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

Justine Ryu,[1,2*] Jennifer La,[1,3*] Rushad Patell,[3,4] Ang Li,[5] Nhan Do,[1,6] Mary Brophy,[1,6] Nathanael Fillmore[1,3#] and Jeffrey I. Zwicker[7,8#]

[1]Massachusetts Veterans Epidemiology Research and Information Center, VA Boston Healthcare System, Boston, MA; [2]Section of Hematology-Oncology, Yale University School of Medicine, New Haven, CT; [3]Harvard Medical School, Boston, MA; [4]Division of Hematology, Beth Israel Deaconess Medical Center, Boston, MA; [5]Section of Hematology-Oncology, Baylor College of Medicine, Houston, TX; [6]Boston University Chobanian and Avedisian School of Medicine, Boston, MA; [7]Hematology Service, Memorial Sloan Kettering Cancer Center, New York, NY and [8]Weill Cornell Medical College, New York, NY, USA

**JR and JL contributed equally as first authors.*
#NF and JIZ contributed equally as senior authors.

Correspondence: J. Zwicker
zwickerj@mskcc.org

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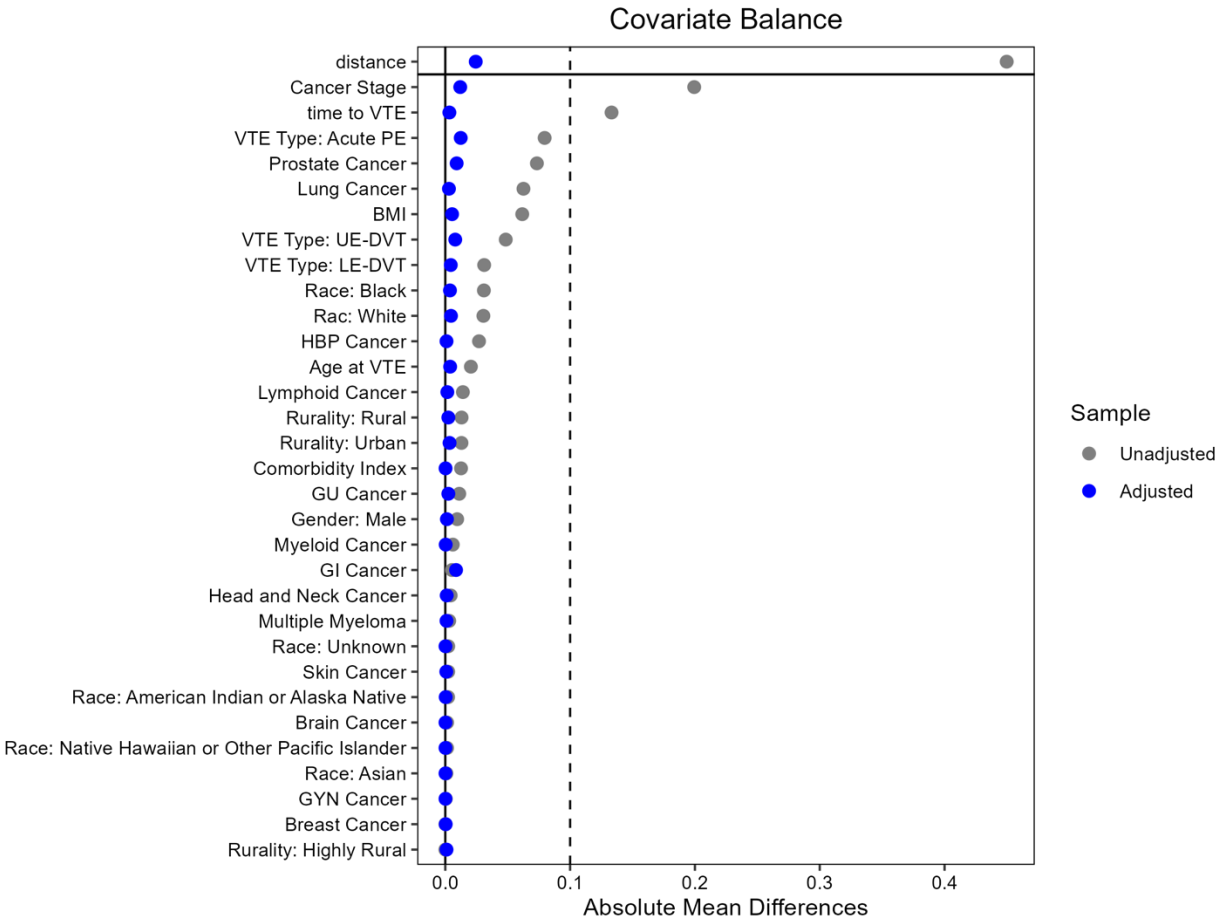
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Supplemental Tables and Figures

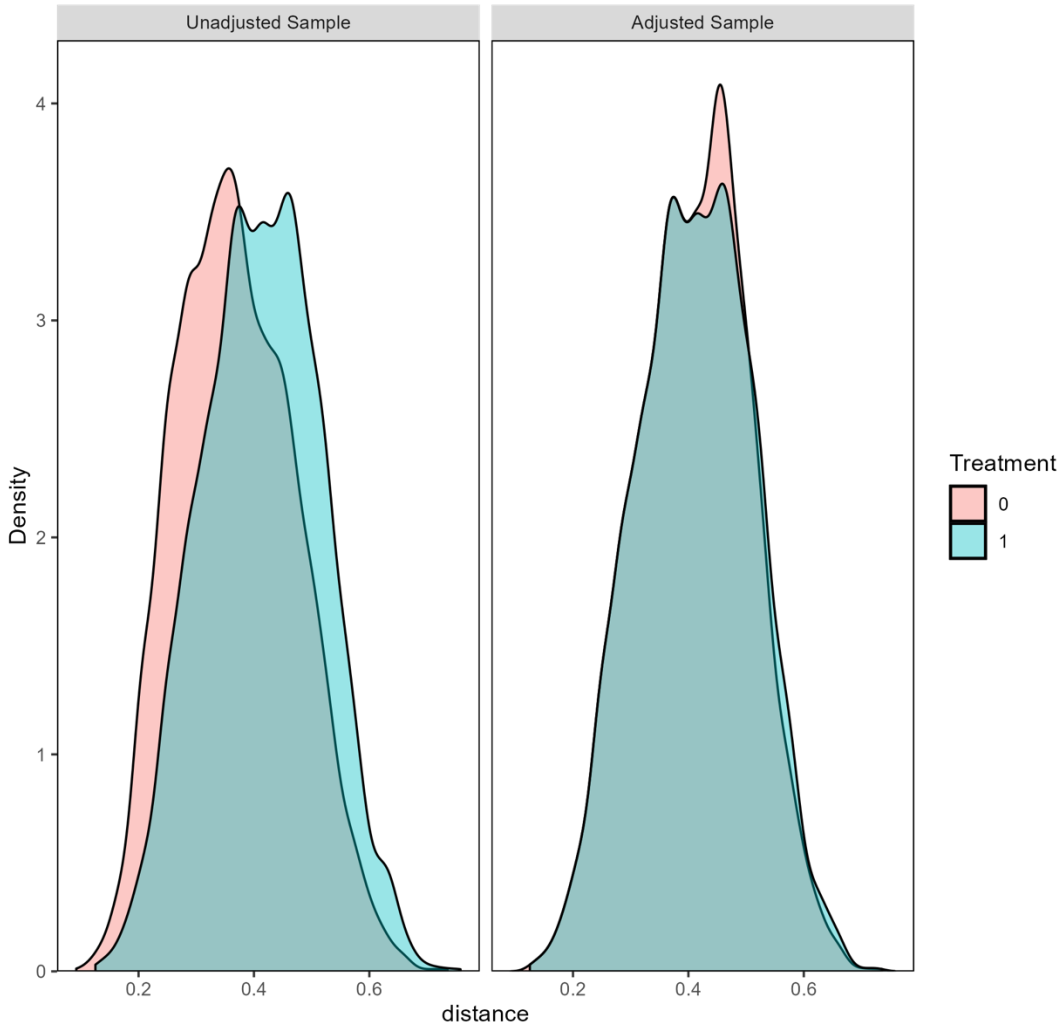
	Non-Warfarin Cohort (N=9911)	Warfarin cohort (N=6222)
Cancer Type		
Prostate	2672 (27.0%)	2134 (34.3%)
Lung	2118 (21.4%)	940 (15.1%)
Gastrointestinal	1446 (14.6%)	941 (15.1%)
Genitourinary	942 (9.5%)	661 (10.6%)
Hepatobiliary	674 (6.8%)	255 (4.1%)
Head and Neck	518 (5.2%)	352 (5.7%)
Lymphoid	514 (5.2%)	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

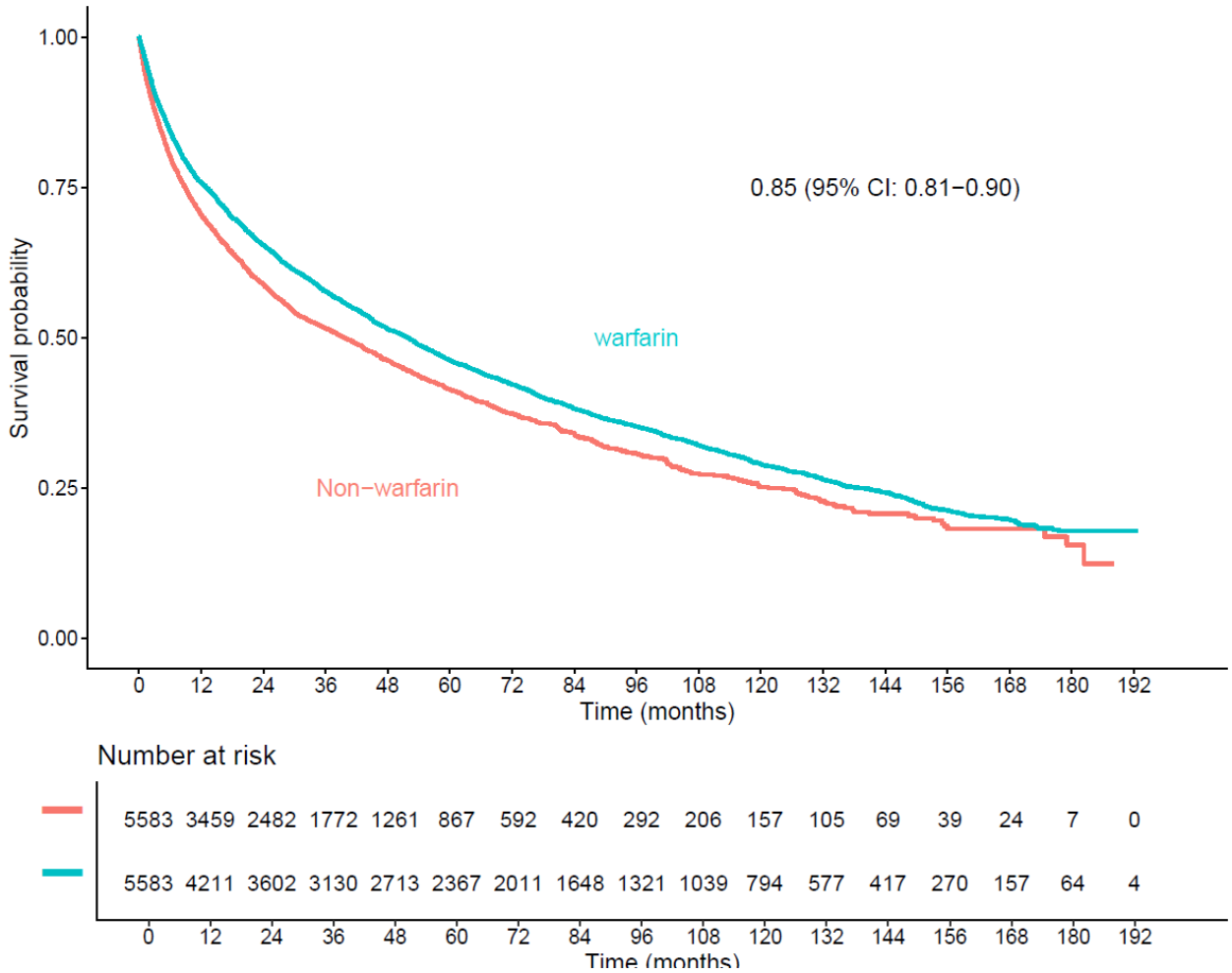


Supplemental Figure 1. Standardized Mean Differences Before and After Matching
Standardized mean differences (SMD) for baseline covariates before (gray) and after (blue) propensity score matching. All covariates achieved SMDs below 0.1 following matching. VTE, venous thromboembolism; BMI, body mass index; 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

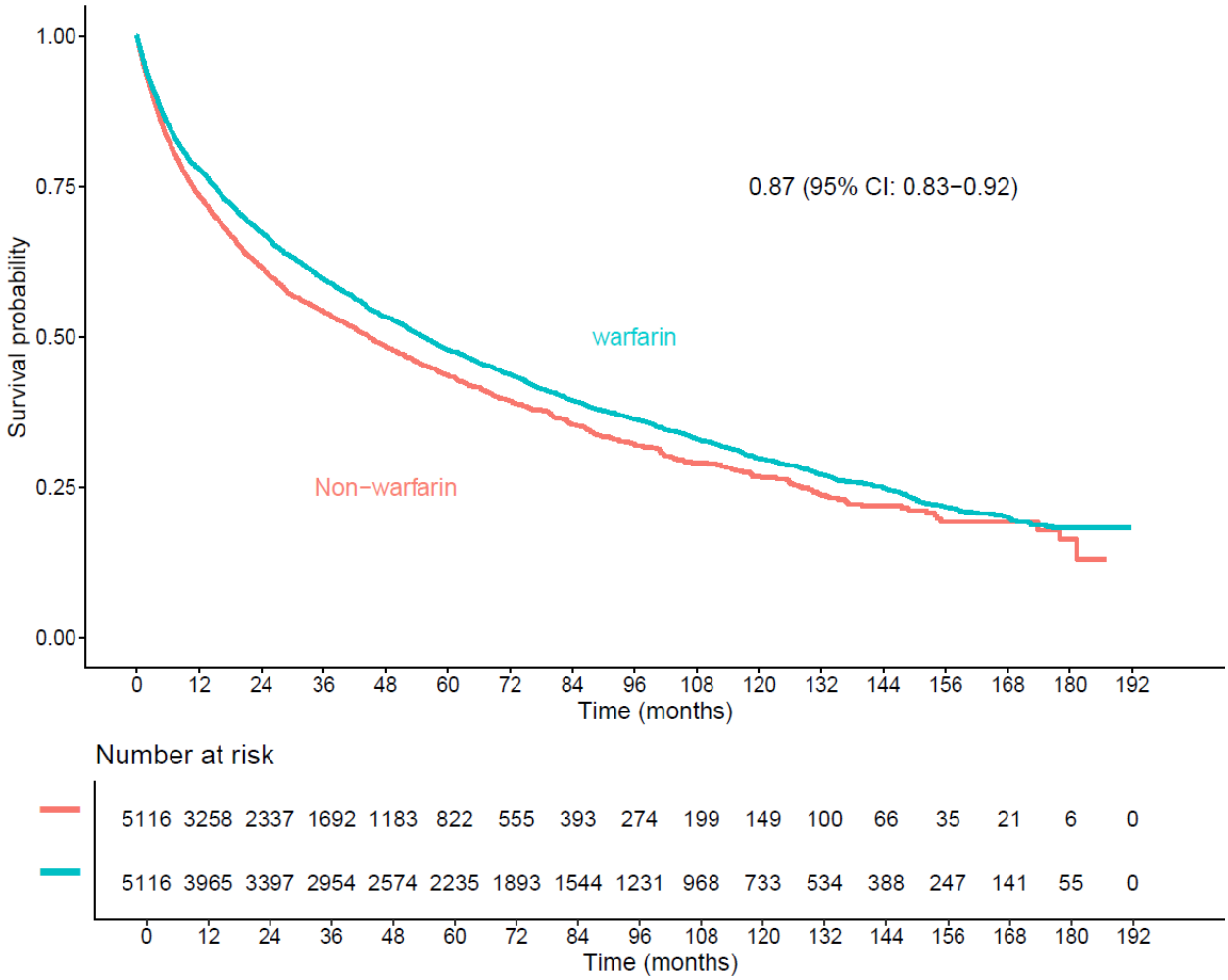


Supplemental Figure 2. Propensity Score Distribution Before and After Matching
Distribution of estimated propensity scores for warfarin (blue) and non-warfarin (pink) groups before (left panel) and after (right panel) matching. Propensity score matching achieved substantial overlap and improved balance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