Thrombosis Research 254 (2025) 109448

Contents lists available at ScienceDirect

Thrombosis Research

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

Letter to the Editors-in-Chief

D-dimer as a predictive biomarker for cancer-associated thrombosis: A prospective cohort study

ARTICLE INFO

Keywords:
Cancer-associated thrombosis
D-dimer
Khorana risk score
Thromboprophylaxis
Predictive biomarker
Venous thromboembolism

1. Introduction

Cancer-associated thrombosis (CAT) is a frequent and severe complication in cancer patients, significantly worsening clinical outcomes [1]. While the Khorana Risk Score (KRS) [2] is a widely used tool for identifying high-risk patients, its predictive performance is limited, particularly in patients with advanced or high-risk tumors [3].

More accurate models, such as the modified Vienna CATScore (mVC) [4], integrate biomarkers like D-dimer, which reflects hemostatic activation. Although the mVC has demonstrated superior predictive accuracy [5], its clinical adoption is hindered by the complexity of its calculations. In contrast, D-dimer as a standalone biomarker, has shown promising results in predicting venous thromboembolism (VTE) in select high-risk populations [6–9].

This study aimed to evaluate the predictive value of D-dimer for VTE at six months in ambulatory patients with high-risk, metastatic cancer initiating chemotherapy.

2. Methods

This was a prospective cohort study conducted at the UC-CHRISTUS Cancer Center in Santiago, Chile. We enrolled patients with metastatic cancers known to have a high risk of VTE, including esophageal, gastric, lung, ovarian, colorectal, pancreatic, and biliary tract cancers. All participants were about to start systemic therapy and had no prior anticoagulation. We determined a sample size of 100 patients to achieve an alpha error of 0.05 and a beta error of 0.2, based on an estimated VTE incidence of 10 % and an anticipated area under the curve (AUC) of 0.75.

Patients were identified by their oncologists and then screened by the research team. A hybrid informed consent process was used, which included a virtual form followed by an in-person signature.

We collected venous blood samples for D-dimer (DD) measurement by a nursing team before the initiation of systemic therapy. D-dimer levels were measured using the ELFA technique (Vidas®, Biomerieux kit) and reported in ng/mL. During the study's execution, a second D-dimer measurement was added for an exploratory analysis, collected between one and two months after the start of therapy. Patients who experienced a VTE event between the two measurement time points were excluded from the analysis of the second measurement.

Patient outcomes were longitudinally assessed at three and six months. We utilized electronic health records from the UC-CHRISTUS Health Network and death certificates as primary sources for follow-up data. To resolve discrepancies or obtain missing information, direct patient contact was established via telephone.

We included both incidental and symptomatic VTE events. Diagnoses were confirmed by Doppler ultrasound for deep vein thrombosis (DVT) in the upper or lower extremities, CT angiography for pulmonary embolism (PE) or DVT, or documented on a death certificate. Routine VTE screening was not performed, and superficial thrombosis cases were excluded. Treating physicians were not blinded to the D-dimer levels when assessing for VTE.

The primary analysis assessed the predictive performance of baseline D-dimer levels (DD1) for VTE development by calculating the AUC of the receiver operating characteristic (ROC) curve. We defined statistical significance as an AUC > 0.5, with the lower bound of the 95 % confidence interval also exceeding 0.5. When the result was significant, the optimal cutoff value was determined using the Youden Index, and we calculated the corresponding performance metrics.

A secondary analysis evaluated the predictive utility of established risk assessment models, including the KRS and mVC, by calculating their respective AUCs. We calculated the Net Reclassification Index (NRI) to determine the added value of the KRS to DD1 risk stratification.

Finally, an exploratory analysis was conducted to assess the predictive value of the second D-dimer measurement (DD2) using the AUC. If significant, the optimal cutoff was determined using the Youden Index.

3. Results

A total of 327 patients were screened, of whom 104 met the inclusion criteria. We successfully recruited 70 patients between January and December 2023. Three of these patients were later excluded due to ineligibility. The 34 potential participants who were not recruited were due to: refusal to participate ($n = 10$), screening failure ($n = 9$), sample-related errors ($n = 6$), transition to care outside the healthcare system ($n = 5$), and insufficient personnel for sample collection ($n = 4$).

For the final cohort, data collection was achieved for 67 cases for DD1 and mVC (100 %), 66 cases for KRS (98.5 %), and 43 cases for DD2

https://doi.org/10.1016/j.thromres.2025.109448
Received 11 July 2025; Received in revised form 6 August 2025; Accepted 25 August 2025
Available online 27 August 2025

(64.2 %). The recruitment for DD2 began mid-study, creating logistical challenges for coordinating a second sample collection, which accounts for the high number of missing data. We completed the six-month follow-up for all participants.

In this cohort, colorectal tumors were the predominant primary site (55 %). The prevalence of other tumor sites ranged from 2 % to 12 %. 19 patients (28 %) were categorized as high-risk by a KRS score ≥2, and 30 (45 %) by an mVC risk ≥8 %. The incidence of VTE was higher than anticipated, at 16 % (n = 11) (Table 1). 10 of these events occurred within the initial 3-month follow-up period. The mortality rate was elevated at 13 % (n = 9); however, no VTE was recorded as a direct cause of death.

The three D-dimer-based tests demonstrated acceptable discriminatory performance: DD1 (AUC 0.70; 95 % CI: 0.57–0.85), DD2 (AUC 0.75; 95 % CI: 0.55–0.95), and mVC (AUC 0.67; 95 % CI: 0.53–0.82). In contrast, the KRS showed poor prognostic performance (AUC 0.52; 95 % CI: 0.33–0.71) (Fig. 1).

Given the observed statistical significance, we determined optimal cutoff values for DD1 and DD2. For DD1, the optimal cutoff via the Youden Index was 1062 ng/mL, yielding a sensitivity of 100 % and a specificity of 46 %. For DD2, the optimal cutoff was 2745 ng/mL, with a sensitivity of 56 % and a specificity of 94 %. By comparison, a KRS score ≥2 demonstrated a sensitivity of 36 % and a specificity of 76 %, while an mVC value ≥8 % yielded a sensitivity of 64 % and a specificity of 59 %. The adjusted NRI for KRS with DD1 was −0.309 (−30.9 %), indicating that adding the KRS to DD1 worsens the model's performance.

4. Discusion

In this prospective cohort study, we evaluated the performance of D-dimer levels in predicting VTE in ambulatory cancer patients initiating systemic therapy and compared it with the widely used KRS.

Although the KRS is a validated and commonly used predictive tool, it had limited discriminative ability in our study population. This result is consistent with prior studies that highlight its limitations, particularly in patients with metastatic or high-risk tumors.

Table 1
Baseline patient characteristics.

Characteristic	Value
Age yr. - median (range)	65 (32–80)
Male sex - no. (%)	37 (40 %)
Primary tumor - no. (%)	
Colorectal	37 (52 %)
Pancreatic	5 (7 %)
Biliar	4 (6 %)
Gastroesofagic	6 (9 %)
Lung	7 (10 %)
Ovarian	8 (12 %)
ECOG-PS - no. (%)	
0–1	62 (91 %)
≥2	5 (7 %)
Previous VTE - no. (%)	0 (0 %)
Antiplatelet therapy - no. (%)	6 (9 %)
Hemoglobin <10 g/dL - no. (%)	9 (14 %)
White blood count >11.000 mm^3 - no. (%)	6 (9 %)
Platelets >350.000 mm^3 - no. (%)	14 (21 %)
BMI >35 kg/m^2 - no. (%)	3 (5 %)
KRS - no. (%)	
0–1	48 (73 %)
≥2	19 (28 %)
mVC - no. (%)	
<8 %	37 (55 %)
≥8 %	30 (45 %)
DD1 - median (range) ng/mL	1271 (246–23,629)
DD2 - median (range) ng/mL	1393 (224–5838)

ECOG PS: Eastern Cooperative Oncology Group Performance Status, VTE: Venous Thromboembolism, BMI: Body mass index. KRS: Khorana Risk Score, mVC: modified Vienna CATScore, DD1: Baseline D-dimer, DD2: one-month post-treatment D-dimer.

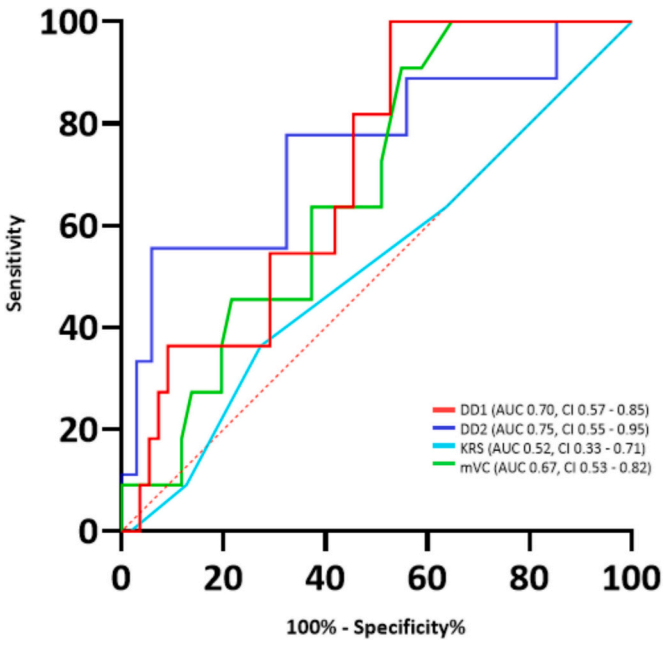

Fig. 1. ROC analysis for thromboembolic disease.
Footnote: DD1: Baseline D-dimer, DD2: one-month post-treatment D-dimer, mVC: modified Vienna CATScore, KRS: Khorana Risk Score, AUC: Area under the curve- c statistic. CI Confidence interval.

In contrast, D-dimer levels measured at baseline (DD1) and one month after therapy initiation (DD2) demonstrated superior predictive performance for VTE, with AUC values of 0.70 and 0.75, respectively. These findings suggest that D-dimer may be a more accurate and reliable biomarker for thrombotic risk stratification in cancer patients. Importantly, DD1 at its optimal cutoff had a 100 % sensitivity, highlighting its value as a rule-out test for VTE. Its ability to reliably identify low-risk patients supports its use in guiding decisions to withhold unnecessary thromboprophylaxis.

Several limitations of this study should be acknowledged. First, we did not achieve our estimated sample size, which may impact the precision of our findings. While the higher-than-anticipated VTE incidence allowed us to reach statistical significance with a smaller cohort, this high VTE rate is likely less accurate due to our limited sample size. Furthermore, our small population limits the value of any subgroup analyses. Second, the inclusion of the second D-dimer measurement (DD2) mid-study and the substantial number of missing values (35.8 %) mean these findings are only hypothesis-generating and require future validation. Third, the predominance of colorectal cancers and the exclusive inclusion of patients with intermediate-to-high-risk metastatic cancers may limit the applicability of our findings to other tumor types and non-metastatic patients. Fourth, there is considerable variability among D-dimer assays due to different methodologies (ELFA, ELISA, or latex immunoturbidimetric assays) and target epitopes [10]. Therefore, the generalizability of our results to other D-dimer measurement techniques is limited.

Our study underscores the limitations of the KRS in predicting VTE in ambulatory cancer patients and highlights the superior performance of D-dimer as a predictive biomarker. Given its simplicity, practicality, and high negative predictive value, D-dimer offers a promising tool for refining risk assessment.

Future research should focus on validating these findings in larger and more diverse cohorts. Randomized controlled trials that incorporate D-dimer into thromboprophylaxis strategies could help determine if its implementation improves clinical outcomes, particularly in high-risk cancer populations.

CRediT authorship contribution statement

E. Elsaca: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **J. López:** Writing – original draft, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **A. Valenzuela:** Writing – review & editing, Project administration. **A. González:** Resources, Investigation. **J. Cerda:** Supervision, Formal analysis. **B. Nervi:** Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization. **A. Aizman:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used Chat-GPT-4 for assistance during the process of translation. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Funding

This study was supported by grants of the Internal Medicine Department and Oncology Department, School of Medicine Pontificia Universidad Católica de Chile, and by the fund ANID FONDAP 152220002 (CECAN).

Declaration of competing interest

None of the authors have any conflicts of interest to declare.

Data availability

The corresponding authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Data of this study are available upon reasonable request from corresponding authors.

References

[1] H.T. Sørensen, L. Mellemkjaer, J.H. Olsen, J.A. Baron, Prognosis of cancers associated with venous thromboembolism, N. Engl. J. Med. 343 (25) (Dec 21 2000) 1846–1850.
[2] A.A. Khorana, N.M. Kuderer, E. Culakova, G.H. Lyman, C.W. Francis, Development and validation of a predictive model for chemotherapy-associated thrombosis, Blood 111 (10) (May 15 2008) 4902–4907.
[3] F.I. Mulder, M. Candeloro, P.W. Kamphuisen, M. Di Nisio, P.M. Bossuyt, N. Guman, et al., The Khorana score for prediction of venous thromboembolism in cancer patients: a systematic review and meta-analysis, Haematologica 104 (6) (June 2019) 1277–1287.
[4] I. Pabinger, N. van Es, G. Heinze, F. Posch, J. Riedl, E.M. Reitter, et al., Development and validation of a clinical prediction model for cancer-associated venous thromboembolism in two independent prospective cohorts, Lancet Haematol. 5 (7) (July 1 2018) e289–e298.
[5] C. Englisch, S. Nopp, F. Moik, A.M. Starzer, P. Quehenberger, M. Preusser, et al., The Vienna CATScore for predicting cancer-associated venous thromboembolism: an external validation across multiple time points, ESMO Open. 10 (2) (Feb 2025) 104130.
[6] M. Nakamura, M. Sakon, M. Sasako, T. Okusaka, H. Mukai, K. Fujiwara, et al., Association of D-dimer level with thrombotic events, bleeding, and mortality in Japanese patients with solid tumors: a Cancer-VTE Registry subanalysis, Int. J. Clin. Oncol. 29 (4) (Apr 2024) 407–416.
[7] V. Kumar, J.R. Shaw, N.S. Key, A. Ilich, R. Mallick, P.S. Wells, et al., D-dimer enhances risk-targeted thromboprophylaxis in ambulatory patients with cancer, Oncologist 25 (12) (Dec 2020) 1075–1083.
[8] Y. Yang, J. Zhan, X. Li, J. Hua, H. Lei, X. Chen, A nomogram to predict the risk of venous thromboembolism in patients with colon cancer in China, Cancer Med. 13 (9) (May 2 2024) e7231.
[9] D. Faille, M.C. Bourrienne, E. de Raucourt, L. de Chaisemartin, V. Granger, R. Lacroix, et al., Biomarkers for the risk of thrombosis in pancreatic adenocarcinoma are related to cancer process, Oncotarget 9 (41) (May 29 2018) 26453–26465.
[10] L.A. Linkins, S. Takach Lapner, Review of D-dimer testing: good, bad, and ugly, Int. J. Lab. Hematol. 39 Suppl 1 (May 2017) 98–103.

E. Elsaca[a,e], J. López[b,e], A. Valenzuela[a,e], A. González[b,e], J. Cerda[c,e], B. Nervi[b,d,e], A. Aizman[a,e,*]

[a] *Department of Internal Medicine, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile*
[b] *Department of Hematology and Oncology, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile*
[c] *Department of Public Health, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile*
[d] *Center for Cancer Prevention and Control (FONDAP-CECAN), Pontificia Universidad Católica de Chile, Santiago, Chile*
[e] *Red de Salud UC CHRISTUS, Santiago, Chile*

[*] Corresponding author at: Diag. Paraguay 362, Santiago, Región Metropolitana, Chile.
E-mail address: asaizman@uc.cl (A. Aizman).