

# Supplementary Material

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# **Impact of venous thromboembolism on the mortality in patients with cancer: a population-based cohort study**

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## **Description of the Danish registries**

The present study was based on routinely collected nationwide Danish registry data. Denmark has a state-funded healthcare system ensuring free access to healthcare for all residents.<sup>1</sup> We used the following data sources:

- The Danish National Patient Registry contains complete nationwide information on hospital inpatient admissions since 1977 and hospital outpatient clinic and emergency contacts since 1995.<sup>2</sup> Each hospital discharge or outpatient visit is recorded with one primary diagnosis and one or more secondary diagnoses coded according to the *International Classification of Diseases, Eighth Revision* between 1977 and 1993 and *Tenth Revision* thereafter. We used the Patient Registry to identify the patients with venous thromboembolism and comorbidities included in Table 1.
- The Danish Cancer Registry has recorded all incident cases of malignant neoplasms in Denmark since 1943 (mandatory since 1987), including information on morphology, histology, and cancer stage at time of diagnosis.<sup>3</sup> Diagnoses in the Cancer Registry generally have high validity, with 95%–98% completeness and accuracy of recorded diagnoses. For example, it has been shown that only 3·6% of lung cancers and 1·2% of breast cancers have a missing or incorrect diagnosis code. Cancer cases are coded according to the *International Classification of Diseases, Tenth Revision*. We used this Registry to

identify all incident cancers recorded concurrent or before a venous thromboembolism diagnosis. We considered all cancers, as well as site-specific cancers, grouped according to the annual cancer report published by the Danish Health Data Authority.

- The Danish Civil Registration System, established in 1968, is updated daily with changes in vital status and migration for the entire Danish population.<sup>4</sup> A unique 10-digit personal identifier is assigned to all residents at birth or upon immigration, which enables accurate and unambiguous linkage across all data sources at the individual level.
- The Danish National Prescription Registry has recorded detailed data on all prescription drugs sold in Danish pharmacies since 1995. The Registry contains variables that characterize each redeemed prescription, including those describing the patient, the drug dispensed, the health provider issuing the prescription and the dispensing pharmacy. Prescription drugs are coded using the Anatomical Therapeutic Chemical (ATC) coding system.

## References

1. Schmidt M, Schmidt SAJ, Adelborg K, et al. The Danish health care system and epidemiological research: from health care contacts to database records. *Clin Epidemiol.* 2019;**11**:56391.
2. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol.* 2015;**7**:44990.
3. Gjerstorff ML. The Danish Cancer Registry. *Scand J Public Health.* 2011;**39**(7 Suppl):425.
4. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol.* 2014;**29**:5419.

	<b>Coding</b>	<b>Inclusion codes</b>	<b>Exclusion codes</b>
Exposure			
Venous thromboembolism			
Pulmonary embolism	ICD-8	450.99	
	ICD-10	I26	
Deep vein thrombosis	ICD-8	451.00	
	ICD-10	I80.1, I80.2, I80.3	
Covariates			
Antihypertensives			
ACE inhibitors	ATC	C09A, C09B	
Angiotensin receptor blockers	ATC	C09C, C09D	
Calcium channel blockers	ATC	C07FB, C08CA, C09BB, C09DB, C09DX01	
Thiazides/diuretics	ATC	C03AA01, C03AA03, C03AB01, C03AB03, C03AX01, C03EA, C07B, C09BA, C09DA, C09DX01, C09DX03, C09XA52, C09XA54	C07BA06 C09BA04
Beta-blockers	ATC	C07	
Other antihypertensives	ATC	C02AC, C02CA, C03BA11, C09XA C02AB01	C09XA54
Vitamin K antagonists	ATC	B01AA	
Direct oral anticoagulants	ATC	B01AE07, B01AF01, B01AX06, B01AF02, B01AF03	

Low-molecular-weight heparin	ATC	B01AB
Statins	ATC	C10AA, C10B
Aspirin	ATC	B01AC06, N02BA01, N02BA51
Opioid use	ATC	N02A, N07BC02
Glucocorticoids	ATC	H02AB
Loop diuretics	ATC	C03C
Surgical procedures	Surgery	KA-KQ, KX, KY
Central venous catheter	Procedure	BMBD00, BMBD01, BMBZ51

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**Table S1. Diagnosis, medication, and treatment codes used in the study**

	Venous thromboembolism concurrent with a cancer diagnosis			Venous thromboembolism after a cancer diagnosis		
	VTE cohort	Comparison cohort	Mortality rate	VTE cohort	Comparison cohort	Mortality rate
Calendar	mortality risk	mortality risk	ratio	mortality risk	mortality risk	ratio
period	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)
<b>1995-1999</b>	<b>N = 316</b>	<b>N = 930</b>		<b>N = 1814</b>	<b>N = 5414</b>	
0-1 month	40.5 (35.3–46.1)	9.0 (7.4–11.1)	10.53 (6.87–16.14)	18.5 (16.8–20.4)	2.4 (2.0–2.8)	8.21 (6.41–10.52)
0-3 months	57.6 (52.2–63.1)	19.7 (17.3–22.4)	6.80 (5.06–9.14)	29.4 (27.3–31.5)	6.0 (5.4–6.7)	5.88 (4.96–6.98)
0-1 year	72.2 (67.1–77.0)	40.1 (37.0–43.3)	5.42 (4.25–6.90)	49.8 (47.5–52.1)	18.2 (17.2–19.3)	3.88 (3.45–4.35)
0-5 years	85.4 (81.3–89.1)	68.9 (65.9–71.9)	4.02 (3.27–4.93)	72.0 (69.9–74.0)	46.8 (45.4–48.1)	2.63 (2.41–2.87)
<b>2000-2004</b>	<b>N = 417</b>	<b>N = 1223</b>		<b>N = 2856</b>	<b>N = 8505</b>	
0-1 month	32.1 (27.9–36.9)	7.9 (6.5–9.5)	7.01 (4.87–10.10)	16.4 (15.1–17.8)	2.5 (2.1–2.9)	6.79 (5.60–8.24)
0-3 months	52.0 (47.3–56.9)	18.07 (16.03–20.34)	6.73 (5.13–8.83)	27.9 (26.3–29.6)	6.4 (5.9–6.9)	5.10 (4.46–5.84)
0-1 year	68.8 (64.4–73.2)	38.76 (36.09–41.55)	4.82 (3.90–5.96)	49.3 (47.5–51.1)	18.5 (17.7–19.4)	3.86 (3.52–4.24)
0-5 years	84.9 (81.3–88.1)	67.47 (64.83–70.08)	3.55 (2.98–4.24)	72.1 (70.4–73.7)	46.7 (45.7–47.8)	2.59 (2.42–2.78)
<b>2005-2009</b>	<b>N = 359</b>	<b>N = 1067</b>		<b>N = 4611</b>	<b>N = 13 766</b>	
0-1 month	25.6 (21.2–30.2)	8.53 (7.00–10.37)	6.14 (3.98–9.47)	15.1 (14.1–16.2)	2.5 (2.2–2.8)	6.05 (5.20–7.04)
0-3 months	51.0 (45.9–56.2)	17.90 (15.73–20.34)	5.26 (3.97–6.97)	27.7 (26.4–29.0)	6.7 (6.2–7.1)	4.54 (4.10–5.04)
0-1 year	71.3 (66.6–75.9)	41.33 (38.44–44.35)	4.12 (3.32–5.11)	46.6 (45.2–48.1)	18.9 (18.2–19.5)	3.25 (3.03–3.50)

0-5 years	83.8 (79.9–87.4)	67.70 (64.88–70.49)	3.32 (2.75–4.00)	70.4 (69.1–71.8)	44.4 (43.6–45.3)	2.47 (2.34–2.61)
<b>2010-2014</b>	<b>N = 464</b>	<b>N = 1362</b>		<b>N = 7106</b>	<b>N = 21 217</b>	
0-1 month	20.7 (17.3–24.7)	6.90 (5.67–8.38)	5.55 (3.68–8.36)	12.7 (12.0–13.5)	2.1 (2.0–2.3)	5.81 (5.07–6.67)
0-3 months	41.6 (37.7–46.2)	14.76 (12.98–16.75)	5.00 (3.83–6.53)	24.5 (23.5–25.5)	5.6 (5.3–5.9)	4.64 (4.24–5.08)
0-1 year	67.5 (63.2–71.7)	35.54 (33.06–38.14)	4.26 (3.48–5.20)	43.70 (42.6–44.9)	16.4 (15.9–16.9)	3.46 (3.26–3.68)
0-5 years	84.5 (81.0–87.6)	63.66 (61.10–66.21)	3.39 (2.86–4.02)	68.1 (67.1–69.2)	40.4 (39.8–41.1)	2.61 (2.49–2.73)
<b>2015-2018</b>	<b>N = 326</b>	<b>N = 967</b>		<b>N = 6979</b>	<b>N = 20 833</b>	
0-1 month	22.1 (18.0–27.0)	5.48 (4.21–7.11)	9.95 (5.63–17.58)	11.6 (10.8–12.3)	1.8 (1.6–2.0)	5.82 (5.02–6.76)
0-3 months	43.6 (38.4–49.1)	15.00 (12.90–17.41)	8.17 (5.68–11.77)	22.7 (21.8–23.7)	5.0 (4.7–5.3)	4.55 (4.13–5.01)
0-1 year	61.4 (56.1–66.6)	37.57 (34.60–40.70)	3.91 (3.08–4.96)	41.5 (40.4–42.7)	14.8 (14.3–15.3)	3.43 (3.21–3.65)
0-5 years	81.3 (76.6–85.5)	65.97 (62.58–69.34)	3.26 (2.66–3.99)	65.6 (64.2–66.9)	39.5 (38.7–40.3)	2.55 (2.43–2.68)

**Table S2. Mortality risks and mortality rate ratios by calendar period of venous thromboembolism and by follow-up time**



	Venous thromboembolism concurrent with a cancer diagnosis			Venous thromboembolism after a cancer diagnosis		
	VTE cohort	Comparison cohort	Mortality rate	VTE cohort	Comparison cohort	Mortality rate
	mortality risk	mortality risk	ratio	mortality risk	mortality risk	ratio
	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)
<b>Pulmonary embolism</b>						
0-1 month	36.5 (33.8–39.4)	7.6 (6.7–8.5)	9.19 (7.37–11.46)	18.6 (17.9–19.3)	2.2 (2.1–2.4)	8.58 (7.80–9.44)
0-3 months	56.1 (53.3–59.0)	17.0 (15.8–18.3)	7.62 (6.48–8.97)	30.3 (29.5–31.1)	5.9 (5.7–6.2)	5.94 (5.56–6.34)
0-1 year	73.0 (70.4–75.6)	39.3 (37.6–41.0)	5.10 (4.51–5.78)	49.3 (48.4–50.2)	17.3 (17.0–17.7)	4.00 (3.82–4.18)
0-5 years	87.1 (85.1–89.0)	67.5 (65.9–69.2)	4.05 (3.64–4.51)	72.8 (72.0–73.7)	43.3 (42.8–43.8)	2.92 (2.82–3.02)
<b>Deep venous thrombosis</b>						
0-1 month	14.3 (12.0–17.1)	7.5 (6.5–8.7)	2.96 (2.18–4.03)	8.2 (7.7–8.8)	2.1 (2.0–2.3)	3.35 (2.98–3.76)
0-3 months	37.5 (34.1–41.1)	16.9 (15.4–18.6)	3.89 (3.17–4.77)	19.8 (19.0–20.5)	5.5 (5.3–5.8)	3.39 (3.15–3.66)
0-1 year	60.9 (57.4–64.4)	37.3 (35.3–39.3)	3.50 (3.00–4.10)	39.6 (38.7–40.6)	16.2 (15.8–16.6)	2.93 (2.78–3.07)
0-5 years	79.5 (76.6–82.4)	65.2 (63.2–67.2)	2.79 (2.45–3.18)	63.7 (62.8–64.7)	41.2 (40.7–41.8)	2.21 (2.13–2.30)

**Table S3. Mortality risks and mortality rate ratios for patients with pulmonary embolism and venous thrombosis and their comparison cohorts by follow-up time**

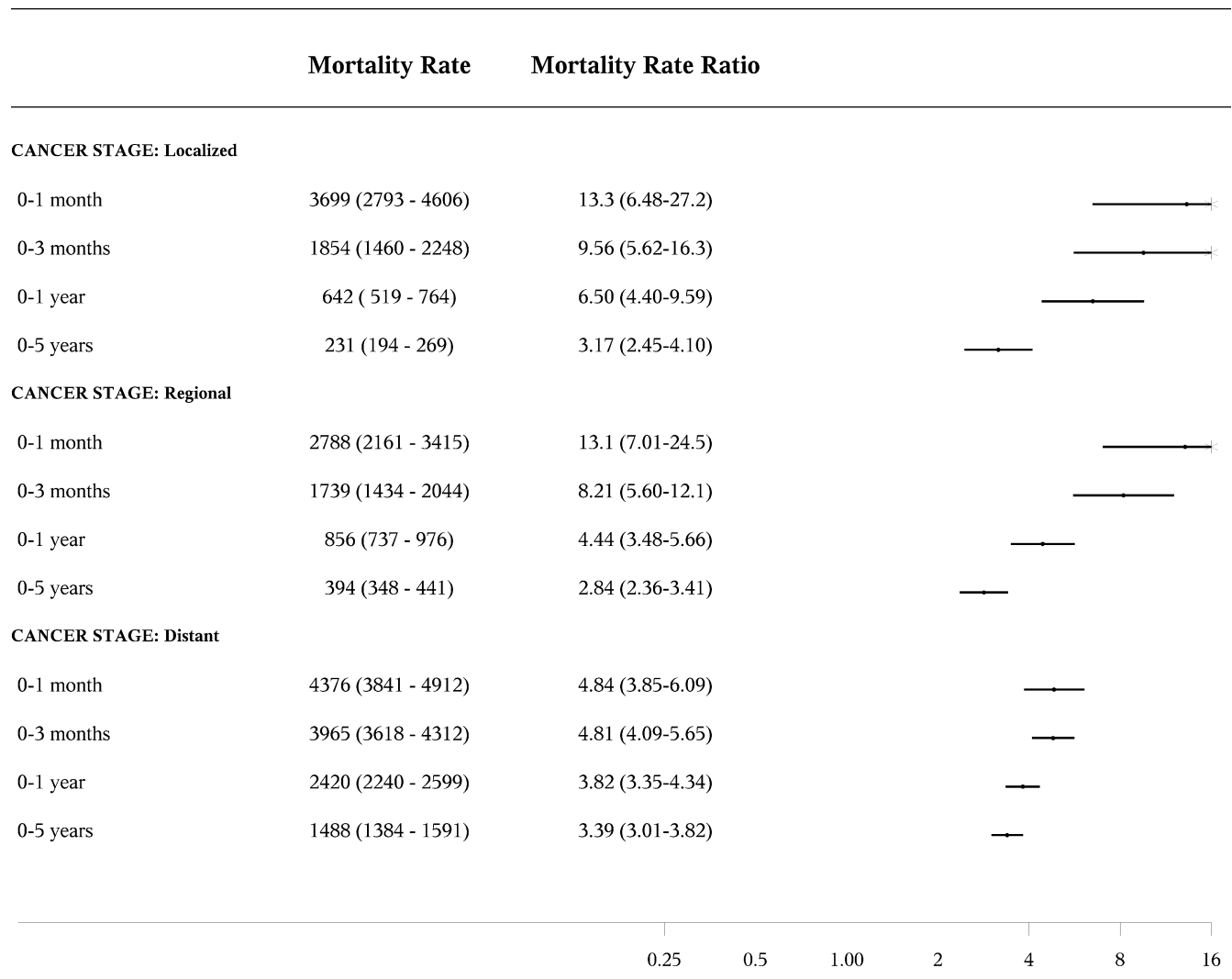
		Venous thromboembolism concurrent with a cancer diagnosis			Venous thromboembolism after a cancer diagnosis		
		VTE cohort	Comparison	Mortality rate	VTE cohort	Comparison	Mortality rate
		mortality risk	cohort	ratio	mortality risk	cohort	ratio
		(95% CI)	mortality risk	(95% CI)	(95% CI)	mortality risk	(95% CI)
			(95% CI)			(95% CI)	
Stomach	0-1 year	96.4 (89.1–99.3)	53.5 (45.9–61.4)	7.19 (3.89–13.30)	64.2 (59.6–68.9)	32.4 (29.8–35.1)	3.15 (2.56–3.88)
	0-5 years	96.4 (89.1–99.3)	77.3 (70.4–83.5)	5.85 (3.34–10.24)	81.5 (77.6–85.2)	60.5 (57.7–63.8)	2.60 (2.17–3.10)
Colon	0-1 year	54.1 (48.3–60.2)	23.3 (20.5–26.4)	4.76 (3.54–6.38)	42.6 (40.7–44.5)	13.8 (13.1–14.6)	3.71 (3.33–4.12)
	0-5 years	74.9 (69.6–78.0)	50.1 (46.8–53.7)	3.27 (2.60–4.10)	67.6 (65.7–69.5)	40.7 (40.0–42.0)	2.55 (2.36–2.76)
Rectal	0-1 year	51.2 (41.0–62.3)	23.8 (18.9–29.6)	4.60 (2.49–8.49)	36.8 (34.4–39.4)	13.1 (12.1–14.1)	3.20 (2.77–3.70)
	0-5 years	68.5 (58.3–78.3)	49.9 (43.7–56.4)	3.13 (1.98–4.94)	66.3 (63.8–68.8)	39.6 (38.1–41.1)	2.49 (2.25–2.75)
Liver	0-1 year	87.5 (76.6–94.9)	46.8 (38.5–56.0)	5.13 (2.69–9.77)	74.8 (66.4–82.4)	47.7 (42.4–53.5)	2.75 (1.91–3.96)
	0-5 years	100.0	82.4 (74.9–88.8)	5.14 (2.81–9.41)	91.9 (85.9–96.0)	82.6 (77.7–87.0)	2.38 (1.72–3.31)
Pancreas	0-1 year	97.6 (95.2–99.0)	74.0 (70.8–77.1)	5.64 (4.38–7.25)	88.7 (86.2–90.8)	61.0 (58.8–63.0)	2.61 (2.29–2.96)
	0-5 years	98.4 (96.3–99.5)	90.6 (88.3–92.6)	5.28 (4.14–6.75)	96.5 (94.9–97.7)	85.0 (83.4–86.6)	2.43 (2.15–2.75)
Non-small cell lung	0-1 year	84.4 (80.9–87.6)	54.0 (51.4–56.7)	3.81 (3.20–4.53)	71.5 (69.7–73.3)	39.7 (38.6–40.8)	2.76 (2.55–2.98)
	0-5 years	97.6 (95.8–98.8)	82.4 (80.3–84.5)	3.51 (2.98–4.13)	89.7 (88.4–90.9)	70.2 (69.1–71.2)	2.43 (2.27–2.60)
Breast	0-1 year	44.9 (34.1–57.4)	7.8 (4.8–12.4)	10.28 (3.50–30.22)	32.0 (30.6–33.4)	6.7 (6.3–7.2)	4.66 (4.20–5.18)

	0-5 years	64.3 (53.0–75.5)	41.19 (34.6–48.2)	4.06 (2.35–7.04)	57.8 (56.3–59.4)	28.1 (27.3–28.9)	2.61 (2.44–2.79)
Ovary	0-1 year	54.81 (46.7–63.4)	27.4 (23.3–32.1)	4.67 (3.12–7.01)	59.8 (56.4–63.2)	16.8 (15.4–18.4)	4.67 (3.91–5.58)
	0-5 years	81.8 (74.8–87.8)	65.0 (60.3–69.8)	3.42 (2.50–4.68)	82.2 (79.3–84.9)	48.3 (46.2–50.4)	3.13 (2.73–3.59)
Prostate	0-1 year	29.8 (22.0–39.6)	20.51 (16.4–25.4)	2.92 (1.62–5.26)	38.7 (37.0–40.6)	10.5 (9.8–11.2)	4.05 (3.62–4.53)
	0-5 years	67.4 (58.2–76.4)	62.13 (56.7–67.6)	1.92 (1.34–2.76)	66.9 (65.1–68.7)	41.1 (41.0–42.2)	2.59 (2.40–2.80)
Kidney	0-1 year	55.7 (43.8–68.4)	20.00 (14.9–26.6)	10.28 (4.11–25.71)	35.9 (32.0–40.2)	12.5 (11.0–14.2)	2.96 (2.29–3.83)
	0-5 years	72.4 (60.8–83.0)	50.0 (43.0–57.6)	4.10 (2.38–7.07)	64.5 (60.2–68.8)	38.8 (36.3–41.4)	2.10 (1.77–2.51)
Non- Hodgkin's lymphoma	0-1 year	44.3 (34.2–55.9)	12.3 (8.7–17.3)	11.37 (4.88–26.51)	32.1 (29.3–35.0)	9.3 (8.3–10.4)	3.73 (3.09–4.52)
	0-5 years	63.6 (53.1–74.1)	41.8 (35.6–48.5)	4.55 (2.75–7.52)	56.1 (53.0–59.20)	30.3 (28.6–32.0)	2.32 (2.04–2.65)
Leukemia	0-1 year	54.1 (42.2–66.9)	12.6 (8.5–18.3)	38.02 (9.23–156.6)	32.4 (29.0–36.0)	10.9 (9.6–12.3)	3.31 (2.66–4.13)
	0-5 years	72.7 (61.0–83.2)	43.4 (36.5–51.0)	6.14 (3.38–11.15)	61.1 (57.4–64.9)	36.9 (34.8–39.2)	2.29 (1.97–2.67)

**Table S4. Mortality risks and mortality rate ratios by cancer type and by follow-up time**

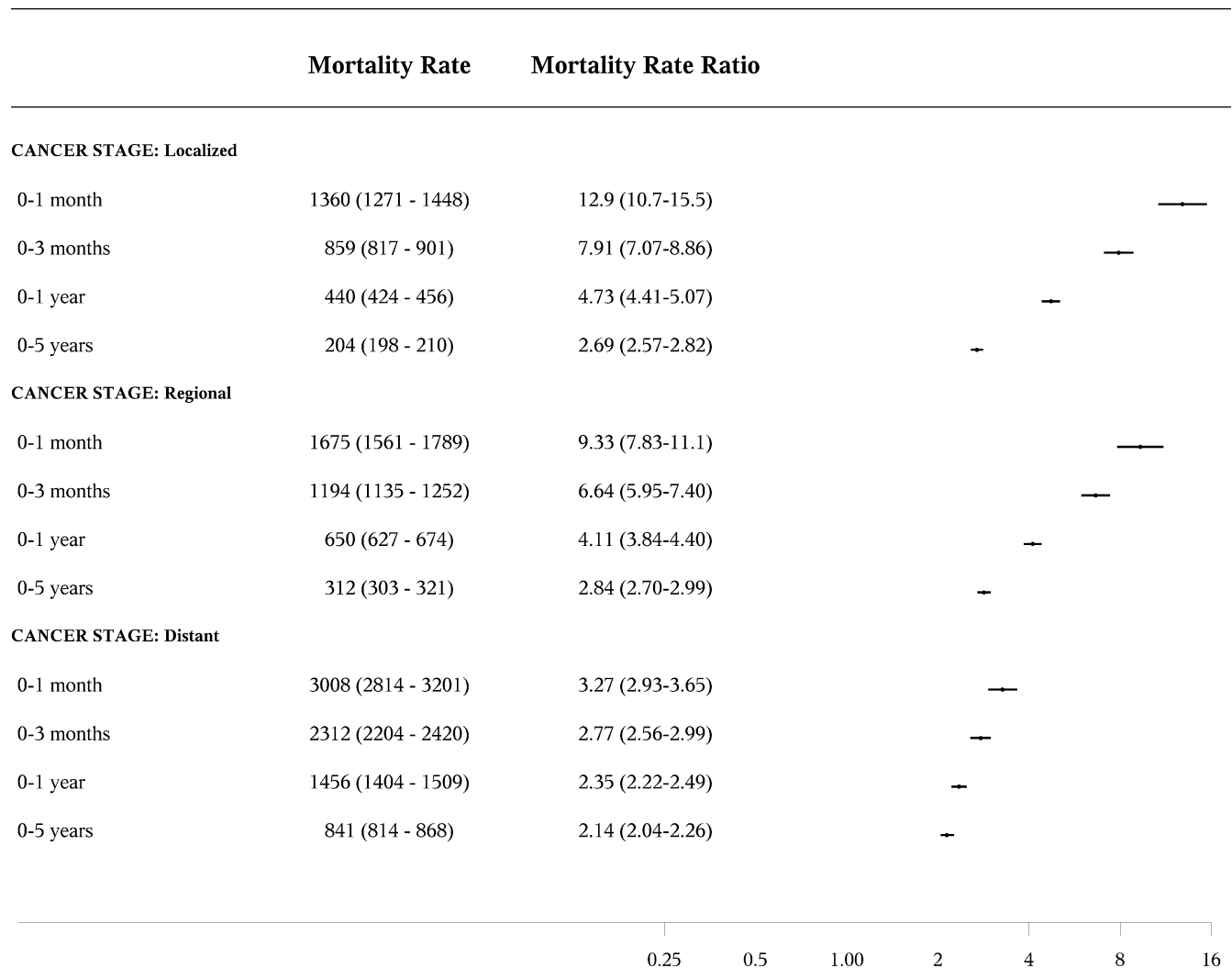
		Venous thromboembolism concurrent with a cancer diagnosis			Venous thromboembolism after a cancer diagnosis		
Follow-up time	Cohort	Mortality risk (95% CI)	Mortality rate per 1000 person-years (95% CI)	Mortality rate ratio (95% CI)	Mortality risk (95% CI)	Mortality rate per 1000 person-years (95% CI)	Mortality rate ratio (95% CI)
<b>1-3 months</b>	Comparison	10.2 (9.4–11.1)	662 (605-718)		3.7 (3.5–3.8)	229 (220-238)	
	VTE	29.1 (26.8–31.6)	2196 (1980-2413)	5.56 (4.61–6.70)	13.5 (13.0–14.0)	896 (863-930)	3.72 (3.48–3.98)
<b>1 month-1 year</b>	Comparison	33.5 (32.2–34.8)	459 (437-481)		15.0 (14.7–15.2)	178 (175-182)	
	VTE	56.1 (53.4–58.7)	1030 (957-1104)	3.63 (3.22–4.09)	36.0 (35.3–36.7)	513 (501-525)	2.93 (2.82–3.04)
<b>1 month-5 years</b>	Comparison	63.9 (62.5–65.2)	247 (238-255)		41.1 (40.7–41.4)	115 (113-116)	
	VTE	78.0 (75.8–80.2)	469 (441-497)	2.80 (2.54–3.08)	63.6 (62.9–64.2)	254 (249-258)	2.22 (2.16–2.28)

**Table S5. Mortality risks, rates, and mortality rate ratios for patients with venous thromboembolism and their cancer cohorts after excluding patients with less than one month of follow-up.**



Mortality rates calculated per 1,000 person-years.

**Figure S1. Overall mortality in patients with venous thromboembolism concurrent with a cancer diagnosis and matched comparison cancer cohort, stratified by cancer stage**



Mortality rates calculated per 1,000 person-years.

**Figure S2. Overall mortality in patients with venous thromboembolism after a cancer diagnosis and matched comparison cancer cohort, stratified by cancer stage**