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Effect of comorbidity on risk of venous thromboembolism in patients with renal cell carcinoma¹

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Abstract

Purpose—Venous thromboembolism (VTE) is associated with renal cell carcinoma (RCC), but data on the effect of comorbidities are limited. Therefore, our purpose was to determine the effect of comorbidity on VTE risk among patients with RCC.

Materials and methods—A population-based cohort of all patients with RCC ($n = 8,633$) diagnosed in Denmark between 1995 and 2010 and a comparison cohort selected from the general population and matched on age, sex, and comorbidities ($n = 83,055$) were identified. Risk of subsequent VTE was estimated with 95% CI for the first 3 months, 1 year, and 5 years following cancer diagnosis. We stratified by Charlson comorbidity index (CCI) scores to estimate excess risk in patients with RCC vs. the comparison cohort within comorbidity strata. We also performed subanalyses for postoperative VTE and metastases.

Results—VTE risk was higher in the RCC compared with comparison cohort, particularly during the initial year following diagnosis (risk difference = 9.9 per 1,000 persons [95% CI: 7.7–12.2]). After stratifying by CCI, excess risk declined with increasing comorbidities. The risk difference was 12.3 per 1,000 persons (95% CI: 9.1–15.5) for CCI = 0 and 0.5 (95% CI: 6.0–7.0) for CCI = 4. Excess risk also declined with increasing comorbidities among patients with postoperative VTE and among those with metastases.

Conclusions—RCC is associated with increased risk of VTE when compared with a matched general population cohort. Risk did not appear to increase with added comorbidity burden.

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Clinical attention to VTE risk in patients with RCC is appropriate regardless of the presence or absence of comorbidities.

Keywords

Carcinoma; Renal cell; Venous thromboembolism; Incidence; Epidemiology; Comorbidity

1. Introduction

Venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), has been widely linked to malignancy [1–3]. A number of factors have been implicated, including tumor-induced hypercoagulability, vascular injury from surgical treatment, chemotherapy, radiation, and venous stasis due to immobilization [4,5]. Recently, increased attention has been focused on other factors for VTE such as comorbidities, which may help to identify patients at highest risk for VTE [6]. In most earlier studies, risk has been examined in cohorts of patients with cancers at different sites [7,8]. Incidence of VTE and associated risk factors among patients with specific cancers, such as renal cell carcinoma (RCC), has been largely unstudied.

RCC is a common malignancy with increasing incidence [9]. Among newly diagnosed patients with RCC who had localized disease, occurrence of VTE has been linked to increased risk of death within 1 year of cancer diagnosis [10]. To our knowledge, no studies have addressed VTE risk specifically in patients with RCC (outside of those focusing on postoperative VTE). In addition, no population-based study has evaluated in detail the effect of comorbidity and disease stage on incidence of VTE among patients with RCC. Estimating the incidence of VTE among patients with RCC is important for better understanding the association between this malignancy and VTE and identifying patients at highest risk. Targeted thromboprophylaxis may be useful for patients with high-risk RCC [11], but defining this risk category is necessary before recommending changes in clinical practice.

We assembled a large cohort of patients with RCC and a matched comparison general population cohort using Danish registries to determine the incidence and time course of VTE development. We hypothesized that VTE absolute risk would be higher among patients with RCC when compared with the general population, and excess risk is highest among those with recent surgery and more comorbidity. We therefore stratified our analyses using the Charlson comorbidity index (CCI) score, disease stage, and history of surgery before VTE. Ethical principles were followed according to the Declaration of Helsinki.

2. Materials and methods

2.1. Study population

We conducted a nationwide, population-based cohort study among all patients with RCC recorded in the Danish Cancer Registry (DCR) between 1995 and 2010. In Denmark, all medical and administrative registry records for individuals can be linked through a unique personal registration number. We used this number to link data from the DCR, Danish National Registry of Patients (DNRP), and the Danish Civil Registration System (CRS) [12–14].

2.2. Cancer cohort

We first identified individuals from the DCR with an incident RCC diagnosis (10th revision of the *International Classification of Diseases* [ICD-10] code: C64) recorded between January 1, 1995 and December 31, 2010. This period was chosen to ensure homogeneity of VTE diagnostic procedures and RCC treatment [15]. We used the date of cancer diagnosis specified in the DCR as the index date. Because VTE has been associated with undiagnosed cancer, we excluded all patients with RCC ($n = 232$) with a VTE diagnosis before or concurrent with the RCC index date.

2.3. Matched comparison cohort

For each patient with RCC, we used the CRS to select 10 individuals from the general population who were alive and free of RCC on the patient's index date, matched on year of birth (in 5-y intervals), sex, and presence (but not exact date of diagnosis) of comorbidities included in the CCI [16]. As in the cancer cohort, we excluded persons with VTE diagnosed before the index date. We also excluded patients with RCC who could not be matched to persons in the general population comparison cohort ($n = 131$). Members of the comparison cohort who developed RCC were moved to the RCC cohort on the date of diagnosis and corresponding matched comparison individuals were selected.

2.4. VTE data

The DNRP has tracked nonpsychiatric inpatient hospitalizations since 1977, with diagnoses coded according to ICD-10 since 1993. Since 1994, outpatient hospital visits, including essentially all specialist care in the country, have also been coded and included in the DNRP. The RCC and general population cohorts were linked to records in the DNRP and in the CRS, which tracks vital status and nationwide migration.

VTE was defined as the first inpatient diagnosis of PE (an embolic thrombus in the pulmonary artery; ICD-8: 450.99; ICD-10: I26) or DVT (ICD-8: 451.00; ICD-10: I80.1–3), excluding superficial thrombophlebitis, at any time after the index date. Only those with an inpatient diagnosis were included, as an analysis of VTE diagnosed in outpatient clinics or the emergency room within 5 years of the index date yielded only an additional 98 of 91,688 total cases with equal proportions noted for RCC and the comparison cohorts (0.12% and 0.11%, respectively). Patients coded as having both PE and DVT were classified as patients with PE. Postoperative VTE, in this study, was defined as any VTE occurring in patients who underwent any surgical procedure within 3 months (90 d) preceding the VTE event.

Patients were followed up from their RCC diagnosis/index date until occurrence of an inpatient VTE diagnosis, death, emigration, or December 31, 2011. Members of the matched comparison cohort were followed up from the index date until occurrence of a RCC cancer diagnosis or for 5 years, whichever came first. Patients with RCC were also followed up for 5 years after diagnosis.

2.5. Comorbidity data

We used both inpatient and outpatient diagnoses in the DNRP to ascertain presence of potential confounding comorbidities. The following conditions were tracked: myocardial

infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes types 1 and 2, hemiplegia, moderate to severe renal disease, diabetes with end-organ damage, any tumor (except RCC), leukemia, lymphoma, moderate to severe liver disease, metastatic solid tumors, and AIDS. Using these comorbidities, CCI scores were computed and divided into 4 categories (0: none; 1: little; 2–3: moderate; and 4+: high) (Refer to Table 1 for ICD-8, ICD-10 codes, and CCI calculation) [16].

2.6. Statistical analyses

We computed the distribution of persons in the RCC and comparison cohorts in categories of demographics, and for those in the RCC cohort, the distribution of cancer characteristics. Risk of hospitalization for VTE in the cancer and comparison cohorts was calculated using the Kaplan-Meier statistics, with survival curves compared using log-rank tests [17]. The associated 95% CI were calculated using the method described by Marubini and Valsecchi [18]. Among patients with RCC, we estimated VTE risk overall and by comorbidity level, disease stage, and time since cancer diagnosis. To compare VTE risk in patients with RCC with that in the comparison cohort, risk differences with corresponding 95% CI were calculated overall and for stratified analyses. Multivariable Cox proportional hazard regression analysis was used to compute hazard ratios by taking into account the confounding effects of age (as a continuous variable), sex (males vs. females), year of RCC diagnosis (1995–1999 vs. 2005–2010 and 2000–2004 vs. 2005–2010), and CCI score (1 vs. 0, 2–3 vs. 0, 4+ vs. 0).

A subanalysis included the comparison stratified by cancer stage (metastatic, localized, and nonmetastatic). To examine the role of recent surgery in VTE incidence, postoperative VTE risks were calculated. Risk of VTE was calculated at 3 months, 1 year, and 5 years, stratified by VTE type for RCC and the comparison cohort, treating death as a competing risk [17].

3. Results

3.1. Descriptive data

We identified 8,633 patients with the first RCC diagnosis between 1995 and 2010, after excluding 232 patients with previous or concurrent VTE and 131 patients with no corresponding match available, and followed them up for 19,832 person-years. We followed up 83,055 matched members of the general population for 331,494 person-years. Overall, 62% of patients with RCC were men, and no important differences between the RCC and comparison cohorts were noted among sex, age, and comorbidity (Table 2).

3.2. Overall VTE

Overall, risk of VTE among patients with RCC increased within the first year after diagnosis. Subsequently, the risk increased at a rate similar to that of the matched comparison cohort (Fig.). RCC was associated with an increased risk of any VTE diagnosis (DVT or PE), as compared with risk in the general population cohort (Table 3). The hazard ratio for any VTE in the first year of follow-up was 8.3 (95% CI: 6.4–10.6). The risk difference between patients with RCC and the comparison cohort was highest for any VTE

in the first year of follow-up: 9.9 per 1,000 persons (95% CI: 7.7–12.2). The risk difference after 5 years of follow-up was 8.2 per 1,000 persons (95% CI: 5.1–11.3). Risk differences did not differ substantially between 1 year and 5 years of follow-up for any VTE, DVT, or PE cases.

3.3. Comorbidity and VTE

As the largest differences in VTE risk occurred within the first year following RCC diagnosis, we performed a subanalysis to evaluate whether comorbidity affected VTE risks for RCC patients during this time period. The risks across comorbidity strata were similar in the RCC cohort while risks increased with comorbidity level within the matched comparison cohort (Table 4). Thus, risk differences decreased with increasing comorbidity, e.g., from 12.3 per 1,000 persons (95% CI: 9.1–15.5) at 1 year for CCI score = 0 to 0.5 per 1,000 persons (95% CI: –6.0–7.0) for CCI score = 4. These decreasing point estimates reflect the similar VTE risks in each comorbidity stratum within the RCC cohort, in contrast to increasing VTE risk with increasing comorbidity levels within the matched comparison cohort. Similar risk patterns were noted for DVT and PE. Broadly similar results were observed in analyses of patients with RCC with and without metastases and their matched comparators (data not shown). Likewise, adjusted hazard ratios also decreased as CCI scores increased, e.g., from 14.2 (95% CI: 10.0–20.1) for CCI = 0 to 1.8 (95% CI: 0.4–8.0) for CCI = 4 at 1 year. Regardless of the presence or absence of metastases, VTE risk was consistently higher in all comorbidity strata of the RCC patient cohort than in the matched comparison cohort.

3.4. Comorbidity and postoperative VTE

The RCC patient cohort had an elevated risk of postoperative VTE at 3 months, 1 year, and 5 years, both overall and in all comorbidity strata when compared with the matched general population cohort (Table 5). The risk differences decreased with increasing comorbidity, e.g., from 6.6 per 1,000 persons (95% CI: 4.3–8.9) at 1 year for CCI score = 0 to 0.9 per 1,000 persons (95% CI: –3.6 to 5.4) for CCI score = 4. The adjusted hazard ratios also decreased with increasing comorbidity, with a hazard ratio at 1 year of 35.9 (95% CI: 18.2–71.0) for CCI score = 0 and 2.7 (95% CI: 0.3–24.7) for CCI score = 4.

4. Discussion

In a large population-based cohort study, we found convincing evidence that patients with RCC have a greater risk of VTE than a comparison population matched on age, gender, and comorbidity, most markedly during the year following RCC diagnosis. When evaluating those who have had surgery in the prior 3 months or metastasis, VTE risk was found to be even higher. Interestingly, our results also demonstrated that VTE risk decreases with increasing comorbidity indices, when compared with that of the population cohort.

Our study extends the literature regarding comorbidity and VTE incidence. Its results disprove the hypothesis that comorbidity increases risk of VTE in RCC. Patients in the lowest comorbidity category had higher hazard ratios than patients in higher comorbidity categories. The combination of a rising VTE risk with increasing comorbidity among

persons in the comparison cohort and decreased risk among patients in the RCC cohort suggests a consistently elevated risk of VTE among all comorbidity strata of patients with RCC.

As in earlier studies [19], we found that surgery within 3 months of VTE conferred a significant increased risk of any VTE. However, the pattern noted for comorbidity status remained consistent in this setting as well, with a stable risk of VTE with increasing comorbidity burden. Furthermore, this pattern held among patients with both metastatic and nonmetastatic disease, suggesting that this finding is not driven by stage alone.

As with all studies that rely on registry data, limitations include lack of data on subjects' personal and clinical characteristics. Furthermore, our findings may be affected by unmeasured confounders such as obesity, aggressive tumor histology, and functional status, which may increase the observed effect of cancer on VTE risk. In addition, the effect of RCC treatment may also affect this risk. Finally, temporal changes in the diagnostic workup for VTE occurring during the study period may have influenced our results. However, an analysis of computed tomography scan and ultrasound utilization revealed that 65% of those in the RCC cohort were diagnosed with VTE using imaging as compared with 71% in the comparison cohort. Thus, our results should estimate VTE risk conservatively, as slightly less imaging use may have underestimated the incidence of VTE diagnosed in the RCC cohort. Another consideration involves incidental diagnosis of VTE through imaging of patients with RCC; however, given that VTE diagnosis through imaging was similar in both cohorts, the likelihood that this is a significant bias is low. It must also be noted that a proportion of patients with VTE may be managed as outpatients, and this may differ between those with RCC and the general population. As another possible source of variation between cohorts, upper extremity VTE can occur as a complication of indwelling catheters used in patients with cancer during chemotherapy treatment. RCC is not often treated with traditional systemic chemotherapy however, so it is unlikely that many patients in our study received this treatment.

Despite these limitations, the study advances our understanding of the relation between VTE incidence and RCC, as well as the association of VTE with comorbidity. An increased risk of VTE was noted for patients with RCC in comparison to the matched general population cohort during 3 months following diagnosis and persisted during 1 to 5 years of follow-up. However, VTE risks among patients with RCC did not vary within strata of CCI scores. Thus, clinical attention to VTE risk should be paid to patients with RCC regardless of the presence or absence of comorbidities, as all patients are at substantially higher risk than the general population, particularly in the year after their cancer diagnosis. This finding may translate to other cancer sites, and further investigation is warranted to clarify whether comorbidity status (an often-used basis for risk stratification) is a predictor of VTE risk among patients with other cancers.

5. Conclusions

In a population-based cohort of patients with RCC diagnosed in Denmark and a matched comparison population cohort, VTE risk remained constant and elevated among those with

RCC throughout all comorbidity strata. This finding persisted with stratification by prior surgery as well as the presence or absence of metastases. Comorbidity status may not be a useful risk stratification tool for patients with RCC when determining VTE risk.

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Fig.
Risk of VTE for RCC patient cohort and matched comparison cohort, Denmark, 1995 to 2010.

Table 1

Charlson comorbidity index with ICD-8 and ICD-10 codes

	Diseases	ICD-8	ICD-10	Score
1	Myocardial infarction	410	I21; I22; I23	1
2	Congestive heart failure	427.09; 427.10; 427.11; 427.19; 428.99; 782.49	I50; I11.0; I13.0; I13.2	1
3	Peripheral vascular disease	440; 441; 442; 443; 444; 445	I70; I71; I72; I73; I74; I77	1
4	Cerebrovascular disease	430–438	I60–I69; G45; G46	1
5	Dementia	290.09–290.19; 293.09	F00–F03; F05.1; G30	1
6	Chronic pulmonary disease	490–493; 515–518	J40–J47; J60–J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3	1
7	Connective tissue disease	712; 716; 734; 446; 135.99	M05; M06; M08; M09; M30; M31; M32; M33; M34; M35; M36; D86	1
8	Ulcer disease	530.91; 530.98; 531–534	K22.1; K25–K28	1
9	Mild liver disease	571; 573.01; 573.04	B18; K70.0–K70.3; K70.9; K71; K73; K74; K76.0	1
10	Diabetes type 1	249.00; 249.06; 249.07; 249.09	E10.0; E10.1; E10.9	1
	Diabetes type 2	250.00; 250.06; 250.07; 250.09	E11.0; E11.1; E11.9	1
11	Hemiplegia	344	G81; G82	2
12	Moderate to severe renal disease	403; 404; 580–583; 584; 590.09; 593.19; 753.10–753.19; 792	I12; I13; N00–N05; N07; N11; N14; N17–N19; Q61	2
13	Diabetes with end-organ damage type 1	249.01–249.05; 249.08	E10.2–E10.8	2
	type 2	250.01–250.05; 250.08	E11.2–E11.8	
14	Any tumor (except RCC)	140–194 (excluding 189.0x)	C00–C75 (excluding C64)	2
15	Leukemia	204–207	C91–C95	2
16	Lymphoma	200–203; 275.59	C81–C85; C88; C90; C96	
17	Moderate to severe liver disease	070.00; 070.02; 070.04; 070.06; 070.08; 573.00; 456.00–456.09	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85	3
18	Metastatic solid tumor	195–198; 199	C76–C80	6
19	AIDS	079.83	B21–B24	6

Table 2

Characteristics of RCC patient cohort and matched comparison cohort, Denmark, 1995 to 2010

Characteristic	RCC cohort (<i>n</i> = 8,633)		Matched comparison cohort ^a (<i>n</i> = 83,055)	
	Total number	Percentage (%)	Total number	Percentage (%)
Sex				
Female	3,284	38.0	31,653	38.1
Male	5,349	62.0	51,402	61.9
Age at diagnosis/index date, y				
59	2,554	29.6	25,415	30.5
60–69	2,488	28.8	23,967	28.9
70–79	2,417	28.0	22,586	27.2
80+	1,174	13.6	11,087	13.3
Year of cancer diagnosis				
1995–1999	2,401	27.8	23,132	27.9
2000–2004	2,566	29.7	24,834	29.9
2005–2010	3,666	42.5	35,089	42.2
Cancer stage				
Nonmetastatic	4,732	54.8	–	–
Metastatic	2,597	30.1	–	–
Unknown	1,304	15.1	–	–
Comorbidity				
Myocardial infarction	528	6.1	4,684	5.6
Congestive heart failure	448	5.2	3,703	4.5
Peripheral vascular disease	414	4.8	3,498	4.2
Cerebrovascular disease	723	8.4	6,576	7.9
Dementia	58	0.7	474	0.6
Chronic obstructive pulmonary disease	686	7.9	6,192	7.5
CTD	217	2.5	1,919	2.3
Ulcer disease	446	5.2	3,888	4.7
Mild liver disease	85	1.0	746	0.9
Hemiplegia	13	0.2	115	0.1
Moderate to severe renal disease	265	3.1	2,068	2.5
Diabetes type 1 or 2	531	6.2	4,653	5.6
Diabetes with end-organ damage	221	2.6	1,776	2.1
Any tumor (except RCC)	930	10.8	8,539	10.3
Leukemia	22	0.3	155	0.2
Lymphoma	50	0.6	382	0.5
Moderate to severe liver disease	33	0.4	266	0.3
Metastatic solid tumor (except RCC)	132	1.5	1,048	1.3
AIDS	3	0.0	20	0.0
Charlson comorbidity index score				
0	4,980	57.7	49,170	59.2

Characteristic	RCC cohort (<i>n</i> = 8,633)		Matched comparison cohort ^a (<i>n</i> = 83,055)	
	Total number	Percentage (%)	Total number	Percentage (%)
1	1,532	17.7	14,924	18.0
2–3	1,667	19.3	15,871	19.1
4+	454	5.3	3,090	3.7

CTD = connective tissue disease.

Table 3

Risk of VTE among persons in the RCC and comparison cohorts at 3 mo, 1 y, and 5 y after RCC diagnosis/
index date

Time since index date	Risk, RCC cohort ^a (95% CI)	Risk, matched comparison cohort ^{a,b} (95% CI)	Risk difference ^a (95% CI)	Adjusted hazard ratio ^c (95% CI)
3 mo				
Any VTE	7.1 (5.5, 9.0)	0.5 (0.4–0.7)	6.6 (4.8, 8.3)	16.0 (10.8, 23.8)
DVT	2.9 (1.9, 4.2)	0.3 (0.2, 0.4)	2.6 (1.5, 3.8)	12.2 (6.9, 21.6)
PE	4.2 (3.0, 5.7)	0.2 (0.1, 0.4)	3.9 (2.6, 5.3)	20.4 (11.7, 35.6)
1 y				
Any VTE	11.8 (9.7, 14.3)	1.9 (1.6, 2.2)	9.9 (7.7, 12.2)	8.3 (6.4, 10.6)
DVT	5.4 (4.1, 7.2)	1.1 (0.9, 1.3)	4.4 (2.8, 5.9)	6.6 (4.6, 9.4)
PE	6.4 (4.9, 8.2)	0.8 (0.6, 1.0)	5.6 (3.9, 7.3)	10.5 (7.3, 15.0)
5 y				
Any VTE	18.7 (15.9, 21.9)	10.5 (9.8, 11.3)	8.2 (5.1, 11.3)	3.5 (2.9, 4.1)
DVT	9.3 (7.4, 11.6)	5.5 (5.0, 6.1)	3.8 (1.6, 6.0)	3.2 (2.5, 4.2)
PE	9.4 (7.5, 11.7)	5.0 (4.5, 5.5)	4.4 (2.2, 6.6)	3.7 (2.9, 4.7)

^a Risk per 1,000 persons over 3 mo, 1 y, or 5 y of follow-up.

^b Matched on year of birth (in 5-y intervals), sex, and presence of comorbidities.

^c Adjusted for age, sex, year of RCC diagnosis, and comorbidities.

Table 4

Risks of VTE, PE, and DVT by CCI score among persons in the RCC and matched comparison cohorts in the initial year following diagnosis date/index date

Charlson comorbidity index score	Risk, RCC ^a (95% CI)	Risk, matched comparison cohort ^{a,b} (95% CI)	Risk difference ^a (95% CI)	Adjusted hazard ratio ^c (95% CI)
Any VTE				
0	13.5 (10.5, 17.0)	1.2 (0.9, 1.5)	12.3 (9.1, 15.5)	14.2 (10.0, 20.1)
1	9.8 (5.8, 15.8)	2.3 (1.6, 3.2)	7.5 (2.5, 12.5)	6.1 (3.3, 11.2)
2–3	10.8 (6.7, 16.7)	3.2 (2.4, 4.2)	7.6 (2.5, 12.6)	4.6 (2.7, 7.9)
4	4.4 (0.9, 14.9)	3.9 (2.1, 6.7)	0.5 (–6.0, 7.0)	1.8 (0.4, 8.0)
DVT				
0	6.2 (4.3, 8.7)	0.8 (0.6, 1.1)	5.5 (3.3, 7.7)	10.2 (6.3, 16.4)
1	5.2 (2.5, 10.0)	1.6 (1.1, 2.4)	3.6 (–0.1, 7.3)	4.6 (2.0, 10.2)
2–3	3.6 (1.5, 7.6)	1.3 (0.9, 2.0)	2.3 (–0.7, 5.2)	3.5 (1.4, 8.7)
4	4.4 (0.9, 14.9)	2.3 (1.0, 4.6)	2.1 (–4.2, 8.5)	3.5 (0.7, 17.0)
PE				
0	7.2 (5.2, 9.9)	0.4 (0.3, 0.6)	6.8 (4.5, 9.2)	21.4 (12.4, 37.1)
1	4.6 (2.1, 9.1)	0.7 (0.4, 1.2)	3.9 (0.5, 7.3)	9.8 (3.7, 25.9)
2–3	7.2 (4.0, 12.3)	1.9 (1.3, 2.7)	5.3 (1.2, 9.4)	5.4 (2.8, 10.6)
4	–	1.6 (0.6, 3.7)	–	–

^a Risk per 1,000 persons during 1 y of follow-up.

^b Matched on year of birth (in 5-y intervals), sex, and presence of comorbidities.

^c Adjusted for age, sex, and year of RCC diagnosis.

Table 5

Risks of postoperative VTE overall and by Charlson comorbidity index score among persons in the RCC and matched comparison cohorts at 3 mo, 1 y, and 5 y after RCC diagnosis date/index date

Time since index date	Charlson comorbidity index score	Risk, RCC ^a (95% CI)	Risk, matched comparison cohort ^{a,b} (95% CI)	Risk difference ^a (95% CI)	Adjusted hazard ratio ^c (95% CI)
3 mo	Overall	5.0 (3.7, 6.7)	0.1 (0.1, 0.2)	4.8 (3.4, 6.3)	41.7 (21.5, 80.9)
	0	5.4 (3.7, 7.8)	0.1 (0.03, 0.2)	5.4 (3.3, 7.4)	96.8 (29.4, 319.2)
	1	4.6 (2.1, 9.1)	0.1 (0.01, 0.4)	4.5 (1.1, 7.9)	76.5 (9.4, 622.4)
	2-3	4.8 (2.3, 9.2)	0.3 (0.1, 0.7)	4.5 (1.2, 7.8)	17.4 (5.7, 53.2)
1 y	4	2.2 (0.2, 11.8)	0.6 (0.1, 2.3)	1.6 (-2.8, 6.0)	4.7 (0.4, 52.9)
	Overall	6.4 (4.9, 8.2)	0.4 (0.3, 0.6)	5.9 (4.3, 7.6)	18.0 (11.8, 27.4)
	0	6.8 (4.8, 9.4)	0.2 (0.1, 0.4)	6.6 (4.3, 8.9)	35.9 (18.2, 71.0)
	1	6.5 (3.4, 11.7)	0.5 (0.3, 1.0)	6.0 (1.9, 10.0)	15.7 (6.2, 40.0)
5 y	2-3	6.0 (3.1, 10.7)	0.8 (0.5, 1.4)	5.2 (1.4, 8.9)	9.3 (4.1, 21.3)
	4	2.2 (0.2, 11.8)	1.3 (0.5, 3.2)	0.9 (-3.6, 5.4)	2.7 (0.3, 24.7)
	Overall	7.6 (5.9, 9.6)	2.6 (2.2, 3.0)	5.0 (3.1, 6.9)	5.5 (4.1, 7.3)
	0	8.7 (6.3, 11.6)	1.8 (1.5, 2.3)	6.8 (4.2, 9.5)	8.7 (5.9, 12.7)
	1	6.5 (3.4, 11.7)	2.5 (1.8, 3.6)	4.0 (-0.1, 8.1)	5.2 (2.5, 10.6)
	2-3	6.6 (3.6, 11.6)	4.5 (3.5, 5.8)	2.1 (-1.9, 6.2)	3.0 (1.6, 5.7)
	4	2.2 (0.2, 11.8)	6.3 (3.7, 10.2)	-4.1 (-9.5, 1.2)	0.8 (0.1, 5.9)

^aRisk per 1,000 persons during 3 mo, 1 y, or 5 y of follow-up.

^bMatched on year of birth (in 5-y intervals), sex, and presence of comorbidities.

^cAdjusted for age, sex, year of RCC diagnosis, and comorbidities (only in overall analyses).