

ORIGINAL ARTICLE

The Vienna CATScore for predicting cancer-associated venous thromboembolism: an external validation across multiple time points

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Background: Patients with cancer undergoing systemic therapies have a high risk for venous thromboembolism (VTE). Risk assessment models were developed to select high-risk subgroups that might benefit from primary thromboprophylaxis, yet currently available models reportedly underperform in contemporary cancer treatment populations and risk models across multiple time points throughout therapy are not available.

Patients and methods: We, therefore, aimed to validate the Vienna CATScore, a nomogram-based model including tumor type and continuous D-dimer levels, in a prospective cohort study of patients initiating contemporary systemic anticancer therapies. The validity of the model was tested at study inclusion, 3 weeks, and 3 months after start of therapy.

Results: Overall, 598 patients were included [49% women, median age 62 years (interquartile range 53–70 years)]. Most patients had stage IV disease (68.2%). The 6-month cumulative incidence of VTE was 9.2% [95% confidence interval (CI) 6.8% to 11.5%]. The Vienna CATScore demonstrated good discriminatory ability (c-statistics: 0.69, 95% CI 0.61–0.76) at study baseline and across all evaluated time points (c-statistics: 0.68, 95% CI 0.63–0.73). Applying a 6-month predicted VTE risk threshold of 8%, the CATScore effectively distinguished between low- and high-risk groups at study inclusion (7.1% versus 15.1% observed VTE risk, $P = 0.004$) and across all three time points (6.3% versus 13.6% observed VTE risk, $P < 0.001$). Assuming a 50% risk reduction with thromboprophylaxis, this threshold resulted in a number needed to treat (NNT) of 13 and 15, respectively, in the high-risk group, while the NNT was 28 and 32, respectively, in the low-risk group.

Conclusions: This external validation of the Vienna CATScore confirms its effectiveness in predicting VTE risk in the initial months of state-of-the-art systemic anticancer therapies and across multiple time points.

Key words: venous thromboembolism, cancer, risk prediction

INTRODUCTION

Venous thromboembolism (VTE) is an important complication in patients with cancer, with an increase in risk by a factor of 4–9 compared with individuals without malignancies, with the highest risk observed in patients undergoing systemic anticancer therapies.^{1,2} VTE represents a significant cause of morbidity and mortality in patients with cancer.³ The occurrence of VTE is a negative prognostic

factor with a threefold increase in mortality, across different cancer types and stages.^{4–8} Considerable efforts have been directed toward the development of prevention strategies, including primary thromboprophylaxis, which reduces the risk of VTE in cancer patients by ~50%.⁹ Based on concurrent bleeding risks, the identification of high-risk subgroups of patients is crucial to derive a net clinical benefit of primary thromboprophylaxis. When primary thromboprophylaxis is considered, the availability of tools for identification of patients with high or low risk of VTE is crucial.

Various risk assessment models were developed to help identify patients at high risk of VTE who would profit from primary thromboprophylaxis. The most frequently validated risk score is the Khorana score¹⁰; however, the predictive performance was moderate in external validation cohorts.^{11–13} Thus, the Vienna CATScore, which is a

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nomogram-based model including tumor type and D-dimer, was created and showed a good discriminatory capacity in the derivation cohort and upon external validation.^{14,15}

The treatment landscape in medical oncology has significantly changed over the past years, with targeted treatments and immune checkpoint inhibitors (ICIs) affecting the risk profiles for VTE by creating a heightened inflammatory environment, as previously hypothesized.^{16,17} Further, development of established risk assessment models was done in patients receiving mostly chemotherapy, questioning the applicability to contemporary cancer therapies. Importantly, recent data suggest limited discriminatory utility of the Khorana score in patients undergoing novel targeted therapies and ICI therapy.^{18,19} Furthermore, most risk prediction models were developed for prior assessment of VTE risk in patients initiating anticancer treatment. Thus, currently available risk assessment models were not evaluated across multiple, longitudinal time points and, therefore, might not capture changes in risk category assignment over time. Furthermore, the implementation of risk assessment models including hemostatic biomarkers was hampered as unclarity exists about the predictive utility of biomarker-based prediction models during anticancer treatment, as levels might change over time and longitudinal evaluations are not available. Thus, it is crucial to evaluate the predictive performance of VTE prediction scores longitudinally, considering the potential significant impact of cancer and anticancer therapy on hemostatic biomarkers. This could significantly improve the clinical utility of risk assessment scores.

In this study, we aimed to externally validate the Vienna CATScore in a prospective cohort of patients with cancer undergoing contemporary cancer therapies across multiple longitudinal time points.

PATIENTS AND METHODS

Study population

This project was carried out within the framework of the Vienna Cancer, Thrombosis and Bleeding study (CAT-BLED study), a single-center, prospective, observational cohort study conducted at the Medical University of Vienna (Vienna, Austria) to investigate the risk and risk factors of VTE and bleeding in a cohort of patients with cancer initiating a regimen of systemic anticancer therapy. Consecutive ambulatory patients with cancer referred to the oncology day clinic (a clinic which patients attend to receive their therapy) with histologically confirmed cancer, comprising both patients with newly diagnosed and with recurrent/progressive cancer after previous anticancer therapies, were eligible for inclusion. All included patients provided written informed consent for study participation. Exclusion criteria were incapacity or refusal of informed consent, age <18 years, and therapeutic anticoagulation at study inclusion. Patients who were included in this project were recruited between July 2019 and March 2023. Biobanking of blood samples was done within the Translational Research Unit (TRU) Biobanking Program for Personalized

Immunotherapy of the Division of Oncology at the Medical University of Vienna (EK 1164/2019). The study has been approved by the Ethics Committee of the Medical University of Vienna (approval number: EK 1533/2019) and has been conducted in full conformity with the International Conference of Harmonization guidelines on Good Clinical Practice and the Declaration of Helsinki by the World Medical Association.

Baseline blood sampling was carried out before the first administration of systemic anticancer therapy at the oncology day clinic upon study enrollment. Patients underwent in-person follow-ups during routine visits and repeated blood samples were drawn. Data about outcome events were collected through personal interviews, questionnaires, and regular screening of electronic medical records. All reported outcome events were cross-validated through screening of electronic medical records. All study participants were followed over the course of therapy and for a maximum of 2 years.

Vienna CATScore and study outcomes

The Vienna CATScore is a nomogram-based risk assessment model that includes two variables: continuous D-dimer levels and tumor type¹⁴ (current link to the risk calculator: <https://catscore.shinyapps.io/catscore/>). Tumor types were grouped according to their VTE risk into very high, high, and low/intermediate risk. In the CATScore derivation study, tumor types considered as very high risk were pancreas and stomach, while lung, colorectal, esophagus, kidney, lymphoma, bladder or urothelial, uterus, cervical, ovarian, sarcoma, and testicular germ-cell tumors were grouped in the high-risk group. Tumor types considered as low/intermediate risk were breast and prostate cancer.¹⁴ As brain tumor and head and neck cancer patients were not included in the derivation cohort, we grouped brain cancer patients in the very-high-risk category as previously done²⁰ and head and neck cancer in the high-risk group, based on the underlying VTE risk associated with this cancer type.¹ The Khorana score was calculated as previously described.¹⁰ Accordingly, we assigned 2 points for very-high-risk (stomach, pancreas) tumors and 1 point for high-risk (lung, lymphoma, gynecologic) tumors, while all other cancer sites were assigned to have 0 points. Additionally, 1 point each was added for a platelet count of $\geq 350 \times 10^9/\text{L}$, hemoglobin <10 g/dL and/or use of erythropoiesis-stimulating agents, leukocyte count $>11 \times 10^9/\text{L}$, and body mass index of $\geq 35 \text{ kg/m}^2$.¹⁰

The primary outcome of interest was the occurrence of VTE within 6 months after study inclusion or after the time point of repeated blood sampling and risk reassessment. VTE was defined as incidental or symptomatic deep vein thrombosis, pulmonary embolism (PE), catheter-related thrombosis, symptomatic visceral vein thrombosis, and symptomatic lower-limb superficial vein thrombosis with an extension of at least 5 cm according to the study protocol and previous studies. All VTE events were adjudicated by an

independent committee including experts in the field of radiology, dermatology, or angiology (vascular medicine).

Laboratory measurements

Venous blood samples were collected into Vacutainer sodium citrate tubes (Vacuette; Greiner Bio-One, Kremsmünster, Germany; containing 1/10 volume sodium citrate stock solution at 0.129 mmol/l) by sterile venipuncture. Samples were centrifuged to obtain platelet-poor plasma, and until analysis, biomaterial was processed and stored according to standard operating procedures by the MedUni Wien Biobank in an ISO 9001:2015-certified environment.²¹ Samples were coded before laboratory analysis, but technicians were unaware of the patients' characteristics at all times.

For this project, plasma samples from the following time points were used: study inclusion (baseline), 3 weeks after start of therapy (follow-up 1), and 3 months after start of therapy (follow-up 2). D-dimer levels were measured with the Tina-quant® D-Dimer Gen2 Assay (Roche Diagnostics, Rotkreuz, Switzerland) carried out on the cobas t 711 coagulation analyzer at the Department of Laboratory Medicine at the Medical University of Vienna.

Statistical analyses

Statistical analyses were carried out using SPSS 28.0 (IBM SPSS Statistics, Chicago, IL) and R Studio (v4.2.0; R Studio, Vienna, Austria) and predefined in the statistical analysis plan (see [Supplementary Material](https://doi.org/10.1016/j.esmoop.2024.104130), available at <https://doi.org/10.1016/j.esmoop.2024.104130>). Standard summary statistics were used to report patient baseline characteristics [absolute frequencies, percentages, median, interquartile range (IQR)]. Median follow-up time was calculated using the reverse Kaplan–Meier method.

Due to the anticipated high risk of underlying mortality, all-cause mortality was treated as a competing event during the follow-up period, and thus, VTE endpoints were studied in a competing risk framework.²² Cumulative VTE incidence was computed using competing risk cumulative incidence functions. The individual risk according to the Vienna CATScore¹⁴ was calculated for each patient. The discriminatory performance of the score in this cohort was evaluated by calculating c-statistics obtained in logistic regression. Calibration was assessed visually with calibration plots, plotting observed against predicted risks. Furthermore, the observed cumulative VTE incidence was compared between groups designated as low risk and high risk according to the Vienna CATScore predictions, utilizing an 8% threshold as a cut-off, according to the recommendation for selecting high-risk ambulatory patients with cancer for primary thromboprophylaxis of the European Society for Medical Oncology (ESMO) guideline.²³ Furthermore, according to a reviewer suggestion, a threshold of 5% was evaluated as this is a commonly used cut-off in recurrent VTE follow-up studies to decide when anticoagulant treatment is stopped. Cumulative VTE incidences were obtained in a proportional subhazard regression model according to Fine and Gray and compared with a Gray's test in a competing risk framework.²⁴ To

visualize the transitions between risk categories over time, an alluvial plot was constructed. Furthermore, we calculated the number needed to treat (NNT) in the two risk groups assuming that primary thromboprophylaxis leads to a risk reduction of 50% according to data from a recent meta-analysis.⁹ Finally, a decision curve analysis was carried out to evaluate the clinical usefulness of the model in comparison to two approaches: thromboprophylaxis for everyone (treat all) or no thromboprophylaxis at all (treat none). The net clinical benefit of the decision curve analysis was calculated as the true-positive rate minus the weighted false-positive rate. The analyses were carried out for every time point (baseline, follow-up 1, follow-up 2) separately and for all three time points combined. A sensitivity analysis excluding superficial vein thrombosis as outcome of interest was carried out additionally.

RESULTS

Cohort characteristics

Overall, 598 patients were included ([Supplementary Figure S1](https://doi.org/10.1016/j.esmoop.2024.104130), available at <https://doi.org/10.1016/j.esmoop.2024.104130>). Of those 49% were female and the median age was 62 years (IQR 53–70 years). Approximately half of the cohort (49.7%) had newly diagnosed cancer, while the remaining patients had progressive or recurrent cancer after previous therapies (50.3%). The most common cancer types were lung (22.9%), breast (10.5%), and head and neck (10.5%) cancer. Overall, 408 (68.2%) patients had stage IV disease at study inclusion. The three most common therapies initiated after study inclusion were chemotherapy (45.1%), followed by ICI monotherapy (16.1%), combined ICI–chemotherapy (17.2%), and chemotherapy combined with targeted therapy (11.7%). The majority of patients had tumor types categorized as high VTE risk (67.1%), while fewer patients had tumor types regarded as very high risk (21.6%) or low/intermediate risk (11.4%) according to the CATScore.¹⁴ Detailed patient characteristics are summarized in [Table 1](#).

Median levels of D-dimer were 0.71 µg/ml (IQR 0.40–1.32 µg/ml) in all samples ($n = 1381$), 0.69 µg/ml (IQR 0.38–1.33 µg/ml) in the baseline samples ($n = 589$), 0.74 µg/ml (IQR 0.41–1.47 µg/ml) at study follow-up after 3 weeks ($n = 408$), and 0.73 µg/ml (IQR 0.41–1.21 µg/ml) at follow-up after 3 months after study inclusion ($n = 384$).

D-dimer levels at study inclusion did not differ between the single tumor types ([Supplementary Figure S2A](https://doi.org/10.1016/j.esmoop.2024.104130), available at <https://doi.org/10.1016/j.esmoop.2024.104130>); however, upon grouping patients according to the VTE risk categories of the CATScore,¹⁴ patients with very-high-risk tumor types had the highest D-dimer levels at study inclusion ([Supplementary Figure S2B](https://doi.org/10.1016/j.esmoop.2024.104130), available at <https://doi.org/10.1016/j.esmoop.2024.104130>).

Study outcomes

Overall, 54 patients were diagnosed with VTE in the first 6 months after study inclusion [6-month cumulative

Table 1. Patient characteristics at study inclusion

	<i>n</i> of available data	Median (IQR)/ <i>n</i> (%)
Age (years)	598	62 (53-70)
Female	598	292 (49.0)
BMI (kg/m ²)	598	23.7 (20.9-26.8)
Tumor type	598	
Lung		137 (22.9)
Breast		63 (10.5)
Head and neck		63 (10.5)
Pancreatic		62 (10.4)
Other		49 (8.2)
Sarcoma		45 (7.5)
Colorectal		44 (7.4)
Brain		36 (6.0)
Stomach		31 (5.2)
Liver		21 (3.5)
Esophagus		20 (3.3)
Urinary		11 (1.8)
Lymphoma		9 (1.5)
Prostate		5 (0.8)
Gynecological		2 (0.3)
Tumor VTE risk category	598	
Very high risk		129 (21.6)
High risk		401 (67.1)
Low/intermediate risk		68 (11.4)
Newly diagnosed cancer	596	297 (49.7)
Stage IV disease	598	408 (68.2)
Systemic therapy after study inclusion	598	
Chemotherapy		270 (45.1)
Chemotherapy + ICI therapy		103 (17.2)
ICI therapy		96 (16.1)
Targeted therapy + chemotherapy		70 (11.7)
Targeted therapy		34 (5.7)
No systemic therapy		15 (2.5)
Targeted + ICI therapy		10 (1.7)

BMI, body mass index; ICI, immune checkpoint inhibitor; IQR, interquartile range; VTE, venous thromboembolism.

incidence: 9.2%, 95% confidence interval (CI) 6.8% to 11.5%; [Figure 1A](#)]. During the same observation period, 95 patients died (6-month cumulative mortality: 16.1%, 95% CI 13.1% to 19.0%; [Figure 1B](#)). During the 6-month observation period after follow-up 1 at 3 weeks after study inclusion (i.e. until 6 months and 3 weeks of overall follow-up), 38 VTE events occurred (cumulative incidence: 7.3%, 95% CI 5.1% to 9.6%). During the 6-month observation period after follow-up 2 at 3 months (i.e. until 9 months of overall follow-up), 24 VTE events occurred (cumulative incidence: 4.9%, 95% CI 3.0% to 6.9%). Details on the characteristics of the VTE events are summarized in [Supplementary Table S1](#), available at <https://doi.org/10.1016/j.esmoop.2024.104130>.

Validation of the Vienna CATScore

The Vienna CATScore was calculated for every patient as described previously, using the formula given in the derivation and validation study.¹⁴ The median predicted 6-month cumulative VTE risk for all included patients at all time points was 5.3% (IQR 4.7%-7.9%). The model achieved good discriminatory performance when applied at study baseline (c-statistics: 0.69, 95% CI 0.61-0.76). The predictive performance at follow-up 1 (at 3 weeks) and follow-up 2 (at

3 months of follow-up) was very similar and a comparable discriminatory performance was observed (c-statistics at follow-up 1: 0.65, 95% CI 0.55-0.74; c-statistics at follow-up 2: 0.70, 95% CI 0.57-0.83). When assessing the performance of all predicted VTE risks including all D-dimer measurements (up to three per patient, *n* = 1381), the model showed overall good discriminatory performance (c-statistics: 0.68, 95% CI 0.63-0.73, [Figure 2A](#)). The performance was comparable when used to assess the 3-month VTE risk (data not shown). The assessment of the calibration plot revealed a good calibration for patients with a 0%-10% predicted 6-month VTE risk ([Figure 2B](#)), whereas the model tended to underestimate VTE risk in patients with a predicted 6-month risk exceeding 10%.

Applying a 6-month predicted VTE risk threshold of 8%, the CATScore effectively distinguished between low- (*n* = 440) and high-risk (*n* = 149) groups at study inclusion [cumulative 6-month incidence of VTE: 7.1% (95% CI 4.7% to 9.5%) versus 15.1% (95% CI 9.3% to 21.0%), Gray's test *P* = 0.004, subdistribution hazard ratio (SHR) for VTE high- versus low-risk group: 2.21 (95% CI 1.28-3.81); [Figure 3](#)]. This clear distinction of risk groups was also seen when assessing follow-up 1 and follow-up 2 time points ([Supplementary Figure S3B and C](#), available at <https://doi.org/10.1016/j.esmoop.2024.104130>). When applying the 8% cut-off to all time points and carrying out a joint analysis, again a clear difference between the low-risk (*n* = 961) and high-risk (*n* = 367) group was observed [6.3% (95% CI 4.8% to 7.8%) versus 13.6% (95% CI 10.0% to 17.1%) 6-month observed VTE risk, Gray's test *P* < 0.001, SHR high- versus low-risk group: 2.25 (95% CI 1.54-3.27); [Supplementary Figure S3D](#), available at <https://doi.org/10.1016/j.esmoop.2024.104130>]. The sensitivity of the 8% cut-off was 76.3% when applied to the prediction at study inclusion and 74.4% when all time points together were assessed. The specificity was 41.5% and 44.6%, respectively. During the follow-up period, six patients (1.0%) moved from the low- to the high-risk group as their predicted 6-month VTE risk increased above 8% during follow-up compared with study baseline. In contrast, eight patients (1.3%) transitioned from the high-risk group at baseline to the low-risk group during follow-up as their predicted risk decreased below 8% ([Supplementary Figure S4](#), available at <https://doi.org/10.1016/j.esmoop.2024.104130>). Similarly, a 5% 6-month predicted VTE risk threshold effectively distinguished between low- (*n* = 235) and high-risk (*n* = 354) groups at study inclusion and at all time points together ([Supplementary Figure S5](#), available at <https://doi.org/10.1016/j.esmoop.2024.104130>).

The decision curve analysis revealed that the model exhibited higher clinical utility for evaluating thromboprophylaxis at study inclusion compared with the strategies of universal treatment (i.e. thromboprophylaxis for all) or no treatment (i.e. thromboprophylaxis for none; [Supplementary Figure S6A](#), available at <https://doi.org/10.1016/j.esmoop.2024.104130>). This higher net clinical benefit was also observed when a decision curve analysis assessing all three time points was carried out

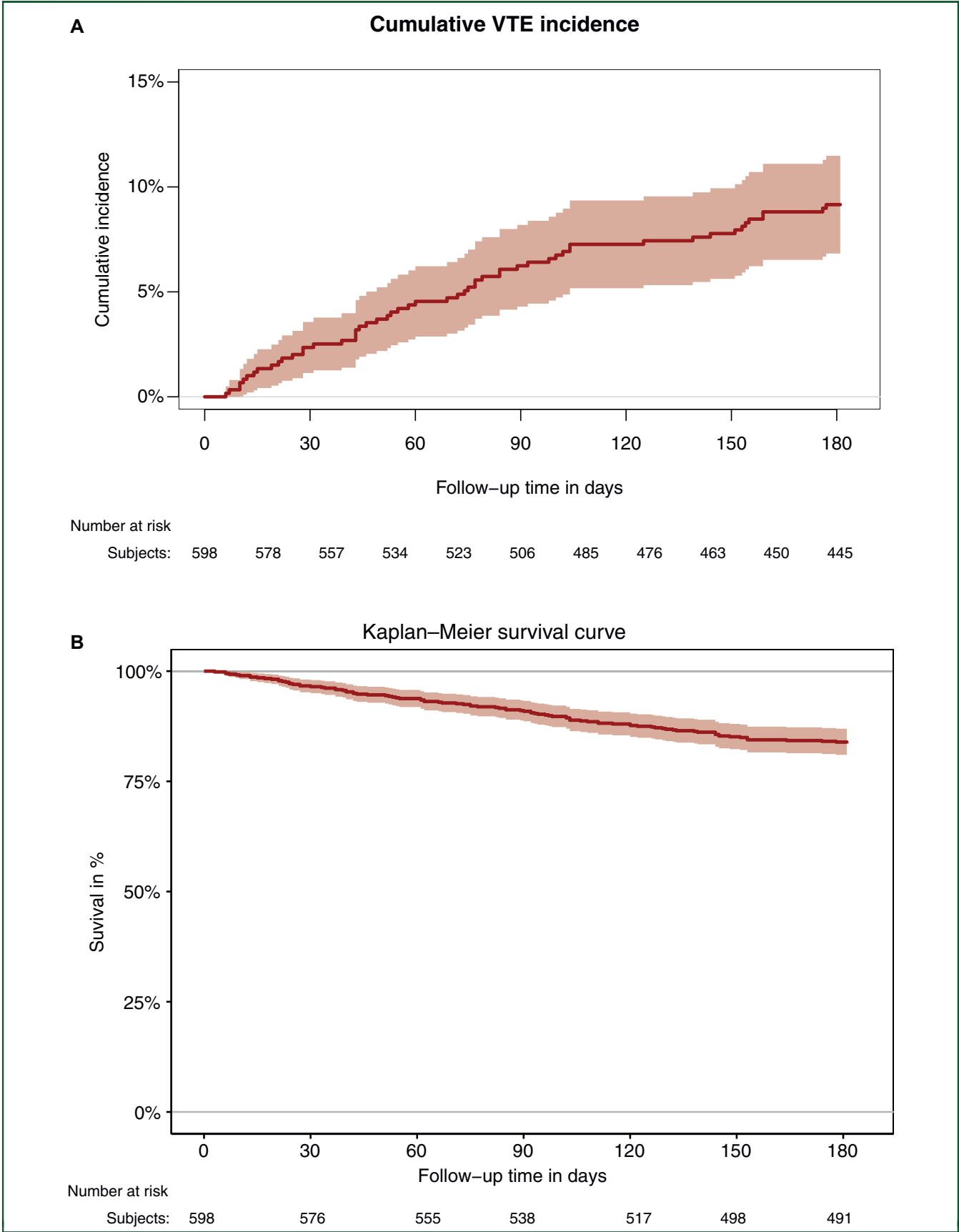


Figure 1. Cumulative venous thromboembolism (VTE) incidence (A) and overall survival (B) during the first 6 months of follow-up.

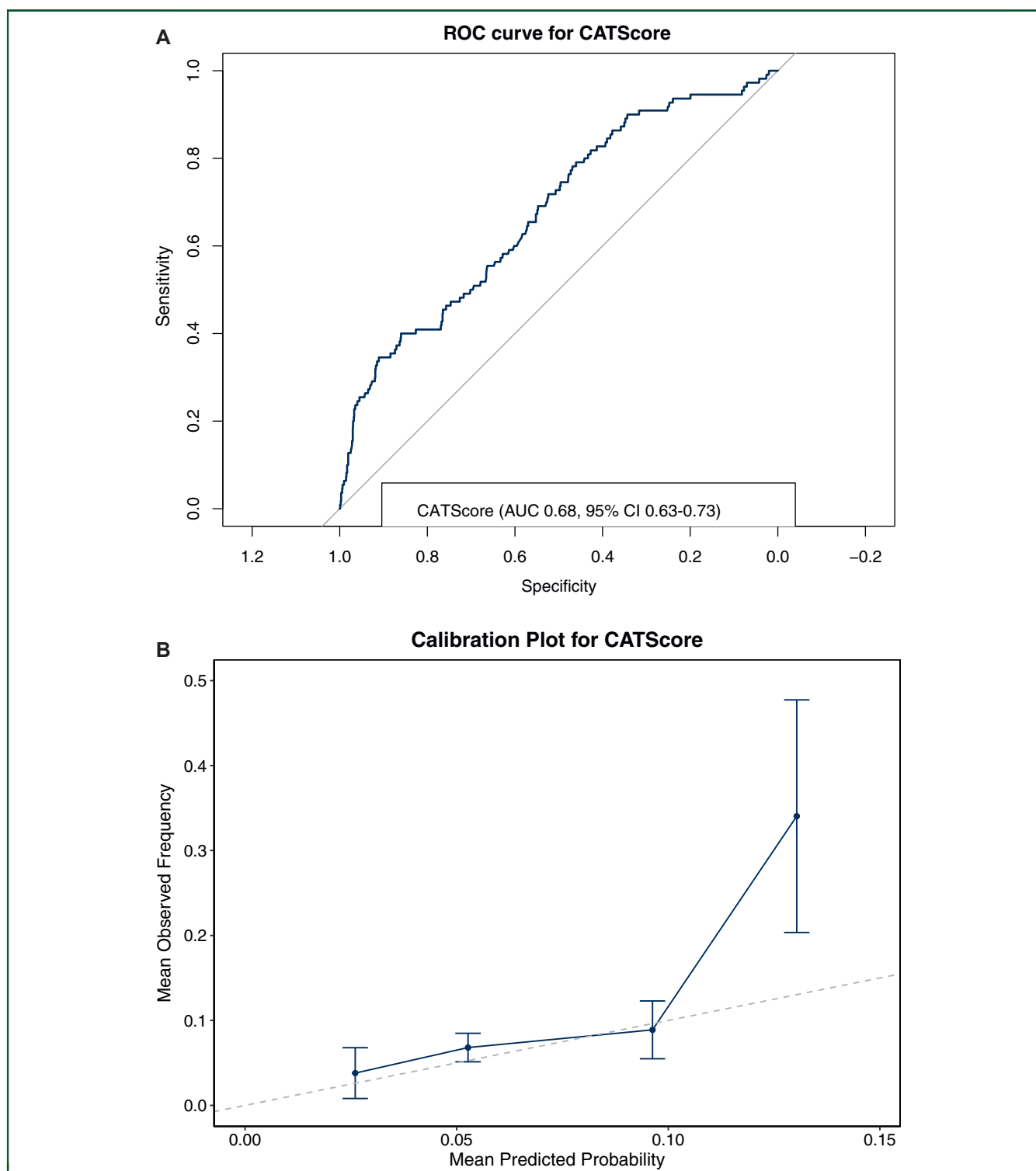


Figure 2. ROC curve analysis (A) and calibration curve (B) for the Vienna CATScore including all three time points of D-dimer measurements. AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristic.

(Supplementary Figure S6B, available at <https://doi.org/10.1016/j.esmoop.2024.104130>). Assuming a 50% risk reduction with primary thromboprophylaxis,⁹ the NNT to prevent one VTE event in the high-risk group was 13 at baseline and 15 when all time points together were assessed, indicating a clear benefit with a relatively low NNT across all time points. In contrast, the NNT was 28 at baseline and 32

across all time points in the low-risk group, reflecting a much smaller benefit in this population.

Sensitivity analysis

We conducted a sensitivity analysis excluding superficial vein thrombosis as study outcome and assessed the performance

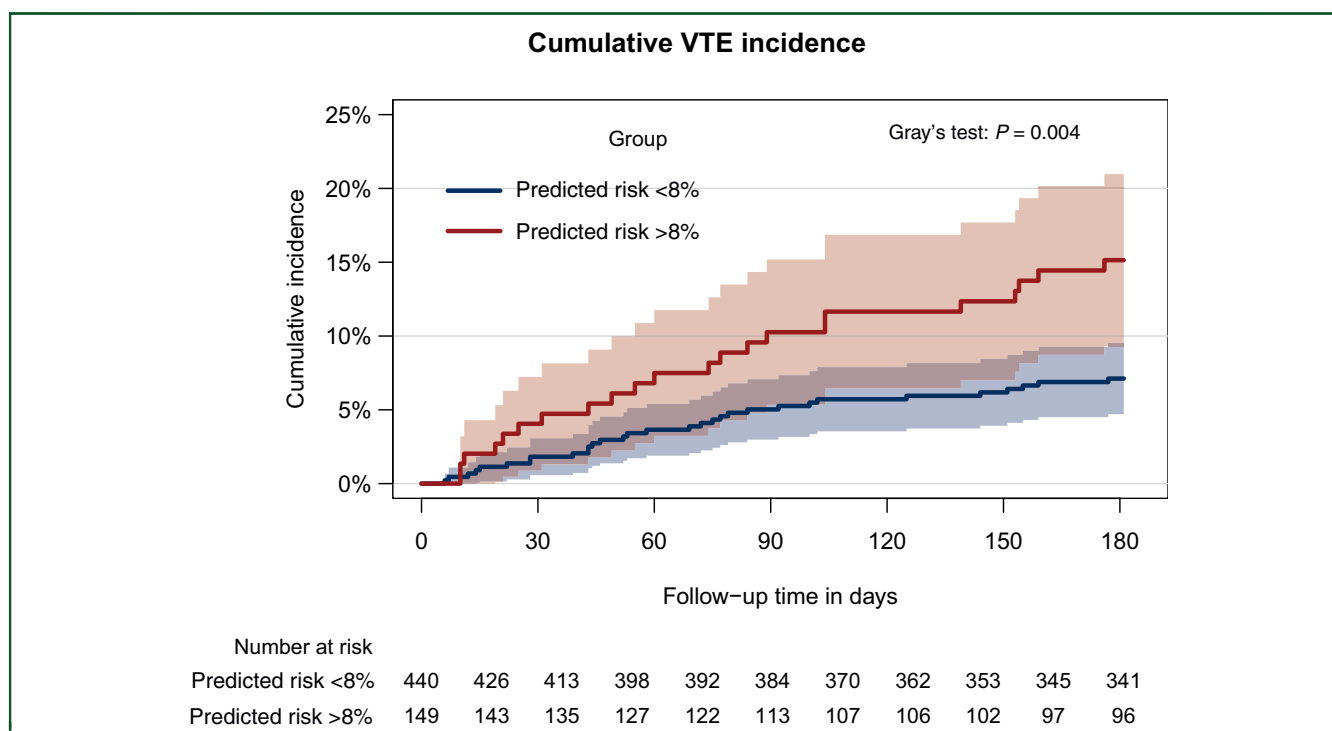


Figure 3. Cumulative VTE incidence between predicted risks below ($n = 440$) or above ($n = 149$) 8% at study inclusion. Patients were divided according to their predicted 6-month VTE risk using 8% as a cut-off and the groups were compared within a Fine and Gray subdistribution hazard model, $P < 0.001$. VTE, venous thromboembolism.

of the Vienna CATScore in this context. The discriminatory ability at study inclusion was consistent (Supplementary Table S2, available at <https://doi.org/10.1016/j.esmoop.2024.104130>). Using the 8% cut-off for predicted risk again resulted in a clear distinction between groups (Supplementary Figure S7, available at <https://doi.org/10.1016/j.esmoop.2024.104130>) and showed comparable sensitivity and specificity (Supplementary Table S3, available at <https://doi.org/10.1016/j.esmoop.2024.104130>).

Comparative performance of the Vienna CATScore and the Khorana score

The Khorana score showed a poor discriminatory performance when evaluated at study inclusion (c-statistics: 0.56, 95% CI 0.48-0.64) and a similarly poor performance was seen at follow-up 1, follow-up 2, and when all three time points together were assessed (Supplementary Table S4 and Figure S8, available at <https://doi.org/10.1016/j.esmoop.2024.104130>). Using a Khorana score ≥ 2 as a cut-off did not result into low- and high-risk groups with a clear difference in observed 6-month VTE incidence [8.4% (95% CI 5.7% to 11.1%) versus 10.7% (95% CI 6.3% to 15.2%), Gray's test $P = 0.36$]. This cut-off led to a sensitivity of 68.4% at study inclusion and of 67.7% when all time points were combined. The specificity was 37.7% and 39.0%, respectively. The decision curve analysis comparing the Khorana score and the CATScore showed a higher net clinical benefit for using the CATScore at study inclusion (Figure 4) and at all time points combined for evaluating thromboprophylaxis.

DISCUSSION

In the present study, we report the validation of the Vienna CATScore in patients receiving contemporary anticancer therapies including targeted treatments and ICI. Overall, the Vienna CATScore demonstrated good predictive performance for assessing the 6-month risk of VTE in our cohort. Moreover, this validation confirmed the model's dynamic applicability by demonstrating consistent predictive performance across three distinct time points within the first 3 months of anticancer therapy.

Patients with cancer at high risk for VTE are recommended to be offered primary thromboprophylaxis.^{23,25-27} To estimate if a patient is at high VTE risk, the use of a validated risk assessment tool is suggested. Most guidelines recommend the Khorana score; however, this score demonstrated only moderate discriminatory performance in a recent large-scale meta-analysis evaluating almost 35 000 patients with cancer.¹¹ The Vienna CATScore was developed more recently, which showed promising discriminatory ability in both its derivation and subsequent validation cohorts.^{14,15}

Our study now not only corroborates the strong predictive capacity of the Vienna CATScore but also broadens its utility in several aspects. Firstly, previous risk assessment models were developed in cohorts of patients mostly undergoing chemotherapy. With the introduction of novel anticancer therapies, the risk profiles of VTE in treated patients were changed, affecting the potential predictive utility of previously developed VTE risk prediction models.^{1,16,17} Novel oncologic therapies

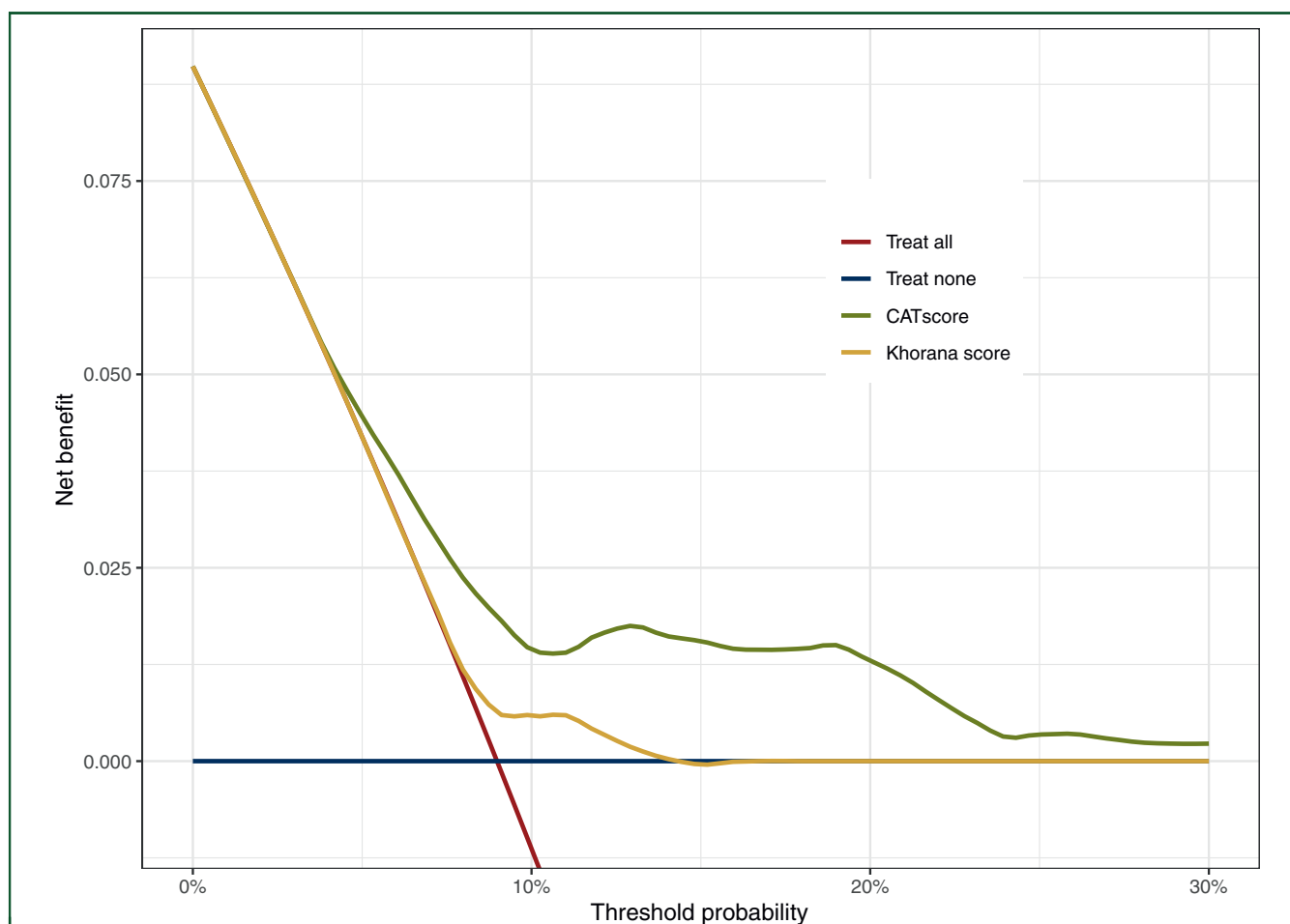


Figure 4. Decision curve analysis. The threshold probability represents the predicted 6-month risk of venous thromboembolism in CAT-BLED for recommending primary thromboprophylaxis at study inclusion. The net clinical benefit balances the risk of venous thromboembolism with the potential harms of unnecessary thromboprophylaxis and was calculated as the true-positive rate minus the weighted false-positive rate.

including ICI and targeted therapies might affect VTE risk.¹⁸ Previously, known risk factors and risk assessment models were shown to have a lower or absent predictive capacity in cohorts including patients receiving novel therapies, especially ICIs.²⁸⁻³⁵ Also, a more recently developed, promising risk assessment score with a modern derivation cohort only included a small proportion of patients with ICI therapy,³⁶ and further validation in ICI cohorts is needed. In our cohort, nearly one-third of patients received ICIs either as monotherapy or as a combination therapy. Agreeing with the literature, the Khorana score showed a poor predictive performance in our cohort. Apart from the possibility that the Khorana score may underperform in a contemporary cohort of cancer patients as demonstrated previously,²⁸⁻³⁵ another reason for its poor performance could be the low proportion of real low-risk cancer types included in our study. In contrast, we observed a good predictive performance of the Vienna CATScore which also includes cancer type as variable.

Secondly, in everyday clinical practice, it would be useful to have a risk assessment tool that remains applicable even after the initiation of anticancer therapy. Most risk

assessment tools were developed within cohorts where patients were assessed before the start of the treatment. It is known that systemic therapy influences certain hemostatic biomarkers; however, their changes are very heterogeneous questioning the predictive abilities of biomarker-based models after the start of systemic therapy.³⁷ Previously, D-dimer was shown to increase in patients who will develop VTE in the future.³⁸ Therefore, we also assessed the predictive utility of the CATScore after the start of therapy. The score showed similar predictive performance at all three time points, indicating that it might be a useful tool at different time points throughout ongoing cancer treatment. Another concern when utilizing hemostatic biomarkers to assess individual risk in cancer patients is the frequent lack of standardization, with institutions often employing different assays from various manufacturers. For this validation, we employed a different assay than the one used in the derivation cohort. Additionally, in the initial validation cohort (Multinational Cohort Study to Identify Cancer Patients at High Risk of Venous Thromboembolism [MICA] cohort), another assay was utilized.¹⁴ Despite the use of different assays across the three cohorts, the predictive performance remained highly

comparable, suggesting that assay variation may not significantly impact the score's performance.

Thirdly, in the derivation cohort¹⁴ and in one of the external validation cohorts,¹⁵ mainly deep vein thrombosis, PE, and, to a lesser extent, also symptomatic visceral vein thrombosis were outcome events. The present study also included incidental PE, catheter-related thrombosis, and extended superficial vein thrombosis of the lower limb. We observed that the predictive performance was still very comparable with the results reported before in the other cohorts, even when we extended the outcomes of interest, suggesting that the score is also capable of predicting risk for these VTE events.

According to the ESMO clinical practice guidelines, thromboprophylaxis in cancer patients at a predicted VTE risk >8%-10% is recommended.²³ Our analysis of the Vienna CATScore revealed that, while it tends to underestimate the risk in patients whose predicted risk exceeds 10%, it offers exceptional accuracy for predictions below this threshold. The Vienna CATScore holds the capacity to accurately differentiate between low- and high-risk groups in accordance with the 8% guideline-recommended cut-off. Furthermore, when using 8% predicted 6-month VTE risk as cut-off, we observed a sensitivity of 76.3% at study inclusion and of 74.4% when all time points together were assessed, indicating that three-fourths of patients who will develop a VTE can be captured and classified as high risk before the event. Thus, these results render it a valuable tool in clinical decision making for the prediction of VTE risk in patients with cancer. This is also supported by the decision curve analysis indicating that application of the CATScore to decide on primary thromboprophylaxis in patients with cancer yields greater net benefit compared to universal or no thromboprophylaxis.

Two pivotal randomized controlled trials, the AVERT and CASSINI trials, evaluated the efficacy of direct oral anticoagulants (DOACs) for primary thromboprophylaxis in cancer patients identified as intermediate to high risk according to the Khorana score.^{39,40} While the CASSINI trial could not show a significant reduction of VTE occurrence,⁴⁰ the AVERT trial showed a significantly lower rate of VTE with DOACs compared with placebo.³⁹ However, the net clinical benefit was debatable as the NNT was suboptimal and the risk of major bleeding seemed to be elevated.³⁹ In a subsequent *post hoc* analysis of the AVERT trial, stratifying patients according to the CATScore into high- and low-risk groups using the 8% predicted risk threshold uncovered a substantial net clinical benefit of primary thromboprophylaxis with a DOAC within this high-risk group, resulting in a notable low NNT of 6.⁴¹ This benefit was not seen in the low-risk group, suggesting that the CATScore was more effective than the Khorana score in clearly distinguishing a high-risk group that would benefit from primary thromboprophylaxis. This is further supported by our decision curve analysis revealing that the utilization of the CATScore had a higher net clinical benefit than using the Khorana score for evaluating thromboprophylaxis. Further evidence for using D-dimer or biomarker-based models for risk assessment to

decide on thromboprophylaxis as a promising approach comes from a recent randomized controlled trial including patients with lung and gastrointestinal cancer. Using a D-dimer- and fibrinogen-based risk assessment model led to a clear benefit of low-molecular-weight heparin prophylaxis in the high-risk group and a comparably low NNT of 6.7.⁴² Future research on enhancing the prediction of adverse bleeding events could further improve outcomes for patients with cancer receiving primary thromboprophylaxis.

Our analysis has several limitations that merit consideration. First of all, our cohort consisted of cancer patients undergoing anticancer therapy at a single tertiary center, which may limit the generalizability of our findings, particularly to patients receiving oral therapy alone. However, this cohort is representative of cancer patients receiving systemic therapy at an oncology day clinic. The data demonstrate that the Vienna CATScore shows a robust performance in a heterogeneous cohort of cancer patients, highlighting its utility in assessing VTE risk in daily oncological clinical practice. Secondly, samples were not available from every patient for all three time points of biomarker measurements. However, we believe that only including patients with samples from all time points available would have introduced a validation conditional on survival, meaning that only patients with cancer who survived at least 3 months would have been included in the analysis. Thirdly, the number of patients with predicted risk available at a single time point was rather small, whereas taking all time points of risk assessment together yielded a larger group (over 1300 patient time points). Nevertheless, to our knowledge, this is the first study that evaluated a biomarker-based risk assessment model for cancer-associated VTE longitudinally during systemic anticancer therapy and assessed the CATScore in a cohort receiving contemporary anticancer therapies.

In conclusion, the Vienna CATScore demonstrates good predictive performance in estimating 6-month VTE risk when applied before or during systemic anticancer therapies. Moreover, the model is precisely calibrated to employ the guideline-recommended 8%-10% risk threshold for stratifying patients into low- and high-risk groups, demonstrating its utility in selecting cancer patients for primary thromboprophylaxis in routine oncological practice.

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DISCLOSURE

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REFERENCES

- Mulder FI, Horváth-Puhó E, van Es N, et al. Venous thromboembolism in cancer patients: a population-based cohort study. *Blood*. 2021;137(14):1959-1969.
- Grilz E, Posch F, Nopp S, et al. Relative risk of arterial and venous thromboembolism in persons with cancer vs. persons without cancer—a nationwide analysis. *Eur Heart J*. 2021;42(23):2299-2307.
- Ay C, Pabinger I, Cohen AT. Cancer-associated venous thromboembolism: burden, mechanisms, and management. *Thromb Haemost*. 2017;117(2):219-230.
- Moik F, Zöchbauer-Müller S, Posch F, Pabinger I, Ay C. Systemic inflammation and activation of haemostasis predict poor prognosis and response to chemotherapy in patients with advanced lung cancer. *Cancers (Basel)*. 2020;12(6):1619.
- Moik F, Posch F, Grilz E, et al. Haemostatic biomarkers for prognosis and prediction of therapy response in patients with metastatic colorectal cancer. *Thromb Res*. 2020;187:9-17.
- Moik F, Prager G, Thaler J, et al. Hemostatic biomarkers and venous thromboembolism are associated with mortality and response to chemotherapy in patients with pancreatic cancer. *Arterioscler Thromb Vasc Biol*. 2021;41(11):2837-2847.
- Chew HK, Wun T, Harvey D, Zhou H, White RH. Incidence of venous thromboembolism and its effect on survival among patients with common cancers. *Arch Intern Med*. 2006;166(4):458-464.
- Crobach MJT, Anijis RJS, Braekkan SK, et al. Survival after cancer-related venous thrombosis: the Scandinavian Thrombosis and Cancer Study. *Blood Adv*. 2023;7(15):4072-4079.
- Bosch FTM, Mulder FI, Kamphuisen PW, et al. Primary thromboprophylaxis in ambulatory cancer patients with a high Khorana score: a systematic review and meta-analysis. *Blood Adv*. 2020;4(20):5215-5225.
- Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood*. 2008;111(10):4902-4907.
- Mulder FI, Candeloro M, Kamphuisen PW, et al. The Khorana score for prediction of venous thromboembolism in cancer patients: a systematic review and meta-analysis. *Haematologica*. 2019;104(6):1277-1287.
- van Es N, Di Nisio M, Cesarman G, et al. Comparison of risk prediction scores for venous thromboembolism in cancer patients: a prospective cohort study. *Haematologica*. 2017;102(9):1494-1501.
- Di Nisio M, van Es N, Rotunno L, et al. Long-term performance of risk scores for venous thromboembolism in ambulatory cancer patients. *J Thromb Thrombolysis*. 2019;48(1):125-133.
- Pabinger I, van Es N, Heinze G, et al. A clinical prediction model for cancer-associated venous thromboembolism: a development and validation study in two independent prospective cohorts. *Lancet Haematol*. 2018;5(7):e289-e298.
- Verzeroli C, Giaccherini C, Russo L, et al. Utility of the Khorana and the new-Vienna CATS prediction scores in cancer patients of the HYPER-CAN cohort. *J Thromb Haemost*. 2023;21(7):1869-1881.
- Moik F, Riedl JM, Englisch C, Ay C. Update on thrombosis risk in patients with cancer: focus on novel anticancer immunotherapies. *Haemostaseologie*. 2024;44(1):40-48.
- Moik F, Ay C. Venous and arterial thromboembolism in patients with cancer treated with targeted anti-cancer therapies. *Thromb Res*. 2022;213(suppl 1):S58-S65.
- Moik F, Chan WE, Wiedemann S, et al. Incidence, risk factors, and outcomes of venous and arterial thromboembolism in immune checkpoint inhibitor therapy. *Blood*. 2021;137(12):1669-1678.
- West MT, Smith CE, Kaempf A, et al. CDK 4/6 inhibitors are associated with a high incidence of thrombotic events in women with breast cancer in real-world practice. *Eur J Haematol*. 2021;106(5):634-642.
- Ay C, Dunkler D, Marosi C, et al. Prediction of venous thromboembolism in cancer patients. *Blood*. 2010;116(24):5377-5382.
- Haslacher H, Gerner M, Hofer P, et al. Usage data and scientific impact of the prospectively established fluid bioresources at the hospital-based MedUni Wien Biobank. *Biopreserv Biobank*. 2018;16(6):477-482.
- Ay C, Posch F, Kaider A, Zielinski C, Pabinger I. Estimating risk of venous thromboembolism in patients with cancer in the presence of competing mortality. *J Thromb Haemost*. 2015;13(3):390-397.
- Falanga A, Ay C, Di Nisio M, et al. Venous thromboembolism in cancer patients: ESMO Clinical Practice Guideline. *Ann Oncol*. 2023;34(5):452-467.
- Fine JP, Gray RJ. A Proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94(446):496-509.
- Key NS, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO guideline update. *J Clin Oncol*. 2023;41(16):3063-3071.
- Lyman GH, Carrier M, Ay C, et al. American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer. *Blood Adv*. 2021;5(4):927-974.
- Farge D, Frere C, Connors JM, et al. 2022 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer, including patients with COVID-19. *Lancet Oncol*. 2022;23(7):e334-e347.
- Alma S, Eloi D, Léa V, et al. Incidence of venous thromboembolism and discriminating capacity of Khorana score in lung cancer patients treated with immune checkpoint inhibitors. *J Thromb Thrombolysis*. 2022;54(2):287-294.
- Icht O, Darzi N, Shimony S, et al. Venous thromboembolism incidence and risk assessment in lung cancer patients treated with immune checkpoint inhibitors. *J Thromb Haemost*. 2021;19(5):1250-1258.

30. Sheng IY, Gupta S, Reddy CA, et al. Thromboembolism in patients with metastatic renal cell carcinoma treated with immunotherapy. *Target Oncol.* 2021;16(6):813-821.
31. Nichetti F, Ligorio F, Zattarin E, et al. Is there an interplay between immune checkpoint inhibitors, thromboprophylactic treatments and thromboembolic events? Mechanisms and impact in non-small cell lung cancer patients. *Cancers (Basel).* 2019;12(1):67.
32. Guven DC, Aksun MS, Sahin TK, et al. Poorer baseline performance status is associated with increased thromboembolism risk in metastatic cancer patients treated with immunotherapy. *Support Care Cancer.* 2021;29(9):5417-5423.
33. Hill H, Robinson M, Lu L, et al. Venous thromboembolism incidence and risk factors in non-small cell lung cancer patients receiving first-line systemic therapy. *Thromb Res.* 2021;208:71-78.
34. Kewan T, Ko T, Flores M, Sallam Y, Haddad A, Daw H. Prognostic impact and risk factors of cancer-associated thrombosis events in stage-IV cancer patients treated with immune checkpoint inhibitors. *Eur J Haematol.* 2021;106(5):682-688.
35. Bjørnhart B, Kristiansen C, Asmussen J, et al. Clinical impact of venous thromboembolism in non-small cell lung cancer patients receiving immunotherapy. *Thromb Res.* 2023;221:164-172.
36. Li A, La J, May SB, et al. Derivation and validation of a clinical risk assessment model for cancer-associated thrombosis in two unique US health care systems. *J Clin Oncol.* 2023;41(16):2926-2938.
37. Reitter EM, Kaider A, Ay C, et al. Longitudinal analysis of hemostasis biomarkers in cancer patients during antitumor treatment. *J Thromb Haemost.* 2016;14(2):294-305.
38. Posch F, Riedl J, Reitter EM, et al. Dynamic assessment of venous thromboembolism risk in patients with cancer by longitudinal D-dimer analysis: a prospective study. *J Thromb Haemost.* 2020;18(6):1348-1356.
39. Carrier M, Abou-Nassar K, Mallick R, et al. Apixaban to prevent venous thromboembolism in patients with cancer. *N Engl J Med.* 2019;380(8):711-719.
40. Khorana AA, Soff GA, Kakkar AK, et al. Rivaroxaban for thromboprophylaxis in high-risk ambulatory patients with cancer. *N Engl J Med.* 2019;380(8):720-728.
41. Kumar V, Shaw JR, Key NS, et al. D-Dimer enhances risk-targeted thromboprophylaxis in ambulatory patients with cancer. *Oncologist.* 2020;25(12):1075-1083.
42. Alexander M, Harris S, Underhill C, et al. Risk-directed ambulatory thromboprophylaxis in lung and gastrointestinal cancers: the TARGET-TP randomized clinical trial. *JAMA Oncol.* 2023;9(11):1536-1545.