Chronic Obstructive Pulmonary Disease Mortality in Bladder Cancer Patients: A SEER-Based Competing Risk Analysis

Shunde Wang[1], Chengguo Ge[2]*

Purpose: This study was designed to evaluate risk of mortality from chronic obstructive pulmonary disease (COPD) in patients with bladder cancer (BC).

Methods and Materials: Data on patients diagnosed with BC by pathology between 2000 and 2016 were collected from the Surveillance, Epidemiology, and End Results (SEER) database. Based on reference data from the general population, the standardized mortality rate (SMR) is calculated. Nelson-Aalen cumulative hazard curves were used for assessment of the risk of COPD mortality in BC patients. Multivariable competing risk models were conducted. The proportional hazards assumption was tested using Schoenfeld residuals, which were scaled and plotted over time for each risk factor.

Results: A total of 237,563 BC patients were identified for further analysis from the SEER database, 5,198 of these patients experienced COPD mortality; the overall SMR for COPD mortality in BC patients was 1.58 (95% CI: 1.54-1.63). Age, race, year of diagnosis, histologic type, summary stage, surgery, marital status, college education level, and median household income independently predicted COPD mortality in BC patients.

Conclusion: In comparison to the general population, the risk of COPD mortality is significantly higher in patients with BC. Pre-identification of high-risk groups and respiratory care provisions are important measures to effectively improve survival in this group of patients.

Keywords: bladder cancer; COPD; mortality; SEER; competing risk regression

INTRODUCTION

It is estimated that there are more than 500,000 newly diagnosed cases of bladder cancer (BC) worldwide each year, with approximately 40% of these patients died. However, the US alone accounts for 16% of all new cases worldwide each year(1-3).

Chronic obstructive pulmonary disease (COPD) and lung cancer are almost universally associated with smoking. Tobacco burning can produce a variety of carcinogens, which have been linked to at least 17 types of human cancer, including lung, throat, and bladder cancer(4). Because COPD and cancer share common risk factors(5), they can occur in the same patient at the same time, leading to challenges for clinicians. Furthermore, this trend is further exacerbated by an aging population. In 1990, COPD was identified as the sixth leading cause of death worldwide, and the prevalence and death rate will continue increasing over the coming decades(6,7). Smoking and being exposed to air pollution both contribute to COPD(8-10). Impaired lung function can lead to a reduction in the effective cleaning mechanisms of the lungs, increasing the exposure of carcinogens in the lungs(11,12). Presence of chronic obstructive pulmonary disease (COPD) is related to cancer stage at diagnosis and can interfere with aggressive cancer treatment, leading to reduced effective lifespan in cancer patients(13,14). A detailed literature search revealed no reports of COPD mortality in patients with BC. Therefore, our discoveries may help to establish a more targeted follow-up strategy for BC patients as well as more effective COPD mortality prevention measures.

MATERIALS AND METHODS

Data Source and Patient Selection

Information related to patients with BC diagnosed from 2000 to 2016 was downloaded from the SEER database using SEER*Stat software (version 8.3.9.2, Database: Incidence - SEER 18 Regs excluding AK Research Data, Nov 2018 Sub (2000 - 2016) for standardized mortality ratios (SMRs)).

Patients diagnosed with BC with positive pathology from 2000 to 2016 were included. Exclusions included cases identified only through autopsies or death certificates, and cases with incomplete data on age, gender, race, and other factors. COPD mortality is defined as death of a patient with BC due to the onset or acute exacerbation of COPD during the period of cancer, and a two-month latency is allowed. Of all included patients, cases that experienced COPD mortality will be included in further analysis of this study. COPD mortality was the primary endpoint of interest, while competing event being death from BC, other cancers, and other non-cancer diseases.

[1]Department of Urology, The ChenJiaqiao Hospital of ShaPingba District of Chongqing city, Chongqing, China, 401331.
E mail: rainbow951222@outlook.com.
[2]Department of Urology, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China, 400010.
Shunde Wang. . ORCID: 0000-0001-5973-8390.
*Correspondence: No.76, Linjiang road, Yuzhong District, Chongqing, 400010, PR China.E mail: gcg2022@hospital.cqmu.edu.cn.
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Table 1. Baseline features and standardized mortality ratios of COPD mortality in patients with bladder cancer

	Observed Deaths	Expected Deaths	SMR [95% CI]	AER Per 10,000	Persons	Person Years at Risk
Overall	5198	3285.27	1.58# [1.54–1.63]	17.73	237563	1079006.59
Age, year						
0–50	27	13.33	2.03# [1.34–2.95]	1.48	13009	92394.95
51–60	229	125.69	1.82# [1.59–2.07]	5.26	32856	196551.81
61–70	1026	578.83	1.77# [1.67–1.88]	14.49	61201	308691.31
71–80	2265	1412.68	1.60# [1.54–1.67]	26.41	75277	322772.51
81+	1651	1154.75	1.43# [1.36–1.50]	31.29	55220	158596.01
Race						
White	4943	3130.23	1.58# [1.54–1.62]	18.41	214764	984523.07
Black	138	88.56	1.56# [1.31–1.84]	9.74	13045	50763.83
AIAN	9	2.30	3.91# [1.79–7.43]	27.68	619	2420.49
API	108	64.19	1.68# [1.38–2.03]	10.61	9135	41299.21
Sex						
Male	3868	2594.12	1.49# [1.44–1.54]	15.71	179880	810942.96
Female	1330	691.16	1.92# [1.82–2.03]	23.83	57683	268063.63
Year of diagnosis						
2000–2003	1862	1173.34	1.59# [1.52–1.66]	18.34	53447	375401.43
2004–2007	1612	1018.38	1.58# [1.51–1.66]	17.92	56320	331202.90
2008–2011	1162	727.45	1.60# [1.51–1.69]	17.75	57139	244822.26
2012–2016	562	366.10	1.54# [1.41–1.67]	15.36	70657	127580.00
Histologic Type						
Tcc	5021	3199.89	1.57# [1.53–1.61]	17.38	226823	1047766.11
Scc	73	34.77	2.10# [1.65–2.64]	31.79	3815	12026.36
Nec	20	7.79	2.57# [1.57–3.97]	46.93	1555	2602.70
Ac	23	14.69	1.57# [0.99–2.35]	11.65	2308	7134.40
Oet	57	26.79	2.13# [1.61–2.76]	36.66	2731	8240.26
Summary stage						
In situ	2949	2024.15	1.46# [1.40–1.51]	13.70	125403	675257.36
Localized	2016	1135.57	1.78# [1.70–1.85]	24.82	86178	354786.32
Regional	179	107.67	1.66# [1.43–1.92]	17.31	17170	41207.66
Distant	54	17.88	3.02# [2.27–3.94]	46.58	8812	7755.25
Surgery						
No	229	134.57	1.70# [1.49–1.94]	21.66	11915	43585.52
TURBT	4710	2961.66	1.59# [1.55–1.64]	18.30	201251	955166.63
PC	55	38.44	1.43# [1.08–1.86]	12.31	3340	13451.45
RC	204	150.59	1.35# [1.18–1.55]	7.99	21057	66803.00
Marital status						
Married	2878	2238.30	1.29# [1.24–1.33]	8.59	153408	744788.58
Separated	38	14.39	2.64# [1.87–3.63]	35.48	1589	6654.38
Divorced	451	178.12	2.53# [2.30–2.78]	33.00	19239	82686.26
Widowed	1350	632.56	2.13# [2.02–2.25]	54.28	37708	132164.93
Unmarried	481	221.91	2.17# [1.98–2.37]	22.99	25619	112712.43
Education level						
College level ≤50%	4912	3026.54	1.62# [1.58–1.67]	19.01	219153	991670.08
College level >50%	286	258.65	1.11# [0.98–1.24]	3.13	18403	87303.01
Median household income						
≤$50,000 USD	1144	561.8	2.04# [1.92–2.16]	30.18	44102	192881.08
$50,000–100,000 USD	3859	2560.49	1.51# [1.46–1.56]	15.59	182473	832950.98
>$100,000 USD	195	162.91	1.20# [1.03–1.38]	6.04	10981	53141.02

Abbreviation: COPD: Chronic obstructive pulmonary disease; SMR: standardized mortality ratio; CI: confidence interval; AER: absolute excess risk; AIAN: American Indian/Alaska Native; API: Asian or Pacific Islander; Tcc: transitional cell carcinoma; Scc: squamous cell carcinoma; Nec: neuroendocrine carcinoma; Ac: adenocarcinoma; Oet: other epithelial tumors; TURBT: transurethral resection of bladder tumor; PC: partial cystectomy; RC: radical cystectomy.
# $P < .05$

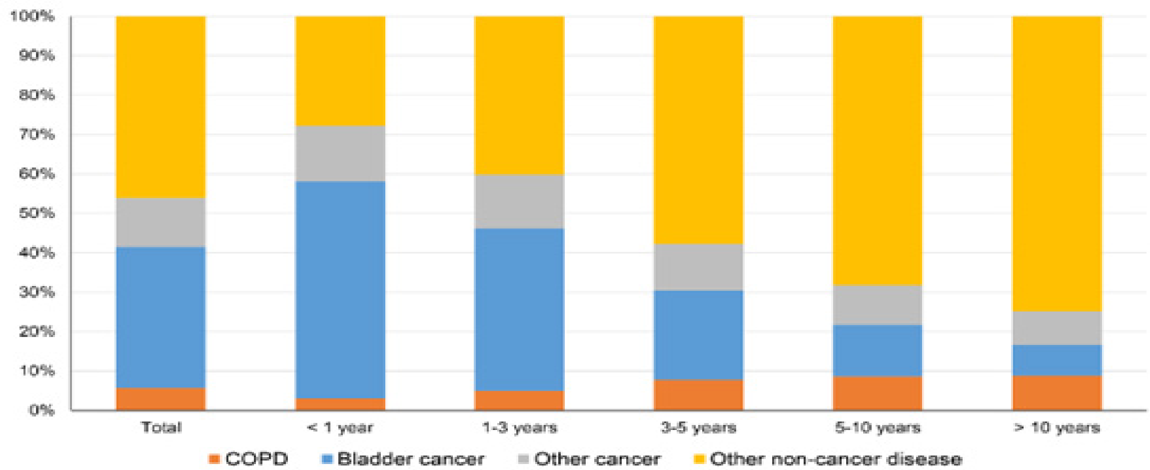

Figure 1. Causes of death in each latency period following bladder cancer diagnosis.

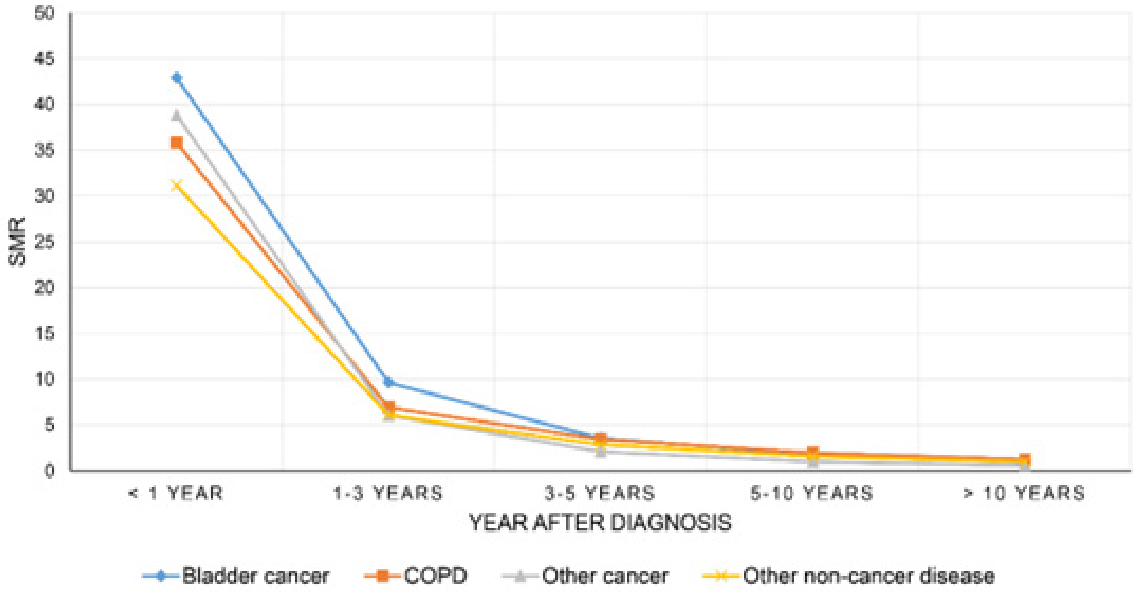

Figure 2. Overall SMR of all causes of death in bladder cancer patients decreased with increasing follow-up time.

Study Variables

The definitions and information regarding variables are mentioned in **Table 1**.

Statistical Analysis

SMR is the ratio of observed deaths to expected deaths of COPD mortality[15]. We calculate 95% confidence intervals (95% CIs) for all SMRs using the exact method. Absolute excess risks (AERs) were also calculated, which proxy for the excess number of deaths per 10,000 person-years in different subgroups. To investigate the risk of COPD mortality in different subgroups of BC patients, the Nelson-Aalen cumulative hazard curve was used. Multivariable competing risk analyses using Fine-Gray model were conducted to identify risk factors related to COPD mortality. The proportional hazards assumption (PHA) was tested using Schoenfeld residuals, which were scaled and plotted over time for each factor[16-18].

All analyses were performed with SEER*Stat software (version 8.3.9.2), Stata/MP version 16.0 (StataCorp LP, College Station, TX, US), R 4.2.3 (R foundation for Statistical Computing, Vienna, Austria), and Microsoft Excel 2019 (Microsoft, Redmond, WA). A two-side p-value < 0.05 being considered statistically significant.

RESULTS

Patient Characteristics

A total of 237,563 BC patients were identified for fur-

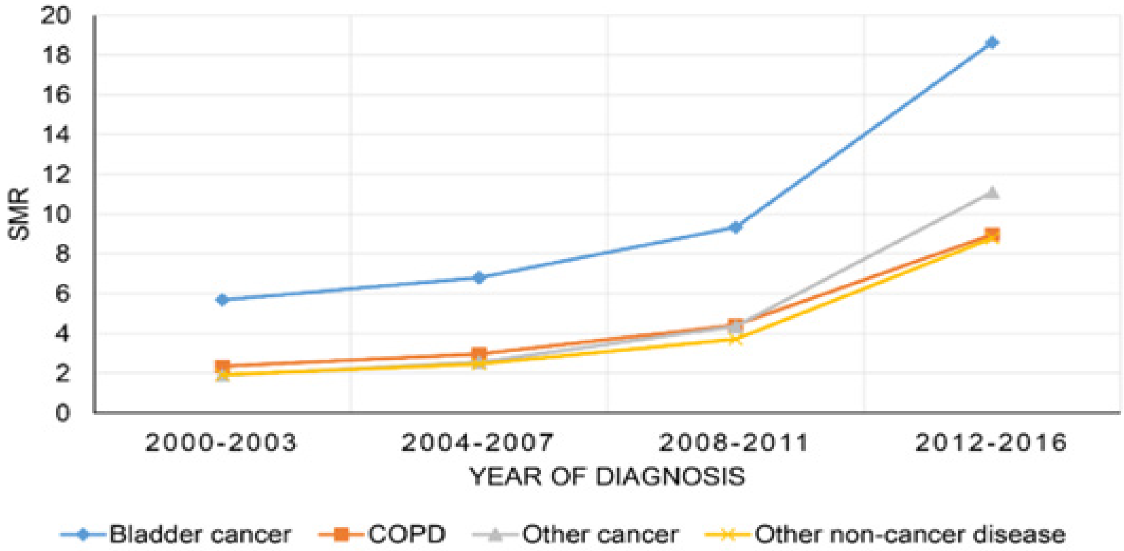

Figure 3. Overall SMR of all causes of death of bladder cancer patients elevated year by year.

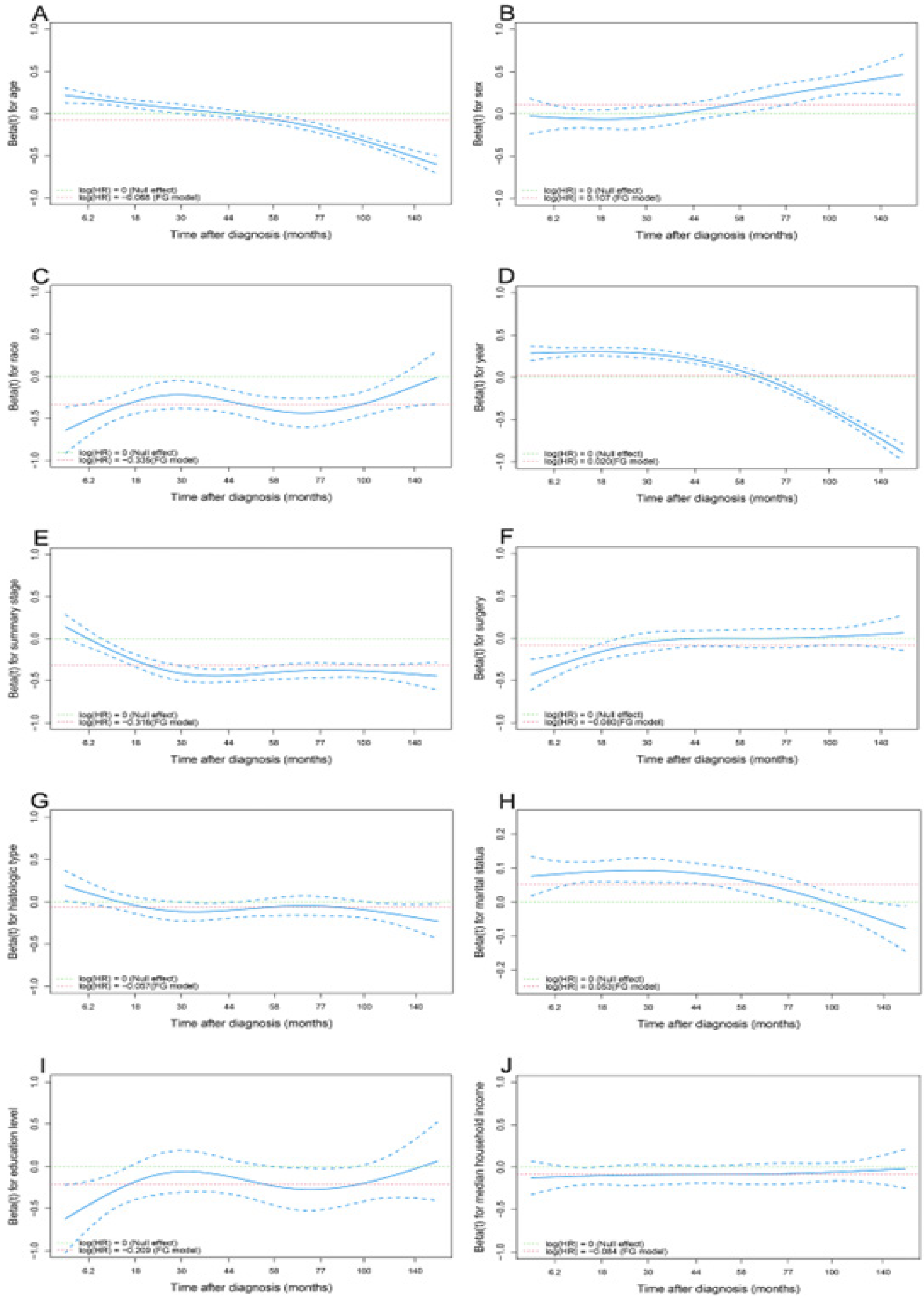

Figure 4. Scaled Schoenfeld residuals for different factors with 95% confidence intervals. Residuals were used to visualize the log cause-specific hazard rates for each factor over time: age **(A)**, sex **(B)**, race **(C)**, year of diagnosis **(D)**, summary stage **(E)**, surgery **(F)**, histologic type **(G)**, marital status **(H)**, education level **(I)**, and median household income **(J)**. Green lines represent the null effect (no effect on survival outcomes when Log (HR) is equal to 0), and red lines represent the average log cause-specific hazard rate as estimated using the Fine-Gray model. The FG model in the figure represents the Fine-Gray model, and HR represents the subdistribution hazard rate.

ther analysis from the SEER database, and 5,198 patients experienced COPD mortality. The mean age was 75.98 ± 8.58 years, and the median follow-up time was 45 months. Most patients were over 71 years old (75.34%), white (83.52%), male (74.41%), married (55.37%), and had carcinoma in situ (56.73%). The histologic types of BC consisted of Tcc (96.59%), Scc (1.40%), Ac (0.38%), Nec (0.44%) and Oet (1.10%). A total of 4,710 (90.61%) patients underwent TURBT, 55 (1.06%) patients underwent PC, 204 (3.92%) patients underwent RC, and 229 (4.41%) patients did not undergo surgery. Most deaths were observed during the follow-up period of < 1 year (32.81%), followed by the follow-up period of1 to 3 years (28.07%).

A total of 30,057 BC patients died within 1 year after diagnosis, including 16,536 (55.02%) deaths from BC, 920 (3.06%) deaths from COPD, 4,263 (14.18%) deaths from other cancers, and 8,338 (27.74%) deaths from other non-cancer diseases. The proportion of cancer-related deaths decreased gradually at < 1 year, 1 - 3 years, 3 - 5 years, 5 - 10 years, and > 10 years (including BC and other cancers), while the proportion of noncancer disease-related deaths increased gradually (including COPD and other non-cancer diseases) (**Figure 1**).

SMR and AER

The overall SMR for COPD mortality was 1.58 (95% CI: 1.54-1.63), and the AER was 17.73/10,000 person-years in BC patients. Baseline characteristics and SMRs for COPD mortality in BC patients are shown in **Table 1**.

Figure 2 shows that the SMR of all causes of death for BC patients decreased with the increase in the follow-up time. However, the SMR of COPD gradually overtakes other mortality factors at 3 - 5 years after diagnosis.

Figure 3 shows that the SMR of all causes of death for BC patients increased each year, with BC having the highest SMR of all.

Nelson-Aalen Cumulative Hazard Curve

Supplementary Figure 1 illustrates the risk of COPD mortality with increasing follow-up time for different factors, with the following subgroups being associated with a higher risk of COPD mortality: age between 61 and 80 years, white, carcinoma in situ and localized tumors, undergoing TURBT, Tcc and Nec pathological types, a college education level less than 50%, widowed and separated, and a median household income less than $50,000 USD.

Supplementary **Figure 2** demonstrates the results of a progressive increase in the risk of all mortality factors in BC patients at different ages with increasing follow-up time. The risk of BC-related death was highest in patients at all ages. In patients aged 51-80 years, the risk of COPD surpassed that of other noncancer diseases and ranked third (**Supplementary Figure 2B, C and D**), more significantly at the age of 61-70 years (**Supplementary Figure 2**C). However, in patients older than 81 years, the risk of COPD-related mortality was the lowest (**Supplementary Figure 2E**).

Predictors of Death from COPD

Multivariable competing risk regression analysis was performed to identify risk factors associated with COPD mortality in BC patients (**Table 2**). We identified that the following indicators were independently related to higher risks of COPD mortality: age between 71 and 80 years (95% CI: 2.89-6.16, HR: 4.22, $P < .001$), diagnosed between 2012 and 2016 (95% CI: 1.47-1.80, HR: 1.63, $P < .001$), and separated (95% CI: 1.11-2.09, HR: 1.52, $P = .010$). On the contrary, the following indicators were independently related to lower risks of COPD mortality: black (95% CI: 0.40-0.56, HR: 0.47, $P <.001$), Nec histological type (95% CI: 0.40-0.96, HR: 0.61, $P = .031$), regional summary stage (95% CI: 0.18-0.26, HR: 0.22, $P <.001$), undergoing RC (95% CI: 0.62-0.92, HR: 0.76, $P = .005$), college education level > 50% (95% CI: 0.65-0.86, HR: 0.75, $P < .001$), and median household income between $50,000 USD and $100,000 USD (95% CI: 0.80-0.92, HR: 0.86, $P < .001$). Supplementary **Figure 3** shows the CIF curves using Fine-Gray competing risk analyses. The PHA was tested, and the corresponding P-values and the P-value associated with a global test of nonproportionality are reported (**Table 3**). Scaled Schoenfeld residuals were plotted over time for each factor (**Figure 4**). The results of the global test suggested strong evidence of nonproportionality ($P < .001$).

DISCUSSION

In this large population-based study using the SEER database, we analyzed the long-term COPD mortality in patients with BC. Our findings showed that patients with BC diagnosed in recent years have a lower SMR than those diagnosed earlier. This may be related to the advancement of BC treatment strategies and the improved quality of comprehensive cancer management[19,20]. At the same time, the treatment of COPD and the ability to cope with COPD events have also improved, which has been effective in reducing the incidence of death from COPD. Nevertheless, the risk of COPD mortality was significantly higher (95% CI: 1.47-1.80, HR: 1.63, $P < .001$) among BC patients diagnosed in 2012-2016, possibly because the data in the SEER database is mainly from the U.S. population and published studies have shown that smoking to be the major risk factor for COPD in the US[21]), regardless of sex. Additionally, several studies have shown that smoking has a long-term delayed effect on COPD mortality[22,23], and the increase in smoking rate in the 1960s (up to 42.4%) is largely responsible for the increase in COPD mortality in the United States.

Published studies have illustrated that the risk of COPD mortality varies considerably between patients with cancer at different primary sites(8, 14), in this study, our focus was only on COPD mortality in patients with BC. By studying 5,198 patients, we found that the risk of COPD mortality was approximately 58% higher in BC patients compared with the general US population (95% CI: 1.54-1.63, SMR: 1.58, $P <.05$). Over the entire follow-up period, patients with BC had an increased risk of COPD mortality. Our study identified age, race, year of diagnosis, histologic type, summary stage, surgery, marital status, college education level, and median household income as independent predictors for the development of COPD mortality in patients with BC.

Multivariable competing risk regression analysis was used to identify COPD mortality risk factors in BC patients. We observed that patients with BC aged 71-80 years had the highest COPD mortality (95% CI: 2.89-6.16, HR: 4.22, $P < .001$) and lower SMR (95% CI: 1.54-1.67, SMR: 1.60, $P < .05$), while patients aged less than 50 years had the highest SMR (95% CI: 1.34-2.95, SMR: 2.03, $P < .05$). One possible reason is that young-

Table 2. Multivariable competing risk analysis for predictors of COPD mortality in patients with bladder cancer1

Characteristics	Adjusted HR [95%CI]	*P*-value2
Age, year		
0–50	Ref.	
51–60	2.44 [1.64–3.62]	< 0.001
61–70	4.11 [2.81–6.01]	< 0.001
71–80	4.22 [2.89–6.16]	< 0.001
81+	3.17 [2.17–4.63]	< 0.001
Race		
White	Ref.	
Black	0.47 [0.40–0.56]	< 0.001
AIAN	0.68 [0.56–0.82]	< 0.001
API	0.75 [0.39–1.45]	0.390
Sex		
Male	Ref.	
Female	0.95 [0.89–1.02]	0.166
Year of diagnosis		
2000–2003	Ref.	
2004–2007	1.23 [1.16–1.32]	< 0.001
2008–2011	1.55 [1.43–1.67]	< 0.001
2012–2016	1.63 [1.47–1.80]	< 0.001
Histologic Type		
Tcc	Ref.	
Scc	0.82 [0.66–1.04]	0.100
Nec	0.61 [0.40–0.96]	0.031
Ac	0.70 [0.47–1.04]	0.078
Oet	1.03 [0.80–1.35]	0.803
Summary stage		
In situ	Ref.	
Localized	0.55 [0.52–0.59]	< 0.001
Regional	0.22 [0.18–0.26]	< 0.001
Distant	0.09 [0.07–0.11]	< 0.001
Surgery		
No	Ref.	
TURBT	1.12 [0.98–1.27]	0.102
PC	1.07 [0.80–1.44]	0.634
RC	0.76 [0.62–0.92]	0.005
Marital status		
Married	Ref.	
Separated	1.52 [1.11–2.09]	0.010
Divorced	1.34 [1.22–1.49]	< 0.001
Widowed	1.32 [1.23–1.42]	< 0.001
Unmarried	1.25 [1.14–1.38]	< 0.001
Education level		
College level ≤50%	Ref.	
College level >50%	0.75 [0.65–0.86]	< 0.001
Median household income		
≤$50,000 USD	Ref.	
$50,000–100,000 USD	0.86 [0.80–0.92]	< 0.001
>$100,000 USD	0.93 [0.78–1.11]	0.405

Abbreviation: COPD: Chronic obstructive pulmonary disease; HR: hazard ratio; CI: confidence interval; AIAN: American Indian/Alaska Native; API: Asian or Pacific Islander; Tcc: transitional cell carcinoma; Scc: squamous cell carcinoma; Nec: neuroendocrine carcinoma; Ac: adenocarcinoma; Oet: other epithelial tumors; TURBT: transurethral resection of bladder tumor; PC: partial cystectomy; RC: radical cystectomy.

1 The origin of the survival analysis was at the time of bladder cancer diagnosis, and the survival analysis was started after a 2-month latency period and ended when the patient developed COPD mortality.

2 A two–side P–value < .05 being considered statistically significant.

er BC patients are subjected to more psychological and physical stress, which in part contributes to the development of COPD mortality risk factors, such as smoking[24]. At the same time, their physical condition allows them to receive more aggressive cancer treatment, which gives them a longer life expectancy to experience COPD mortality. Male patients had a higher risk of COPD mortality than female patients, but there was no significant difference. Although COPD is primarily a male disease, COPD prevalence and mortality have increased more rapidly in women than in men over the past two decades(25, 26). Published studies have shown that male and female patients have different susceptibilities to COPD risk factors, which may be related to biological and hormonal mechanisms[27, 28]. Additionally, our study demonstrated that separated BC patients are at a higher risk of COPD mortality (95% CI: 1.11-2.09, HR: 1.52, P = .010), which may be associated with the fact that married patients are more likely to receive encouragement and support from their spouses, both emotionally and physically. Patients with a lower socioeconomic status have been reported to be at higher risk for non-cancer mortality, and our findings demonstrated that patients with a lower college education level and lower median household income had a higher risk of COPD mortality, in accordance with previous results.

In this study, the majority of patients underwent surgery (95.59%), including TURBT (90.61%), PC (1.06%) and RC (3.92%). Although only 229 (4.41%) patients in this study did not receive surgery, the SMR was the highest (95% CI: 1.49-1.94, SMR: 1.70, $P < .05$). Multivariable competing risk analysis showed that patients with BC who underwent RC had the lowest risk of experiencing COPD mortality (95% CI: 0.62-0.92, HR: 0.76, P = .005), which is probably explained by the fact that most patients who underwent RC surgery had an advanced tumor stage and did not have enough life-expectancy to experience a COPD mortality event (median survival time: 28 months for TURBT, 20 months for PC, 16 months for RC, and 11 months for no surgery). Although some studies have found a greater risk of dyspnea in BC patients receiving open RC[29], however, the studies did not mention whether the patients presented with a history of COPD, so we cannot determine whether the dyspnea in these patients was due to COPD. In addition, the physical status of BC patients with COPD often does not allow them to undergo radical surgical treatment. Our results showed that patients with BC who were not treated with surgery had the highest SMR and a higher risk of COPD mortality, although the median survival time was only 11 months. One possible reason is that the diagnosis of BC often causes a longer period of psychological and emotional distress, and psychological factors such as depression and anxiety may be associated with smoking behavior after a cancer diagnosis[24], and for most patients, smoking is a common way to seek solace[30,31]. Encouraging cancer patients to quit smoking is essential to improve treatment outcomes and cancer survival. However, patients are at increased risk of COPD mortality as up to 68% of patients continue to smoke after a cancer diagnosis[32,33].

There are still some shortcomings in our study. First, information related to COPD, such as the number of years of smoking and the number of cigarettes smoked, was not recorded in the SEER database. Second, there was no further analysis of the effects of chemotherapy, radiotherapy, and some other new therapeutic strategies. Meanwhile, some studies reported that the causes of death on death certificates might have been overestimated, which might have affected the accuracy of our study to some extent[34]. Lastly, a causal interpretation of our results is risky because the HR estimated from our analysis may change with the addition of different risk factors (such smoking, pneumonia, or lung cancer), and the HR has a built-in selection bias due to the inclusion of only those who died during the follow-up periods[35].

Table 3. Results of the Fine-Gray model and tests of the proportional hazard assumption

Factor	Coefficient	Standard Error	*P** > |z|	HR [95% CI]	*p**(PH)
Age	-0.068	0.014	< 0.001	0.934 [0.912-0.957]	< 0.001
Sex	0.107	0.033	< 0.001	1.113 [1.045-1.186]	< 0.001
Race	-0.335	0.043	< 0.001	0.715 [0.653-0.783]	0.251
Year	0.020	0.014	0.143	1.020 [0.993-1.047]	< 0.001
Histologic type	-0.057	0.029	0.049	0.945 [0.893-0.999]	0.004
Summary stage	-0.316	0.023	< 0.001	0.729 [0.699-0.760]	< 0.001
Surgery	-0.080	0.029	0.003	0.923 [0.877-0.972]	< 0.001
Marital status	0.053	0.009	< 0.001	1.054 [1.036-1.072]	< 0.001
Education level	-0.209	0.064	< 0.001	0.812 [0.717-0.916]	0.155
Median household income	-0.084	0.032	0.007	0.919 [0.865-0.977]	0.573

Abbreviation: HR: Hazard ratio; PH: Proportional hazard.
*A two-side *p*-value < .050 being considered statistically significant.
Proportional hazard assumption test: GLOBAL < .001.

CONCLUSIONS

In summary, patients with BC have a significantly increased risk of developing COPD mortality than the general population. Whites aged 61-80 years, with carcinoma in situ, separated from their spouse, and with lower levels of education and income were at higher risk of experiencing COPD mortality. These findings should be considered by physicians. Physicians can counsel BC patients regarding survivorship with death causes screening and focus on the prevention of COPD mortality.

AVAILABILITY OF DATA AND MATERIALS

Publicly available datasets were analyzed in this study. These data can be found in the SEER database (https://seer.cancer.gov/).

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest that might be relevant to the contents of this manuscript.

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APPENDIX

https://journals.sbmu.ac.ir/urolj/index.php/uj/libraryFiles/downloadPublic/60

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