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

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Abbreviations

BC: Bladder cancer; COPD: Chronic obstructive pulmonary disease; SMR:
Abstract

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.

Conclusions: 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,
1. 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\textsuperscript{(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 \textsuperscript{(4)}. Because COPD and cancer share common risk factors\textsuperscript{(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\textsuperscript{(6, 7)}. Smoking and being exposed to air pollution both contribute to COPD\textsuperscript{(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\textsuperscript{(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\textsuperscript{(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.

2. Materials and Methods
2.1. 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.

2.2. Study Variables

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

2.3. 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.

3. Results

3.1. Patient Characteristics

A total of 237,563 BC patients were identified for further 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 of 1 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).

3.2. 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.

3.3. 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 2C). However, in patients older than 81 years, the risk of COPD-related mortality was the lowest (Supplementary Figure 2E).

3.4. 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 ($P < .001$).

4. 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 younger 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. 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.

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. 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.

5. 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.
Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

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/).

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

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References:


[33] Bell RJ, Lijovic M, Fradkin P, Schwarz M, Davis SR. Changes in patterns of use


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

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

**Supplementary Figure 1** Independent Nelson–Aalen cumulative hazard curves for various factors of CVM in bladder cancer patients: age (A), sex (B), race (C), summary stage (D), surgery (E), histologic type (F), education level (G), marital status (H), and...
median household income (I).

Supplementary Figure 2 Nelson–Aalen cumulative hazard curves for all causes of death in primary bladder cancer patients in different age groups: 0 - 50 years (A), 51 - 60 years (B), 61 - 70 years (C), 71 - 80 years (D), and 81 + years (E).
**Supplementary Figure 3** Cumulative incidence curves for various factors of CVM in bladder cancer patients after competing risk regression analysis: age (A), sex (B), year of diagnosis (C), summary stage (D), surgery (E), histologic type (F), education level (G), marital status (H), and median household income (I).