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Orginal article

Venous thromboembolism and effect of comorbidity in bladder cancer: A danish nationwide cohort study of 13,809 patients diagnosed between 1995 and 2011

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Abstract

Objectives: Bladder cancer (BC) is associated with venous thromboembolism (VTE), but data on the effect of comorbidities are scarce.

Materials and methods: Population-based cohort study with 13,809 patients with BC diagnosed in Denmark (1995–2011) and a general population comparison cohort matched on age, sex, and comorbidities ($n = 132{,}421$). Risk of VTE, pulmonary embolism and deep venous thrombosis was computed for the first month, 3 months, 1 year, and 5 years following cancer diagnosis and stratified by Charlson Comorbidity Index (CCI) scores, cystectomy, and metastases.

Results: VTE risk was higher among the patients with BC than in the comparison cohort during five years of follow-up (risk difference = 20 per 1,000 persons [95% CI: 16–23]). Excess risk was relatively stable with increasing comorbidity score. In the first year, the risk difference was 17 per 1,000 persons (95% CI: 14–21) and 16 (95% CI: 4.8–27) for CCI score = 0 and CCI score = 4, respectively, and similar results were observed by stratification on pulmonary embolism and deep venous thrombosis. For patients with BC undergoing cystectomy, VTE risk was 70-fold higher than in the general population cohort within 3 months after diagnosis.

Conclusions: BC is associated with increased risk of VTE, compared with the general Danish population. Risks are particularly high for VTE after cystectomy. Risk did not increase with higher comorbidity burden, as the relative risk of VTE was greatest among patients without comorbidity. Clinical attention to VTE risk, particularly cystectomy-related VTE, in patients with BC is appropriate irrespective of comorbidities.

Keywords: Carcinoma; Urinary bladder neoplasms; Venous thromboembolism; Epidemiology; Comorbidity

1. Introduction

Venous thromboembolism (VTE) has been associated with cancer since the 19th century [1–3], likely due to immobilization, cancer induced hypercoagulability, cancer treatment, and vascular injury from surgical procedures [4,5]. Among patients with cancer, those with VTE have considerably poorer survival and VTE is a common cause of death [6–9]. Recently, increased attention has been focused on other risk factors for VTE in cancer patients, such as comorbidities, which may help to identify patients at highest VTE risk [10]. In the United States, the number of new bladder cancer (BC) cases increased from stable rates of approximately 50,000 per year in the 1990s to more than 70,000 per year since 2010 [11,12], whereas incidence rates have declined and are now relatively stable in many

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European countries [13,14]. A recent meta-analysis suggests that postsurgery VTE rates are higher in the United States than in Europe, but the risk varies considerable among subgroups of patients [15]. To our knowledge, no population-based study has evaluated in detail the effect of comorbidity on VTE incidence among patients with BC. This information is needed to inform our understanding of the association between BC and VTE and to identify patients at highest risk. Although targeted thromboprophylaxis may be effective for patients with high-risk BC [16,17], it is still necessary to identify whether those patients with comorbidity have a higher risk. Our objective was to evaluate the impact of comorbidity on VTE incidence among patients with BC in a population-based cohort. We hypothesized that VTE risk would raise with increasing comorbidity burden. The conduct of this study was approved by the Danish Data Protection Agency (record number: 1-16-02-1-08).

2. Patients and methods

This study was conducted using national medical and administrative databases, which cover the entire Danish population of 5.6 million inhabitants. [18] The Danish databases record individual-level data on health care uses and vital status with daily updates, which can be linked accurately with a unique personal identification number that has been assigned to all Danish residents since 1968 at birth or upon imigration [18]. We used this number to link data from the Danish Cancer registry, the Danish National Patient Registry (DNPR), and the Danish Civil Registration System (CRS) [19–21].

2.1. Bladder cancer cohort

We identified incident cases of BC recorded in the Danish Cancer registry, which hold information on all incident cancers diagnosed in Denmark since 1943 [19]. We included patients diagnosed between January 1, 1995 and December 31, 2011. This period was chosen to ensure homogeneity of VTE diagnostic procedures and BC treatment and inclusion of all VTEs diagnosed in hospitals [20]. As VTE can be a marker of occult cancer, we excluded all patients with BC ($n = 382$) with a VTE diagnosis before or concurrent to the BC index date.

2.2. Matched general population comparison cohort

We used the CRS to select up to 10 individuals from the general population who were alive and free of a BC diagnosis and matched them to each patient with BC on the date of BC diagnosis for the corresponding patient with BC, year of birth (in 5-y intervals), sex, and presence of the specific individual comorbidities included in the Charlson Comorbidity Index (CCI) [22]. We excluded comparison individuals diagnosed with VTE prior to the index date. We also excluded patients with BC who could not be matched to any individuals in the general population comparison cohort ($n = 162$). Members of the comparison cohort diagnosed with BC during follow-up were switched to the BC cohort on the diagnosis date and corresponding matched individuals were selected from the general population and added to the comparison cohort. The index date was defined as the date of BC diagnosis for the BC cohort and as the date of calendar time matching for the general population comparison cohort.

3. Comorbidity, venous thromboembolism, and follow-up

The DNPR has tracked nonpsychiatric inpatient hospitalizations since 1977 using the 8th revision of the *International Classification of Diseases*, with diagnoses coded according to the *International Classification of Diseases* 10 from 1994 [20]. Since 1995, outpatient hospital clinic visits were included in the DNPR, including nearly all specialist care in the country [20]. The BC and general population cohorts were linked to records in the DNPR and in the CRS, which tracks vital status, nationwide migration, and emigration [20,21]. We used both inpatient and outpatient diagnoses in the DNPR to ascertain presence of comorbidities using the Charlson Comorbidity Index (CCI) [22]. VTE was defined as the first inpatient or outpatient diagnosis of pulmonary embolism (PE) or deep venous thrombosis (DVT) after the index date. Patients recorded with both a PE and DVT were classified as PE patients. Postoperative VTE was defined as VTE occurring in patients who underwent any surgical procedure (including nonurologic procedures) within 3 months preceding VTE.

The cohorts were followed from the index date until occurrence of an inpatient or outpatient VTE diagnosis, death, emigration, December 31, 2012, or 5 years of follow-up, whichever came first. The general population comparison cohort was also followed until occurrence of a BC cancer diagnosis. (Supplemental Table 1 for diagnostic codes).

4. Statistical analyses

We characterized the cohorts with respect to demographics, and stage for the BC cohort. Risk of VTE was calculated with survival curves, using death as a competing risk [23]. Among patients with BC, we computed VTE risk overall and by comorbidity level, and time since cancer diagnosis. To compare VTE risk in patients with BC with that in the comparison cohort, we calculated risk differences with corresponding 95% confidence intervals (CIs) overall and for stratified analyses. We computed hazard ratios as a