Poor performance of D-dimer in excluding venous thromboembolism among patients with lymphoma and leukemia

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Supplementary Material

Supplemental Methods

Study subjects and data collection

All consecutive patients who visited the emergency department (ED) of The University of Texas MD Anderson Cancer Center, Houston, Texas, between January 1, 2009, and December 31, 2012, with a laboratory request for measurements of D-dimer were identified by querying billing and laboratory databases. Exclusion criteria were 1) non-cancer patients, 2) lost to follow-up before determining the presence or absence of VTE, 3) incomplete data, and 4) duplicate cases (e.g., multiple D-dimer measurements within two days of the diagnostic imaging). Patients lacking appropriate diagnostic imaging studies (upper or lower extremity Doppler ultrasound, chest computed tomography with contrast, or ventilation/perfusion (V/Q) scans) within 2 days of the visit and those who had arterial thrombosis were also not included in the analysis.

Potential study subjects were identified using an electronic medical record system. Patient demographic, clinical, and laboratory data, including D-dimer levels were collected. D-dimer is on the diagnostic panels for the evaluation of chest pain, shortness of breath or limb swelling. The majority of the ED patients had D-dimer ordered for the evaluation of these symptoms. The presence or absence of VTE was determined by reviewing the imaging reports by investigators not aware of the D-dimer results. Questionable imaging results were further reviewed by a board-certified thoracic radiologist and classified as either positive or negative. VTE was defined as venous thromboembolism excluding superficial venous thrombosis and thrombophlebitis with evidence from imaging studies. This includes pulmonary embolism (PE) as evidenced by

at least one PE identified anywhere in the pulmonary arterial system on CT scan or a high-probability V/Q scan. Lower limb deep vein thrombosis (LL-DVT) is considered positive if proximal or distal venous thrombus was identified in the lower limb, and "other VTE" includes upper limb DVT, inferior vena cava thrombosis … etc.).

To validate the results, we analyzed data from a second cohort of patients who presented to the emergency department of King Hussein Cancer Center, Amman, Jordan, between January 1, 2009, and December 31, 2015. Our collaborators at the King Hussain Cancer Center used a similar work flow. Institutional Review Boards of MD Anderson and King Hussein Cancer Center approved the study and granted waivers of informed consent.

Sample size

We estimated the minimum sample size required based on the prevalence of VTE in cancer patients presented to the ED and 0.90 as the lowest tolerable sensitivity for D-dimer in excluding VTE. To detect a sensitivity of 0.96 with a power of 0.80 and a significance level of 0.05, at least 106 patients in each cancer type were needed. Therefore, our final sample size of 5238 was needed such that there were >106 patients for the top 10 cancer types presented to the ED.

D-dimer analysis

D-dimer for all patients in the MD Anderson cohort was detected using the Liatest(r) D-Di immuno-turbidimetric assay (Diagnostica Stago). For patients in the King Hussain cohort, D-dimer was detected using Liatest(r) D-Di Plus immunoassay (Diagnostica Stago). Both

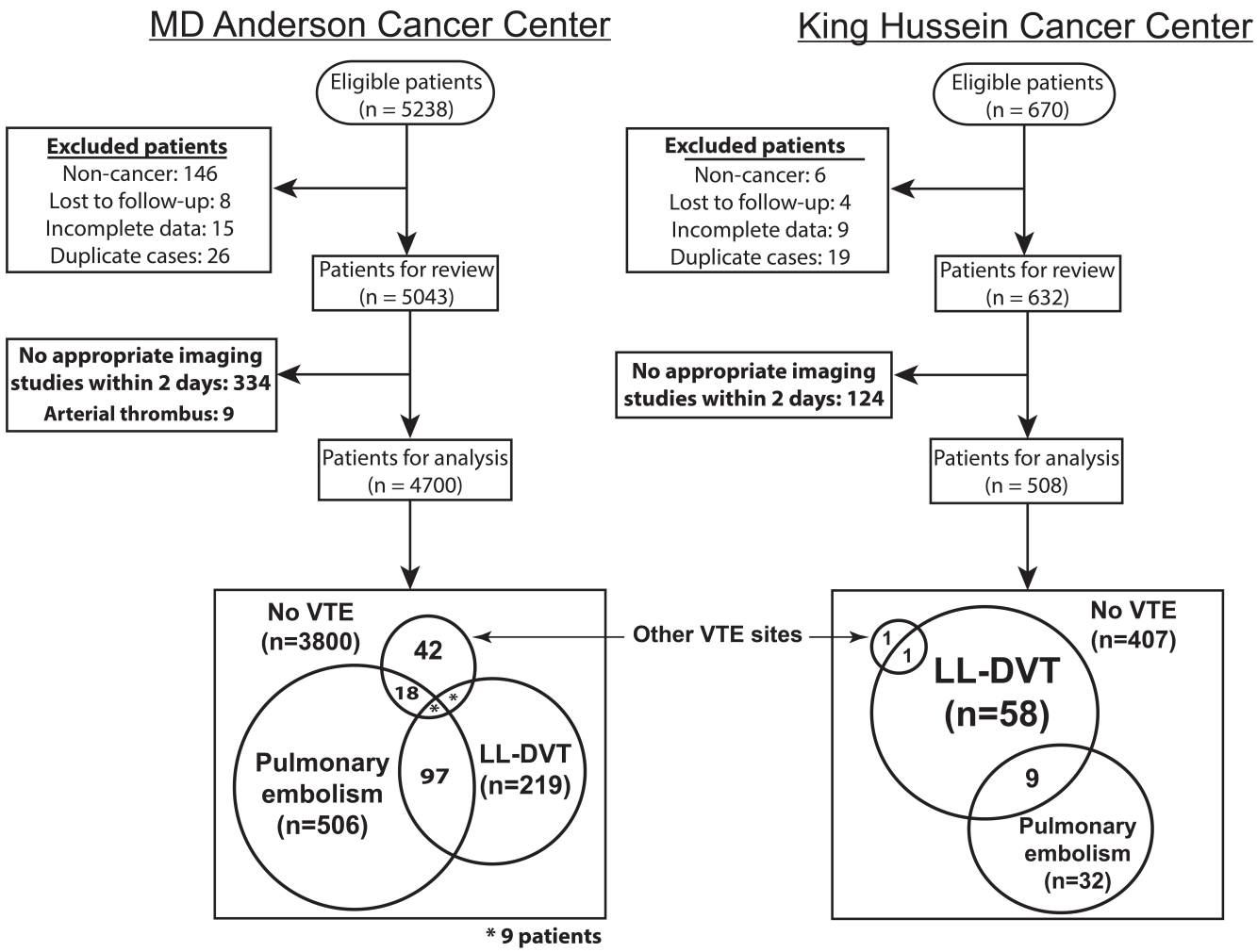
assays have a 0.5 μg/mL cutoff value and a range of 0.27-20 μg/mL. D-dimer levels were analyzed for each cancer type to determine the difference in mean D-dimer levels between VTE and non-VTE groups. The sensitivity, specificity, NPV, and positive predictive value (PPV) of D-dimer for a range of D-dimer values were determined for each cancer type, and cancer types with similar results were grouped together. Receiver operating characteristic (ROC) analysis of each group was performed, and the area under the curve (AUC) was calculated. These AUC values were compared with each other. The Delong test was used to evaluate the statistical significance of differences between ROC curves. A two-tailed *P* value of <0.05 was considered statistically significant.

Analysis of different D-dimer cutoff point determination methods

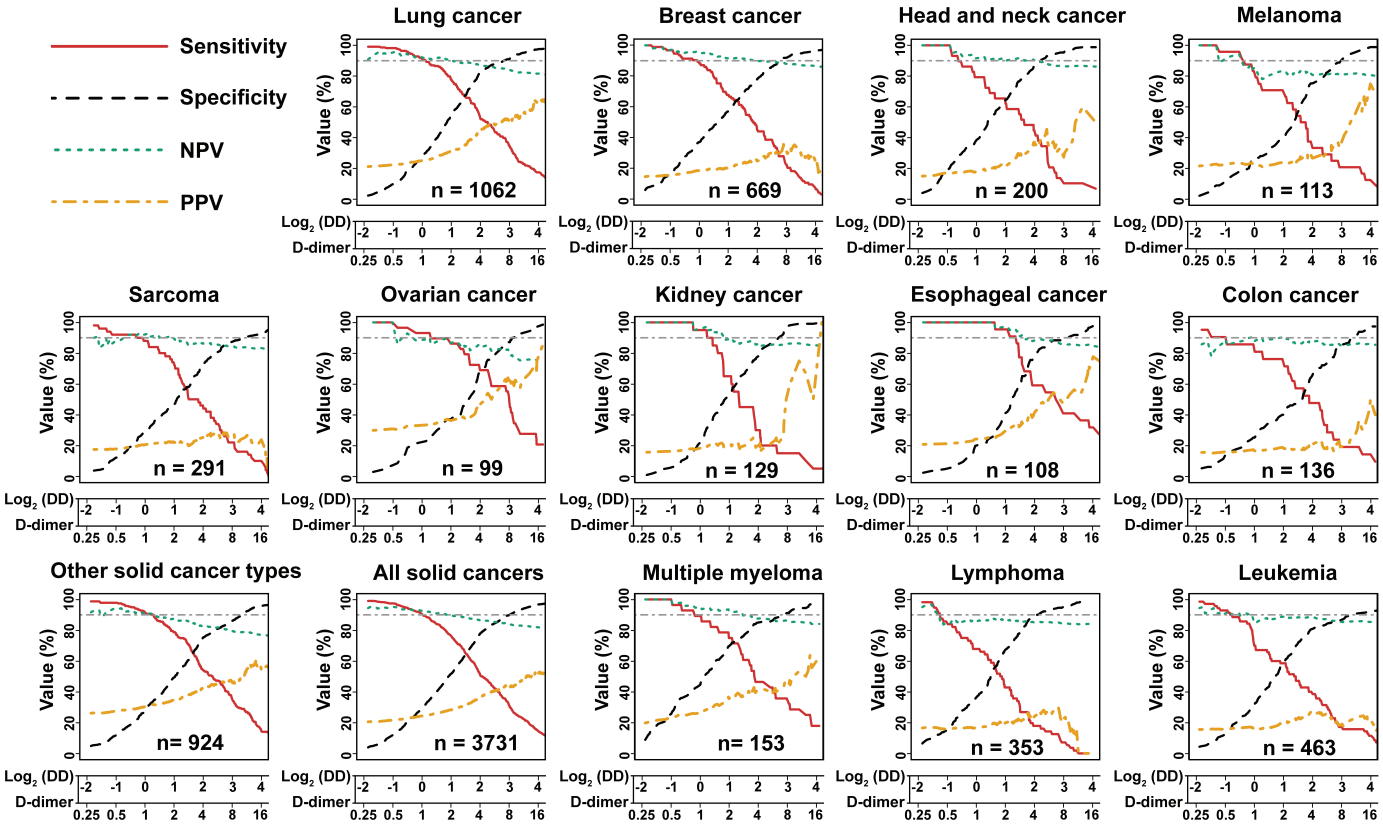
The performance of the current conventional cutoff point (0.5 μg/mL) specified by most of the commercially available D-dimer assays, the age-adjusted cutoff point, and the seventy-fifth percentile level of the study population as a cutoff point were analyzed for their usefulness in detecting VTE. The sensitivity, specificity, NPV, and the PPV of each method was calculated and compared for different cancer groups. The McNemar test and generalized score statistic test were used to evaluate the statistical significance of differences between the sensitivity and NPV for each method.

All statistical analyses were performed using R software (version 3.4.1, The R Foundation, http://www.r-project.org).

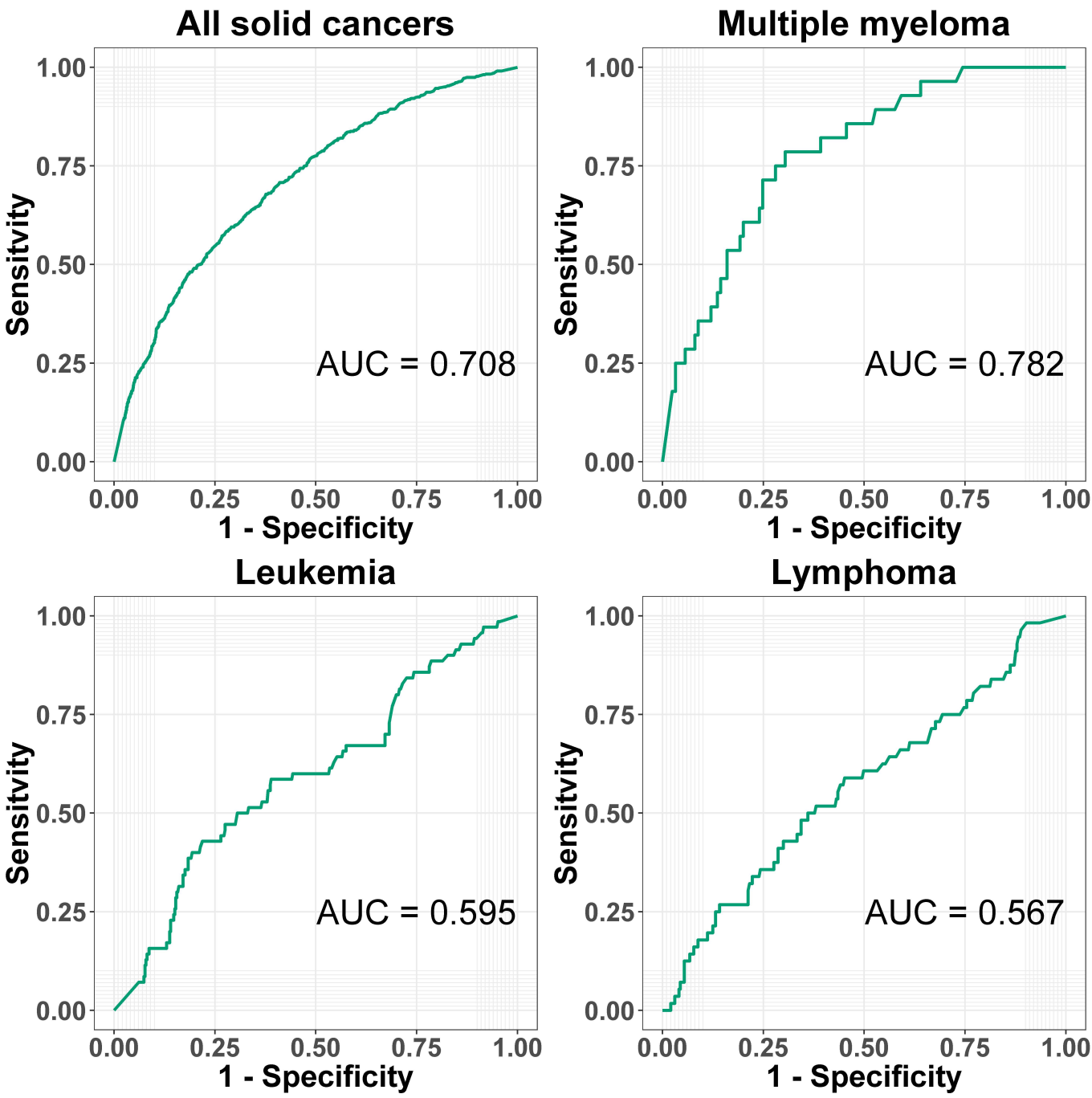
Supplemental Figures



Supplemental Figure S1: Flow chart of exclusion criteria for the MD Anderson and King Hussein cohorts. VTE, venous thromboembolism; LL-DVT, lower limb deep venous thrombosis.



Supplemental Figure S2: Sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) of D-dimer for each cancer type. Low-prevalence solid cancers were grouped into a miscellaneous category of “other solid cancer types.”



Supplemental Figure S3: Receiver operating characteristic curve analysis of D-dimer for the prediction of venous thromboembolism in all solid cancers, multiple myeloma, leukemia, and lymphoma. AUC, area under the curve.