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The Investigation between Voiding Function Medication and the Risk of Bladder Cancer in Patients with Spinal Cord Injury

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Original Article

The Investigation between Voiding Function Medication and the Risk of Bladder Cancer in Patients with Spinal Cord Injury

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Bladder cancer (BC) is a chronic complication of spinal cord injury (SCI). Limited studies have focused on the risks of BC in SCI patients using voiding function medication for bladder dysfunction.

In this retrospective, national-wide, population-based cohort study, SCI patients with registration in the National Health Insurance Research Database (NHIRD) from 1998 to 2013 were included. We investigated the risk of BC in SCI patients administered voiding function medications and other comorbidities by 2-year landmark analysis. SCI patients were divided into medication user (bethanechol, oxybutynin, or tolterodine) and non-medication user groups at landmark period. They were followed until the development of BC, death, or any other reason for loss to follow-up. Cox regression models and competing risk regression were used to investigate BC risks.

In our study, 47,373 SCI patients registered in our database met the inclusion criteria. After exclusion, 22,974 patients were divided into medication user and non-medication user groups. There were no increased BC risks in medication user group, comparing to non-medication user group, neither in different cDDD nor subgroup analyses. In the subgroup analysis of medication user group, age more than 45 years (aHR: 1.93–2.45), male (aHR: 1.62), higher economic levels (aHR: 1.82), renal stone (aHR: 2.43), and chronic urinary tract infection (aHR: 2.18) were independent factors increased BC. Voiding dysfunction medication did not increase the risk of BC in SCI. Physician should still pay attend on other risk factors of BC in SCI patients. (Tw J Phys Med Rehabil 2021; 49(1): 91 - 104)

Key Words: bladder cancer, medication, risk factor, spinal cord injury

INTRODUCTION

1. Risk factors of Bladder cancer (BC) in spinal cord injury (SCI) patients

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BC is a chronic complication of SCI.[1] According to recent studies, 0.6% of SCI patients have bladder tumors, which is higher than that of the general population.[1,2] The average age of these patients is 50 years (95% confidence interval [CI]: 45–55 years), which was also younger than that of the general population.[1] Long-term use of urine catheterization has also been observed in SCI patients with BC.[1] In addition, several studies demonstrated that urine catheterization increases the risk of BC.[3-8] However, Kalisvaart et al. (2010) reported up to 48% of 38 BCs in 1,319 SCI patients without urine catheterization, suggesting that BC may be related to bladder dysfunction but not urine catheterization.[8] Until now, limited studies have focused on the risk factors of BC in patients using medication for bladder dysfunction. Because a higher risk of metastasis, cancer-specific mortality, and overall mortality was already reported in the general population with untreated BC,[9] the studies to determine the risk factors, predictors, and prognostic factors of BC are ongoing.[1,5,7,8,10-15]

2. Voiding function medication in SCI patients with bladder dysfunction

In addition to non-pharmacological treatments (i.e., abdominal tapering and intermittent cauterization), medication plays an important role in the management of bladder dysfunction.[16] SCI patients with bladder dysfunction can experience voiding difficulty or an inability to store urine.[16] To improve the voiding function, different types of medication are administered.[16] When voiding difficulty occurs, cholinergic medications (bethanechol) increase bladder emptying, and alpha-sympathetic receptor blockers (e.g., prazosin and terazosin) relax internal sphincter contractions.[16]When urine storage difficulty occurs, anticholinergic medications (e.g., oxybutynin and tolterodine) can inhibit bladder contraction, and alpha receptors (ephedrine and phenylpropanolamine) increase internal sphincter contractions.[16] Among these medications, only cholinergic (bethanechol) and anticholinergic (e.g., oxybutynin and tolterodine) medications act directly on the detrusor muscle of the urinary bladder. It is unclear if these medications induced BC in patients with SCI. In contrast, in a recent study, Lofling et al reported that anticholinergic medications for overactive bladder showed protective effects on lung and colon cancers.[17] Thus, it is necessary to investigate further if cholinergicand anticholinergic medicationshave any carcinogenic or protective effect on BC in patients with SCI.

3. Study aims

We designed this study to determine factors of BC in patients with SCI. This study aimed to investigate whether the use of voiding function medication, mainly focusing oncholinergicand anticholinergic medications, and other factors are risk factors of BC in patients with SCI.

MATERIALS AND METHODS

1. General design

In this national-wide, population-based study, SCI patients with registration in the national health insurance research database (NHIRD) from 1998 to 2013 were included. A retrospective, cohort, 2-year landmark analysis was conducted to investigate the risk of BC after SCI with or without the use of voiding function medications. A subgroup analysis of SCI with use of voiding function medication was conducted using competing risk regression. This study was approved by the Institutional Review Board in our hospital (IRB No. 201801230B0).

2. NHIRD

In the NHIRD database, 99% of medical claims data in our country are enrolled, with protection of the privacy of the patients. The patients' demographic characteristics, diagnoses, catastrophe illness cards, medical expenditures, and prescription claims data were recorded. The diagnostic codes indicated in the records of the participants were based on the clinical modification of the international classification of diseases, ninth revision, clinical modification (ICD-9-CM) codes. BC is classified as a catastrophic disease. Patients with BC were recorded as ICD-9-CM code 188.* in the database.

3. Participants

Patients with the first registration of the catastrophic illness card of SCI (ICD-9 CM code: 806, 952), at least one admission, or two outpatient visits within 365 days

from 1998–2013 were enrolled in this study. The index date was defined as the first date of the catastrophic illness card identified, SCI admission, or the first diagnosis at an outpatient visit. If the patient had met 2 or 3 conditions, the earliest date was defined as the index date. Exclusion criteria included: (1) patients with missing demographic data (i.e. gender and birth date), (2) patients diagnosed with neurogenic bladder (ICD-9 CM codes: 596.5*, 788.3*), multiple sclerosis (ICD-9 CM code: 340), and any malignancy (ICD-9 CM codes: 140–149, 150–159, 160–165, 170–176, 179–189, 190–199, 200–209, 230–239) before the index date, (3) patients previously administered the cholinergic agent bethanechol (ATC code: N07AB02), the anticholinergic agent oxybutynin (ATC code: G04BD04), and tolterodine (ATC: G04BD07) before the index date. When the patients met one or more of the exclusion criteria, they were counted in each exclusion criterion but only counted as one case in the total number of cases excluded. Because this study was a 2-year landmark analysis designed (mentioned in detail in "statistical analysis"), the patients with a follow-up period less than the 2-year landmark period and no diagnosis of BC after the index date were excluded.

After exclusion, all SCI patients were divided into two groups, depending on the use of voiding function medication. These medications included the cholinergic agent bethanechol, the anticholinergic agent oxybutynin, and tolterodine. SCI patients administered one of these medications during the landmark period were defined as a "medication user." The remaining SCI patients who were not administered any of these medications were defined as a "non-medication user.". In the medication user group, the defined daily dose (DDD) (defined by the World Health Organization (WHO)) was used to measure the exposure of different doses of certain medications.[18] DDD is defined as the assumed average maintenance dose per day for a drug used for its main indication in adults. In this study, the dose of cumulative DDD (cDDD) in medication users was classified into three groups for subgroup analysis: (1) 0 cDDD (no exposure of certain cholinergic or anticholinergic medications), (2) 1–28 cDDD (at least 1–28 days of an adult dose of certain cholinergic or anticholinergic medications), (3) >28 cDDD (>28 days of an adult dose of certain cholinergic or anticholinergic medications).

4. Covariates

Factors related to the development of BC in previous studies were listed as covariates, including chronic obstructive pulmonary disease(COPD, an indicator of smoking, ICD-9 CM code: 490.*–496.*),[14,15,19,20] renal stone (ICD-9 CM code: 592.0),[5,21] bladder stone (ICD-9 CM code: 594.1),[3,5] chronic urinary tract infection (ICD-9 CM code: 599.0), pioglitazone (ATC code: A10BD06, A10BD05, A10BG03, A10BD09, and A10BD12),[11] and indwelling urinary catheter.[3,5] The Charlson comorbidity index (CCI) score was used to measure the disease burden.[22] In this study, the CCI score was measured within 1 year before the index date.

5. Primary outcome

To investigate whether the use of voiding function medication increases the risk of BC in patients with SCI, BC was the primary outcome in this study. BC was defined as patients who had a new registration of ICD-9 CM code:188.* in either the medication user or non-medication user group after the landmark period and either during the outpatient visit or upon admission.

6. Statistical analysis

6.1. Landmark analysis

Landmark analysis is one of the methods for survival analysis or evaluation of certain outcomes.[23] This method requires participants to be followed-up for a certain period (known as the landmark time or period) and subsequent investigation of only those participants who have survived until the landmark period.[23] All subjects were classified or divided into different groups at the landmark time.[23] In our study, the landmark period was set at 2 years and was defined as the "exposure period" of medication within 2 years after the index date. In addition to other exclusion criteria, participants who were followed-up for less than 2 years were excluded. Then, all remaining participants with SCI were divided into the medication use group or non-medication use group depending on the DDD of exposure to cholinergic or anticholinergic medication at the 2-year landmark period. After the landmark period, all patients were followed until the development of BC, death, or any other reason for loss to follow-up. Only outcomes (i.e., BC)

that occurred after the 2-year landmark period were included in our analysis.

Landmark analysis can avoid immortal time bias. The benefit of landmark analysis is that it allowed exclusion of other causes of death in the early stage of injury and sufficient time to observe any time-dependent event (i.e., cholinergic or anticholinergic medication). In our study, participants with SCI may die of acute pneumonia or other complications of acute injury. If these participants were included in the analysis of the association of BC and use of voiding function medication, they may have been wrongly grouped into no development of BC group. In fact, these participants died too early, and there was no opportunity to observe if BC developed. This bias is called immortal or guarantee time bias. By excluding participants who cannot be followed-up until the landmark period, this type of immortal time bias can be minimized.[23] Another cause of immortal time bias is when a time-dependent event is analyzed.[24] In the early diagnosis of SCI, information about which patients needs voiding function medication is unknown. If the participants were classified at baseline, i.e., at the time of SCI diagnosis, the patients who later need voiding function medication may have been wrongly categorized into the non-medication user group. In the 2-year landmark analysis, the patients with SCI were grouped after a 2-year follow-up. This allowed sufficient time to observe patients who needed or did not need voiding function medication. Therefore, we performed a 2-year landmark analysis to prevent misgrouping and to minimize immortal time bias in our analysis.

6.2. Comparison between medication and non-medication users

Categorical variables of medication or non-medication users at baseline were compared using the chi-square test. The cumulative incidence of BC was estimated by the cause-specific hazard model. Cox regression analysis with competing risk regression was performed to evaluate the relationship between BC and certain doses of medication before and after adjusting the covariates, and the results were expressed as crude hazard ratios (HRs) and adjusted HRs (aHRs). For sensitivity tests, a subgroup analysis was performed, including different age groups, sexes, economic levels, urbanization levels, CCI scores, comorbidities, medications, and treatments. For further investigation of any other risk of BC in patients with SCI, a subgroup analysis with at least one of the covariates under the use of cholinergic or anticholinergic medication was performed using competing risk regression. The aHRs of each factor were calculated after adjusting for the covariates.

6.3. Software

SAS version 9.4 (SAS Institute, Cary, NC, USA) was used for all statistical analyses. A p-value of <0.05 indicated statistical significance.

RESULTS

1. Patient selection and demographic data

In 1998–2013, 47,373 SCI patients were identified in our database. Of these, 24, 399 who met one or more of the following exclusion criteria were excluded: neurogenic bladder diagnosis before the index date (n = 6,211), multiple sclerosis diagnosis before the index date (n = 165), any malignancy diagnosis before the index date (n = 11,112), BC diagnosis before the index date (n = 471), using medication for neurogenic bladder (i.e., bethanechol, oxybutynin, or tolterodine) before the index date (n = 11,802), an interval less than 2 years between the BC diagnosis and index date (n = 168),no diagnosis of BC after the index date and a follow-up period less than 2 years (n = 8,733), and missing data (i.e., gender and birth date) (n = 5) (Figure 1). The remaining 22,974 SCI patients were divided into the medication user group (n = 3,256) and non-medication user group (n = 19,718) according to the use of bethanechol, oxybutynin, or tolterodine.

In the analysis of demographic data between the two groups (Table 1), the number of SCI patients with COPD and who used pioglitazone or alpha-adrenergic medication was similar ($p< 0.05$). However, the differences in age, sex, economic level, urbanization level, CCI score, renal stone, bladder stone, chronic urinary tract infection, use of alpha-blockers, and tricyclic antidepressants, catheterization, and invasive bladder procedure (e.g., Cystofix or cystostomy) were statistically significant between the two groups ($p< 0.05$ for all). The follow-up time after SCI was 6.45 ± 3.99 years (median, 6.24 year) in medication user group and 6.93 ± 3.94 years (median: 6.97 years) in the non-medication user group.The inci-

dence rate of BC was 0.9% (29/3256) in the medication user group and 1.0% (200/19718) in the non-medication user group. There was no significant difference in the cumulative incidence of BC between the two groups (Figure 2).

Table 1. Demographic characteristics of the two groups.

	Medication user		Non-medication user		Total		p value
	SCI patients with cholinergic or anticholinergic medication for voiding function.		SCI patients without cholinergic or anticholinergic medications for voiding function.				
Patients	3,256	100.0%	19,718	100.0%	22,974	100.0%	
Catastrophic illness card	1,663	51.1%	3,383	17.2%	5,046	22.0%	<0.001
Age on index date, year							<0.001
< 18	58	1.8%	438	2.2%	496	2.2%	
18–44	995	30.6%	5,225	26.5%	6,220	27.1%	
45–64	1,106	34.0%	6,322	32.1%	7,428	32.3%	
≧65	1,097	33.7%	7,733	39.2%	8,830	38.4%	
Sex							<0.001
Female	1,130	34.7%	8,561	43.4%	9,691	42.2%	
Male	2,126	65.3%	11,157	56.6%	13,283	57.8%	
Economic level (NT$/month)							<0.001
0	392	12.0%	2,824	14.3%	3,216	14.0%	
1-15,840	467	14.3%	3,117	15.8%	3,584	15.6%	
15,841-25,000	1,593	48.9%	9,553	48.4%	11,146	48.5%	
≧25,001	804	24.7%	4,224	21.4%	5,028	21.9%	
Urbanization level							0.026
Very high	1,136	34.9%	6,603	33.5%	7,739	33.7%	
High	1,120	34.4%	6,544	33.2%	7,664	33.4%	
Moderate	460	14.1%	3,114	15.8%	3,574	15.6%	
Low	540	16.6%	3,457	17.5%	3,997	17.4%	
CCI score							<0.001
0	1,792	55.0%	10,053	51.0%	11,845	51.6%	
1	550	16.9%	4,047	20.5%	4,597	20.0%	
2	418	12.8%	2,490	12.6%	2,908	12.7%	
≧3	496	15.2%	3,128	15.9%	3,624	15.8%	
Comorbidities							
COPD	1,576	48.4%	9,421	47.8%	10,997	47.9%	0.509
Renal stone	381	11.7%	1,615	8.2%	1,996	8.7%	<0.001
Bladder stone	234	7.2%	463	2.3%	697	3.0%	<0.001
Chronic Urinary tract infection	2,663	81.8%	9,659	49.0%	12,322	53.6%	<0.001
Medications or treatments							
Pioglitazone	34	1.0%	176	0.9%	210	0.9%	0.400
Alpha-blockers	1,672	51.4%	1,972	10.0%	3,644	15.9%	<0.001
Tricyclic antidepressants	1,205	37.0%	2,783	14.1%	3,988	17.4%	<0.001
Alpha adrenergic medications	14	0.4%	81	0.4%	95	0.4%	0.874
Catherization	127	3.9%	184	0.9%	311	1.4%	<0.001
Invasive bladder procedure[1]	2,708	83.2%	8,042	40.8%	10,750	46.8%	<0.001
MRI	1,960	60.2%	6,819	34.6%	8,779	38.2%	<0.001
Catherization or surgery before index date	2,393	73.5%	9,571	48.5%	11,964	52.1%	<0.001

* The values were expressed as number (n) or percentage (%).

Note 1. Invasive bladder procedure, such as cystofix or cystostomy was included for comparison between two groups.

Abbreviations: CCI,Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; MRI, magnetic resonance imaging; SCI, spinal cord injury.

Table 2. Competing risk regression of different doses of voiding function medications.

Medication use	Crude HR	95%CI		p-value	Adjusted HR*	95%CI		p value
Cholingeric or anticholingeric medication								
No use	1.00				1.00			
Use	0.94	0.64	1.39	0.752	1.01	0.67	1.54	0.953
Cholingeric or anticholingeric medication levels								
0 cDDDs	1.00				1.00			
1-28 cDDDs	1.09	0.66	1.82	0.737	1.10	0.65	1.85	0.731
> 28 cDDDs	0.80	0.46	1.41	0.440	0.91	0.50	1.66	0.762
Bethanechol levels								
0 cDDDs	1.00				1.00			
1-28 cDDDs	0.73	0.32	1.63	0.440	0.85	0.37	1.92	0.693
> 28 cDDDs	1.02	0.57	1.83	0.936	1.20	0.65	2.23	0.565
Oxytobulin levels								
no use	1.00				1.00			
1-28 cDDDs	1.58	0.92	2.71	0.097	1.55	0.88	2.73	0.131
> 28 cDDDs	0.55	0.14	2.23	0.405	0.61	0.15	2.44	0.480
Tolterodine level								
no use	1.00				1.00			
1-28 cDDDs	1.97	0.73	5.29	0.179	1.99	0.73	5.42	0.180
> 28 cDDDs	0.41	0.06	2.89	0.367	0.51	0.07	3.70	0.507

*HRs were adjusted by age, sex, economic level, urbanization level, CCI score, COPD, renal stone, bladder stone, chronic urinary tract infection, alpha-blockers use, tricyclic antidepressant use, invasive bladder procedure.

Abbreviations: CCI, Charlson comorbidity index; cDDD, cumulative defined daily dose; COPD, chronic obstructive pulmonary disease; HR: hazard ratio.

2. Risk of BC under the use of cholinergic or anticholinergic medication

As the primary outcome was the risk of BC in SCI patients administered voiding function medications in this study, the results of competing risk regression for the subgroup analysis of different types and doses of medication were shown in Table 2. First, we found that the risk of BC in SCI patients who were cholinergic or anticholinergic medication users was not increased compared with non-medication users (aHR: 1.02, 95% CI: 0.67–1.55, Table 2). Further subgroup analysis of different doses of these medication in SCI patients revealed that the risk of BC did not increase in medication users compared with non-medication users (aHR in 1–28 cDDD group: 1.10, 95% CI: 0.65–1.85; aHR of >28 cDDD group: 1.92, 95% CI: 0.50–1.66, Table 2).

Similar results were obtained following individual medication analyses with different doses (Table 2). The risks of BC in SCI patients who were administered each type of medication (i.e., bethanechol, oxybutynin, and tolterodine) had not increased in either the 1–28 cDDDs or >28 cDDDs subgroups compared with non-medication users (p> 0.05, Table 2).

3. Risk of BC in different subgroups who use cholinergic or anticholinergicmedication

As shown in Table 3, the presence of any risk of BC was determined in the different subgroups of SCI patients under the use of medication. These subgroups included different ages, sex, economic levels, urbanization levels, CCI scores, certain comorbidities (COPD, renal stone, bladder stone, chronic urinary tract infection), coexisting use of alpha-blockers, coexisting use of tricyclic antidepressants, and those treated with invasive bladder procedures. Similarly, the risk of BC in the medication user group was not increased in any of the subgroup analyses (p> 0.05 for all, Table 3).

Table 3. Competing risk regression analysis of the risk of bladder cancer and the effects of cholinergic or anticholinergic medication use in differentsubgroups.

Subgroup	Adjusted HR[2]	95%CI		p value
Age on index date, year				
< 18	-	-	-	-
18–44	1.44	0.52	4.02	0.482
45–64	0.74	0.34	1.60	0.438
≧65	1.19	0.69	2.06	0.535
Sex				
Female	0.75	0.36	1.59	0.459
Male	1.14	0.67	1.94	0.620
Economic level (NT$/month)				
0	0.81	0.23	2.83	0.740
1-15,840	1.27	0.50	3.20	0.615
15,841-25,000	1.24	0.67	2.29	0.499
≧25,001	0.67	0.28	1.60	0.368
Urbanization level				
Very high	1.22	0.57	2.58	0.608
High	0.91	0.46	1.81	0.785
Moderate	0.33	0.07	1.53	0.157
Low	2.06	0.82	5.18	0.125
CCI score				
0	1.39	0.74	2.59	0.304
1	1.02	0.46	2.29	0.961
2	0.59	0.17	2.08	0.411
≧3	0.92	0.35	2.41	0.866
Comorbidities				
COPD				
Without	0.99	0.49	1.98	0.975
With	1.04	0.62	1.75	0.879
Renal stone				
Without	0.89	0.52	1.51	0.658
With	1.38	0.68	2.82	0.377
Bladder stone				
Without	0.99	0.64	1.53	0.951
With	1.20	0.25	5.77	0.819
Chronic urinary tract infection				
Without	0.72	0.18	2.79	0.631
With	1.07	0.68	1.68	0.778
Medications or treatments				
Alpha-blockers				
No use	0.87	0.49	1.55	0.639
Use	1.36	0.69	2.68	0.378
Tricyclic antidepressants				
No use	0.89	0.52	1.53	0.666
Use	1.40	0.70	2.78	0.338
Invasive bladder procedure[1]				
Without	0.95	0.46	1.96	0.892
With	1.07	0.63	1.84	0.798
MRI				
Without	1.10	0.64	1.89	0.737
With	1.01	0.55	1.83	0.986

Note:1. Invasive bladder procedure, such as cystofix or cystostomy. 2. HRs were adjusted by age, sex, economic level, urbanization level, CCI score, COPD, renal stone, bladder stone, chronic urinary tract infection, alpha-blockers use, tricyclic antidepressant use, invasive bladder procedure.

Abbreviations: CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; HR: hazard ratio; MRI, magnetic resonance imaging.

Table 4. Competing risk regression analysis of the risk of bladder cancer in SCI patients using voiding function medications with certain factors.

Parameter	aHR	95%CI		p value
Exposure: 1 - 28 cDDDs (ref: non-exposure)	1.10	0.65	1.85	0.731
Exposure: >28 cDDDs (ref: non-exposure)	0.91	0.50	1.66	0.762
Age: <18 (ref: 18-44)	0.57	0.08	4.21	0.578
Age: 45-64 (ref: 18-44)	1.93	1.26	2.96	0.002
Age: 65+ (ref: 18-44)	2.45	1.58	3.79	<0.001
Sex: male (ref: female)	1.62	1.19	2.19	0.002
Economic level: 1-15,840 (ref: 0)	1.22	0.73	2.05	0.456
Economic level: 15,841-25,000 (ref: 0)	1.30	0.83	2.03	0.257
Economic level: ≧25,001 (ref: 0)	1.82	1.09	3.04	0.023
Urbanization level: very high (ref: low)	0.99	0.64	1.53	0.968
Urbanization level: high (ref: low)	1.46	0.97	2.19	0.071
Urbanization level: moderate (ref: low)	1.53	0.99	2.38	0.059
CCI score: 1 (ref: 0)	1.05	0.75	1.46	0.780
CCI score: 2 (ref: 0)	0.93	0.62	1.40	0.733
CCI score: 3+ (ref: 0)	0.83	0.57	1.22	0.346
COPD (ref: without)	1.11	0.84	1.47	0.475
Renal stone (ref: without)	2.43	1.76	3.37	<0.001
Bladder stone (ref: without)	1.68	0.96	2.93	0.068
Chronic Urinary tract infection (ref: without)	2.18	1.59	2.97	<0.001
Alpha-blockers use (ref: no use)	0.90	0.62	1.31	0.570
TCA use (ref: no use)	0.98	0.69	1.41	0.922
Invasive bladder procedure (ref: without)	0.48	0.35	0.65	<0.001

*HRs were adjusted by age, sex, economic level, urbanization level, CCI score, COPD, renal stone, bladder stone, chronic urinary tract infection, alpha-blockers use, TCA use, invasive bladder procedure.

Abbreviations: CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; HR, hazard ratio;TCA, tricyclic antidepressant.

4. Risk of BC when SCI patient using voiding function medications with certain factors

We further investigated the risk of BC in the medication user group to identify any coexisting factors that may increase the risk of BC. The analysis was summarized in Table 4. Age older than 45 years, male sex, renal stone history, chronic urinary tract infection history, and high economic level were independent risk factors of BC in SCI patients using voiding function medication. The aHRs in the age group 45–64 years indicated a 2-fold increase in the risk of BC compared with the age group of 18–44 years (aHR: 1.93, p= 0.002). Similarly, the aHRs of the old age group (>65 years) indicated a ~2.5-fold increase in the risk of BC (aHR: 2.45, p< 0.001). The aHRs of sex indicated that men had an approximately 1.6-fold increased risk of BC (aHR, 1.62; p = 0.002). The aHRs of renal stones and chronic urinary tract infections indicated that patients had a ~2.4- and ~2.2-fold increased risk of BC, respectively (aHR of renal stone: 2.43, p< 0.001; aHR of chronic urinary tract infection: 2.18, p< 0.001).

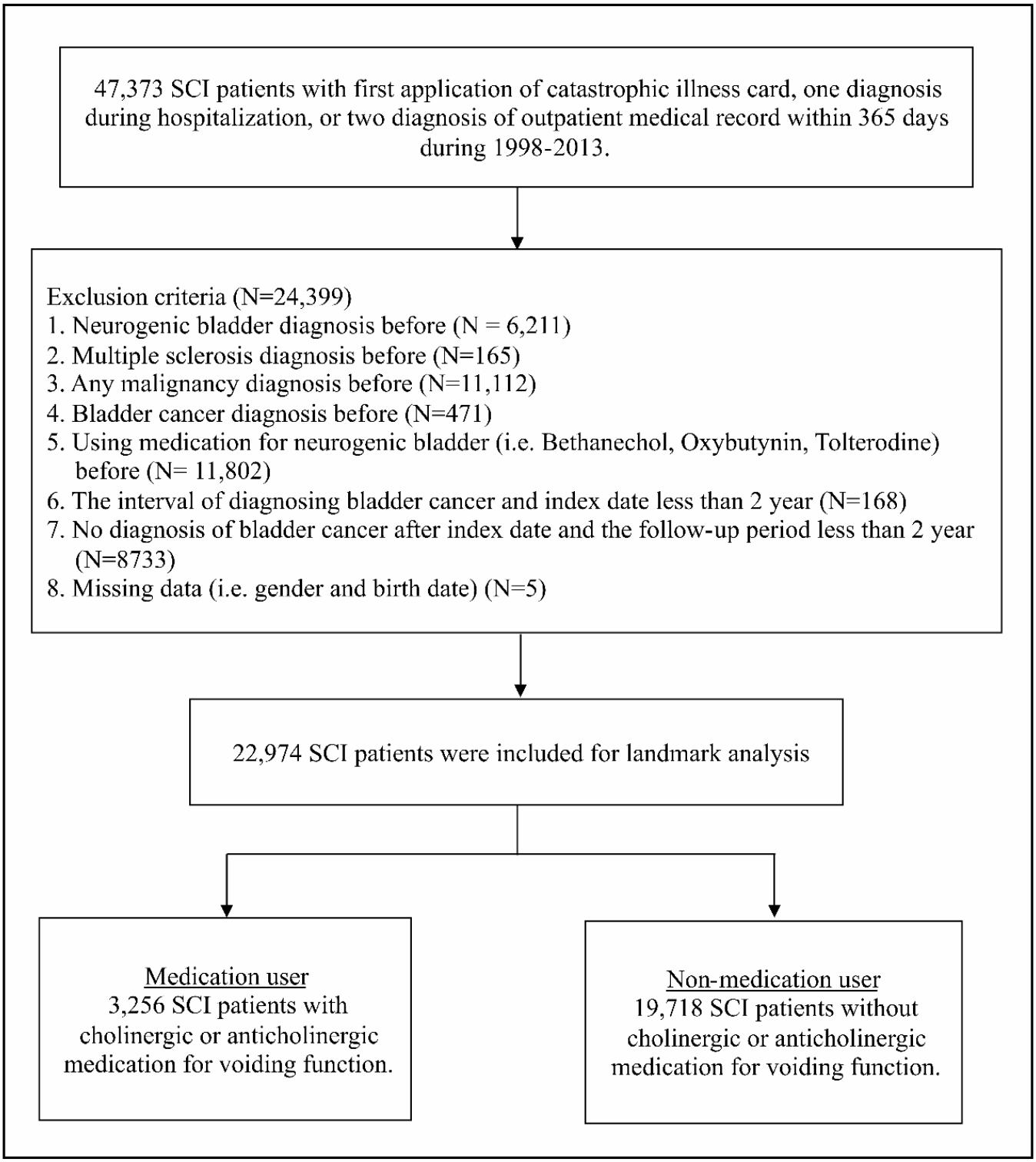

Figure 1. Flow chart of patient selection.
Abbreviation: SCI, spinal cord injury.

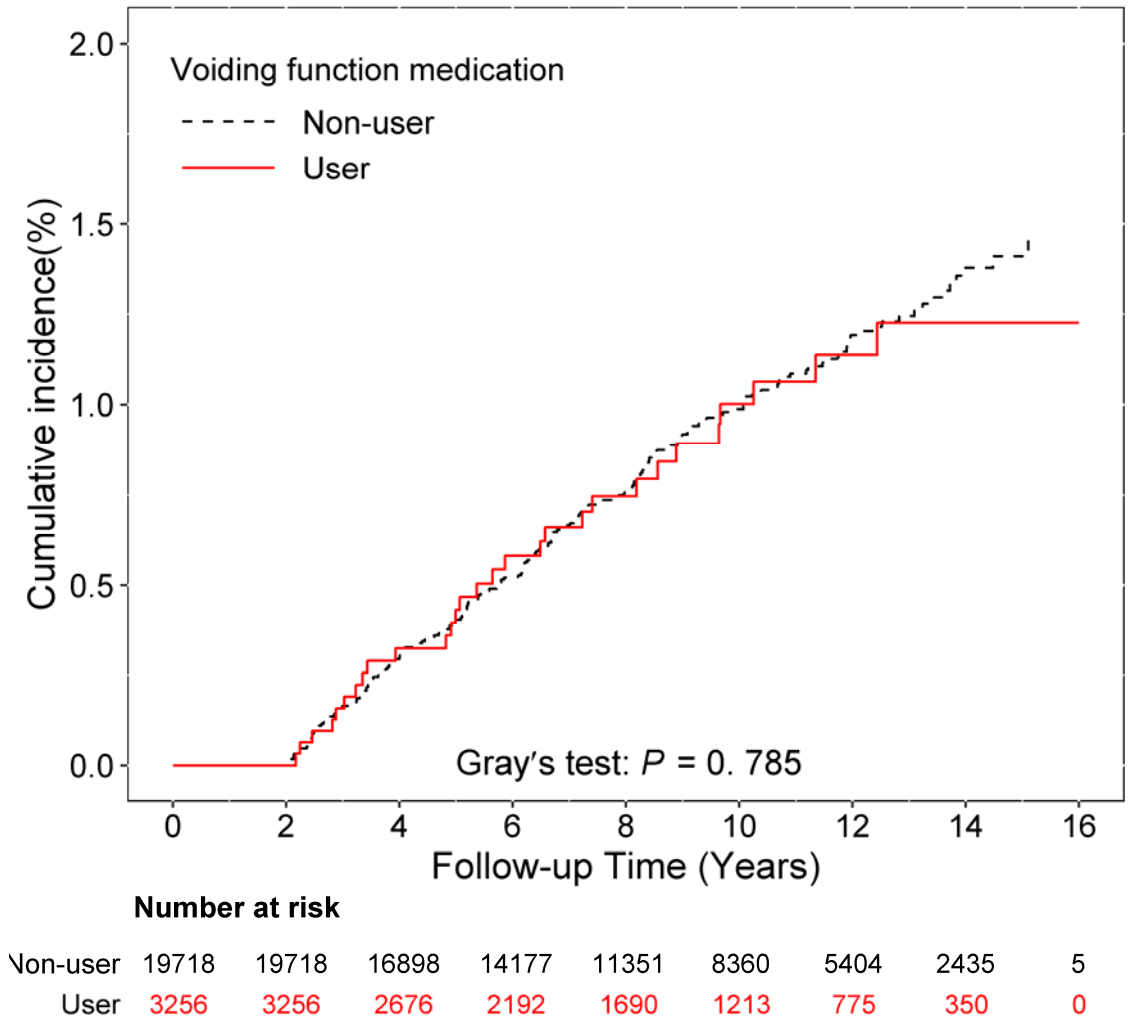

Figure 2. The cumulative incidence of bladder cancer estimated by the cause-specific hazard model.
Note: Non-user, non-medication user group; User, medication user group.

DISCUSSION

To the best of our knowledge, this is the first population-based study that investigated the association of voiding function medication with other factors and the risk of BC in SCI patients. In our study, two important findings were observed. First, voiding function medications (i.e., bethanechol, oxybutynin, and tolterodine) did not increase the risk of BC in SCI patients in the different cDDD or subgroup analyses. Second, several independent factors were found to increase the risk of BC in SCI patients administered voiding function medication, including age between 45–64 years (aHR: 1.93), age older than 65 years (aHR: 2.45), male sex (aHR: 1.62), higher economic levels (aHR: 1.82), renal stone history (aHR: 2.43), and chronic urinary tract infection (aHR: 2.18).

1. Medication and risks of BC

In the literature, some medications have been reported to increase the risk of BC in other populations.[11,25] However, whether voiding function medication is associated with an increased risk of BC in SCI patients remains unknown. One of the well-known medications reported as

a risk factor of BC is the antidiabetic drug pioglitazone.[11,25] In a large population-based study involving 145,806 patients treated with antidiabetic drugs in the United Kingdom, the use of pioglitazone was associated with an approximately 63% increased risk of BC, which further increased when the duration and dose of the drug increased.[11] In our study, pioglitazone was listed as a covariate to control for this confounding factor. We focused on medications that act on the detrusor muscle function of the urinary bladder, including cholinergic and anticholinergic drugs, which can change the smooth muscle contractility in the urinary bladder. In addition to their effect on bladder function, whether these drugs are associated with bladder carcinogenesis remains unknown. Although the effects of these medications on the risk of BC is a negative finding of this study, the information provided here is essential for the SCI population. SCI patients have poor locomotor ability and poor sensation below the neurological injury level. If typical symptoms or discomfort of secondary commodities only present below the neurological injury level, then they may not feel these symptoms until their family or caregiver notices or a systemic symptom develops. In addition, the early diagnosis of these diseases is difficult. Atypical presentation of BC in the SCI population has been previously reported.[7] Thus, primary prevention or regular screening tests for certain chronic complications in the high-risk group are considered in clinical health settings. In our study, voiding function medications were initially assumed to increase the risk of BC in SCI patients, suggesting that these patients may need regular screening tests after using certain doses of medications during the long-term care period. Fortunately, we found that the use of bethanechol, oxybutynin, and tolterodine was not associated with an increased risk of BC, at least in our study. These findings suggest that there is no carcinogenic effect of these medications in SCI patients, which can reduce the concern regarding their long-term use.

2. Other risk factors of BC in SCI

Aside from medications, several risk factors related to BC in SCI patients have been discussed in the literature,[3-7,13,26-29] such as age,[7,28] sex,[26] use of indwelling urinary catheters,[3-7,27,29] urinary tract infection,[7,11,13,26] smoking exposure,[5,6]renal stone,[5,26] and bladder stone.[3,5-7,26] For the most part, our findings were consistent with previous studies.[3-7,13,26-29] For example, in a review by Welk et al. (2013), the mean age at which BC is diagnosed in SCI patients was between 48 and 61 years, which was younger than that in the general population.[7] We also found that age was an independent risk factor for BC. Specifically, the risk was higher in patients older than 44 years. Our findings also support the study by Bejany et al. (1987) in which men had a 1.62-fold higher risk of BC than women. Similar to Bejany et al. and Hess et al.,[5,26] our findings also supported that renal stones were another risk factor ofBC. We also found patients with urinary tract infection have a 2.18-fold higher risk of BC compared with patients without urinary tract infections, which is consistent with previous studies.[7,26]

In addition to previous studies, we found that a higher economic level was associated with a 1.82-fold increased risk of BC. Although previous studies explaining the relationship between economic level and BC are limited, higher economic levels are known to be associated with increased health alertness and motivation of seeking healthcare systems, which may lead to more opportunities for medical examinations and BC diagnoses.

In previous studies, smoking was reported as a carcinogen agent related to BC.[5,6] In our study, data on smoking were not recorded in the database. Instead, we used COPD, a smoking-related disease, as a proxy for heavy smoking and listed it as a covariate. However, COPD did not increase the risk of BC. It seemed that direct record of smoking status is more suitable for detect risk of BC.

3. Strengths and limitations

This study has some limitations. In our population-based cohort study, the two study groups have different characteristics. To avoid the effect of selection bias, all these factors were listed as covariates, and HR was calculated after adjustment for these covariates. Moreover, a sensitivity test was also performed for each covariate in the subgroup analysis, and the aHR of BC in the medication use group was calculated. After this adjustment, there was still no difference in BC risk between the two groups. Patients with SCI who need voiding function medication may not be noticed in the early stage of injury, which may lead to immortal time bias. The 2-year landmark analysis was used to avoid

immortal time bias. Additionally, because patients who were followed-up for less than 2 years and those who had BC that developed within 2 years after the index date were excluded in the 2-year landmark analysis, and thus reverse causality was also avoided.

CONCLUSION

Our study demonstrated that voiding function medications (i.e., bethanechol, oxybutynin, and tolterodine) did not increase the risk of BC in patients with SCI in the different cDDD or subgroup analyses. The safety of these voiding function medications in SCI patients was confirmed, which can reduce the concern regarding their long-term use. In additions, several independent factors were found to increase the risk of BC in SCI patients administered voiding function medication. These included age between 45–64 years, age older than 65 years, male sex, higher economic levels, renal stone history, and chronic urinary tract infection. We should pay close attention to SCI patients with these identified risk factors.

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DISCLOSURE OF INTEREST

The authors report no conflicts of interest.

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探究影響膀胱功能的藥物與脊髓損傷病患罹患膀胱腫瘤的風險

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膀胱癌是脊髓損傷患者的慢性併發症。過往文獻甚少探討治療膀胱功能異常的排尿功能藥物對脊髓損傷患者罹患膀胱癌的風險。在本篇回溯性全國性世代研究中，以健保資料庫中已登錄罹患脊髓損傷患者爲納入條件，採用標誌性分析(landmark analysis)探討使用排尿功能藥物及合併其他共病時脊髓損傷患者發生膀胱癌的風險。患者分爲藥物使用組和非藥物使用組，並以 Cox 回歸模型(Cox regression analysis)和競爭風險回歸(competing risk regression)分析膀胱癌的風險。

本研究共計 22,974 名患者進入標誌性分析，研究發現藥物使用組和非藥物使用組之間在膀胱癌風險沒有統計學上的顯著差異。在藥物使用組的亞組分析中，發現以下幾個獨立因子增加罹患膀胱癌的風險，包括年齡大於 45 歲、男性、較高的經濟水平、腎結石病史和慢性尿道感染。本研究結論是排尿功能藥物並不會增加脊髓損傷患者的膀胱癌風險，醫師仍應注意患者是否具有前述膀胱癌的危險因子。（台灣復健醫誌 2021；49(1)：91 - 104）

關鍵詞：膀胱癌(bladder cancer)，藥物(medication)，危險因子(risk factor)，脊髓損傷(spinal cord injury)

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