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Anijs, R.J.S.; Chen, Q.; Hulle, T. van der; Versteeg, H.H.; Klok, F.A.; Lijfering, W.M.; Cannegieter, S.C.

Thrombosis Research 229 (2023) 90–98

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Venous and arterial thromboembolism after colorectal cancer in the Netherlands: Incidence, predictors, and prognosis

R.J.S. Anijs [a,b], Q. Chen [a], T. van der Hulle [c], H.H. Versteeg [b], F.A. Klok [b], W.M. Lijfering [d], S.C. Cannegieter [a,b,*]

[a] Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, the Netherlands
[b] Department of Medicine, Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, the Netherlands
[c] Department of Medical Oncology, Leiden University Medical Center, Leiden, the Netherlands
[d] The Knowledge Institute of the Federation of Medical Specialists, Utrecht, the Netherlands

ARTICLE INFO

Keywords:
Colorectal cancer
Epidemiology
Risk factor
Venous thrombosis
Arterial thrombosis

ABSTRACT

Background: Colorectal cancer (CRC) is the third most prevalent cancer type. CRC-patients are at increased risk of venous and arterial thromboembolism (TE), but the magnitude of the risks, their predictors and consequences are not exactly known.

Objectives: We aimed to determine incidence, predictors and prognosis of TE after incident CRC in a large, unselected population.

Methods: Using data from Statistics Netherlands and the Netherlands Comprehensive Cancer Organization, all incident CRC-patients were identified between 2013 and 2018 plus a sample of 1:2 age- and sex-matched control subjects. Incidence rates and cumulative incidences for TE were estimated. Predictor variables for TE were explored by univariable Cox regression. The association between TE and all-cause mortality was evaluated by multivariable time-dependent Cox regression.

Results: 68,238 incident CRC-patients were matched to 136,476 controls. CRC-patients had a 1-year cumulative venous TE (VTE) incidence of 1.93 % (95%CI 1.83–2.04), versus 0.24 % (95%CI 0.21–0.27) in controls (HR 8.85; 95%CI 7.83–9.99). For arterial TE (ATE), this was 2.74 % (95%CI 2.62–2.87) in CRC versus 1.88 % (95%CI 1.81–1.95) in controls (HR 1.57; 95%CI 1.47–1.66). Cancer stage, surgery, chemotherapy and asthma were predictors for VTE, whereas age, prior ATE and Parkinson's disease were predictors for ATE. CRC patients with TE had an increased risk of all-cause mortality (VTE HR; 3.68 (95%CI 3.30–4.10, ATE HR; 3.05 (95%CI 2.75–3.39)) compared with CRC-patients without TE.

Conclusions: This Dutch nationwide cohort study adds detailed knowledge on the risk of VTE and ATE, their predictors and prognosis in CRC-patients. These findings may drive TE prophylactic management decisions.

1. Introduction

Cancer patients are at increased risk of cancer-associated thrombosis (CAT), manifesting in venous thromboembolism (VTE) or arterial thromboembolism (ATE), and leading to increased morbidity and mortality [1]. For VTE, being the most extensively studied, cancer patients have an up to ~9-fold increased 1-year risk compared to the general population [2]. Far less is known on the increased risk of ATE in cancer patients, comprising myocardial infarction (MI) or a (transient) ischemic attack (TIA/ischemic stroke/systemic arterial embolism). Only two recent cohort studies demonstrated a ~ 2-fold increased 6-month risk of ATE in cancer patients compared to the general population [3,4].

For CAT patients, anticoagulant treatment is recommended for at least 6 months and is continued as long as the patient has an active malignancy, but this is accompanied by a relevant risk of bleeding complications [5]. Despite the fact that the increased risk of thrombosis in cancer has been studied extensively, the biological mechanism is not yet fully understood. Accurate risk prediction therefore is still challenging. Both CAT types have worsened prognoses, with 1-year mortality rates being 2.5-fold and 3.3-fold higher in VTE and ATE patients, respectively, compared to cancer patients without thrombosis [6].

In The Netherlands, colorectal cancer (CRC) is the third most

* Corresponding author at: Department of Clinical Epidemiology, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, the Netherlands.
E-mail address: s.c.cannegieter@lumc.nl (S.C. Cannegieter).

https://doi.org/10.1016/j.thromres.2023.06.028
Received 9 April 2023; Received in revised form 26 June 2023; Accepted 28 June 2023
Available online 4 July 2023

prevalent cancer type, with 13.000 cases yearly and an overall 5-year survival rate of 67 % [7]. Worldwide, approximately 1930.000 new cases are diagnosed yearly, with an ever rising incidence [8]. Being associated with a moderately high risk for VTE [5], CRC presents a fast-rising disease burden globally, which makes thorough investigation clinically relevant. So far, studies on CAT after CRC reported inconsistent findings, which was mostly due to limited sample sizes, relatively outdated data, and only few investigations addressing ATE [9,10].

With recent data, we conducted a nationwide cohort study to examine the incidence, predictors, and subsequent mortality risk of developing both venous and arterial TE after incident CRC diagnosis in The Netherlands, aiming to provide updated and better estimated epidemiology on thromboembolism in CRC patients.

2. Methods

2.1. Study design

Using data from nationwide registries, we formed a cohort of incident CRC patients and an age- and sex- matched control cohort from the general population, included between 1 January 2013 and 31 December 2018. The objectives were [1] to determine the incidence of VTE/ATE after incident CRC, and compare to the general population; [2] to identify predictors for developing VTE/ATE after incident CRC; [3] to estimate the mortality risk after developing VTE/ATE.

The study received approval from the Science Committee of the department of Clinical Epidemiology at Leiden University Medical Centre with a waiver for participant consent due to the use of pre-existing, de-identified data (#A161).

2.2. Data sources and study population

The two data sources, Statistics Netherlands ('Centraal Bureau voor de Statistiek', CBS) and the Netherlands Comprehensive Cancer Organization ('Integraal Kankercentrum Nederland', IKNL) were linked on an individual level with 98.8 % match. In the supplementary material, a detailed description of these data sources and the inclusion and exclusion criteria of the cohorts are described. Table S1 presents the codes used for variable extraction and fig. S1 presents the flowchart of the study populations.

2.3. Baseline characteristics

At baseline (CRC diagnosis), several characteristics were registered; [1] age, sex, immigration background, and standard household income; [2] various comorbidities (identified by examining hospitalization diagnosis data within 3 years before index date), shown in table S1; [3] cancer characteristics and treatment, including topography, cancer stage (pathological TNM and clinical TNM), surgery, systemic chemotherapy, and/or radiotherapy; [4] variables only available for individuals who had participated in the Dutch Health Monitor (DHM), including highest education level, body mass index (BMI), physical health, feeling of loneliness, feeling of depression, ability to meet financial needs, alcohol use, smoking history, living alone, and being unemployed.

2.4. Clinical events and follow up

For the first and second objective, the following clinical outcomes were defined using ICD-10 codes: VTE, including DVT and/or PE, and ATE, including MI, Ischemic stroke, TIA, and/or systemic arterial thromboembolism. For the third objective, the clinical outcome was defined as all-cause mortality. Except for all-cause mortality, all subjects were followed from the index date (date of cancer diagnosis) until first occurrence of the clinical outcome (TE) studied, date of death or end of follow-up (31 December 2019), whichever occurred first.

2.5. Statistical analyses

Summary statistics of the baseline characteristics of the two cohorts were expressed as numbers (percentages), or mean ± standard deviation. As the number of missing values was relatively low, a complete case analysis was performed when necessary.

For the first objective, cumulative incidences with 95 % confidence intervals (95 % CI) were estimated for developing the outcomes VTE/ATE within 3, 6, 9 and 12 months after the index date using the cumulative incidence competing risk (CICR) method, in which death (for non-thromboembolic reasons) was considered as competing event. Furthermore, incidence rates (IR) were calculated per 100 person-years and survival graphs were plotted to visualize the incidences. To compare the risk of the study outcomes between cohorts, multivariable Cox regression models were used to estimate hazard ratios. In addition to a crude model, the following adjustment models were used: model 1, immigration status and standardized household income; model 2, model 1 plus history of comorbidities. To examine the robustness of the associations, a sensitivity analysis was performed by repeating all the analyses described above, after excluding patients with VTE/ATE within 3 years before the index dates.

Using univariable Cox regression analyses, predictors for developing VTE/ATE in CRC patients were explored for the second objective. For variables extracted from the DHM surveys, only CRC patients who were also DHM participants were included.

The last objective, the association between developing VTE/ATE and subsequent all-cause mortality, was evaluated by multivariable Cox regression analyses where the occurrence of thrombosis was treated as time-dependent exposure, using the Mantel-Byar method. In addition to a crude model, the following adjusted models were used: model 1, age, sex, immigration status and standardized household income; model 2, adjusting for model 1 plus history of comorbidities (as described in table S1); model 3, adjusting for model 2 plus tumor characteristics; model 4, adjusting for model 3 and time-dependent confounding, namely developing other types of TE during follow-up (except when the event(s) itself (themselves) was (were) studied as the exposure). As there might be causal associations between different types of TE, this raised a concern about time-varying confounding, affected by past exposure where the conventional time-dependent Cox regression becomes inappropriate [11]. For this reason, the inverse-probability-of-treatment weighting (IPTW) method was used in model 5, in which all covariates included in model 4 were used as denominator to calculate the (stabilized) weight.

For all the above analyses, we restricted the follow-up to one year in the main analysis, but results for a follow-up until 31/12/2019 were also presented. All statistical analyses were performed with SPSS® Statistics (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) and R program (R Core Team (2018). R Foundation for Statistical Computing, Vienna, Austria.

3. Results

3.1. Baseline characteristics

Between 1 January 2013 and 31 December 2018, 68.238 subjects developed incident CRC and were matched to 136.476 control subjects (fig. S1). The baseline characteristics of both cohorts are shown in table S2, with a mean age of 69.8 ± 11.1 years and a male sex proportion of 55.5 %. At baseline, 35.5 % of the tumors were proximal, 33.2 % was distal, 29.8 % was rectal and 1.7 % of undetermined or unspecified topography. Clinical stage 1 was identified for 22.2 % of all tumors, 25.6 % had stage 2, 30.3 % stage 3, 20 % stage 4 and 1.9 % of the tumors had an unclassified stage. For patients receiving cancer treatment, 78.4 % underwent surgery, 32.6 % received systemic chemotherapy and 16.2 % received radiotherapy. Comorbidities were mostly similar between cohorts, apart from anemia, hypertension, atrial fibrillation, diabetes mellitus and major bleeding history, which were more frequent in the

cancer patients.

A total of 6.665 cancer patients and 14,220 controls also participated in the DHM survey (table S3), with similar baseline characteristics compared to the total cancer cohort, except for a slightly older age distribution (mean age 73 versus 70 years). Overall, in both cohorts, 44.2 % had a BMI ranging between 25 and 30 kg/m2, 64.4 % had a very good or good physical health and 63.6 % had a history of smoking.

The baseline characteristics of CRC patients excluded from the study due to inconsistent registration years between the two data sources, were similar to that of the total CRC cohort, except for a higher proportion of rectal cancer and lower proportion of receiving surgery (Table S4).

3.2. Incidence of thromboembolism in the colorectal cancer cohort and control cohort

In total, 1324 CRC patients developed VTE and 1817 developed ATE during 1 year follow-up. Fig. 1 and table S5 show a cumulative incidence of VTE at 1 year follow-up in the cancer cohort of 1.93 % (95%CI 1.83–2.04), versus 0.24 % (95%CI 0.21–0.27) in the controls, which was 8.85-fold (95 % CI 7.83–9.99) higher, after adjusting for person characteristics and comorbidities (Table 1). A similar trend was seen for DVT and PE separately (HRs 8.40 (95%CI 6.85–10.29) and 8.86 (95%CI 7.69–10.21), respectively).

The 5-year cumulative VTE incidence in CRC patients was 3.24 % (95%CI 3.10–3.39) versus 1.10 % (95%CI 1.04–1.17) in the control subjects (HR 3.97 (95%CI 3.69–4.27)) (table S7 and S9).

For ATE, CRC patients had a 1-year incidence of 2.74 % (95 % CI 2.62–2.87), versus 1.88 % (95%CI 1.81–1.95) in controls (Fig. 1, table

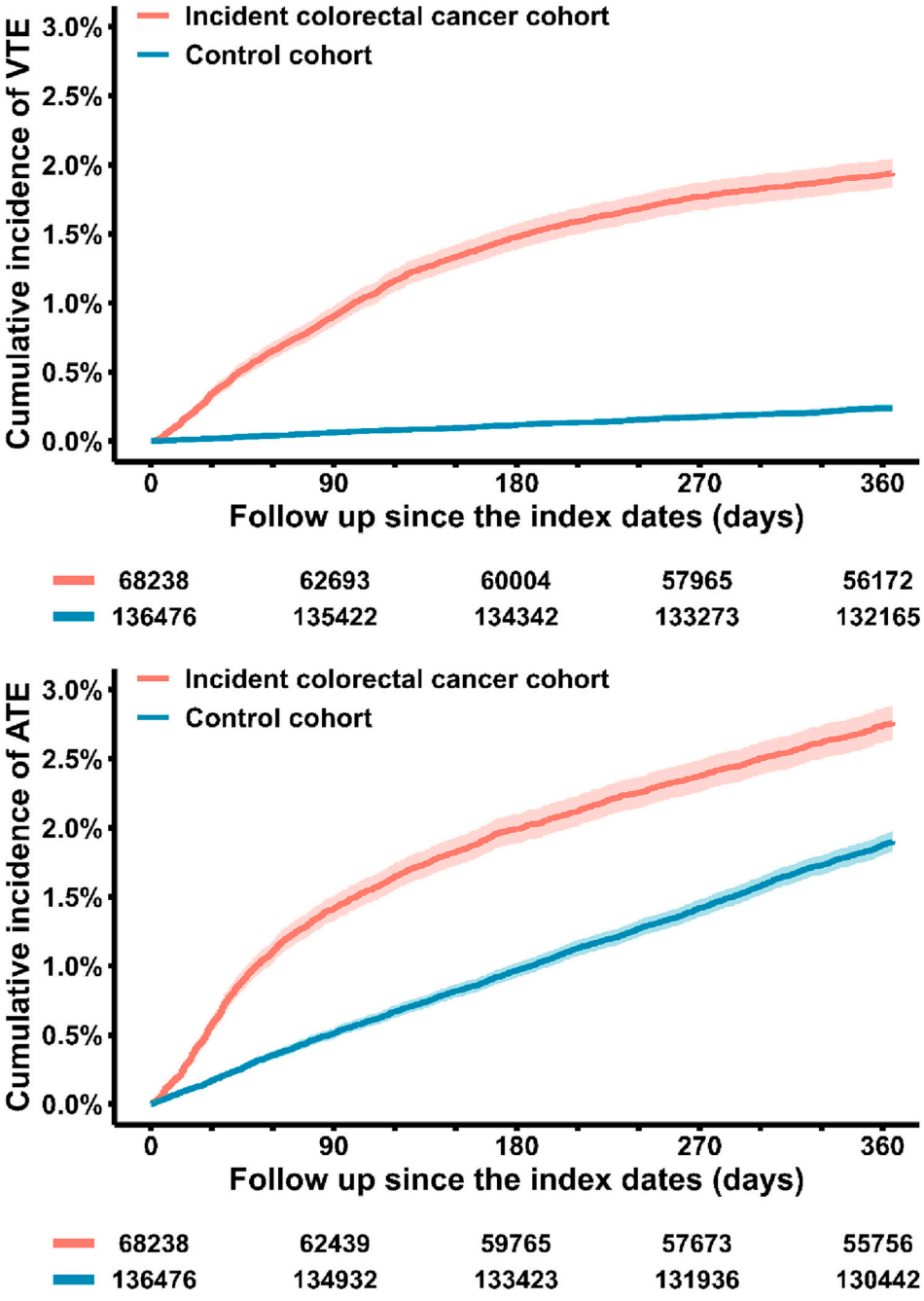

Fig. 1. Cumulative incidence curves of developing venous or arterial thromboembolism within one year after incident colorectal cancer diagnosis compared to the age and sex matched general population (control cohort)
Note: Estimated by the cumulative incidence competing risk method, in which all-cause death not due to VTE or ATE was considered as the competing event. VTE included deep vein thrombosis and/or pulmonary embolism; ATE included myocardial infarction, ischemic stroke, and/or systemic arterial embolism. Abbreviations: VTE, venous thromboembolism; ATE, arterial thromboembolism; CRC, colorectal cancer.

Table 1
Incidence rates and hazard ratios of study outcomes in colorectal cancer patients versus cancer-free control subjects after 1 year follow up.

Outcome	Cohort	No. at risk	Observation time (PYs)	No. events	Incidence rate (/100PYs)	HR (95 % CI)		
						Crude	Model 1	Model 2
VTE	Control subjects	136,476	134,213	327	0.24 (0.22–0.27)	1 (Reference)	1 (Reference)	1 (Reference)
	Colorectal cancer patients	68,238	60,451	1324	2.19 (2.07–2.31)	8.82 (7.82–9.96)	8.72 (7.72–9.85)	8.85 (7.83–9.99)
DVT	Control subjects	136,476	134,296	119	0.09 (0.07–0.11)	1 (Reference)	1 (Reference)	1 (Reference)
	Colorectal cancer patients	68,238	60,902	454	0.75 (0.68–0.82)	8.28 (6.76–10.13)	8.23 (6.72–10.08)	8.40 (6.85–10.29)
PE	Control subjects	136,476	134,250	240	0.18 (0.16–0.20)	1 (Reference)	1 (Reference)	1 (Reference)
	Colorectal cancer patients	68,238	60,634	981	1.62 (1.52–1.72)	8.88 (7.71–10.23)	8.74 (7.59–10.07)	8.86 (7.69–10.21)
ATE	Control subjects	136,476	133,289	2601	1.95 (1.88–2.03)	1 (Reference)	1 (Reference)	1 (Reference)
	Colorectal cancer patients	68,238	60,194	1887	3.13 (3.00–3.28)	1.59 (1.50–1.69)	1.60 (1.51–1.70)	1.57 (1.47–1.66)
MI	Control subjects	136,476	133,975	931	0.69 (0.65–0.74)	1 (Reference)	1 (Reference)	1 (Reference)
	Colorectal cancer patients	68,238	60,857	568	0.93 (0.86–1.01)	1.33 (1.20–1.48)	1.31 (1.18–1.46)	1.28 (1.15–1.42)
Ischemic stroke/TIA/ systemic arterial embolism	Control subjects	136,476	133,647	1716	1.28 (1.22–1.35)	1 (Reference)	1 (Reference)	1 (Reference)
	Colorectal cancer patients	68,238	60,467	1353	2.24 (2.12–2.36)	1.72 (1.61–1.85)	1.75 (1.63–1.88)	1.72 (1.60–1.85)

Model 1 was adjusted for immigration status and standardized household income; Model 2 was adjusted for model 1, asthma, chronic obstructive pulmonary disease, other chronic lung diseases, heart failure, hypertension, atrial fibrillation, aortic plaque, myocardial infarction history, valvular heart disease (rheumatic mitral stenosis and mechanical heart valves), other valvular heart disease, peripheral artery disease, abnormal liver function, diabetes mellitus, thyroid disease, abnormal renal function, anemia, coagulopathy, stroke/TIA history, arterial systemic embolism and thrombosis, venous thromboembolism, major bleeding history, Parkinson's disease, Alzheimer's disease, autoimmune disease, systemic connective tissue disorders.

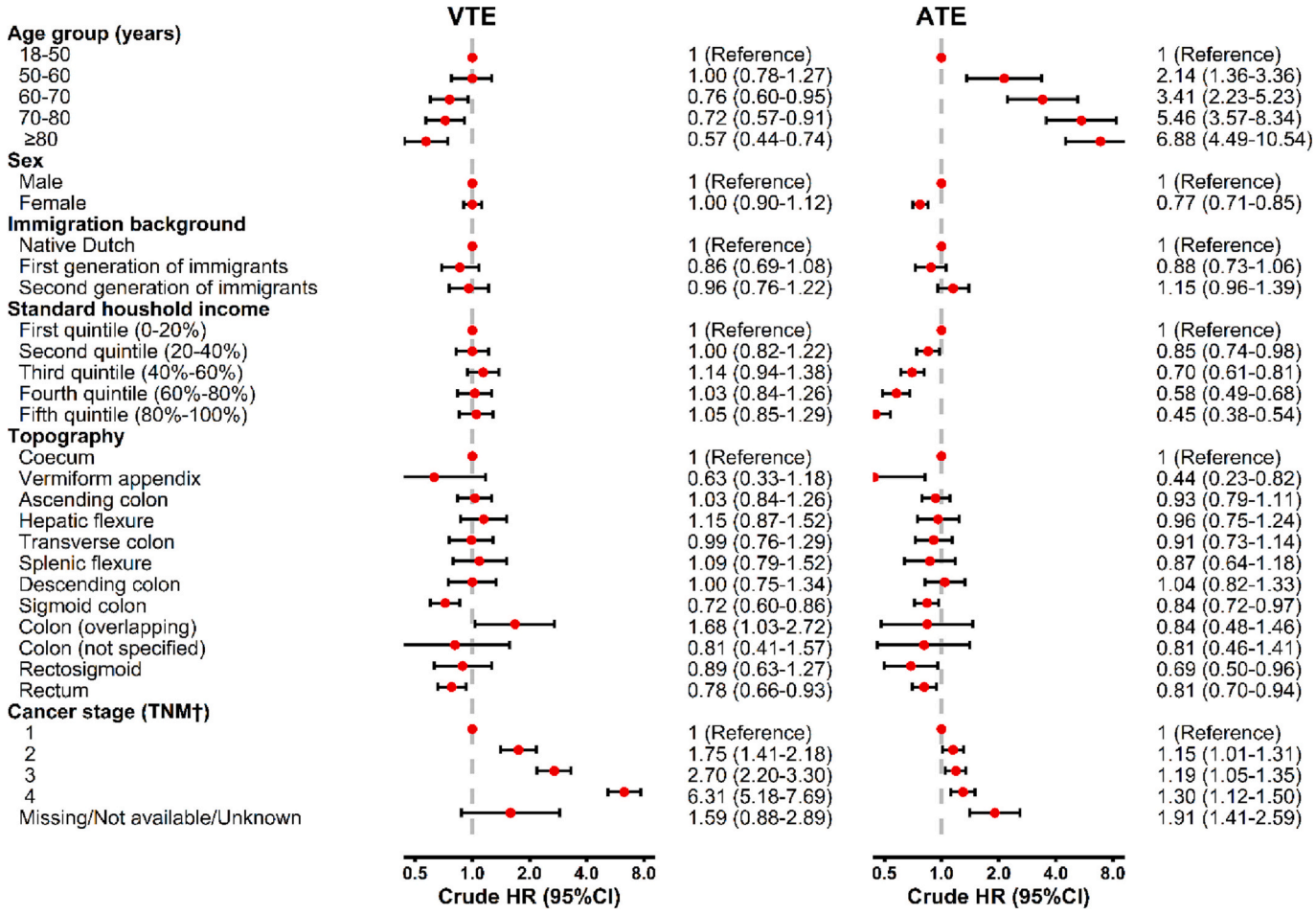

Fig. 2. Predictor variables in colorectal cancer patients for developing venous or arterial thromboembolism after 1 year follow up. Notes: The forest plots present the hazard ratios and 95 % confidence intervals of the associations. VTE included deep vein thrombosis and/or pulmonary embolism; ATE included myocardial infarction, ischemic stroke, and/or systemic arterial embolism. † Based on pathological (pTNM) supplemented with clinical (cTNM). Abbreviations: VTE, venous thromboembolism; ATE, arterial thromboembolism; TNM, the TNM classification of malignant tumors; COPD, chronic obstructive pulmonary disease; MHV, mechanical heart valves; VHD, valvular heart disease; TIA, transient ischemic attack.

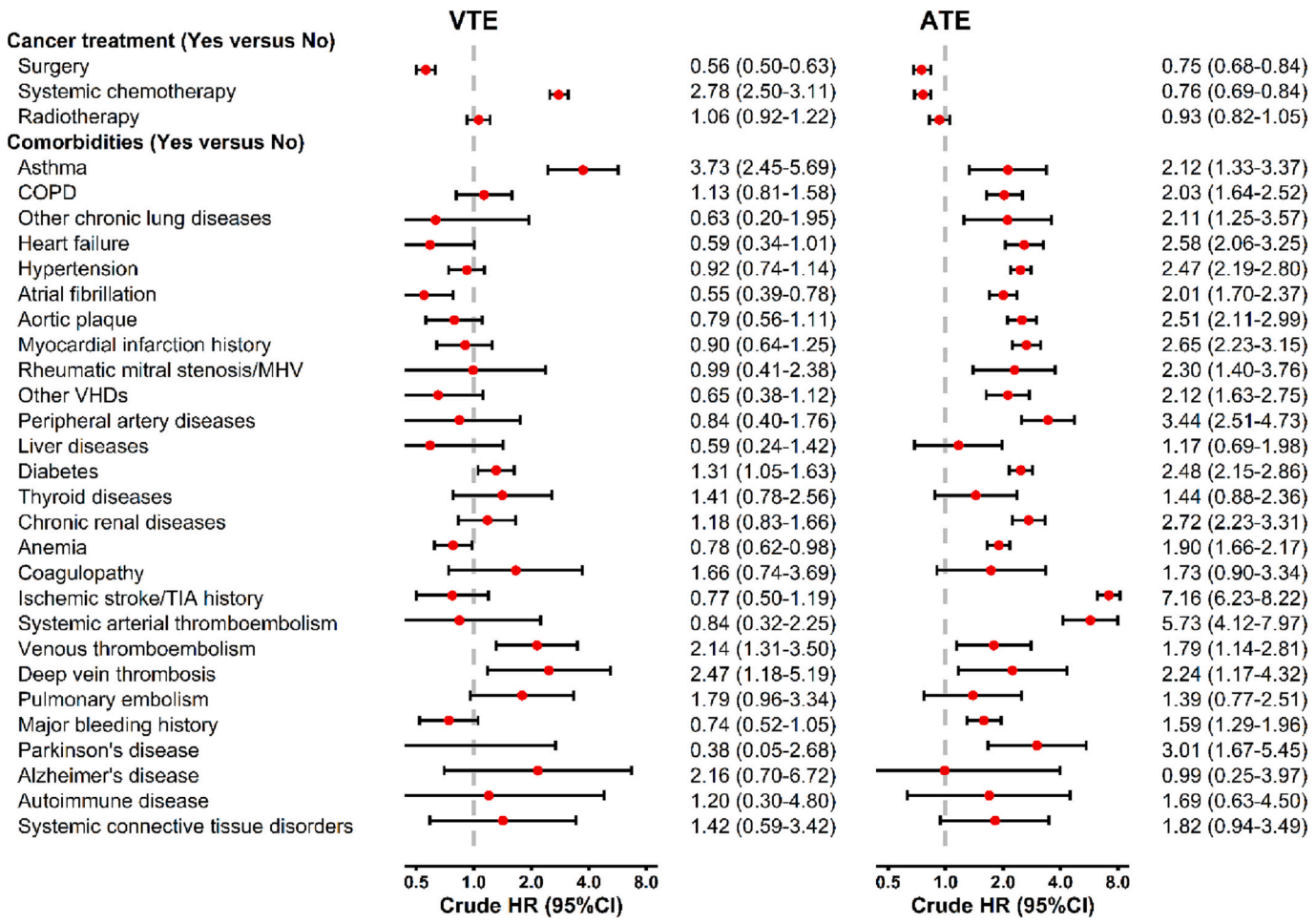

Fig. 2. (*continued*).

S5). The 1-year risk was 1.57-fold (95%CI 1.47–1.66) increased in CRC versus controls, after adjusting for person characteristics and comorbidities (Table 1) and the increase was at its highest at three months follow-up (HR 2.81 (95%CI 2.55–3.11). Both MI and stroke had comparable risk increases (HR 1.28 (95%CI 1.15–1.42) and 1.72 (95%CI 1.60–1.85), respectively).

After 1 year follow-up, the difference in risk of ATE between cancer patients and control subjects disappeared over time until the end of follow-up (table S8). The 5-year cumulative incidence in CRC patients was 7.02 % (95%CI 6.80–7.25) versus 7.76 % (95%CI 7.59–7.94) in controls, corresponding to an adjusted relative risk of 1.14 (95%CI 1.10–1.18) (table S9).

A similar pattern of results was seen when also adjusting the above analyses for available DHM variables (table S7, S10) and when patients with a history of any thromboembolic event within 3 years before the index date were excluded from the analyses (table S4, S7).

3.3. Predictors for developing thromboembolism in the colorectal cancer cohort

As presented in Fig. 2, advanced cancer stage, comorbid asthma, diabetes, and prior TE were associated with a higher risk of developing both VTE and ATE within one year after incident CRC diagnosis, whereas receiving surgery was associated with a lower risk. Younger age and receiving systemic chemotherapy were associated with higher risk of VTE but with lower risk of ATE. Male sex, lower socioeconomic status, and most studied comorbidities (including cardiovascular diseases and prior ATE) were only associated with ATE, but not VTE. Atrial fibrillation was associated with a lower risk of VTE. Of the DHM variables, only smoking history was associated with higher risk of VTE, while a lower education level, poorer physical health, depression, smoking history, and living alone were associated with a higher risk of ATE (Fig. 2, table S11).

3.4. Risk of all-cause mortality related to developing thromboembolism in colorectal cancer cohort

The occurrence of VTE in CRC patients was associated with a 4-fold increased risk of all-cause mortality (HR 3.99, 95%CI 3.59–4.43), compared to CRC patients without VTE (Table 2). After adjusting for age, sex, tumor topography, stage, comorbidities and developing other thromboembolic events during follow-up, an increased relative risk of 3.68 (95%CI 3.30–4.10) remained. The occurrence of ATE in CRC patients led to a crude 1-year relative risk of 3.29 (95%CI 2.99–3.62) for all-cause mortality, while after adjustment a 3.05-fold risk remained (95%CI 2.75–3.39) (Table 2). Similar patterns were seen for DVT/PE and MI/TIA/ischemic stroke/systemic arterial embolism separately (Table 2) or when follow-up was extended up to five years after CRC diagnosis (table S12).

4. Discussion

In this Dutch nationwide cohort study we provided comprehensive details on the occurrence of both venous and arterial thromboembolism in individuals with incident CRC. We found a 1.9 % 1-year risk of VTE in CRC patients, which was 9-fold higher than in the general population

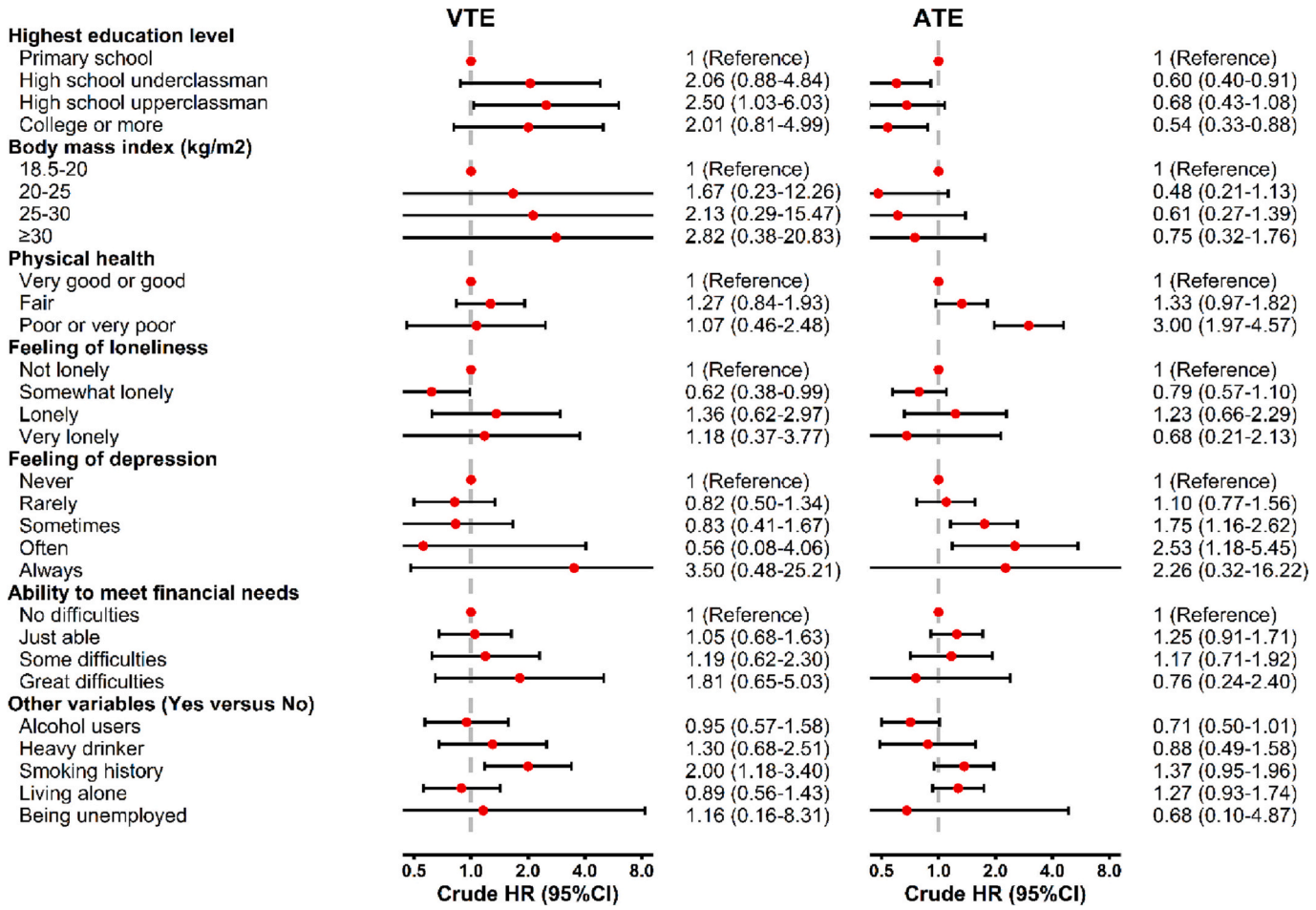

Fig. 2. (*continued*).

and stayed elevated up to five years after cancer. For ATE, the 1-year risk was 2.7 %, which was 1.6-fold higher than the general population, but decreased after the first year after cancer diagnosis to the baseline risk in the general population. Furthermore, various patient characteristics, including demographic characteristics, comorbidities and cancer characteristics were identified as potential predictors for developing VTE or ATE in these patients, which differed to some extent between VTE and ATE. Lastly, we reported a 3-fold increased risk of subsequent mortality after developing either VTE or ATE, independent of cancer stage, treatment and topography.

Numerous studies have investigated the risk of TE in CRC, but their risk estimations varied strongly, possibly due to different study populations, small sample sizes and different methodology. Among these, three other large population studies investigated the risk of VTE after CRC [9,10,12]. In the first, Chew et al. (n = 32.157, 1993–1995 United States) reported incidence rates ranging between 0.9 and 4.3 per 100-py, depending on stage, in accordance with our findings. Alcalay et al. (n = 68,142, 1993–1999 United States) found a slightly higher 1 year cumulative incidence (3.1 vs 2.4 %) than our study [9]. It is worth mentioning that this study may have overestimated the cumulative incidence since competing risk due to death was ignored [13] with a 2-year mortality rate of 35.5 % [9]. Lastly, Ahern et al. (n = 56,189, 1995–2010, Denmark) reported an IR of 0.95 per 100-py, lower than our findings (2.2 per 100-py) [12], possibly by differences in study populations and practices. Of note, all these studies were based on relatively old data which may have affected the results, due to changes in clinical care, diagnosing and treatment.

While VTE has been often investigated in relation to (colorectal) cancer, studies on ATE are limited, let alone studies in which the two are studied simultaneously. Interestingly, in absolute terms, the risk of ATE was higher than that of VTE (2.7 vs 1.9 %), but in relative terms the effect of cancer on risk was much stronger for VTE, with a relative risk of 9, compared to 1.6 for ATE. The higher absolute risk of ATE compared with VTE in CRC patients is obviously the result of a higher baseline risk in the general Dutch population, where the 1 year incidence of ATE compared to VTE was 2 per 100-py vs 0.2 per 100-py which is in accordance with previous data [14]. These findings imply that the burden of ATE in cancer patients is higher than that of VTE, but that the pathophysiological relation between VTE and cancer is much stronger. Additionally in our study, contrary to VTE, the increase in ATE risk was most prominent in the first 3 months after cancer, after which it remained stable and eventually decreased over time back to the baseline risk. This pattern has been previously shown by two large population-based cohort studies [3,4]. Navi et al. (n = 279.719, 2002–2011, United States) showed a 1.3-fold increased relative risk at 6 months, lower than in our cohort (2.2-fold). Mulder et al. (n = 458.462, 1997–2017, Denmark) included colon and rectal tumors separately, corresponding to relative risks of 2.6 and 3.1, respectively. One important difference between these studies that might explain the inconsistent findings, is that Navi et al. used a study population older than 65 years. Aging is known to be associated with an increased risk of ATE in general, which might lead to a decreased relative risk [15]. In addition, our study included only inpatient TE diagnoses, similar to Mulder et al., but not to Navi et al., who also included outpatient data. In outpatient clinics, TE events are more frequent in controls versus cancer patients, which might lead to a lower relative risk. The remarkably different time course of the risks of VTE and ATE after a CRC diagnosis can provide clues on the etiology of both events. This is, however, beyond the scope of our study

Table 2
Incidence rates and hazard ratios of the study outcome all-cause mortality in colorectal cancer patients with thrombotic event versus without thrombotic event at 1 year follow up.

	Observation time (PYs)	No. events	Incidence rate/100 PYs (95 % CI)	Hazard ratio (95 % CI)					
				Standard time-dependent Cox regression					IPTW (stabilized)
				Crude	Model 1	Model 2	Model 3	Model 4	Model 5
VTE									
No	60,451	10,842	17.94 (17.60–18.28)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	689	404	58.62 (53.04–64.63)	3.98 (3.59–4.40)	4.39 (3.97–4.86)	4.35 (3.93–4.82)	2.97 (2.68–3.29)	2.81 (2.54–3.12)	3.68 (3.30–4.10)
DVT									
No	60,902	11,112	18.25 (17.91–18.59)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	238	134	56.41 (47.26–66.81)	3.89 (3.28–4.61)	4.02 (3.39–4.77)	4.00 (3.37–4.75)	2.68 (2.25–3.18)	1.85 (1.55–2.22)	3.85 (3.24–4.58)
PE									
No	60,634	10,940	18.04 (17.71–18.38)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	506	306	60.50 (53.91–67.67)	4.01 (3.57–4.51)	4.51 (4.01–5.07)	4.45 (3.96–5.01)	3.08 (2.74–3.47)	2.65 (2.34–3.00)	3.95 (3.49–4.47)
ATE									
No	60,194	10,708	17.79 (17.45–18.13)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	946	538	56.88 (52.18–61.90)	3.29 (2.99–3.62)	2.70 (2.46–2.97)	2.61 (2.37–2.87)	2.92 (2.66–3.22)	2.83 (2.57–3.11)	3.05 (2.75–3.39)
Stroke/TIA/embolism									
No	60,467	10,863	17.97 (17.63–18.31)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	672	383	56.96 (51.40–62.96)	3.48 (3.13–3.88)	2.83 (2.54–3.16)	2.72 (2.43–3.03)	2.94 (2.63–3.28)	2.80 (2.51–3.13)	3.39 (3.01–3.81)
MI									
No	60,857	11,076	18.20 (17.86–18.54)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Yes	283	170	60.10 (51.41–69.84)	2.87 (2.40–3.44)	2.41 (2.01–2.88)	2.38 (1.99–2.85)	2.95 (2.46–3.54)	2.69 (2.25–3.23)	2.87 (2.37–3.47)

Model 1 was adjusted for age, sex, immigration status, and standard household income; Model 2 was adjusted for model 1, and asthma, chronic obstructive pulmonary disease, other chronic lung diseases, heart failure, hypertension, atrial fibrillation, aortic plaque, myocardial infarction history, valvular heart disease (rheumatic mitral stenosis and mechanical heart valves), other valvular heart disease, peripheral artery disease, abnormal liver function, diabetes mellitus, thyroid disease, abnormal renal function, anemia, coagulopathy, stroke/TIA history, arterial embolism and thrombosis, venous thromboembolism, major bleeding history, Parkinson's disease, Alzheimer's disease, autoimmune disease, systemic connective tissue disorders; Model 3 was adjusted for model 2, and primary topography, and stage based on pTNM supplemented with cTNM, organ surgery, systemic chemotherapy, and radiotherapy; Model 4 was adjusted for model 3, and developing myocardial infarction, stroke/TIA/embolism, deep vein thrombosis, and pulmonary embolism during the follow-up (except when the event(s) itself (themselves) was (were) studied as the exposure). Model 5, was adjusted for model 3, but with Inverse Probability Weighting (IPW). The covariates included in the Model 4 were used as the denominator to calculate the weight (except when the covariate(s) was (were) studied as the exposure), with weights truncated at the 1st /99th percentiles.
Abbreviations: PY, person-year; CI, confidence interval; TIA, transient ischemic attack; VTE, venous thromboembolism; MI, myocardial infarction.

but should be the focus of future research.

For identifying cancer patients at high-risk for VTE, several risk prediction scores have been developed, but none is yet available for ATE. The Khorana score is widely suggested to select VTE patients for primary thromboprophylaxis. However, the performance of this score is found to be suboptimal and over time, adaptations and other risk prediction scores have been published [16]. For our study we focused only on univariable associations, to explore and identify predictors. Therefore, these findings function to indicate an association and any causal explanations should not be sought for. The observed associations may form a basis for development or updating of a CRC-specific model for predicting TE, but this is beyond the scope of the current study.

The predictor profiles found for VTE and ATE differed greatly. For VTE, older age, increasing cancer stage and systemic chemotherapy were associated with a strongly increased risk, while surgery was associated with a decreased risk. Lastly, history of asthma, diabetes, VTE, diabetes and smoking were associated with a highly increased risk of VTE in CRC. For ATE, older age, male sex, and most comorbidities were associated with an increased risk of ATE, the strongest being histories of ATE, stroke/TIA/systemic arterial embolism, peripheral artery disease, abnormal renal function, hypertension and diabetes. Of interest, tumor stage and treatment were not associated with ATE. Only surgery was associated with a decreased risk. Lastly, a higher education was associated with a lower risk of ATE, just as poor general health and depression were associated with an increased risk of ATE. These findings fit in the common cardiovascular risk profile known for ATE [17].

Although the relative risks of VTE and ATE in CRC patients compared to the general population were clearly different, strikingly, the burden thereafter is of the same extent. CRC patients with VTE or ATE both had a 3-fold increased risk of 1-year mortality, compared to those without TE, also previously reported [4,9,10]. Interestingly, adjusting for a confounding effect by tumor stage, treatment, topography, and comorbidities hardly affected this increased risk which suggests a possible synergistic role for the combination of cancer and thrombosis in these patients with resulting higher mortality. The increased mortality risk remained elevated up to 5 years after cancer, demonstrating the need for more awareness of this additional burden in CAT patients as well as more research into the underlying mechanism of the association.

This study had several strengths worth mentioning. Thanks to the nationwide design with no selections, we had a large sample size with complete follow-up and recent data, which enabled us to provide updated, precise, and generalizable epidemiological information on CRC

and TE. Furthermore, we had extensive information on specific tumor variables, such as stage, treatment and topography, due to linkage with IKNL, as well as information on important lifestyle variables such as smoking and general health. Together, these present a comprehensive overview of factors associated with developing thromboembolism including an unbiased estimation of the survival impact of such an event.

However, there were also limitations. Using data registries, misclassification and measurement error cannot be avoided. CBS only registers hospital admissions (also including ER visits of more than 4 h duration), so some events could have been missed when diagnosed and treated in the outpatient clinic only (e.g. DVT and TIA), leading to an underestimation of incidences. Nevertheless, this may not have occurred frequently in cancer patients, as most cancer-associated events in The Netherlands are seen in hospital settings. For the control cohort, however, there might be a possibility of having missed outpatient diagnoses. In the general Dutch population, a large proportion of VTE (PE) or ATE (stroke/TIA) cases are still diagnosed and initially treated in an inpatient setting. Furthermore, since the incidences found for VTE and ATE in the control population are similar to those reported before [14], we think the proportion of missed events is low. In addition, we cannot completely ascertain that no recurrent CRC diagnoses were included, but we tried to minimize this by excluding those with a history of malignancy up to 3 years before diagnosis. As we only had access to CBS data starting from 2010, it was not possible to look further back in time.

Secondly, there were classification differences between IKNL and CBS; IKNL registers cancer at the date of the first histological or cytological confirmation of the tumor, whereas CBS registers at date of hospital admission, accounting for the 5237 mismatched patients excluded in fig. S1. Furthermore, IKNL only collects data on invasive tumors, accounting for approximately 46,000 excluded (fig. S1) patients with in-situ tumors in CBS. In addition, in the excluded patients, a higher portion of rectal cancer and fewer surgery cases were observed. Therefore, our results are less generalizable to the total CRC population, nevertheless, this would have only led to an underestimation of the relative risk compared to the general population. Thirdly, although we took many personal characteristics into account, residual confounding cannot be ruled out. Another limitation was the lack of data on other systemic cancer therapies (immune checkpoint inhibitors, VEGF inhibitors) in the Dutch CRC patients, as previous literature suggests they are associated with both an increased risk of VTE and ATE [2,18–21]. We also did not have sufficiently detailed data available on the use of anti-thrombotic therapy before or during follow-up, nevertheless, we think this could only have led to an underestimation of the risk sizes and taking this into account was not part of our research questions. Lastly, our results might have been biased by the fact that (colorectal) cancer patients are usually better and more carefully monitored, leading to earlier diagnosis of the thromboembolic outcomes in these patients than in the general population, although it is unlikely that TE would be completely missed in the general population.

For clinical practice, several findings are relevant: first, the increase in ATE risk appeared to be predominantly present for the first 3 months, whereas for VTE, the risk remained increased throughout the full follow-up period. This may impact the duration of thromboprophylaxis, if applied. Second, although the increase in VTE was more prominent on a relative scale, developing ATE presented a larger risk in absolute sense. As these risks are below threshold for primary thromboprophylaxis according to current guidelines, they do not justify this for the total CRC population. However, considering that these are average risks, measured in a diverse population, at an individual level there will be subjects with higher risks, who do require prophylactic strategies. Our study provides a novel predictor profile as basis for the development and improvement of current risk stratification models, aiming towards a CRC-specific model to identify high-risk patients. Lastly, more awareness is needed towards the mortality burden in CRC patients in whom thrombosis occurs.

Future mechanistic studies should focus on explaining the differences in relative risk and the different time course for VTE and ATE and on understanding the high mortality rates after CAT. Future clinical studies may concentrate on development and validation of prediction models for VTE and ATE and evaluate (thromboprophylactic) strategies to reduce mortality in cancer patients with established CAT.

To conclude, this large population-based study provided detailed knowledge on the risk of VTE and ATE in CRC patients, on their predictors and related mortality risk. These findings may drive TE prophylactic management decisions.

CRediT authorship contribution statement

RA, QC, SC were involved in the study conceptualization; RA and QC performed formal analyses; RA drafted the first version of the manuscript; QC, TH, HV, FK, WL, and SC interpreted the results, and critically revised the manuscript. All authors read and approved the manuscript. RA and QC had direct access to the data.

Declaration of competing interest

Q. Chen is supported by the Chinese Government Scholarship (No. 201906380148) for his PhD at the Leiden University Medical Center.

Prof. Dr. Klok has received research support from Bayer, Bristol-Myers Squibb, Actelion, Boston Scientific, Leo Pharma, The Netherlands Organization for Health Research and Development, The Dutch Thrombosis Association, The Dutch Heart Foundation and the Horizon Europe program, all outside this work and paid to his institution.

Data availability

The study used non-public microdata from Statistics Netherlands and cancer registry from Netherlands Comprehensive Cancer Organization, but these data cannot be shared directly by the authors. Under certain conditions, these data are accessible for statistical and scientific research. For further information, contact microdata@cbs.nl and gegevensaanvraag@iknl.nl.

Acknowledgements

The authors thank the registration team of the Netherlands Comprehensive Cancer Organization (IKNL) for the collection of data for the Netherlands Cancer Registry. Results are based on calculations by the authors using non-public microdata made available by Statistics Netherlands. The authors also thank the Community Health Services, Statistics Netherlands, and the National Institute for Public Health and the Environment, for making data from the Public Health Monitor Adults and Elderly (2012 and 2016) available.

QC is supported by the Chinese Government Scholarship (No. 201906380148) for his PhD study at the Leiden University Medical Center.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2023.06.028.

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