)	4,852	10.08	481.36* (467.91-495.09)	1,065	7.08	150.41* (141.51-159.73)	590	9.65	61.12* (56.29-66.26)	58	2.47	23.51* (17.85-30.4)
Lung and Bronchus	435	237.33	1.83* (1.66-2.01)	45	46.94	0.96 (0.7-1.28)	147	71.2	2.06* (1.74-2.43)	86	47.15	1.82* (1.46-2.25)	119	58.9	2.02* (1.67-2.42)	38	13.13	2.89* (2.05-3.97)
Prostate	192	87.03	2.21* (1.91-2.54)	64	16.55	3.87* (2.98-4.94)	82	24.95	3.29* (2.61-4.08)	18	17.1	1.05 (0.62-1.66)	23	22.62	1.02 (0.64-1.53)	5	5.8	0.86 (0.28-2.01)
Kidney and Renal Pelvis	95	22.19	4.28* (3.46-5.23)	38	4.16	9.15* (6.47-12.55)	29	6.46	4.49* (3-6.44)	14	4.43	3.16* (1.73-5.31)	11	5.77	1.91 (0.95-3.41)	3	1.38	2.18 (0.45-6.37)
Colon and Rectum	89	76.66	1.16 (0.93-1.43)	13	15.25	0.85 (0.45-1.46)	34	22.66	1.50* (1.04-2.1)	10	15.11	0.66 (0.32-1.22)	24	19.17	1.25 (0.8-1.86)	8	4.48	1.79 (0.77-3.52)
Pancreas	82	56.67	1.45* (1.15-1.8)	13	10.43	1.25 (0.66-2.13)	34	16.34	2.08* (1.44-2.91)	19	11.32	1.68* (1.01-2.62)	15	14.95	1 (0.56-1.66)	1	3.63	0.28 (0.01-1.53)
Colon excluding Rectum	75	63.04	1.19 (0.94-1.49)	11	12.64	0.87 (0.43-1.56)	30	18.66	1.61* (1.08-2.29)	8	12.4	0.65 (0.28-1.27)	19	15.68	1.21 (0.73-1.89)	7	3.65	1.92 (0.77-3.95)
Liver and Intrahepatic Bile Duct	39	32.44	1.2 (0.85-1.64)	6	5.72	1.05 (0.38-2.28)	8	9.28	0.86 (0.37-1.7)	15	6.54	2.29* (1.28-3.78)	8	8.76	0.91 (0.39-1.8)	2	2.14	0.93 (0.11-3.37)
Esophagus	38	25.89	1.47* (1.04-2.01)	4	4.84	0.83 (0.23-2.12)	8	7.63	1.05 (0.45-2.07)	7	5.19	1.35 (0.54-2.78)	15	6.68	2.25* (1.26-3.71)	4	1.56	2.57 (0.7-6.58)
Stomach	34	17.03	2.00* (1.38-2.79)	7	3.39	2.06 (0.83-4.25)	9	5.06	1.78 (0.81-3.38)	8	3.36	2.38* (1.03-4.69)	7	4.24	1.65 (0.66-3.4)	3	0.98	3.06 (0.63-8.95)
Leukemia	30	39.58	0.76 (0.51-1.08)	1	7.44	0.13* (0-0.75)	10	11.4	0.88 (0.42-1.61)	5	7.85	0.64 (0.21-1.49)	10	10.38	0.96 (0.46-1.77)	4	2.51	1.6 (0.44-4.09)
Ureter	21	0.78	26.89* (16.64-41.1)	9	0.14	63.55* (29.06-120.63)	7	0.22	31.78* (12.78-65.47)	3	0.15	19.40* (4-56.71)	1	0.21	4.75 (0.12-26.45)	1	0.05	18.53 (0.47-103.26)
Breast	20	22.44	0.89 (0.54-1.38)	7	4.61	1.52 (0.61-3.13)	5	6.58	0.76 (0.25-1.77)	0	4.38	0.00* (0-0.84)	7	5.58	1.25 (0.5-2.59)	1	1.31	0.77 (0.02-4.27)
Lymphoma	20	36.51	0.55* (0.33-0.85)	1	6.97	0.14* (0-0.8)	2	10.58	0.19* (0.02-0.68)	9	7.22	1.25 (0.57-2.37)	7	9.45	0.74 (0.3-1.53)	1	2.28	0.44 (0.01-2.44)
Non-Hodg-kin Lymphoma	20	35.11	0.57* (0.35-0.88)	1	6.71	0.15* (0-0.83)	2	10.17	0.20* (0.02-0.71)	9	6.94	1.3 (0.59-2.46)	7	9.1	0.77 (0.31-1.59)	1	2.2	0.45 (0.01-2.53)
Non-malignant cancer																		
Diseases of Heart	1,717	1,097.89	1.56* (1.49-1.64)	569	211.8	2.69* (2.47-2.92)	468	312.58	1.50* (1.36-1.64)	261	214.64	1.22* (1.07-1.37)	320	286.09	1.12 (1-1.25)	99	72.77	1.36* (1.11-1.66)

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Chronic Obstructive Pulmonary Disease and Allied Cond	561	256.78	2.18# (2.01-2.37)	162	48.03	3.37# (2.87-3.93)	137	73.21	1.87# (1.57-2.21)	108	50.75	2.13# (1.75-2.57)	122	67.94	1.80# (1.49-2.14)	32	16.86	1.90# (1.3-2.68)
Cerebrovascular Diseases	290	226.65	1.28# (1.14-1.44)	83	43.8	1.89# (1.51-2.35)	89	63.89	1.39# (1.12-1.71)	38	44.11	0.86 (0.61-1.18)	62	59.33	1.04 (0.8-1.34)	18	15.52	1.16 (0.69-1.83)
Nephritis, Nephrotic Syndrome and Nephrosis	170	85.62	1.99# (1.7-2.31)	46	16.3	2.82# (2.07-3.76)	41	24.39	1.68# (1.21-2.28)	26	16.82	1.55# (1.01-2.27)	46	22.47	2.05# (1.5-2.73)	11	5.64	1.95 (0.97-3.49)
Alzheimers	167	171.54	0.97 (0.83-1.13)	39	29.63	1.32 (0.94-1.8)	35	45.18	0.77 (0.54-1.08)	27	33.26	0.81 (0.54-1.18)	54	49.03	1.1 (0.83-1.44)	12	14.44	0.83 (0.43-1.45)
Septicemia	165	57.39	2.88# (2.45-3.35)	80	10.77	7.43# (5.89-9.24)	39	16.32	2.39# (1.7-3.27)	20	11.31	1.77# (1.08-2.73)	21	15.13	1.39 (0.86-2.12)	5	3.85	1.3 (0.42-3.03)
Pneumonia and Influenza	163	101.66	1.60# (1.37-1.87)	50	20.02	2.50# (1.85-3.29)	41	28.89	1.42# (1.02-1.93)	25	19.78	1.26 (0.82-1.87)	35	26.32	1.33 (0.93-1.85)	12	6.65	1.8 (0.93-3.15)
Diabetes Mellitus	153	113.58	1.35# (1.14-1.58)	44	21.52	2.05# (1.49-2.75)	43	32.75	1.31 (0.95-1.77)	32	22.47	1.42 (0.97-2.01)	26	29.54	0.88 (0.57-1.29)	8	7.3	1.1 (0.47-2.16)
Accidents and Adverse Effects	127	112.61	1.13 (0.94-1.34)	30	20.29	1.48 (1.2-1.11)	36	31.64	1.14 (0.8-1.58)	28	22.26	1.26 (0.84-1.82)	22	30.48	0.72 (0.45-1.09)	11	7.94	1.39 (0.69-2.48)
Hypertension without Heart Disease	89	47.1	1.89# (1.52-2.33)	27	8.48	3.19# (2.1-4.64)	21	12.91	1.63# (1.01-2.49)	11	9.24	1.19 (0.59-2.13)	24	12.98	1.85# (1.18-2.75)	6	3.48	1.72 (0.63-3.75)
Symptoms, Signs and Ill-Defined Conditions	83	47.07	1.76# (1.4-2.19)	33	9.13	3.61# (2.49-5.08)	27	13.35	2.02# (1.33-2.94)	10	9.27	1.08 (0.52-1.98)	10	12.51	0.8 (0.38-1.47)	3	2.82	1.06 (0.22-3.11)
Other Infectious and Parasitic Diseases including HIV	78	29.52	2.64# (2.09-3.3)	40	5.72	7.00# (5-9.53)	18	8.7	2.07# (1.23-3.27)	5	5.85	0.85 (0.28-1.99)	13	7.52	1.73 (0.92-2.95)	2	1.73	1.16 (0.14-4.19)
Suicide and Self-Inflicted Injury	67	24.58	2.73# (2.11-3.46)	24	4.51	5.32# (3.41-7.92)	20	7.26	2.76# (1.68-4.26)	9	4.96	1.82 (0.83-3.45)	13	6.37	2.04# (1.09-3.49)	1	1.49	0.67 (0.02-3.73)

Abbreviations: SMR, standardized mortality ratio; CI, confidence interval; #: significant difference.

Cause of death with bladder cancer

Table 5. Main cause of deaths for patients with metastatic bladder cancer

Causes of deaths	Total			<6 months			6 m-1 year			1-3 years			3-5 years			>5 years		
	Ob-served	Expect-ed	SMR (95% CI)	Ob-served	Expect-ed	SMR (95% CI)	Ob-served	Ex-pected	SMR (95% CI)	Ob-served	Ex-pected	SMR (95% CI)	Ob-served	Ex-pected	SMR (95% CI)	Ob-served	Expect-ed	SMR (95% CI)
All Causes of Death	4,392	161.9	27.13* (26.33-27.94)	1,825	38.29	47.67* (45.51-49.91)	1,193	31.64	37.71* (35.6-39.91)	1,159	47.05	24.63* (23.24-26.09)	153	19.96	7.67* (6.5-8.98)	62	24.97	2.48* (1.9-3.18)
All Malignant Cancers	4,034	37.31	108.13* (104.82-111.52)	1,679	8.94	187.84* (178.96-197.04)	1,112	7.6	146.31* (137.84-155.17)	1,078	11.18	96.42* (90.75-102.35)	127	4.33	29.33* (24.45-34.89)	38	5.26	7.23* (5.11-9.92)
Urinary Bladder	3,486	1.35	2,575.46* (2490.67-2662.41)	1,431	0.32	4,509.14* (4278.51-4748.97)	983	0.27	3,690.19* (3463.08-3928.29)	948	0.39	2,410.45* (2259.43-2568.91)	103	0.16	638.02* (520.77-773.78)	21	0.22	97.64* (60.44-149.25)
Prostate	57	3.28	17.38* (13.17-22.52)	23	0.81	28.40* (18-42.61)	11	0.66	16.78* (8.38-30.03)	18	0.93	19.40* (11.5-30.66)	5	0.38	13.27* (4.31-30.96)	0	0.51	0 (0-7.25)
Lung and Bronchus	54	10.44	5.17* (3.89-6.75)	26	2.54	10.24* (6.69-15)	13	2.18	5.97* (3.18-10.21)	11	3.17	3.47* (1.73-6.21)	2	1.18	1.7 (0.21-6.15)	2	1.38	1.45 (0.18-5.24)
Kidney and Renal Pelvis	30	0.94	31.93* (21.54-45.58)	19	0.22	85.94* (51.74-134.2)	6	0.19	31.35* (11.51-68.24)	3	0.28	10.59* (2.18-30.95)	0	0.11	0 (0-33.63)	2	0.13	14.91* (1.81-53.87)
Colon and Rectum	20	3.29	6.08* (3.72-9.39)	8	0.8	9.98* (4.31-19.66)	2	0.67	2.98 (0.36-10.77)	7	0.98	7.15* (2.87-14.72)	0	0.38	0 (0-9.66)	3	0.45	6.61* (1.36-19.32)
Liver	11	1.13	9.70* (4.84-17.35)	7	0.25	27.85* (11.2-57.38)	2	0.22	8.89* (1.08-32.13)	2	0.34	5.81 (0.7-21)	0	0.14	0 (0-26.41)	0	0.17	0 (0-21.14)
Ureter	10	0.03	328.79* (157.67-604.65)	5	0.01	710.34* (230.64-1657.69)	3	0.01	504.18* (103.97-1473.41)	1	0.01	111.49* (2.82-621.17)	1	0	270.84* (6.86-1509.04)	0	0	0 (0-774.36)
Non-tumor diseases																		
Diseases of Heart	128	43.28	2.96* (2.47-3.52)	59	10.4	5.67* (4.32-7.32)	23	8.44	2.73* (1.73-4.09)	30	12.42	2.42* (1.63-3.45)	8	5.32	1.5 (0.65-2.96)	8	6.69	1.2 (0.52-2.36)
Chronic Obstructive Pulmonary Disease and Allied Cond	30	10.28	2.92* (1.97-4.17)	9	2.42	3.72* (1.7-7.06)	8	2.03	3.95* (1.7-7.77)	8	3.03	2.64* (1.14-5.21)	3	1.25	2.41 (0.5-7.03)	2	1.56	1.28 (0.16-4.64)
Septicemia	26	2.34	11.11* (7.26-16.28)	10	0.56	17.93* (8.6-32.97)	6	0.46	13.04* (4.79-28.39)	6	0.68	8.78* (3.22-19.1)	2	0.28	7.09 (0.86-25.6)	2	0.36	5.61 (0.68-20.25)
Cerebro-vascular Diseases	23	8.97	2.56* (1.63-3.85)	8	2.15	3.71* (1.6-7.32)	7	1.72	4.07* (1.63-8.38)	5	2.56	1.95 (0.63-4.55)	2	1.13	1.76 (0.21-6.37)	1	1.4	0.72 (0.02-3.98)

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Other Infectious and Parasitic Diseases including HIV	15	1.35	11.15# (6.24-18.38)	5	0.32	15.77# (5.12-36.8)	5	0.27	18.31# (5.94-42.73)	2	0.4	4.98 (0.6-18)	1	0.16	6.2 (0.16-34.56)	2	0.19	10.36# (1.25-37.42)
Symptoms, Signs and Ill-Defined Conditions	12	1.85	6.48# (3.35-11.33)	9	0.44	20.49# (9.37-38.89)	1	0.35	2.83 (0.07-15.77)	2	0.53	3.8 (0.46-13.73)	0	0.24	0 (0-15.55)	0	0.29	0 (0-12.53)

Abbreviations: SMR, standardized mortality ratio; CI, confidence interval; #: significant difference.

Cause of death with bladder cancer

largest and then black skinned people were second to them, the risk of death of blacks was often higher than that of whites. Some scholars had put forward the same view that bladder cancer affected whites twice as much as blacks or Hispanics, but black patients were more likely to be diagnosed at an advanced stage [23]. This may not only reflect genetic differences, but also socioeconomic differences [1]. In NMIBC, we found that there was no significant difference in the SMR between patients with chemotherapy and non-chemotherapy. While radiotherapy can significantly reduce SMR, for non-MMIBC and MBC, neither radiotherapy nor chemotherapy can reduce SMR. Therefore, we look forward to seeking better therapies, such as surgery combined with neoadjuvant chemotherapy, radiotherapy, and immunotherapy, to improve the survival rate of patients [23].

The most common cause of non-neoplastic deaths from bladder cancer was heart diseases. Studies have shown that cancer patients faced a higher risk of death from cardiovascular diseases throughout their lives. The death rate of cardiovascular diseases in cancer patients was 2-6 times that of the general population on average [24]. This may be due to the long-term use of chemotherapeutics, which has dose-dependent cardiotoxicity, leading to cardiomyopathy and heart failure [25, 26]. In addition, other high-risk diseases such as diabetes, nephritis, nephrotic syndrome and nephrosis, diabetes mellitus disease, etc. can change the body's metabolic state and hemodynamics, thereby increasing the burden on the heart. The risk of death from cardiovascular disease was obviously throughout the entire process of cancer treatment, including the early and late follow-up. Considering such serious and persistent consequences, reactive management methods that only work when clinical manifestations and complications occur were no longer applicable. On the contrary, we advocate a proactive approach, which begins before any cancer treatment is given and lasts for a lifetime thereafter. Chronic obstructive pulmonary disease was the second largest non-tumor cause of death after heart diseases. At the same time, lung cancer and bronchial cancer were the most common non-bladder cancer malignancies after diagnosis of bladder cancer. Bladder cancer has such a significant impact on the lungs, but the reason is still

unknown. Another noteworthy point was that the risk of death from septicemia, other infectious and parasitic diseases including HIV was much higher than that of the general population, especially in non-MMIBC and MBC. This may be caused by using chemotherapy drugs causing bone marrow suppression and reduced white blood cell production which is related to the dysfunction of the immune system. Studies have shown that the main suicide patients were male, white, diagnosed with lung cancer, head, neck cancer, testicular cancer, bladder cancer and Hodgkin's lymphoma, which had the highest SMR (>5-10) [27]. A study found that the suicide rate of bladder cancer patients in British Columbia is 2.71 times that of the general population (95% credible interval 2.02, 3.62) [28]. Men, the elderly, unmarried status, whites, and non-localized diseases were risk factors for suicide [26]. Interestingly, the median time from diagnosis to suicide was 43 months [25], which emphasizes the necessity of providing long-term survival support and basic psychological encouragement for patients with bladder cancer.

Compared with the general population, patients with bladder cancer were at a higher risk of dying from other non-neoplastic diseases. High-risk patients should not consider intensive treatment of bladder cancer, nor should they undergo intensive medical management during and after treatment. Therefore, our research on non-cancerous causes of death may help clinicians individualize the risk characteristics of specific early death events, thereby contributing to more individualized clinical decision-making and survival planning. In addition, the survival time and causes of death for patients were also affected to a certain extent by their lifestyle. It was estimated that 30-40% of cancers can achieve primary prevention by changing lifestyle and environmental risk factors known to be associated with cancer morbidity. An active lifestyle can also contribute to tertiary prevention of cancer and reduce cancer mortality [30]. A healthy lifestyle, including avoiding smoking, maintaining a healthy weight, active exercise, avoiding harmful alcohol consumption and maintaining a healthy diet are the best strategies for preventing and treating cancer and other major non-communicable diseases [31]. Previous studies have shown that physical exercise can reduce the risk and

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mortality of breast cancer, colon cancer and bladder cancer [32]. Drinking more water and increasing the intake of vegetables and fruits could prolong the survival time of patients with bladder cancer. Vegetables and fruits contain many micronutrients and phytochemicals that may prevent or inhibit carcinogenicity, thereby prolonging the survival of patients with bladder cancer [33]. However, bladder cancer patients have physical discomfort, reduced exercise, loss of appetite and other conditions, the pursuit of the healthiest lifestyle is not ideal. Given the low proportion of people with healthy lifestyles in many countries, creating an environment more conducive to behavioral change should be a priority for public health worldwide.

There were some limitations in our study. Firstly, we used AJCC TNM 6th edition staging (2004-2015) to distinguish NMIBC, non-MMIBC and MBC, but these classifications are not the same as the current version. Therefore, the results of this study can't fully represent the current staging results. Secondly, the treatment information of patients in this database was incomplete. The database only provided radiotherapy and chemotherapy records, but not detailed treatment information. For non-MMIBC and MBC patients, the treatments varied greatly which had important impacts on the survival time and the death reasons. Our results might be influenced by this missing information. Therefore, high-quality studies are needed in the future to explore the main causes of deaths and related risk of deaths compared with general population.

In summary, during the follow-up period after diagnosis, deaths caused by non-bladder cancer accounted for a considerable proportion of patients with bladder cancer, especially NMIBC and non-MMIBC. Heart disease and other malignant tumors accounted for the largest number of deaths from non-bladder cancer. Other important non-cancer causes of death include chronic obstructive pulmonary disease, nephritis, nephrotic syndrome and nephrosis, diabetes mellitus, sepsis and other infectious diseases, and suicide. Our findings will help guide bladder cancer patients about their future health and life managements.

Disclosure of conflict of interest

None.

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