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Survival assessment of warfarin and international normalized ratio exposure in cancer-associated venous thromboembolism: Veterans Affairs healthcare system-based analysis

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Abstract

Venous thromboembolism (VTE) is a common complication among patients with cancer. While randomized clinical trials have established the safety and efficacy of direct oral anticoagulants (DOACs) and low-molecular-weight heparin (LMWH) relative to warfarin for the treatment of cancer-associated thrombosis, emerging evidence suggests that warfarin may be associated with improved overall survival in patients with malignancy. To evaluate survival outcomes among patients with cancer and VTE treated with warfarin compared with other anticoagulants within the Veterans Affairs (VA) Health Care System and analyze the association of international normalized ratio (INR) exposure and overall survival. Among 12 298 propensity-matched patients (mean age 69 years; 97% men), warfarin use was associated with a 16% lower risk of mortality compared with other anticoagulants (hazard ratio [HR], 0.84; (95% CI, 0.80-0.88); P < .001). Median survival was 1457 days in the warfarin group vs 1045 days in the non–warfarin group. Survival benefits were consistent across subgroups defined by tumor type, stage, and demographic characteristics. In landmark analyses the greatest benefit was observed with extended periods in the INR range of 2.5 to 3.0 (HR, 0.81; 95% CI, 0.75-0.87). In this population-based cohort study of patients with cancer and VTE, warfarin use was associated with improved survival compared with other anticoagulants. The greatest benefit was observed among patients who maintained an INR between 2.5 and 3.0.

Introduction

Venous thromboembolism (VTE) is a serious and potentially life-threatening condition that poses a significant risk to cancer patients due to the hypercoagulable state induced by malignancy. (1, 2) VTE stands as the second leading cause of death in cancer patients.(3, 4) Given this significant burden, effective management of cancer associated VTE is crucial. A pivotal clinical trial comparing low molecular weight heparin (LMWH) to warfarin demonstrated a lower risk of recurrent VTE with LMWH; however no survival advantage was observed.(5) The lack of survival benefit with LMWH was attributed to the potential underpowering of these trials to detect small but clinically meaningful reductions in fatal VTE events.

We previously evaluated whether a survival benefit could be observed in larger cohorts. We performed analyses of population-based studies utilizing data from Surveillance, Epidemiology, and End Results (SEER) – Medicare Linked database. Unexpectedly, we observed warfarin use was associated with improved overall survival compared with LMWH or direct oral anticoagulant (DOAC) for the treatment of cancer-associated VTE.(6, 7) This novel finding was consistent across every subgroup including stage, different cancer sites, age, year of diagnosis, and comorbidity burden. These findings lead to an interesting hypothesis that warfarin may provide overall survival advantage over LMWH or DOACs, independent of anticoagulation effectiveness. This survival advantage may be mediated by modification of cancer biology, consistent with multiple pre-clinical models that have demonstrated that warfarin has anti-neoplastic effects.(8-10) Taken at face value, these could be

considered practice changing. The reticent reception of these findings is understandable with a critique being that these observations may be an idiosyncrasy related to the SEER-Medicare database. As such, we sought to explore survival outcomes among patients within the Veterans Affairs (VA) healthcare system who received warfarin versus alternative anticoagulant for the treatment of cancer associated thrombosis. The VA is the largest integrated health network in the U.S., consisting of 171 medical centers and 1,113 outpatient clinics. An advantage of the VA database relative to SEER is that it is not limited to a cancer registry but is linked to comprehensive electronic health record (EHR) data, including laboratory results and prescription records. This integration enables a more detailed analysis of the relationship between warfarin dose-intensity—measured by INR levels—and survival outcomes. Based on prior SEER-Medicare findings and preclinical evidence, we hypothesized that warfarin use would be associated with improved overall survival compared with DOACs or LMWH, with the greatest benefit observed among patients who maintained INR values in the higher therapeutic range. While both datasets include cases through 2021, the VA's complete EHR infrastructure allows for a more granular assessment of treatment patterns and longitudinal patient follow-up.

Methods

Study Design and Cohort Selection

We conducted a retrospective cohort study of adult patients receiving care within the VA health care system. The VA's comprehensive infrastructure ensures patients have continuous oncologic care and robust longitudinal follow-up. This study was

approved by the VA Boston Research and Development committee as an exempt study before data collection and analysis, with a waiver of informed consent due to the use of existing data, per the Common Rule.

Data standardization and variable extraction were performed as previously described (see Supplemental Methods).(11, 12) VTE was defined as radiographically confirmed symptomatic or incidental pulmonary embolism (PE), proximal or distal lower extremity deep vein thrombosis (LE-DVT), or upper extremity deep vein thrombosis (UE-DVT)(13) Patients with a diagnosis of both cancer and VTE between 2006 and 2021 were eligible for inclusion. Exclusion criteria included lack of follow-up or survival data beyond 30 days post-VTE diagnosis, absence of an anticoagulation prescription within 30 days of the VTE diagnosis, anticoagulation prescription issued more than 30 days prior to VTE, and missing covariate data. Patients were classified as receiving warfarin if they filled a prescription for warfarin within 30 days of VTE diagnosis and, and as non-warfarin if they filled prescription for non-warfarin anticoagulants (DOAC, LMWH, or direct thrombin inhibitor) in the same window. Cohorts were based on initial qualification on an intention-to-treat basis. Renal failure and liver disease were defined using the Charlson Comorbidity Index via the comorbidity R package. Briefly, the algorithm maps ICD-9 or ICD-10 diagnosis codes to predefined comorbidity categories (e.g., myocardial infarction, diabetes, renal disease, liver disease). In our analysis, we used ICD codes recorded within the three years prior to the cancer diagnosis date. Prescription data were captured from the same national pharmacy database for both groups, ensure comparable ascertainment. Similarly, cancer diagnoses were obtained from the VA cancer Registry and VTE diagnosis from imaging reports for all patients,

regardless of treatment group, ensuring uniform outcome definitions and measurement methods. Mortality was captured via death certificate from the National Death Index and linked to VA patient identifiers using the VA mortality Data Repository. Study size was determined by the total number of eligible VA patients with cancer and VTE during 2006-2021; no apriori sample size calculation was performed given the retrospective design.

Propensity matching

To compare outcomes between patients treated with warfarin and those who were not, we utilized a propensity-score matched retrospective cohort design. A propensity score was generated using a multivariable logistic regression model, incorporating the following covariates: cancer type, cancer stage, age at VTE diagnosis, gender, race, body mass index (BMI), rurality, time from cancer diagnosis to VTE event, Charlson Comorbidity Index(14), and VTE type. We used a multivariable logistic regression to estimate the PS and to perform 1:1 nearest matching using a caliper of 0.1 of the propensity score logit.(15) Ultimately, 6,149 patients treated with warfarin were matched to 6,149 patients treated with non-warfarin anticoagulants.

Statistical Analysis

Overall survival was compared between warfarin users and non-users in the matched cohort using Cox proportional hazards regression. The predefined INR categories were <1.5, 1.5–2, 2–2.5, 2.5–3, 3–3.5, and >3.5. INR cut points were selected based on established therapeutic ranges with subcategories reflecting clinical convention. For each landmark time, we calculated the cumulative time spent in each

INR category, expressed in 90-day increments. See Supplemental Methods for additional methodologic details.

Results

Cohort Selection

Between 2006 and 2021, a total of 42,232 adult patients with both cancer and a venous thromboembolism (VTE) diagnosis were identified within the VA healthcare system. After applying exclusion criteria (Figure 1), the final cohort consisted of 17,728 patients. These patients were stratified into two cohorts based on their anticoagulation treatment: 10,858 patients were included in the non-warfarin cohort, while 6,880 patients received warfarin within 30 days of their VTE diagnosis. The index date was the initial prescription date of the anticoagulation treatment. Prior to matching, we identified 9,911 patients in the non-warfarin group and 6,222 in the warfarin group with complete data, while 947 and 525, respectively, were excluded due to missing covariates (Supplemental Table 1). After propensity score matching on cancer type, cancer stage, age at VTE diagnosis, gender, race, body mass index (BMI), rurality, time from cancer diagnosis to VTE event, comorbidity score, and VTE type, there were a total of 6,149 patients were included in both the warfarin and non-warfarin cohorts (Supplemental Figures 1 and 2). These variables were selected as potential confounders because they are established determinants of both anticoagulant selection and overall survival in patients with cancer-associated VTE. Among the non-warfarin cohort, 42.4% received direct oral anticoagulants (DOAC), 56.4% were treated with low-molecular-weight heparin (LMWH), and 1.2% received direct thrombin inhibitors (DTI).

Baseline Characteristics

The demographic and clinical characteristics of the patients were similar in the two groups, with standardized mean differences (SMDs) less than 0.1 for all matched variables (Table 1, Supplemental Figure 1). The most common cancer types in both cohorts were prostate (33.0% vs. 33.9%, respectively), lung (15.0% vs. 15.3%), and gastrointestinal (GI) cancers (16.1% vs. 15.2%). The mean age at the time of VTE diagnosis was 69 years (± 9.3 in the non-warfarin cohort and ± 9.7 in the warfarin cohort). Gender distribution was predominantly male in both cohorts (97.0% vs. 96.9%, respectively). The racial composition was largely White (74.1% in non-warfarin vs. 73.6% in warfarin cohorts). Time from cancer diagnosis to VTE and comorbidity scores were also similar between the groups. And most of the patients had acute pulmonary embolism (46.5% in the non-warfarin cohort vs. 45.3% in the warfarin cohort).

Primary Outcome

The survival analysis (Figure 2) demonstrates that patients treated with warfarin experienced a significantly greater survival probability compared to those not treated with warfarin. The hazard ratio (HR) for the warfarin group of0.84 (95% CI: 0.80-0.88), indicating a 16% risk reduction in the risk of death ($p < 0.001$). The median survival time was 1,457 days for the warfarin cohort, compared to 1,045 days for the non-warfarin cohort. In landmark analyses for patients surviving at least 60 or 90-days post VTE, differences in survival remained apparent (Supplemental Figure 3).

Subgroup Analysis

To explore the heterogeneity of warfarin's effect on overall survival, we conducted a comprehensive subgroup analysis (Figure 3), stratified by cancer type,

stage, year range, and VTE subtype. This analysis revealed important insights into the populations most likely to benefit from warfarin therapy.

Prostate cancer patients (n = 4,114) had the most pronounced benefit from warfarin, with a hazard ratio (HR) of 0.73 (95% CI: 0.67–0.81). Gastrointestinal cancer patients (n = 1,921) also showed improved survival (HR: 0.83, 95% CI: 0.75–0.92). However, no significant effect was observed in lung cancer (n = 1,860) (HR: 0.92, 95% CI: 0.83–1.03) or hematologic malignancies (n = 1,174) (HR: 0.98, 95% CI:0.84–1.14).

Warfarin associated survival benefit for patients with early-stage cancer (n =8,561) (HR: 0.87, 95% CI: 0.82–0.93) rather than advanced-stage cancer (n =1,949) (HR: 0.96, 95% CI: 0.86–1.06). The survival benefit of warfarin was observed in both earlier cohort entailing 2006 through 2013 (n = 5,642) with a HR of 0.67 (95% CI: 0.63–0.72), as well as more contemporary cohort between 2014 and 2021 (n = 6,656) with a HR of 0.82 (95% CI: 0.76–0.88). Survival improvement was noted even when restricting enrollment to patients who survived at least 60 or 90 days following VTE (Supplemental Figure 3).

Landmark Analysis of INR Status and Survival

To evaluate the potential impact of warfarin dosing on long-term survival, we conducted a landmark analysis of survival outcomes across different INR ranges (<1.5, 1.5 – 2.0, 2-2.5, 2.5 – 3.0, 3.0 – 3.5, and >3.5) among patients actively prescribed warfarin. INR measurements were validated by confirming concurrent warfarin prescriptions, with no prescription lapse exceeding 90 days at the time of INR sampling. The analysis was performed at 1-year, 3-year, and 5-year after VTE diagnosis to evaluate the association between INR status and survival over time.

Our findings demonstrated that patients maintaining a therapeutic INR range of 2.5-3 experienced the most favorable survival outcomes (Table 2). At 1 year, every 90 days spent in the INR 2.5-3 range was associated with a hazard ratio (HR) of 0.81 (95% CI: 0.75-0.87), indicating a significant survival benefit. This survival advantage persisted at 3 years (HR: 0.89, 95% CI: 0.84–0.94) and 5 years (HR: 0.94, 95% CI: 0.89–1.00).

In contrast, patients with INR levels between 2-2.5 showed no substantial survival benefit, with HRs of 0.96 (95% CI: 0.91 – 1.01) at 1 year, 0.99 (95% CI: 0.95 - 1.03) at 3 years, and 0.99 (95% CI: 0.95 – 1.03) at 5 years. Notably, INR values falling below 2 or exceeding 3 were associated with worse survival outcomes.

Discussion

The findings of this study contribute to a growing body of literature suggesting that warfarin may offer a survival advantage for cancer patients with venous thromboembolism (VTE) when compared to other anticoagulants.(6, 7, 16) In this large, population-based cohort of patients treated within the Veterans Affairs (VA) healthcare system, we observed that warfarin use was associated with a significant 16% reduction in mortality risk compared to other anticoagulants. The survival advantage persisted even after adjusting for known confounders, such as age, cancer type, stage, and comorbidities.

These findings corroborate the prior unexpected SEER findings.(6, 7) Similarly, a prior Finnish study that included over 6,000 men with cancer, use of warfarin was associated with improved survival relative to other anticoagulants.(17) Another population-based study demonstrated a significantly lower incidence of cancer among individuals receiving warfarin compared with non-users (incidence rate ratio 0.84, 95%

CI 0.82-0.86).(16) While our results align with earlier research, this analysis uniquely leverages the VA's extensive and integrated dataset, ensuring comprehensive follow-up and minimizing loss to follow-up—a common limitation in other cohort studies. The VA database has complete individual level medical record and administrative data including demographics, laboratory data, comorbidity burden, and prescription data. This comprehensive dataset allowed us to consider as many confounding variables as possible to build the best model to assess the difference in survival. Similarly, the VA is a single-payer health care system which minimizes the likelihood of missing data.

The observed survival benefit of warfarin is particularly striking given the context of modern anticoagulation practices. Contemporary clinical guidelines have increasingly favored DOACs due to their ease of use and established efficacy in preventing VTE recurrence.(18) However, despite these shifts in practice, these findings suggest that vitamin K antagonism may confer additional survival benefits that extend beyond its anticoagulant properties; one proposed mechanism is the inhibition of tumor-specific pathways, such as the Axl receptor tyrosine kinase.(19)

Our landmark analysis further revealed that the survival benefit of warfarin was predominantly observed within the therapeutic INR range of 2.0 – 3.0, with a more pronounced benefit in the higher sub-range of 2.5 – 3.0 compared to the lower range of 2.0 – 2.5. For every 30 days spent within the INR range of 2.5-3.0 in year 1, there was an approximate 20% improvement in overall survival at year 1, an effect that persisted up to 3 years later. This finding suggests a dose-dependent association with survival within the therapeutic INR window. Although it could be argued that the observed survival advantage is primarily due to enhanced anticoagulation and reduced thrombotic

events, previous studies have reported similar risks of ischemic stroke or recurrent VTE across therapeutic 2.0 to 3.0 INR values.(20-22) Notably, there is an apparent survival benefit in non-cancer patients within a lower therapeutic INR (between 2-2.5) compared with higher therapeutic INRs as observed in our cancer cohort.(20) Preclinical studies have provided further support for this hypothesis by demonstrating anti-neoplastic effects of warfarin, offering a plausible biological explanation for our findings.(8-10) In a prior randomized trial conducted in the 1970's at the VA, 431 patients with various tumors and stages including lung, prostate, colorectal, and head and neck cancer were randomized to warfarin or no anticoagulant.(23) The mean prothrombin time for the treated cohort was 17.6 seconds compared with 11.6 seconds in the control cohort which translates to an approximate mean INR of 1.5 in the therapeutic arm. In that study there was an improvement in overall survival in the subgroup of patients with small cell carcinoma treated with warfarin but not the other malignancies; an effect likely impacted not only by INR intensity but heterogeneity of cohorts including diagnoses, stage at enrollment and duration of treatment.

While our study provides strong evidence supporting the use of warfarin, it is not without limitations. The retrospective design inherently carries risks of unmeasured confounding, despite propensity score matching. In particular, confounding by indication is possible given the shift in practice from warfarin to LMWH after clinical trial data in 2003 showing reduced recurrent VTE. Residual unmeasured confounders (e.g. socioeconomic status, performance status) could have biased results in either direction, though the magnitude is uncertain. While the median VA Frailty Index were similar between the two groups, we do not have data on relative chemotherapy intensity or

palliative intent status of the patients. To address the issue of immortal time bias (i.e., patients needed to survive PE and transition to warfarin) inclusion mandated survival of at least 30 days as well as landmark analyses at 60 and 90 days post incident VTE (Supplemental Figure 3). The VA population is 97% male and older (age ~70 years), potentially limiting generalizability to broader cancer populations. Improved survival was apparent between INR ranges of 2.5-3.0 but we cannot exclude the possibility that improved INR control was due to improved health status rather than a causal effect. We also do not have information regarding cause-specific death to determine whether the measured survival advantage was due to a reduction in cardiovascular outcomes rather than cancer progression. And although we have access to prescription filling data, we cannot confirm that the patient was adherent to the anticoagulation medications which could be considered in the subgroup of patients with worse outcomes and subtherapeutic INR. Future prospective studies are warranted to confirm these findings and to elucidate the mechanisms underlying the potential anti-cancer effects of warfarin.

In conclusion, what was initially considered an observation is further bolstered by this analysis of outcomes within the VA Healthcare system indicating a significant survival advantage for warfarin over other anticoagulants in cancer-associated VTE. These findings highlight the potential for warfarin as a dual-purpose antithrombotic, both as an anticoagulant and a potential disease modifier. Considering the risk of thrombosis in patients with cancer receiving chemotherapy and observed survival benefit, the next step would be randomized trial of primary prophylaxis with warfarin that is powered for survival.

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	Non-Warfarin Cohort (N=6149)	Warfarin cohort (N=6149)
Cancer Type		
Prostate	2029 (33.0%)	2085 (33.9%)
Gastrointestinal	987 (16.1%)	934 (15.2%)
Lung	921 (15.0%)	939 (15.3%)
Genitourinary	669 (10.9%)	654 (10.6%)
Head and neck	352 (5.7%)	345 (5.6%)
Hepatobiliary	249 (4.0%)	255 (4.1%)
Lymphoid	245 (4.0%)	235 (3.8%)
Skin	199 (3.2%)	194 (3.2%)
Multiple myeloma	172 (2.8%)	178 (2.9%)
Myeloid malignancy	171 (2.8%)	173 (2.8%)
Breast	86 (1.4%)	88 (1.4%)
Brain	49 (0.8%)	50 (0.8%)
Gynecological	20 (0.3%)	19 (0.3%)
Cancer Stage		
Unknown	926 (15.1%)	862 (14.0%)
1	1414 (23.0%)	1283 (20.9%)
2	1828 (29.7%)	2201 (35.8%)
3	921 (15.0%)	914 (14.9%)
4	1060 (17.2%)	889 (14.5%)
Age at VTE (years)		
Mean (SD)	69 (± 9.3)	69 (± 9.7)
Gender		
Female	182 (3.0%)	190 (3.1%)
Male	5967 (97.0%)	5959 (96.9%)
Race		
White	4556 (74.1%)	4528 (73.6%)
Black Or African American	1452 (23.6%)	1475 (24.0%)
Native Hawaiian or Other Pacific Islander	45 (0.7%)	46 (0.7%)
Unknown	49 (0.8%)	50 (0.8%)
American Indian or Alaska Native	41 (0.7%)	43 (0.7%)
Asian	6 (0.1%)	7 (0.1%)
BMI (kg/m^2)		
Mean (SD)	31 (± 6.2)	31 (± 6.5)
Renal Failure	607 (9.9%)	629 (10.2%)
Liver Disease	642 (10.4%)	514 (8.4%)
Rurality		
Highly Rural	88 (1.4%)	82 (1.3%)
Rural	2015 (32.8%)	2000 (32.5%)

Urban	4046 (65.8%)	4067 (66.1%)
Time from Cancer Diagnosis to VTE (days)		
Mean (SD)	1100 (± 1300)	1100 (± 1200)
Comorbidity Score		
Mean (SD)	3.9 (± 8.2)	3.9 (± 7.6)
VAFI Mean (SD)	0.16 (0.09)	0.15 (0.09)
VTE Type		
Acute LE-DVT	2261 (36.8%)	2288 (37.2%)
Acute PE	2861 (46.5%)	2785 (45.3%)
Acute UE-DVT	1027 (16.7%)	1076 (17.5%)

Table 1: Demographic and clinical characteristics of study cohort at baseline after propensity score matching.
LE-DVT, lower extremity deep vein thrombosis; PE, pulmonary embolism; UE-DVT, upper extremity deep vein thrombosis; GI, gastrointestinal; GU, genitourinary; GYN, gynecologic, HBP, hepatobiliary and pancreatic; HN, head and neck; MM, multiple myeloma; VAFI, VA frailty index.

INR Range	*1 year (95% CI)*	*3 year HR (95% CI)*	*5 year HR (95% CI)*
<1.5	1.06 (1.01 - 1.10)	1.07 (1.02 - 1.12)	1.07 (1.00 - 1.13)
1.5-2	1.09 (1.01 - 1.18)	1.20 (1.13 - 1.27)	1.15 (1.09 - 1.21)
2-2.5	0.96 (0.91 - 1.01)	0.99 (0.95 - 1.03)	0.99 (0.95 - 1.03)
2.5-3	**0.81 (0.75 - 0.87)**	**0.89 (0.84 - 0.94)**	**0.94 (0.89 - 1.00)**
3-3.5	0.99 (0.89 - 1.11)	1.08 (0.98 - 1.19)	0.99 (0.89 - 1.10)
>3.5	1.19 (1.06 - 1.32)	1.04 (0.98 - 1.12)	1.00 (0.94 - 1.06)

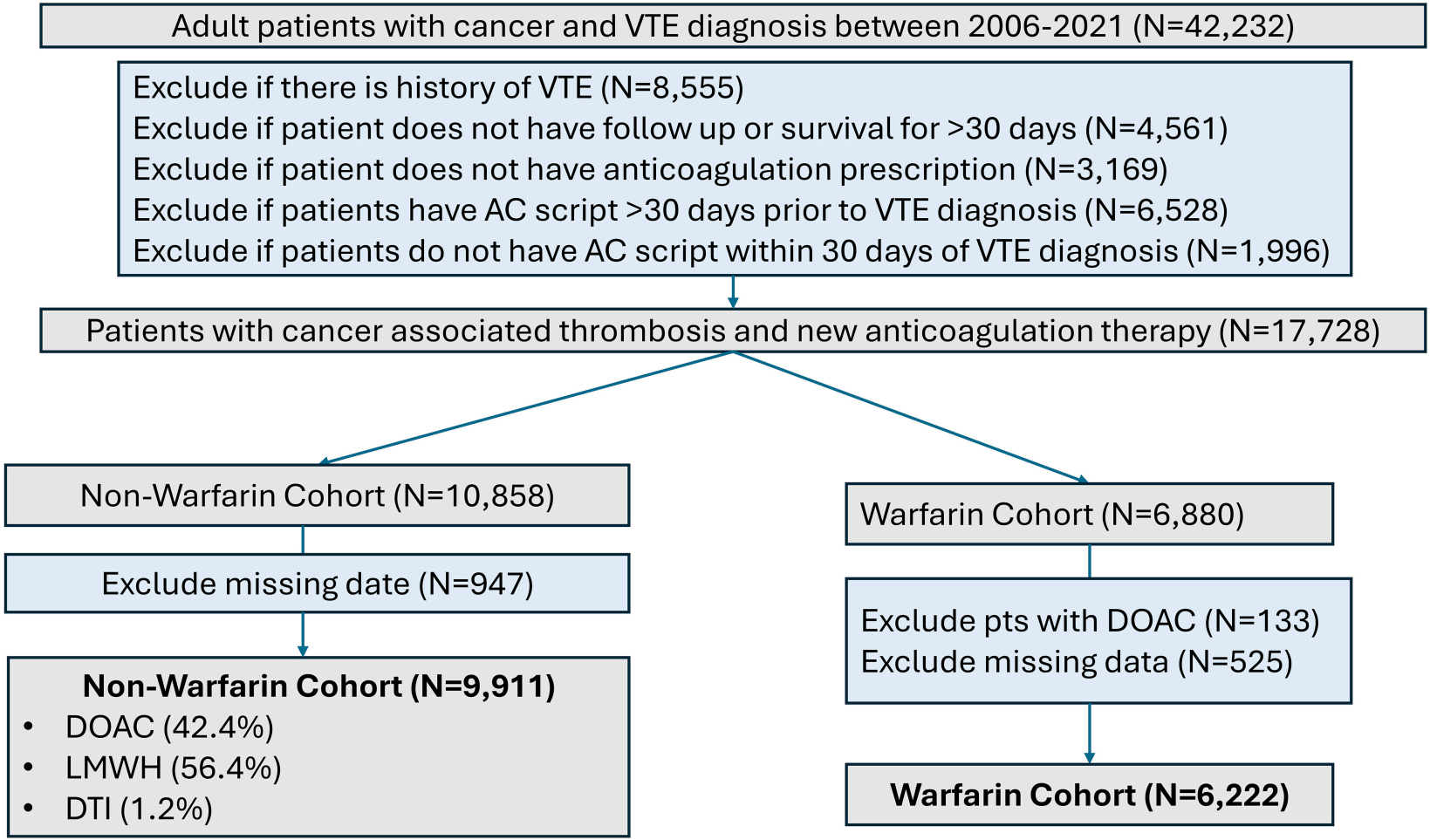
Table 2: Landmark Analysis of INR Ranges and Survival Outcomes in Warfarin-Treated Cancer Patients. Table 2: Landmark Analysis of INR Ranges and Survival Outcomes in Warfarin-Treated Cancer Patients. The duration for which patients in the warfarin cohort remained in each of the predefined INR categories was calculated, including no warfarin, <1.5, 1.5–2, 2–2.5, 2.5–3, 3–3.5, and >3.5. Landmark analyses were performed with index dates set at 1, 3, and 5 years after completion of anticoagulation treatment, and survival analysis was conducted using Cox proportional hazards regression models to evaluate the association between INR control and long-term survival outcomes.

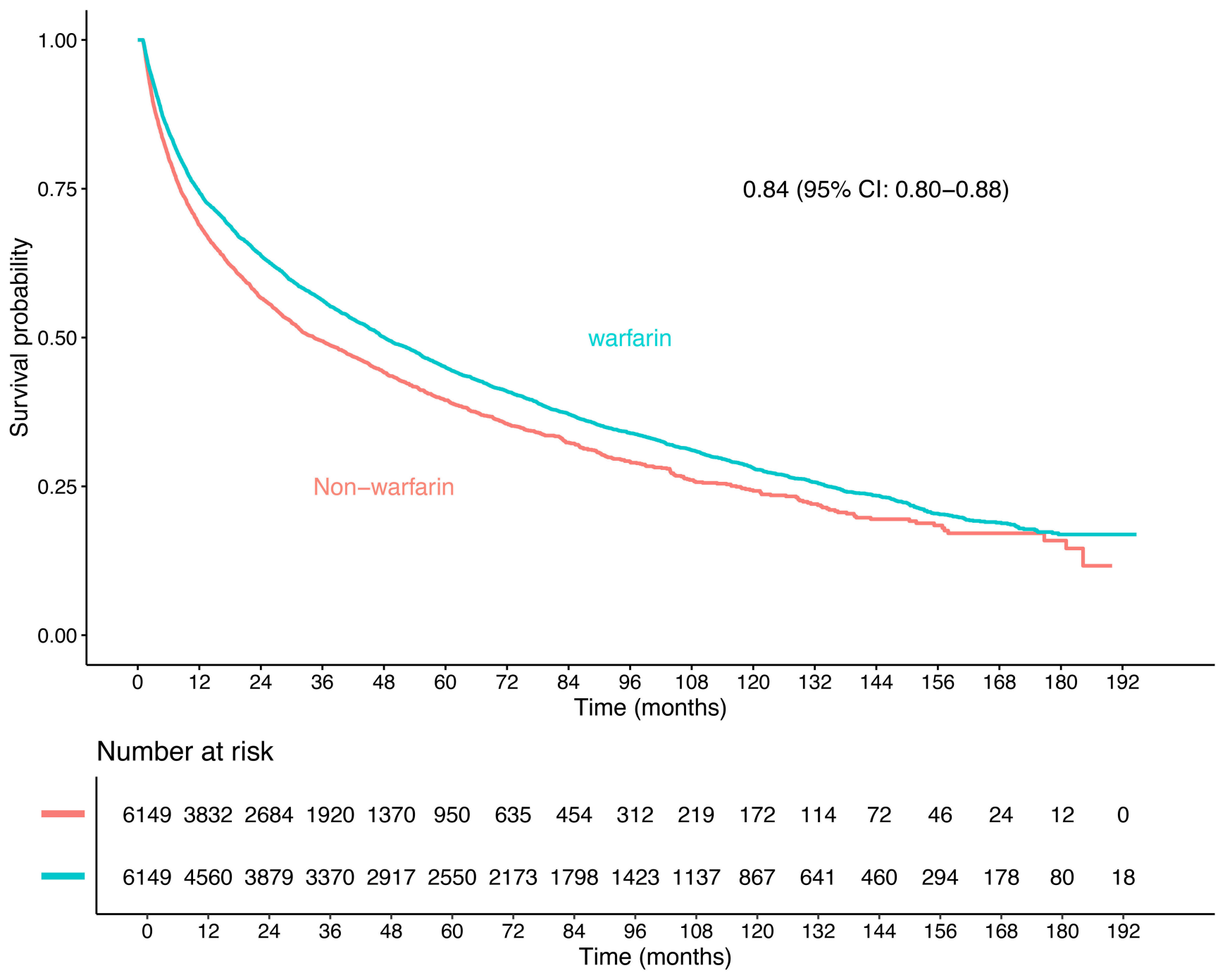
Figure Legends:

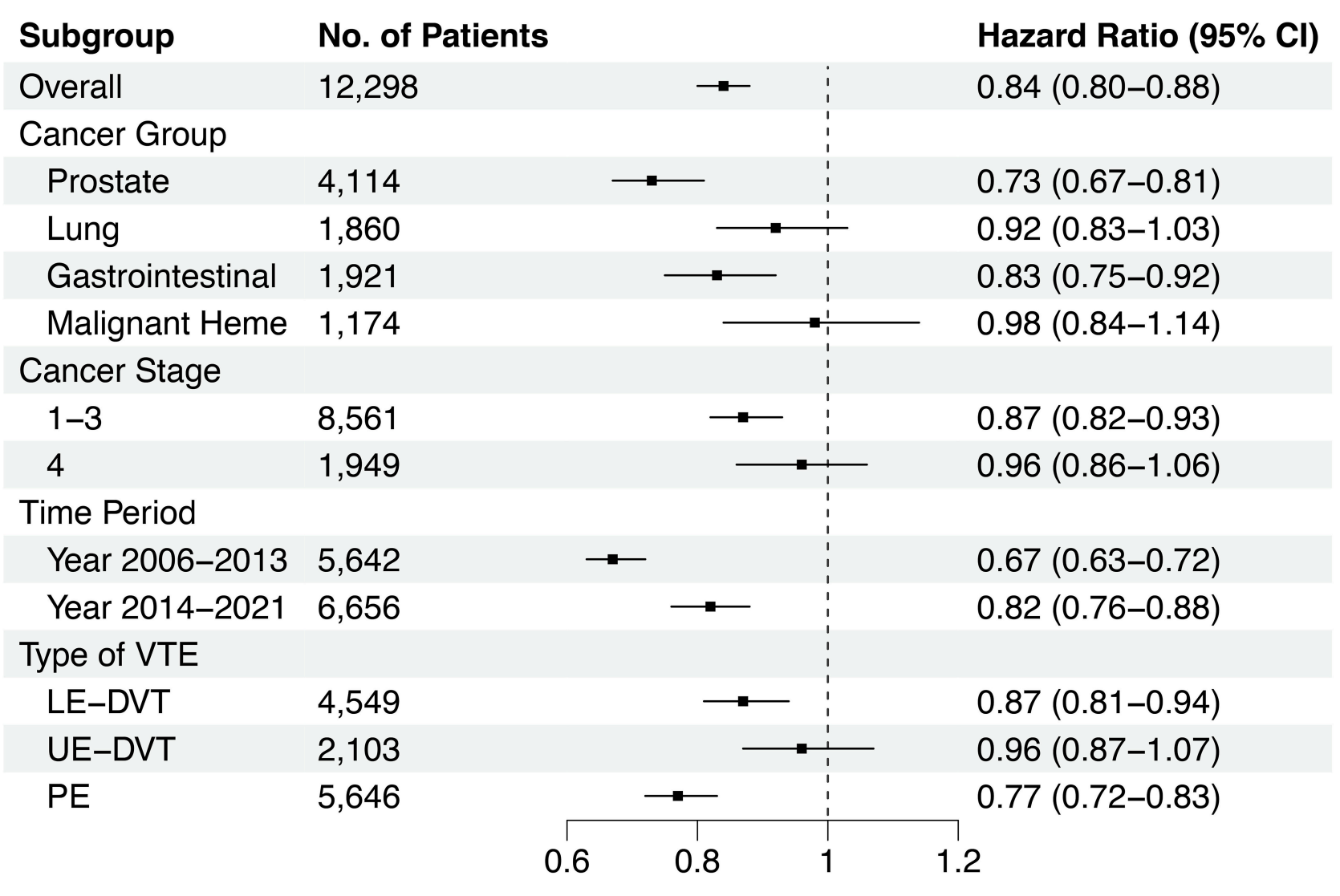
Figure 1: Patient selection and exclusion in cohort selection. A total of 42,232 individuals with a VTE diagnosis between 2006 and 2021 were identified from the cancer registry. After the application of exclusion criteria, the final cohort consistent of 17,729 individuals. This cohort was divided into the non-warfarin or warfarin cohort based on the type of anticoagulation used within the first 30 days of VTE diagnosis. VTE, venous thromboembolism; AC, anticoagulation; DOAC, direct oral anticoagulation; LMWH, low molecular weight heparin; DTI, direct thrombin inhibitor

Figure 2: Overall survival of warfarin compared to the non-warfarin in the matched cohort. Hazard ratios, confidence intervals, and p-values were derived from Cox proportional hazard ratio with bootstrapping with 1000 iterations (N=12,298). Median survival for the non-warfarin cohort was 1045 days and the median survival for warfarin cohort was 1457 days.

Figure 3: Subgroups analysis of overall survival. A cox proportional hazard ratio with bootstrapping was used to estimate the overall survival between the warfarin cohort and the non-warfarin cohort, across the largest cancer subtypes and cancer stages. Malignant Heme cohort comprised of multiple myeloma, lymphoid malignancies, and myeloid malignancies.


Adult patients with cancer and VTE diagnosis between 2006-2021 (N=42,232)
Exclude if there is history of VTE (N=8,555)
Exclude if patient does not have follow up or survival for >30 days (N=4,561)
Exclude if patient does not have anticoagulation prescription (N=3,169)
Exclude if patients have AC script >30 days prior to VTE diagnosis (N=6,528)
Exclude if patients do not have AC script within 30 days of VTE diagnosis (N=1,996)
Patients with cancer associated thrombosis and new anticoagulation therapy (N=17,728)
Non-Warfarin Cohort (N=10,858)
Exclude missing date (N=947)
Non-Warfarin Cohort (N=9,911)
• DOAC (42.4%)
• LMWH (56.4%)
• DTI (1.2%)
Warfarin Cohort (N=6,880)
Exclude pts with DOAC (N=133)
Exclude missing data (N=525)
Warfarin Cohort (N=6,222)


1.00
0.75
0.50
0.25
0.00
Survival probability
0.84 (95% CI: 0.80–0.88)
warfarin
Non–warfarin
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168 180 192
Time (months)
Number at risk
6149 3832 2684 1920 1370 950 635 454 312 219 172 114 72 46 24 12 0
6149 4560 3879 3370 2917 2550 2173 1798 1423 1137 867 641 460 294 178 80 18
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168 180 192
Time (months)

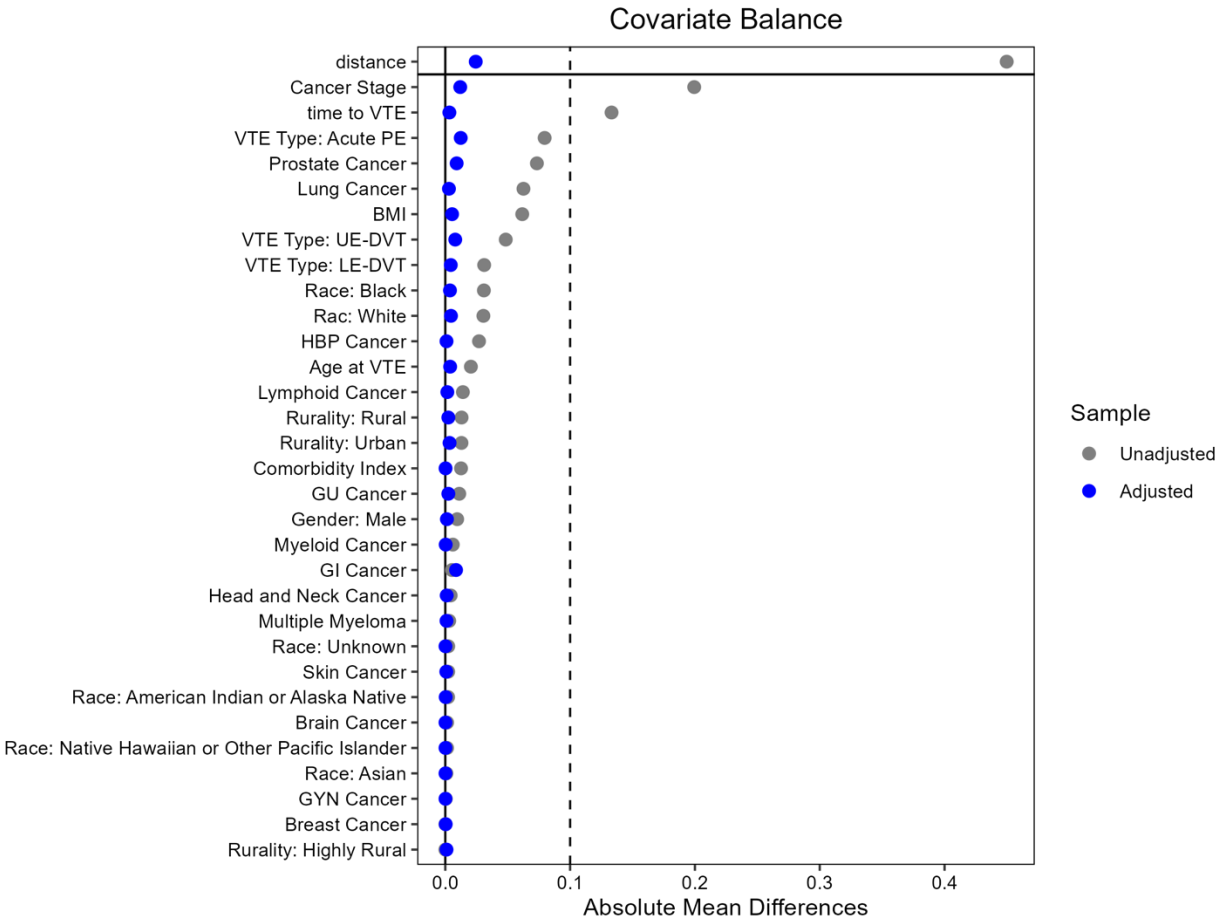

Subgroup
No. of Patients
Hazard Ratio (95% CI)
Overall
12,298
0.84 (0.80–0.88)
Cancer Group
Prostate
4,114
0.73 (0.67–0.81)
Lung
1,860
0.92 (0.83–1.03)
Gastrointestinal
1,921
0.83 (0.75–0.92)
Malignant Heme
1,174
0.98 (0.84–1.14)
Cancer Stage
1–3
8,561
0.87 (0.82–0.93)
4
1,949
0.96 (0.86–1.06)
Time Period
Year 2006–2013
5,642
0.67 (0.63–0.72)
Year 2014–2021
6,656
0.82 (0.76–0.88)
Type of VTE
LE–DVT
4,549
0.87 (0.81–0.94)
UE–DVT
2,103
0.96 (0.87–1.07)
PE
5,646
0.77 (0.72–0.83)
0.6
0.8
1
1.2

Supplemental Tables and Figures

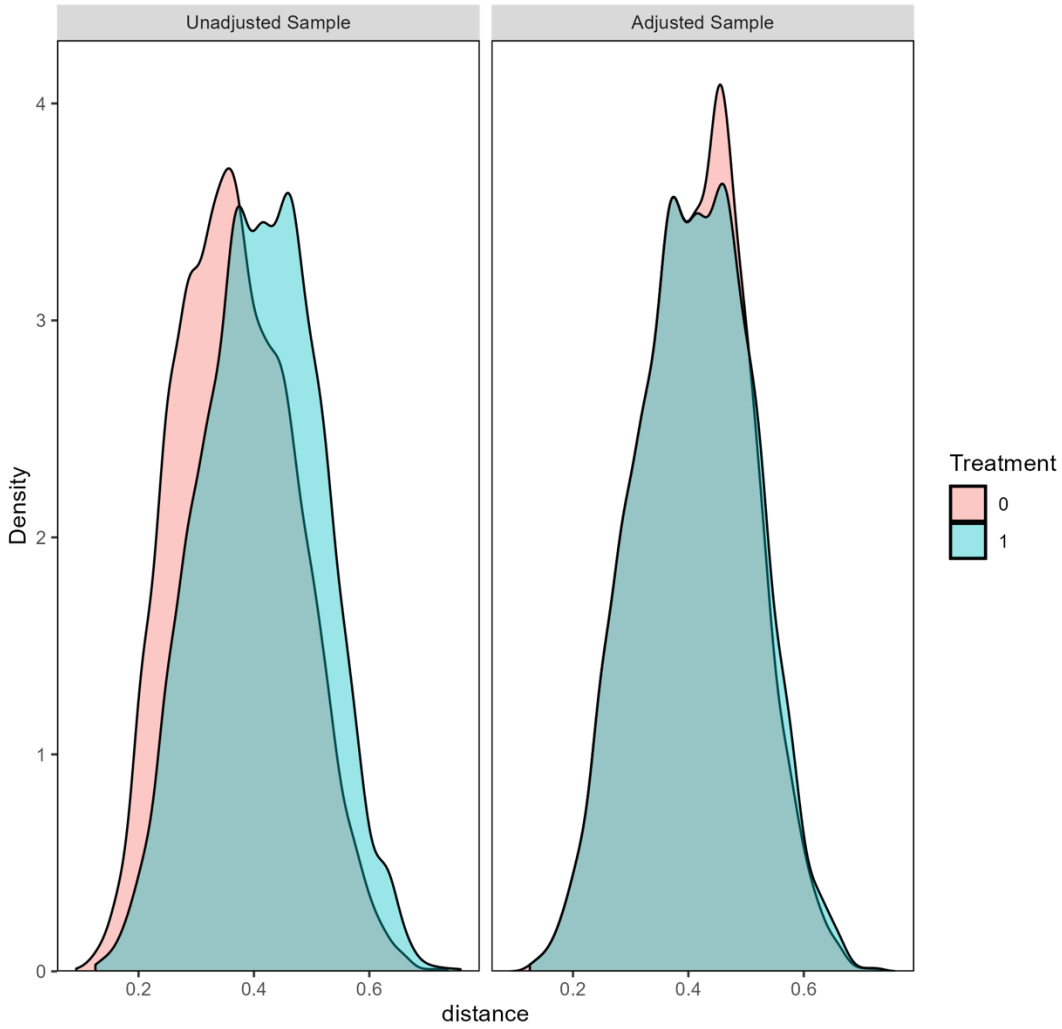
	Non-Warfarin Cohort (N=9911)	Warfarin cohort (N=6222)
Cancer Type		
Prostate	2672 (27.0%)	2134 (34.3%)
Lung	2118 (21.4%)	940 (15.1%)
Gastrointestinal	1446 (14.6%)	941 (15.1%)
Genitourinary	942 (9.5%)	661 (10.6%)
Hepatobiliary	674 (6.8%)	255 (4.1%)
Head and Neck	518 (5.2%)	352 (5.7%)
Lymphoid	514 (5.2%)	235 (3.8%)
Skin	286 (2.9%)	194 (3.1%)
Multiple myeloma	254 (2.6%)	179 (2.9%)
Myeloid malignancy	216 (2.2%)	173 (2.8%)
Breast	143 (1.4%)	89 (1.4%)
Brain	94 (0.9%)	50 (0.8%)
Gynecologic	34 (0.3%)	19 (0.3%)
Cancer Stage		
0	1227 (12.4%)	885 (14.2%)
1	1990 (20.1%)	1303 (20.9%)
2	2718 (27.4%)	2230 (35.8%)
3	1696 (17.1%)	914 (14.7%)
4	2280 (23.0%)	890 (14.3%)
Age at VTE (years)		
Mean (SD)	69 (± 9.4)	69 (± 9.7)
Gender		
Female	397 (4.0%)	190 (3.1%)
Male	9514 (96.0%)	6032 (96.9%)
Race		
WHITE	7012 (70.7%)	4592 (73.8%)
BLACK OR AFRICAN AMERICAN	2664 (26.9%)	1480 (23.8%)
Unknown	103 (1.0%)	50 (0.8%)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	61 (0.6%)	47 (0.8%)
AMERICAN INDIAN OR ALASKA NATIVE	51 (0.5%)	46 (0.7%)
ASIAN	20 (0.2%)	7 (0.1%)
BMI (kg/m^2)		
Mean (SD)	30 (± 6.2)	31 (± 6.6)
Rurality		
Highly Rural	133 (1.3%)	83 (1.3%)

Rural	3098 (31.3%)	2026 (32.6%)
Urban	6680 (67.4%)	4113 (66.1%)
Time from Cancer Diagnosis to VTE (days)		
Mean (SD)	1200 (± 1500)	1100 (± 1200)
Comorbidity Score		
Mean (SD)	3.8 (± 8.1)	3.9 (± 7.7)
VTE Type		
Acute LE-DVT	3374 (34.0%)	2312 (37.2%)
Acute PE	5233 (52.8%)	2790 (44.8%)
Acute UE-DVT	1304 (13.2%)	1120 (18.0%)

Supplemental Table 1: Demographic and clinical characteristics of study cohort at baseline before propensity score matching.
LE-DVT, lower extremity deep vein thrombosis; PE, pulmonary embolism; UE-DVT, upper extremity deep vein thrombosis; GI, gastrointestinal; GU, genitourinary; GYN, gynecologic, HBP, hepatobiliary and pancreatic; HN, head and neck; MM, multiple myeloma

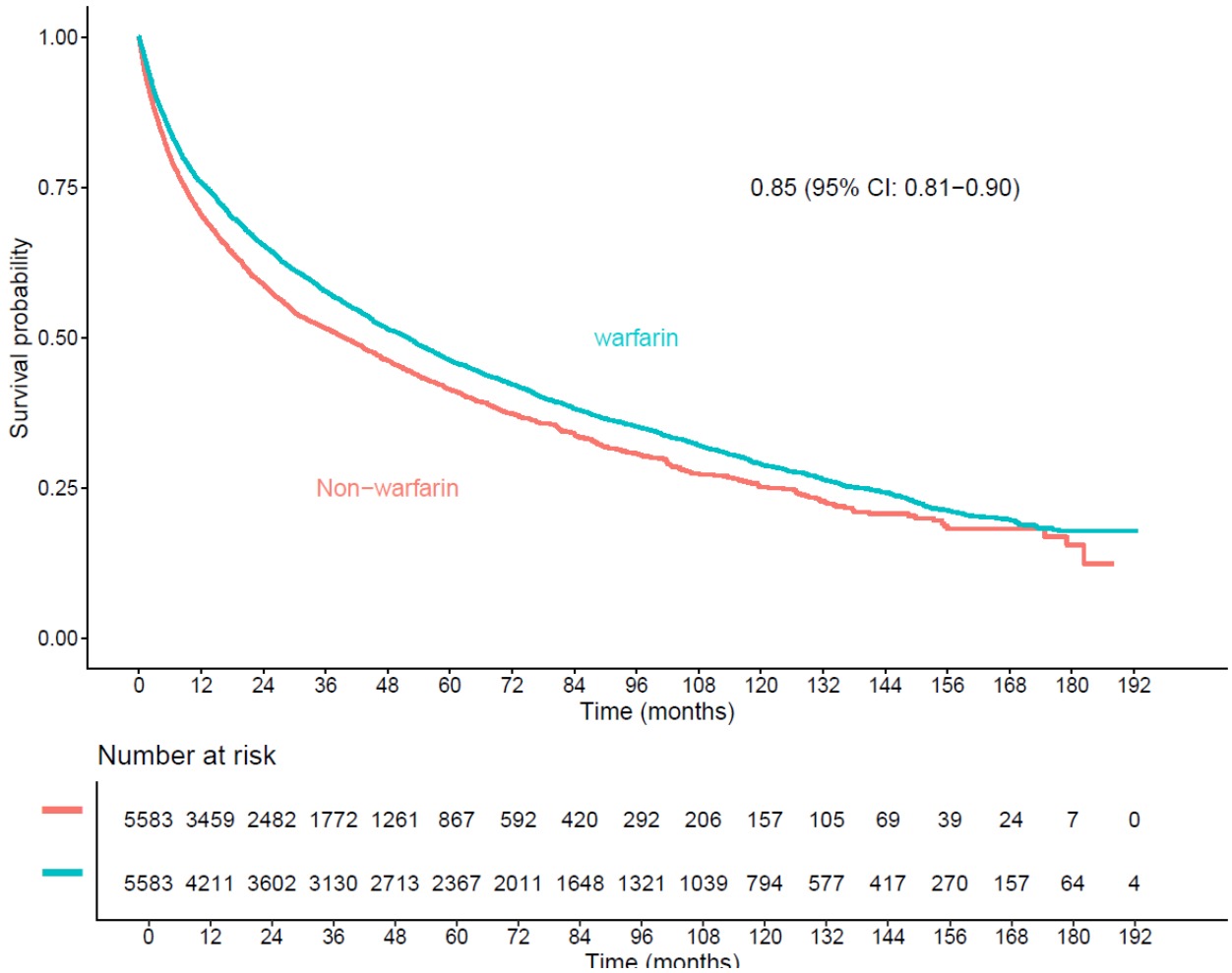


Supplemental Figure 1. Standardized Mean Differences Before and After Matching
Standardized mean differences (SMD) for baseline covariates before (gray) and after (blue) propensity score matching. All covariates achieved SMDs below 0.1 following matching. VTE, venous thromboembolism; BMI, body mass index; LE-DVT, lower extremity deep vein thrombosis; PE, pulmonary embolism; UE-DVT, upper extremity deep vein thrombosis; GI, gastrointestinal; GU, genitourinary; GYN, gynecologic, HBP, hepatobiliary and pancreatic; MM, multiple myeloma

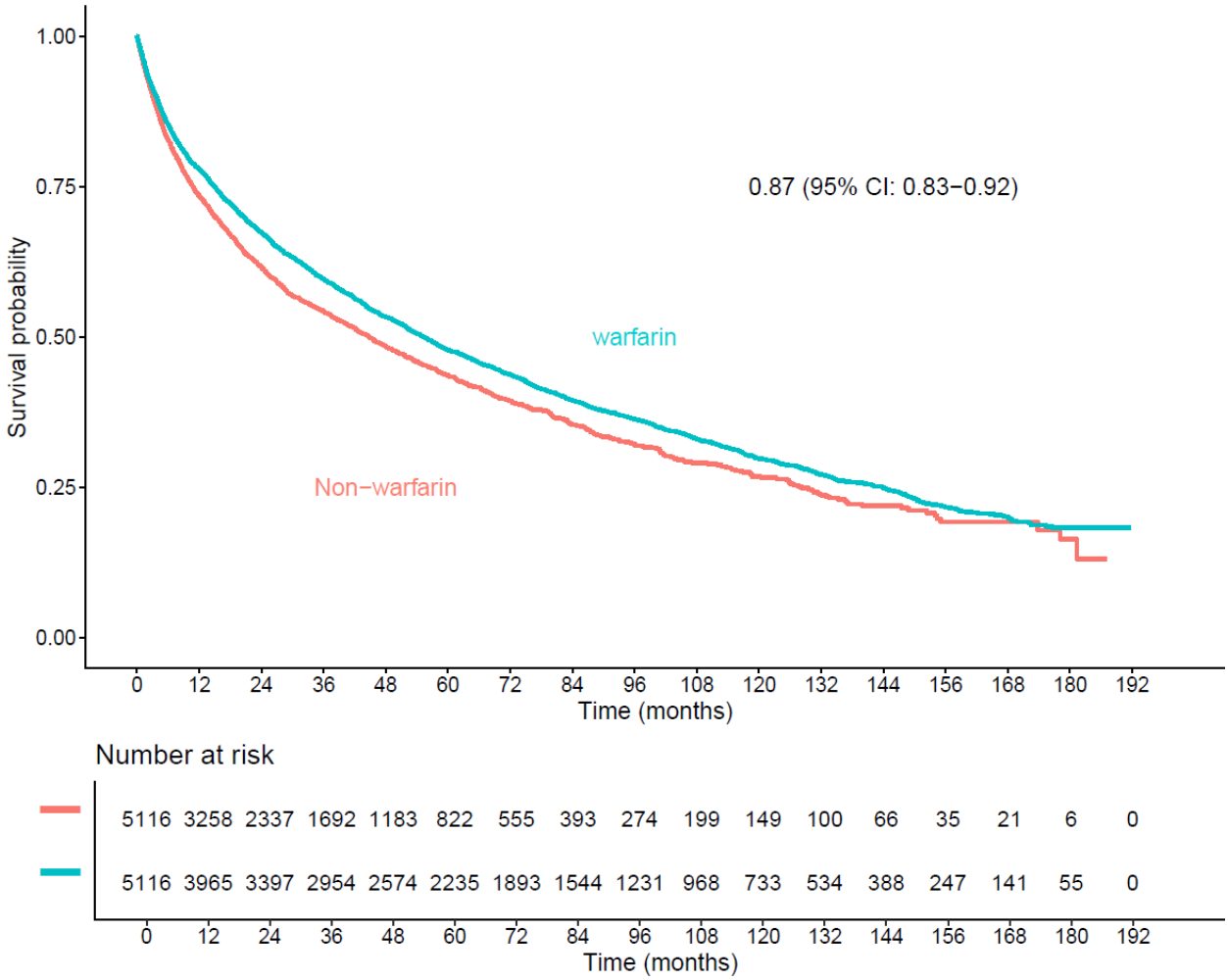


Supplemental Figure 2. Propensity Score Distribution Before and After Matching
Distribution of estimated propensity scores for warfarin (blue) and non-warfarin (pink) groups before (left panel) and after (right panel) matching. Propensity score matching achieved substantial overlap and improved balance in the adjusted sample.

A.


1.00
0.75
0.50
0.25
0.00
Survival probability
0.85 (95% CI: 0.81−0.90)
warfarin
Non−warfarin
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168 180 192
Time (months)
Number at risk
5583 3459 2482 1772 1261 867 592 420 292 206 157 105 69 39 24 7 0
5583 4211 3602 3130 2713 2367 2011 1648 1321 1039 794 577 417 270 157 64 4
0 12 24 36 48 60 72 84 96 108 120 132 144 156 168 180 192
Time (months)

B.



Supplemental Figure 3. Landmark analysis of all patients surviving at least 60 days (A) or 90 days (B) following VTE.

Supplemental Methods:

The Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC) linked eligible patients from the national VA Cancer Registry with the VA Corporate Data Warehouse, which provides comprehensive electronic health record (EHR) data, including demographics, laboratory values, imaging, comorbidities defined by ICD codes, and prescription records. Hazard ratios (HRs), 95% confidence intervals (CIs), and p-values were derived from Cox model with boot strapping (1000 iterations). An alpha level of 0.05 was used to define statistical significance. Analyses were conducted using complete cases with no missing data. Statistical analyses were performed using R v.4.4.1. Survival curves were generated using the Kaplan-Meier method. Subgroup analyses of the overall survival was performed in the four largest cancer subgroups: prostate cancer, lung cancer, gastrointestinal cancer, and hematologic malignancies (including plasma cell, lymphoid, and myeloid disorders).

The primary outcome of interest is overall survival (OS), defined as the duration from the index date to death from any cause, as documented in the VA Corporate Data Warehouse. Death events are identified through death certificates obtained from the National Death Index and are linked to VA patient identifiers via the VA Mortality Data Repository. Due to the high accuracy and completeness of mortality data within the VA system,[16] there was no need to censor the data for loss to follow-up.

To minimize bias, we required at least 30 days of survival after VTE diagnosis to reduce immortal time bias, applied 1:1 propensity score matching to balance measured confounders, and leveraged the VA's comprehensive linked mortality data to minimize outcome misclassification.

Landmark Analysis of Survival Outcomes in Warfarin-Treated Patients

For each INR category landmark time, we calculated the cumulative time spent in each INR category, expressed in 90-day increments. If no time is spent in a specific INR category, then it will take a value of 0. To ensure INR values were recorded during active warfarin use, we confirmed that there was no lapse in warfarin prescriptions for at least 90 days at the time the INR value was recorded. Landmark analyses were conducted at 1, 3, and 5 years from the index date. Cox regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) to assess survival outcomes adjusting for all INR categories. The model was adjusted for potential confounders, including cancer type, stage, age, gender, race, BMI, rurality, time from cancer diagnosis to VTE, Charleson Comorbidity Index, and VTE type.