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Estimating Risk of Venous Thromboembolism in Patients with Cancer in the Presence of Competing Mortality

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Summary

Background—In studies on cancer-associated venous thromboembolism (VTE), patients are not only at risk for VTE but may also die from their underlying malignancy.

Objectives—In this competing-risk (CR) scenario, we systematically compare the performance of standard (Kaplan-Meier-estimator (1-KM), log-rank-test (LRT), Cox model (CM)) and specific CR methods for time-to-VTE-analysis.

Patients & methods—1542 cancer patients were prospectively followed for a median 24 months. VTE occurred in 112 patients (7.3%), and 572 patients (37.1%) died.

Results—In comparison with the CR method, 1-KM slightly overestimated the cumulative incidence of VTE (VTE rate at 12 and 24 months (1-KM vs. CR): 7.22% vs. 6.74%, and 8.40% vs. 7.54%). Greater bias was revealed in tumor entities with high early mortality (e.g. pancreatic cancer, n=99, VTE rate at 24 months: 28.37% vs. 19.30%). Comparing the hazard of VTE between patients with low and high baseline D-Dimer, the CM yielded a higher hazard ratio than the corresponding CR model (Hazard vs. Subhazard ratio (95%CI): 2.85 (1.92–4.21) vs. 2.47 (1.67–3.65)). Similarly, the LRT overestimated the strength of association between D-Dimer and VTE risk (χ^2 test-statistic on 1 degree of freedom; LRT vs. Gray's test = 29.88 vs. 21.34).

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Conceived and designed the study: CA FP IP. Analyzed the data: FP AK. Interpreted the results: CA FP AK CZ IP. Wrote the first draft of the manuscript: CA FP. Contributed to the writing of the manuscript: CA FP AK CZ IP. Agree with the manuscript's results and conclusions: CA FP AK CZ IP. ICMJE criteria for authorship read and met: CA FP AK CZ IP.

Disclosure of Conflicts of Interest

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Conclusion—These results show that in patients with cancer at risk for VTE and death, standard time-to-VTE analysis methods yield biased results. The magnitude of bias is a direct function of competing mortality. Consequently, bias tends to be negligible in cancer patient populations with low mortality, but can be considerable in populations at high risk of death.

Keywords

Bias; Cancer; Competing Risks; Venous thromboembolism

Introduction

Venous thromboembolism (VTE) is a highly prevalent complication in patients with cancer and leads to an increased risk of mortality.[1] During the last decade, cancer-associated VTE has become the subject of several observational and interventional cohort studies [2–4]. While the primary outcome of interest in these studies is the *time-to-VTE* (represented by e.g. a *cumulative VTE incidence* or a *VTE hazard function*), cancer patients recruited into these studies are not only at risk for VTE, but may also die from their underlying malignancy. This represents a so-called *competing risk* scenario, in which the occurrence of one event may significantly alter the probability that the other event occurs.[5] Specifically, death can be considered an important *competing event* in the follow-up of cancer patients enrolled in VTE trials, as it precludes VTE from being observed.[6]

Routinely used time-to-VTE analysis methods like the *complement of the Kaplan-Meier estimator* (1-KM), the *log-rank test* (LRT), and the *Cox proportional hazards model* (CM) ignore these competing risks. Statistically, these methods treat VTE as the only possible event, while patients who remain VTE-free but die or are lost-to-follow-up are censored under the assumption of a *non-informative censoring mechanism* (also known as *independent* or *random* censoring). Non-informative censoring in this setting implies that the future VTE status of a patient is assumed to be unrelated to whether he is censored or not. With death instantly reducing a cancer patient's VTE risk to zero, this assumption is likely untenable, and bias may result.[7, 8]

To address this concern, an alternative *competing risk* (CR) framework has been recommended. These CR methods do not censor patients at the time of death, but treat death as a distinct event that reduces the number of patients at risk for VTE.[5, 6] Thereby the “true” probability of experiencing VTE in the population is disentangled from the influence of competing mortality, which theoretically leads to unbiased and meaningfully interpretable results.[5, 7]

Only with one exception,[9] clinical studies in the cancer and VTE setting uniformly applied traditional methods (1-KM, LRT, CM) for VTE analysis.[8, 9] Despite abundant theoretical work on the competing risk issue, real-world comparisons between standard and CR methodology in empirical data are scarce.[2, 6] Campigotto et al. addressed this issue *in silico* using simulation, and found that the KM method dramatically overestimated VTE rates when death was present as a competing event.[7, 8] In simulations with high early mortality, absolute and relative overestimations of 3-month VTE incidence of more than 100% were observed with the KM approach, respectively.[7] This is worrisome, because

given such a magnitude of bias would be present in clinical studies on cancer-associated VTE, it may be possible that biased VTE rates or treatment effect estimates had lead to wrong conclusions. Hence, the magnitude of bias between standard and CR methodology in VTE studies with competing mortality remains to be explored in the real-world setting.

In this study, we used data from 1542 cancer patients at risk for both VTE and death to systematically compare the real-world performance of the standard and CR approach for time-to-VTE analysis. Our aim was to empirically investigate the source and magnitude of bias between the two approaches. We studied the absolute and relative differences in VTE incidence between the two methods, both in the overall population as well as within different tumour subtypes that feature distinct mortality and VTE rate patterns. Further, we assessed the bias between the two methods according to D-Dimer, a biomarker that is both prognostic for VTE and mortality. A systematic comparison was also performed for hypothesis tests and time-to-event regression techniques. This will allow appreciating how competing deaths influence VTE rate estimates *in vivo*, and give rise to practical recommendations for the analysis of cancer and VTE studies.

Methods

Study population and design

In this analysis, 1542 cancer patients from the Vienna Cancer and Thrombosis Study (CATS) were included. CATS is a prospective observational cohort study that has been implemented to identify prognostic factors and biomarkers for VTE in patients with cancer. The detailed methodology of the study, as well as inclusion and exclusion criteria, have already been described in previous reports.[3] Briefly, patients with newly diagnosed cancer or progression of disease after partial or complete remission were offered to participate in the study. Patients with the following cancer sites were included: breast, lung, stomach, pancreas, brain, colorectal, kidney, prostate, myeloma, lymphoma and others (mainly sarcomas and cancers of the genito-urinary tract). Exclusion criteria were present radiotherapy, recent surgery (within the last 2 weeks) and recent chemotherapy (within the last 3 months) and VTE that has occurred within 3 months prior to study inclusion. At inclusion, venous blood samples were drawn for laboratory analysis, and patients were then prospectively followed for a 2-year observational period until the occurrence of VTE, death, withdrawal of consent, or loss-of-follow-up. The main outcome measure was objectively confirmed symptomatic or fatal VTE (deep vein thrombosis and/or pulmonary embolism) within 2 years after study entry as described previously.[3] The 1542 patients were followed-up for a median duration of 24.0 months. During this period, VTE occurred in 112 (7.3%) patients, and 572 (37.1%) patients died.

Statistical Analysis

We performed all statistical analyses using the packages Stata (Windows version 12.0, Stata Corp, TX, USA) and R (Version 3.0.2., R Core Development Team). For the standard approach, cumulative incidence functions (CIFs) for VTE risk with point estimates and 95% confidence intervals were estimated non-parametrically using the complement of the Kaplan-Meier product limit estimator (denoted in the following as 1-KM). For the

competing risks approach, CIFs were generated using Stata's user-contributed *stcompet* suite, which implements the cumulative incidence and variance estimators proposed by Marubini & Valsecchi, and Choudhury, respectively.[10] Death-from-any-cause was incorporated as the competing event of interest in all following CR calculations. For subgroup analyses within distinct tumor entities of CATS, we excluded the following three cancer sites due to a low number of VTE events to generate meaningful step functions: Kidney (n=40, 1 VTE event), Prostate (n=148, 3 VTE events), Myeloma (n=38, 2 VTE events). Data on baseline D-Dimer levels were available for 1361 patients (11.7% missing). D-Dimer was dichotomized into a binary variable with the upper quartile (Q3) of its distribution as the relevant cut-off (i.e. < or ≥ 75th percentile, as found in Ay et al.).[4] CIFs between patients with high and low baseline D-Dimer were compared using the log-rank test (LRT, standard methodology), and its competing risk correlate, *Gray's test* (GT, CumIncidence package in R).[5, 8] Modeling of time-to-VTE according to D-Dimer level was performed with the Cox proportional hazards model (CM, standard methodology) and the *Fine & Gray proportional subhazards model* (FGM, competing risk methodology, *sterreg* in Stata).[11] The proportional (sub-)hazards assumption was examined for both models by fitting an interaction between the binary D-Dimer variable and the natural logarithm of continuous follow-up time. The full analysis code is available on request from the authors.

Results

Comparison of 1-KM and CR for VTE rate estimation in patients with cancer

In the 1542 study participants, 1-KM consistently overestimated the cumulative incidence of VTE at all times of follow-up (Figure 1, Table 1). Whereas the 1-KM estimator yielded VTE rates of 5.75%, 7.22%, and 8.40% at 6, 12, and 24 months of follow-up, the CR estimator produced lower rates of 5.50%, 6.74, and 7.54%, respectively. Mortality was clearly present as a competing risk in this study population, with 179 deaths during the first 6 months and a cumulative 6-month failure probability from death of 11.86% (95% CI: 10.33 – 13.60).

The difference between 1-KM and CR became apparent after around 6 months of follow-up, and progressively increased thereafter (Figure 1). The absolute difference (in percentage points (%pts)) between the two methods remained small (<1 %pts) at all times of follow-up. In relative terms, 1-KM overestimated the cumulative incidence of VTE by 4.5%, 7.1%, and 11.4% at 6, 12, and 24 months, respectively (Table 1).

Comparison of 1-KM and CR for VTE rate estimation within distinct tumor entities

The bias between 1-KM and CR VTE rate estimates showed considerable variation between the studied tumor entities (Figure 2, Table 1). The differences were consistently higher in tumor subpopulations with higher VTE incidence and mortality (e.g. pancreatic or gastric cancer). The highest absolute and relative bias between the two methods was observed in pancreatic cancer patients (9%pts and 47% at 2 years of follow-up, respectively; Table 1). In tumor entities with only few competing events (e.g. lymphoma or breast cancer), the bias between the two methods was minimal (Table 1, Figure 2).

Time-to-VTE analysis according to baseline D-Dimer levels

Patients with high baseline D-Dimer levels (i.e. 75th percentile (Q3), n=343) had a higher cumulative incidence of both VTE and mortality than patients with low baseline D-Dimer (i.e. < Q3, n=1018, Table 2, Figure 3). Here, 1-KM consistently overestimated VTE incidence in both groups. However, the absolute and relative differences between (1-KM) and CR were considerably higher in patients with D-Dimer ≥ Q3 than in patients with D-Dimer < Q3.

Comparing the VTE cumulative incidence functions (CIFs) of the two D-Dimer groups, both the logrank-test (LRT) and Gray's test (GT) gave strong evidence for a difference in CIFs (both $p < 0.001$). Both tests yield a χ^2 test statistic on 1 degree of freedom. However, the LRT test statistic was greater than the corresponding statistic of GT (29.88 vs. 21.34).

Finally, time-to-VTE according to D-Dimer was modeled with the Cox model (CM) and its competing risk correlate, the Fine & Gray model (FGM). Here, the CM estimated that patients with high D-Dimer have a 2.85 times higher hazard of VTE than patients with low D-Dimer (hazard ratio (HR) = 2.85 (95% CI: 1.92–4.21), $p < 0.001$). In contrast, the FGM estimated the subhazard between the two groups differed only by a factor of 2.47 (subhazard ratio (SHR) = 2.47 (95% CI: 1.67–3.65), $p < 0.001$). During model validation, no (HR for the interaction between D-Dimer and log(time) = 0.77 (95% CI: 0.53 – 1.13), $p = 0.19$) and some (SHR for the interaction between D-Dimer and log(time) = 0.70 (95% CI: 0.49 – 0.99), $p = 0.05$) evidence for non-proportional (sub-) hazards was observed for the CM and FGM, respectively.

Discussion

In this large prospective study of 1542 cancer patients at risk for VTE, we have found that traditional time-to-event methodology yields biased VTE rate estimates, hazard ratios, and p-values when death is present as a competing risk. This raises important methodological and practical issues for the analysis of time-to-VTE studies in patients with cancer.

Exploring the magnitude of bias between 1-KM and CR for VTE rate estimation

In the overall population, death was clearly present as a competing risk, and the KM method consistently overestimated VTE incidence. Nevertheless, the absolute and relative bias between 1-KM and CR was very small. Interestingly, further subgroup analyses in different tumor entities revealed that the bias was highly depending on the extent of competing mortality. In detail, cancers with worse survival exhibited a higher bias between 1-KM and CR. This finding is in line with pertinent theory and simulations, which indicate that the bias is a positive function of competing mortality.[12] Importantly, the VTE rate estimators of the standard and CR approach are statistically identical given no competing deaths are observed. [8] This means that in a cancer and VTE study without competing mortality, the two approaches would yield identical VTE rates and hazard ratios. Our *in vivo* data clearly illustrate this phenomenon; e.g. in lymphoma patients who experienced only minimal competing mortality, we observed nearly identical VTE CIFs according to the KM and CR method. Collectively, this suggests that incorporating competing mortality into VTE rate

estimation may be particularly important when extensive mortality is anticipated (i.e. poor survival prognosis of a cancer cohort and/or tumors with inherently poor prognosis).

Across the different cancer subgroups, we also observed a positive relationship between VTE incidence and magnitude of bias. However, it is important to acknowledge that the statistical drive behind the bias between 1-KM and CR is competing mortality, and not VTE incidence. The number of competing deaths influences the number of VTE events, and subsequently the probability of VTE in the study population.[7] In contrast, this is not the case the other way round. Although a VTE event may clinically increase the probability that a patient dies, this is statistically irrelevant for time-to-VTE studies because the primary endpoint is VTE and not mortality. In time-to-VTE studies, patients that experience VTE only contribute follow-up time until the time of VTE occurrence, and an event that happens thereafter (e.g. death) does not influence the computation of the statistical estimators. Thus, the present relationship between higher magnitude of bias and higher VTE incidence roots in the confounding fact that the tumor subgroups with higher VTE incidence also had higher mortality (e.g. pancreatic or gastric cancer).

Campigotto et al. have addressed the magnitude of bias between the two approaches for VTE rate estimation *in silico* using three simulated cancer cohorts with assumed median survival times of 5 months, 2 months, and <1 month.[7, 8] These simulations produced 1-KM VTE rates that overestimated the “true” CR VTE rates in relative terms by up to 280% at 12 months of follow-up. Our data do not provide an *in vivo* correlate for these simulations. Given that high competing mortality (represented by a short median survival) is the crucial force of bias, this discrepancy may be explained by the different median survivals of our real world and Campigotto et al.’s simulation cohorts. Even in our subgroups with the poorest prognosis (e.g. pancreatic cancer, median survival 1.1 years), competing mortality was substantially lower than what was assumed in the simulations, and relative bias at 12 months was “only” 14.9%. Nevertheless, these simulations clearly illustrate the impact of competing mortality on bias, and might be of interest for selected clinical situations (e.g. trials on the prevention of recurrent VTE in terminally-ill patients with metastasized cancer).

Biomarker analysis: Bias between traditional and CR methods according to D-Dimer

We used baseline D-Dimer as a model biomarker to compare the performance of the LRT and the CM with their CR correlates. D-Dimer is further interesting, because it is known to be both predictive for the primary VTE endpoint as well as for mortality.[4, 13] This has been highlighted by Campigotto et al., who further stressed that it is unclear how the two approaches perform in such a situation of “parallel” prognostic impact.[7] In analogy to our prior results, we found that 1-KM overestimated the cumulative incidence of VTE, and that the extent of overestimation was higher in the group with high baseline D-Dimer. The latter group also featured considerably higher mortality than the group with low D-Dimer, which likely explains the higher bias.

In modeling time-to-VTE, we observed that the CM overestimated the difference in VTE hazard between the two D-Dimer groups (i.e. gave a higher hazard ratio than the FGM). Similarly, the LRT “overestimated” the statistical significance of the difference in CIFs between the two groups (as indicated by a greater χ^2 test statistic and a subsequently smaller

p-value). Synoptically, this shows that competing mortality not only affects the validity of VTE rate estimates, but also the results of between-group VTE rate comparisons (p-values from the LRT) and modeling of time-to-VTE (hazard ratios from the CM). Further, we found evidence for a violation of the proportional hazards assumption (PHA) in the FGM, but not in the CM. A PHA violation may indicate that the “effect” of a predictor variable on an outcome is not constant over time. In detail, the (sub-)hazard ratio of the D-Dimer-log(time)-interaction was <1 in both the CM and the FGM, which is consistent with a decreasing “effect” of baseline D-Dimer on VTE risk over time. Given the adverse impact of high D-Dimer on both survival *and* VTE, this time-dependency is clinically plausible: Higher competing mortality in the D-Dimer Q3-group would preferentially remove the individuals with the highest VTE risk during early follow-up, which *over time* leads to a relative enrichment of the D-Dimer Q3-group with lower-VTE-risk patients, and a progressive dilution of the biomarker’s VTE-predictive potential. While the FGM gave evidence for such a time-dependency, the CM did not. Collectively, this suggests that competing mortality can also obscure potential violations of the PHA, and/or prevent insights about time-specific prediction patterns of a biomarker.

Competing risk consequences and the validity of previous VTE studies in patients with cancer

So far theory, simulation studies, and our empirical findings show that in the competing mortality setting of cancer-associated VTE studies, traditional analysis methods (1-KM, LRT, CM) are biased.[5, 7, 8] However, Parpia et al. have identified an interesting exception from these findings that applies to the LRT and the CM.[6] In 2011, these authors performed a CR re-analysis of a randomized trial that compared the effectiveness of low-molecular weight heparin (LMWH) vs. oral anticoagulation (OAC) for the prevention of recurrent VTE in patients with advanced cancer (the CLOT trial). To our knowledge, this is the only re-analysis of a cancer-associated VTE trial in the present literature. CLOT was originally analyzed with standard methodology (1-KM, LRT, and CM), and published in 2003.[2] Upon re-analysis Parpia et al. found, in accordance with our results, that 1-KM – in comparison to CR analysis - heavily overestimated the cumulative incidence of VTE both in the LMWH group (17.2% vs. 12.0%) and the OAC group (8.7% vs. 6.0%).[6] However, in contrast to our findings, the LRT and the CM estimates were very similar to their CR correlates (LRT vs. GT χ^2 test statistic on 1 degree of freedom: 9.5 vs. 7.6; CM vs. FGM: HR=0.48 vs. SHR=0.47). The authors concluded that bias was absent because mortality was the same in both study arms (complete overlap of KM survival curves at all times of follow-up). Technically, this lead to a similar *relative* overestimation of VTE incidence by around 30% in each study arm, and an unbiased *relative* treatment effect estimate (hazard ratio). However, this constellation of findings can also be interpreted that LMWH and OAC had a comparable effect on mortality, and/or that randomization was effective in generating balanced treatment groups with respect to risk of death. Hence, Parpia et al. highlight a special situation in a randomized trial in which the bias between standard and CR methodology is negligible. However, we believe that the CR approach is superior over standard methods even in this special randomized situation with mortality-risk-balanced treatment arms, because it does not overestimate VTE cumulative incidence. Most importantly, standard methodology will be particularly prone to bias in observational studies

(e.g. VTE biomarker studies), because many predictive biomarkers for VTE such as D-Dimer are also prognostic for mortality.[3, 4, 13] This will distort LRT p-values and CM hazard ratios for VTE, which is clearly illustrated in our study according to D-Dimer. Finally, this allows us to deduce that bias will occur even in a randomized trial if one intervention has a different effect on mortality than the other, or if one intervention exerts a proportional effect on the hazard of VTE in a CM but a non-proportional effect on the subhazard of VTE in an FGM, and vice versa.

As the magnitude of bias between 1-KM and CR is a positive function of competing mortality, our results may allow for the careful speculation that not all prior cancer and VTE studies analyzed with standard methods are invalid. It is conceivable that the bias may be negligible in studies with low overall mortality, balanced mortality between study arms, and/or stable relative treatment or biomarker effects over time. Conversely, a CR re-analysis may be warranted for biomarker studies with high competing mortality, randomized trials with interventions that have a differential effect on mortality, and non-randomized trials with a potential imbalance in mortality risk factors between study groups. Nevertheless, according to these assumptions the effect of competing mortality can only be crudely anticipated, and one only knows its true impact when a CR re-analysis is performed.

Conclusion

In cancer patients at risk for VTE and death, standard time-to-VTE analysis techniques generate biased results. The magnitude of bias is a direct function of competing mortality. Consequently, bias tends to be negligible in cancer patient populations with low mortality, but can be considerable in populations at high risk of death. CR methods that incorporate mortality are unbiased alternatives and should be used instead.

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Figure 1. Comparison of 1-KM vs.

CR for VTE rate estimation in the total study population (n=1542); Risktable indicates the number of patients at risk at the beginning of each time interval and in brackets the number of VTE events during each time interval

Figure 2. Comparison of 1-KM vs.

CR for VTE rate estimation in patients with pancreatic cancer, lung cancer, and lymphoma; Risktable indicates the number of patients at risk at the beginning of each time interval and in brackets the number of VTE events during each time interval

Figure 3. Comparison of 1-KM vs.

CR for VTE rate estimation in patients with high (>75th percentile) and low (< 75th percentile) baseline D-Dimer (n=1361); Risktable indicates the number of patients at risk at the beginning of each time interval and in brackets the number of VTE events during each time interval

Table 1
Comparison of 1-KM and CR for VTE rate estimation in the total study population and according to single tumor entities listed by increasing early mortality at 6 months of follow-up (n=1542)

Population	6-month Mortality (95% CI)	6-month Cumulative Incidence of VTE (95% CI)	abs rel	12-month Cumulative Incidence of VTE (95% CI)	abs rel	24-month Cumulative Incidence of VTE (95% CI)	abs rel
Total study population (n=1542; 112 VTE events, 511 deaths)							
	11.86% (10.33 – 13.60)	1-KM: 5.75% (4.67 – 7.07)	0.25	1-KM: 7.22% (5.98 – 8.71)	0.48	1-KM: 8.40% (7.00 – 10.07)	0.86
		CR: 5.50% (4.43 – 6.72)	4.55	CR: 6.74% (5.55 – 8.08)	7.12	CR: 7.54% (6.27 – 8.96)	11.41
Lymphoma (n=234; 11 VTE events, 28 deaths)							
	2.63% (1.19 – 5.77)	1-KM: 3.02% (1.45 – 6.23)	0.01	1-KM: 4.42% (2.40 – 8.06)	0.06	1-KM: 4.92% (2.75 – 8.71)	0.09
		CR: 3.01% (1.34 – 5.82)	0.33	CR: 4.36% (2.23 – 7.57)	1.38	CR: 4.83% (2.56 – 8.17)	1.86
Breast cancer (n=225; 5 VTE events, 33 deaths)							
	4.98% (2.79 – 8.81)	1-KM: 2.32% (0.97 – 5.47)	0.06	1-KM: 2.32% (0.97 – 5.47)	0.06	1-KM: 2.32% (0.97 – 5.47)	0.06
		CR: 2.26% (0.85 – 4.90)	2.65	CR: 2.26% (0.85 – 4.90)	2.65	CR: 2.26% (0.85 – 4.90)	2.65
Colon cancer (n=159; 13 VTE events, 52 deaths)							
	10.99% (6.98 – 17.09)	1-KM: 6.53% (3.57 – 11.80)	0.17	1-KM: 8.99% (5.30 – 15.05)	0.60	1-KM: 8.99% (5.30 – 15.05)	0.60
		CR: 6.36% (3.25 – 10.90)	2.67	CR: 8.39% (4.70 – 13.42)	7.15	CR: 8.39% (4.70 – 13.42)	7.15
Brain cancer (n=200; 29 VTE events, 82 deaths)							
	16.43% (11.91 – 22.43)	1-KM: 12.75% (8.72 – 18.45)	0.68	1-KM: 14.64% (10.26 – 20.66)	1.01	1-KM: 16.94% (11.88 – 23.85)	1.98
		CR: 12.07% (8.00 – 17.02)	5.63	CR: 13.63% (9.29 – 18.80)	7.41	CR: 14.96% (10.34 – 20.38)	13.24
Lung cancer (n=250; 16 VTE events, 150 deaths)							
	20.52% (15.97 – 26.17)	1-KM: 6.00% (3.52 – 10.13)	0.69	1-KM: 7.90% (4.87 – 12.67)	1.31	1-KM: 7.90% (4.87 – 12.67)	1.31
		CR: 5.31% (2.97 – 8.61)	12.99	CR: 6.59% (3.92 – 10.17)	19.88	CR: 6.59% (3.92 – 10.17)	19.88
Pancreatic cancer (n=99; 18 VTE events, 55 deaths)							
	27.23% (19.41 – 37.38)	1-KM: 14.56% (8.71 – 23.82)	1.36	1-KM: 17.55% (10.90 – 27.59)	2.27	1-KM: 28.37% (16.55 – 45.93)	9.07

Population	6-month Mortality (95% CI)	6-month Cumulative Incidence of VTE (95% CI)	abs rel	12-month Cumulative Incidence of VTE (95% CI)	abs rel	24-month Cumulative Incidence of VTE (95% CI)	abs rel
		CR: 13.20% (7.42 – 20.67)	10.30	CR: 15.28% (9.00 – 23.08)	14.86	CR: 19.30% (11.95 – 27.98)	46.99
Gastric cancer (n=51; 8 VTE events, 32 deaths)							
	27.45% (17.27 – 41.90)	1-KM: 12.73% (5.92 – 26.21)	0.96	1-KM: 19.99% (10.09 – 37.37)	4.01	1-KM: 19.99% 10.09 – 37.37)	4.01
		CR: 11.77% (4.78 – 22.17)	8.15	CR: 15.98% (7.46 – 27.37)	25.09	CR: 15.98% (7.46 – 27.37)	25.09

Abbreviations: 1-KM: Complement of the Kaplan-Meier product limit estimate; CR: Competing risk estimate; VTE: Venous thromboembolism; CI: Confidence interval; abs: Absolute overestimation of VTE cumulative incidence with 1-KM in %age points; rel: Relative overestimation of VTE cumulative incidence with 1-KM in %

Table 2
Comparison of 1-KM and CR for VTE rate estimation by baseline D-Dimer level
(n=1361)

Population	Mortality at 6 months (95% CI)	6-month Cumulative Incidence of VTE (95% CI)	abs rel	12-month Cumulative Incidence of VTE (95% CI)	abs rel	24-month Cumulative Incidence of VTE (95% CI)	abs rel
D-Dimer < Q3 (n=1018; 57 VTE events, 295 deaths)							
	8.66% (7.08 – 10.58)	1-KM: 3.98% (2.92 – 5.41)	0.12	1-KM: 5.12% (3.89 – 6.73)	0.24	1-KM: 6.34% (4.91 – 8.18)	0.56
		CR: 3.86% (2.80 – 5.18)	3.11	CR: 4.88% (3.66 – 6.33)	4.92	CR: 5.78% (4.44 – 7.36)	9.69
D-Dimer Q3 (n=343; 45 VTE events, 179 deaths)							
	23.58% (19.38 – 28.51)	1-KM: 12.40% (9.16 – 16.67)	1.22	1-KM: 14.66% (11.04 – 19.34)	1.96	1-KM: 15.89% (12.01 – 20.88)	2.57
		CR: 11.18% (8.11 – 14.79)	10.91	CR: 12.70% (9.41 – 16.49)	15.43	CR: 13.32% (9.96 – 17.19)	19.29

Abbreviations: 1-KM: Complement of the Kaplan-Meier product limit estimate; CR: Competing risk estimate; VTE: Venous thromboembolism; CI: Confidence interval; abs: Absolute overestimation of VTE cumulative incidence with 1-KM in %age points; rel: Relative overestimation of VTE cumulative incidence with 1-KM in %; Q3: 75th percentile of the distribution of D-Dimer