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Validity of Modified Vienna-CATS Score for Prediction of Venous Thromboembolism in Egyptian Cancer Cases

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ABSTRACT

Background: Modern oncology has a compelling problem in predicting the hazards of venous thromboembolism (VTE) linked with chemotherapy. Although thromboprophylaxis is not now advised for primary prevention, it is typically advised that cases' risks of VTE be evaluated before treatment. Great interest was given to establishing effective predictive methods for VTE in cancer cases.

The aim of this study: The study aimed to detect whether Egyptian cancer cases' VTE risk could be predicted using the modified Vienna Cancer and Thrombosis Study (CATS) score. **Methods*:*** 214 newly diagnosed cancer cases participated in a prospective cohort study completed before receiving chemotherapy. Cases who received chemotherapy were monitored for VTE episodes for six months. The Khorana score was determined. D dimer and soluble P-selectin (sP-selectin) levels were assessed, followed by a modified Vienna CATS score. For each example, the Vienna CATS score was determined.

Results: Only 24 (11.2%) of the 214 cases who had follow-up experienced VTE episodes, and 5 of these (2.3%) were lost.

Conclusion: When compared to the Khorana score, the modified Vienna CATS score was more sensitive in identifying cancer cases at risk for VTE. Implementation of modified Vienna CATS in the clinical workup of cancer cases could help physicians to tailor antithrombotic therapy and lead to the perfect use of thromboprophylaxis.

Keywords: Cancer, Egypt, Vienna CATS.

Abbreviations: venous thromboembolism (VTE), Cancer and Thrombosis Study (CATS), soluble P-selectin (sP-selectin).

INTRODUCTION

VTE is the second cause that leads to death in cancer cases and causes morbidity. In comparison to the general population, a cancer case has more than 4 times the risk of thrombosis. A case with both cancer and VTE has up to 8 times the risk of death from thrombosis compared to cases without cancer **(1).**

By helping to select cancer cases that are at high risk for VTE, risk stratification methods can help in decreasing the number of cases that need treatment. The ideal risk score enables physicians to distinguish between low-risk cases and those at very high risk who require intervention **(2).**

The Korana score is the most well-known risk classification measure. Although the Khorana score is a reliable predictor, it is highly dependent on tumor type and does not take into account many elements that may influence the occurrence of VTE in a cancer case. As a result, its external validation was not entirely conclusive. The main drawback is the sub-average clinical use due to that more than fifty percent of cases were in the intermediate-risk group **(3).**

Other scores have been thought to increase the ability of the Khorana score to predict the outcome by adding new variables such as soluble biomarkers (like the CATS score) **(4)**. Therefore, the goal of this research was to assess the reliability of the modified Vienna CATS scores in predicting VTE in Egyptian cancer cases.

CASES and METHODS

214 newly diagnosed cancer cases participated in this prospective cohort study before starting chemotherapy in February 2021 and February 2022. The Outpatient Hematology and Oncology Clinics at Mansoura University Oncology Center were used to select newly diagnosed cancer cases during 6 months of case monitoring for VTE episodes while they were on chemotherapy.

Cancer cases starting chemotherapy, receiving anticoagulant or thromboprophylaxis therapy, with missing or inadequate data, with a past history of VTE, or with inherited thrombogenic tendency were kept away from the study.

Age, gender, past VTE, therapy history, and concomitant other diseases were all given particular consideration when taking the case's history. Pathology biopsies were used to determine the location, condition, and stage of malignancy.

Calculations included body mass index (BMI), the Khorana score, the neutrophil-lymphocyte (N/L) ratio, and the platelet lymphocyte (P/L ratio). Five clinical and before-therapy lab parameters are given points according to the Khorana score: the primary tumor site (+1 or 2 points), the platelet count of $350x10^9$/L or more, the hemoglobin level 100 g/L or lower, the use of erythropoiesis-stimulating agents, the leukocyte count of

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$11x10^9$/L or higher, and BMI of 35 kg/m^2 or higher. According to the Khorana score, cases with a total score of zero points have a little risk of VTE, those with sum scores of one or two points have an intermediate risk, and those with sum scores of three or more have a great risk. The usual lab testing included CBC, INR, tumor markers, hormones, liver function tests, and kidney function tests were done.

Two milliliters of whole blood were drawn into citrated tubes. The plasma was isolated and maintained at -70°C until the ELISA technique was used to measure D dimer and sP-selectin levels. The assays were performed in the Clinical coagulation Lab, Clinical Pathology Department, Mansoura Faculty of Medicine. Plasma D dimer was assayed with (ZYMUTEST, cata. No: 95000, France), and plasma sP-selectin was assayed with (R&D system, cata. No: DPSE00, USA).

The Vienna CATS score was created by adding 2 markers to the Khorana score. The Vienna CATS score was then modified (by using the new cut-off levels of D dimer & sP-selectin that were obtained from the ROC curve of the results of cancer cases of the present study, d dimer 857.8 ng/ml + 1 point & sP-selectin 50.1 ng/ml + 1 point).

Treatment type (chemotherapy, surgery, radiotherapy, and hormonal therapy) was evaluated during follow-up, after which outcome (VTE, pulmonary embolism, or loss) was documented. VTE is not routinely screened. A diagnosis of VTE was confirmed or ruled out with objective imaging only when cases began to show symptoms. Venography or duplex ultrasound is used to diagnose deep vein thrombosis (DVT).

Ethical Approval:

All cases gave written informed consent to participate in research and ethics efforts. This study was approved by the Institutional Review Board (IRB) of the Faculty of Medicine, Mansoura University MD.21.02.425 - 14 February 2021. All authors have read the author guidelines and consented to the publication of this work. The Declaration of Helsinki, the Code of Ethics of the World Medical Association, is followed in conducting this human study.

Statistical analysis

Computers were fed and used with research data (IBM Corp. Released 2017). Armonk, NY: IBM Corp., IBM SPSS Statistics for Windows, version 25.0. Numbers and percentages were used to describe qualitative data. Quantitative data were described using range (minimum and maximum), mean and standard deviation. At the 5% level, the significance of the results was determined. The Chi-square test, Cox regression analysis, Student's t-test, Mann-Whitney test, and receiver operating characteristic curve (ROC) were used as tests.

RESULTS

The present study was conducted on 219 cancer cases. The mean age of the studied cases was 51.6 ±16.1, females were 144 (65.8%) & males were 75 (34.2%) with mean BMI 27.1 ±5.1 kg/m^2; 127 (58.0%) had localized cancer, 77 (35.2) were not classifiable and 15 (6.8%) had metastatic cancers; most cases had blood cancers 81 (37%) followed by breast cancer 52 (23.7%) and GIT cancers 39 (17.8%).

The least common cancer sites were parotid & thyroid only one case (0.5%) for each; most cases received chemotherapy103 (47.0%), 15 (6.8%) managed with surgical treatment, 7 (3.2%) radiotherapy, 1 (0.5%) neoadjuvant therapy, and 2 (0.9%) hormonal therapy; median WBCs count among studied cases was 8.2×10^9/L, median PLT count was 361×10^9/L, and median hemoglobin count was 13.8 g/dl; median of D dimer was 534.3 ng/ml; median of sP-selectin was 19.8 ng/ml; median observation time was 180 days as shown in **Table (1)**.

Table (1): Study case characteristics (n= 219 cases).

Baseline characteristics	Value
Age, y Mean ±SD	51.6 ± 16.1
Sex, N (%)	
Males	75 (34.2%)
Females	144 (65.8%)
BMI	27.1 ± 5.1
Classification of tumor at study entry, N (%)	
Localized	127 (58.0%)
Metastasis	15 (6.8%)
Not classifiable	77 (35.2%)
Site of cancer, N (%)	
Breast	52 (23.7%)
Uterus	10 (4.6%)
Ovary	8 (3.7%)
Blood	81 (37.0%)
GIT	39 (17.8%)
Lung	4 (1.8%)
Liver	7 (3.2%)
Skin	2 (0.9%)
UB	4 (1.8%)
Renal	4 (1.8%)
Sarcoma	2 (0.9%)
Neuroendocrine	2 (0.9%)
Testis	2 (0.9%)
Thyroid	1 (0.5%)
Parotid	1 (0.5%)
Cancer treatment during the observation period, N (%)	
Chemotherapy	103 (47.0%)
Surgical	15 (6.8%)
Radiotherapy	7 (3.2%)
Neoadjuvant therapy	1 (0.5%)
Hormonal	2 (0.9%)
Median laboratory values, Median (range)	
WBCs count ($\times 10^9$/L)	8.2 (2.2-329)
PLT count ($\times 10^9$/L)	361 (3-910)
Hemoglobin (g/dl)	13.8 (5-16)
D dimer (ng/ml)	534.3 (91.9 - 5150.3)
sP-selectin (ng/ml)	19.8 (12 - 618)
Observation time, d	180 (40- 188)

Mean, Standard deviation (± SD) for parametric numerical data, while Median and range for non-parametric numerical data. Frequency and percentage of non-numerical data. SD, standard deviation; BMI, body mass index; GIT, gastrointestinal tract; UB, urinary bladder; WBCs, white blood cells; PLT, platelet. Median (range) used for nonparametric data.

Breast, uterus, GIT, urinary bladder, and stomach cancers all showed statistically significant associations with VTE (P=0.016, 0.032, 0.001, 0.013, and 0.001, respectively); in addition, VTE showed statistically significant associations with cancer metastasis, WBCs count, PLT count, hemoglobin, N/L ratio, and P/L ratio (P=0.049, 0.001, 0.001, 0.001, 0.001, and 0.010, respectively Otherwise, no statistically significant relationships between VTE and the other investigated factors were found (P> 0.05) as shown in **Table (2)**.

Table (2): Association of VTE with the studied parameters.

		No VTE		VTE		*p*
		N=190		N=24		
Age (years)	**Mean ±SD**	51.2	16	50.9	16.9	0.933
Male	**N, %**	62	32.60%	11	45.80%	0.199
female	**N, %**	128	67.40%	13	54.20%	
BMI	**Mean ±SD**	26.9	4.9	28.3	5.7	0.192
anti-platelet /aspirin	**N, %**	80	42.1%	8	33.3%	0.411
INR	**Median (range)**	1(1-1.9)		1(1-1.5)		0.908
Breast cancer	**N, %**	50	26.30%	1	4.20%	**0.016**
Uterus	**N, %**	6	3.20%	3	12.50%	**0.032**
GIT	**N, %**	26	13.70%	10	41.70%	**<0.001**
UB	**N, %**	2	1.10%	2	8.30%	**0.013**
Stomach	**N, %**	3	1.60%	4	16.70%	**<0.001**
Metastasis	**N, %**	11	5.80%	4	16.70%	**0.049**
WBCs count	**Median (range)**	7.6 (1.8-329)		12.5 (5-309)		**<0.001**
PLT count	**Median (range)**	227(2-539)		373.5 (178-910)		**<0.001**
Hemoglobin	**Median (range)**	11(5-16)		9.1(7-14)		**<0.001**
N/L ratio	**Median (range)**	1.925 (0.005-29.6)		3 (0.06-25.14)		**0.001**
P/L ratio	**Median (range)**	103 (0.029-1110)		144 (32.87-679)		**0.010**
D dimer (ng/ml)	**Median (range)**	487.895 (91.865-4188.05)		1484.4 (622.6-5150.275)		**<0.001**
sP-selectin (ng/ml)	**Median (range)**	18.1 (12-142.6)		91.5 (48.8-618)		**<0.001**
Khorana score	**Median (range)**	1 (0-2)		2 (0-2)		**<0.001**
Vienna CATS score	**Median (range)**	1 (0-4)		4 (1-6)		**<0.001**

Mean, Standard deviation (± SD) for parametric numerical data, while Median and range for non-parametric numerical data. Frequency and percentage of non-numerical data. SD, standard deviation; BMI, body mass index; GIT, gastrointestinal tract; UB, urinary bladder; WBCs, white blood cells; PLT, platelet; N/L neutrophil-lymphocyte ratio; P/L platelet lymphocyte ratio; VTE, venous thromboembolism.

According to the AUC on the ROC curve, D dimer, sP-selectin, Khorana score, Vienna CATS, and modified Vienna CATS are all highly effective predictors of VTE. When compared to the AUC of the modified Vienna CATS score, the AUC of Khorana showed a statistically significant difference (P= 0.013); when compared to the AUC of the modified Vienna CATS score, the AUC of Vienna CATS showed a statistically significant difference (P= 0.026) as shown in **Table (3) & Figure (1).**

Table (3): ROC of D dimer, sP-selectin, Khorana score, Vienna CATS score, and modified Vienna CATS score for prediction of VTE.

Variable	AUC	95% CI		p
D dimer	0.851	.792	.909	Khorana score vs modified Vienna CATS = **0.013**, Vienna CATS vs modified Vienna CATS = **0.026**
sP-selectin	0.981	.965	.997	
Khorana score	0.925	.842	1	
Vienna CATS score	0.932	.875	.988	
Modified Vienna CATS score	0.969	0.937	1	

Modified Vienna CATS score was done for all cases by using the new cut-off levels of D dimer, & sP-selectin that were obtained from the ROC curve.AUC, the area under ROC, receiver operating characteristic curve; CI, confidence interval.

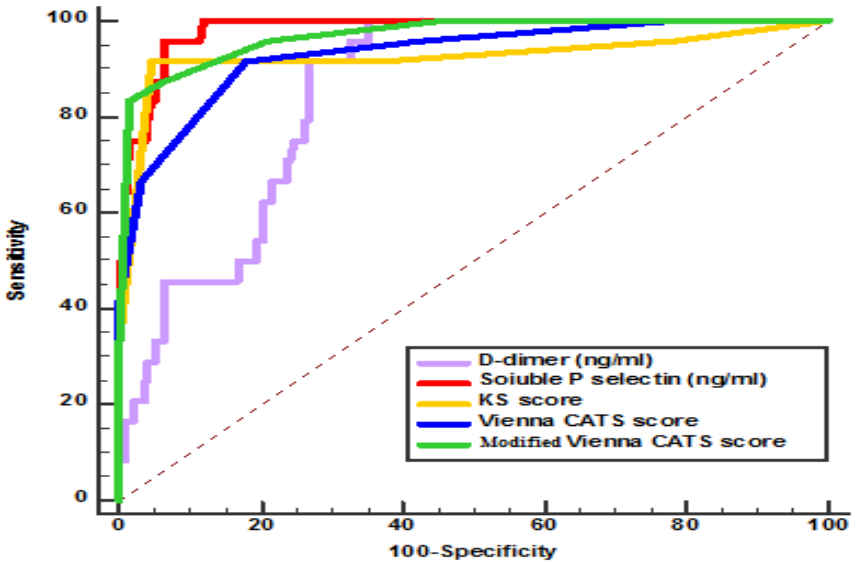

Figure (1): ROC of D dimer, sP-selectin, Khorana score, Vienna CATS score, and modified Vienna CATS score for prediction of VTE.

By using the modified Vienna CATS score 41 cases scored 0 and none of them developed VTE, 62 cases scored 1 none of them developed VTE, 47 cases scored 2 only one of them developed VTE, 28 cases scored 3 two cases of them developed VTE, 10 cases were score 4 one of them developed VTE, 23 cases scored 5 twenty cases of them developed VTE. The increase in modified Vienna CATS score showed a statistically significant association with the decrease in the cumulative proportion survival without VTE and a decrease in survival time without VTE (p <0.001) as shown in **Table (4) & Figure (2)**.

Table (4): Modified Vienna CATS score probability of VTE occurrence.

VCA.5	Total N	No VTE	VTE	Cumulative proportion survived without VTE			Time without VTE (months)		
	N=214	N=190	N=24	6 months	9 months	12 months	Mean	95% CI	p
Score 0	41	41	0	100	100	100	12.0	12.000 to 12.000	**<0.001**
Score 1	62	62	0	100	100	100	12.9	12.900 to 12.900	
Score 2	48	47	1	97.9	97.9	97.9	12.8	12.477 to 13.035	
Score 3	30	28	2	93.3	93.3	93.3	11.7	11.038 to 12.368	
Score 4	10	9	1	90	90	90	10.8	9.627 to 11.933	
Score ≥5	23	3	20	13	13	13	4.7	3.606 to 5.777	

VTE, venous thromboembolism.

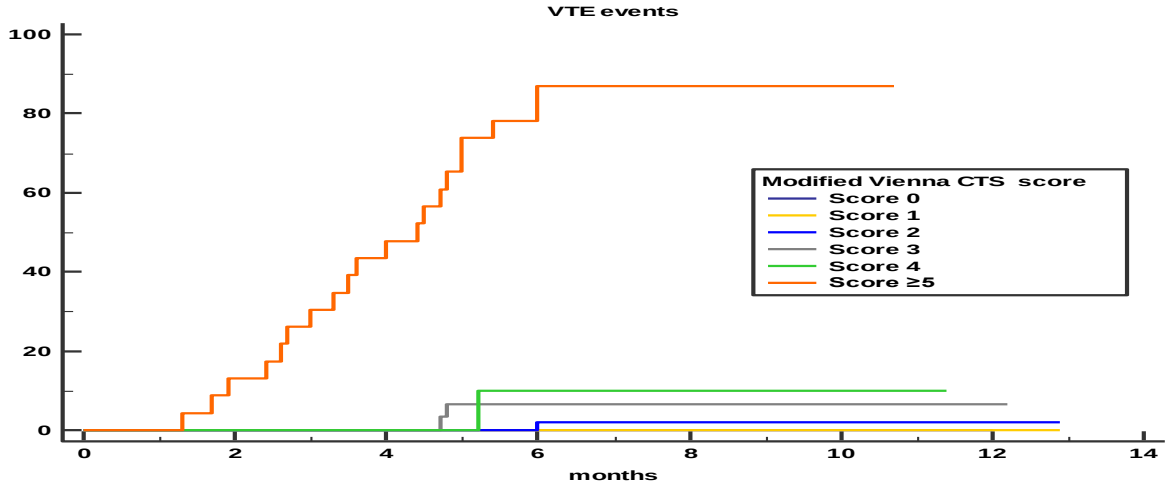

Figure (2). Modified Vienna CATS score probability of VTE occurrence.

Very high-risk tumors, D dimer, sP-selectin, Khorana score, Vienna CATS score, and Modified Vienna CATS score were evaluated as risk predictors of VTE (P= 0.001, 0.001, 0.001, 0.001, & 0.001, respectively); HRs were calculated using the results of the Cox regression analysis (6.144, 1.023, 1.007, 4.586, 3.804, & 4.243, respectively) as shown in **Table (5)**.

Table (5). Cox regression analysis for prediction of VTE.

	p	HR	95% CI	
Age	0.946	0.999	0.974	1.025
Gender	0.213	0.601	0.269	1.341
BMI	0.165	1.050	0.980	1.124
Comorbidities	0.392	1.449	0.620	3.386
Very high-risk tumors	**<0.001**	6.144	2.288	16.499
High-risk tumors	0.829	1.173	0.276	4.990
Chemotherapy	0.286	1.555	0.691	3.501
D dimer	**<0.001**	1.023	1.011	1.056
sP-selectin	**<0.001**	1.007	1.005	1.008
Khorana score	**<0.001**	4.586	1.284	8.981
Vienna CATS score	**<0.001**	3.804	2.821	5.129
Modified Vienna CATS score	**<0.001**	4.243	2.936	6.131

DISCUSSION

In the current study, 214 cases were followed up for 6 months; 190 (88.8%) of them had no VTE, 24 (11.2%) had VTE events, and 5 (2.3%) were lost to follow-up. Only 24 cases experienced VTE episodes.

Ahmed *et al.* [5] stated that among the 277 study participants for 2.5 years, 17 cases (6.13%) experienced VTE episodes. Age, gender, BMI, chemotherapy, the kind of tumor, metastasis, and co-morbidities are some of the risk variables that may be responsible for the high incidence of VTE among the study's participants.

In the current investigation, there was no statistically significant correlation between age, gender, or BMI with VTE. Similar to the findings of the present investigation, **Samuel *et al.*** [6] discovered that the incidence of VTE did not rise progressively with increasing severity of obesity in hospitalized overweight and obese cases who weighed more than one hundred kg and had a BMI of twenty-five kg/m^2 or above.

Hotoleanu, [7] showed that obesity was linked to a six-fold higher risk for VTE, which is in contrast to the findings of the current investigation. Due to the increased blood coagulability and higher prevalence of other risk factors (such as cancer, immobility, and hospital admission), advanced age was revealed to be an independent risk factor for VTE in another investigation [8]. Additionally, it was discovered that gender had an impact on the likelihood of VTE in women compared to males during the reproductive years [9].

The lack of statistical significance regarding age, gender, and BMI in the comparison between VTE and non-VTE cases suggests that the present study's participants were homogeneous concerning these factors. Additionally, VTE in cancer cases is dependent on many factors, including tumor type, stage, type of therapy, age, immobilization, past VTE, and other risk factors, that interact to cause VTE.

The kinds of breast, uterine, GIT and urinary bladder cancer were statistically significantly associated with VTE in the current investigation. Otherwise, VTE & other cancer types did not show any statistically significant connection. This was comparable to the findings of **Khorana *et al.*** [10] who discovered that the pancreas (8.1%), ovary (5.6%), kidney (5.6%), lung (5.1%), stomach (4.9%), and brain (4.7%) were the cancer sites linked to the highest in the occurrence of VTE.

In the current investigation, VTE and cancer metastasis were statistically significantly correlated. These findings were consistent with those of other research, which discovered that metastasis is a significant risk factor for VTE and that the tumor stage was the primary factor affecting the frequency of VTE rather than the kind of cancer [11, 12].

In the current investigation, there was no statistically significant correlation between aspirin use at admission and VTE. These findings were in line with those of **Matsuo *et al.*** [13] who claimed that using aspirin did not lower the frequency of VTE episodes in cancer cases**.**

These findings were at odds with those of **King *et al.*** [14] who claimed that cases who had ever taken aspirin had fewer VTE episodes than those who hadn't. While in another study **Ahmed *et al***. [15] showed that people using aspirin had a higher risk of developing VTE.

Aspirin administration is easy, safe, and doesn't require any monitoring, yet it can't stop VTE in cancer cases on its own. Furthermore, **Rothwell *et al***. [16] observed that individuals with larger weights and heights have decreased clinical effects of low-dose aspirin.

In the current investigation, there was a statistically significant correlation between VTE and higher WBC counts, PLT counts, NLRs, P/L ratios, and lower hemoglobin levels. Although no statistically significant correlation between VTE and INR was discovered, this may be because none of the individuals included in the current investigation were receiving anticoagulant medication.

These findings concurred with those of **Connolly *et al.*** [17] who discovered that cases with raised baseline

WBC counts had a higher likelihood of recurrent VTE. In addition to the research of **Simanek *et al.*** [18] who discovered that higher platelet counts are associated with a higher risk of VTE in cancer cases. Additionally, **Chi *et al.*** [19] showed that anemic cases had a higher probability of developing VTE.

According to **Wu *et al.*** [20] elevated PLR and NLR have been found as biomarkers of cancer-related chronic inflammation, VTE, and death rate. The association of neutrophils with VTE in cancer and the tendency of the cancer microenvironment to predispose neutrophils to release extracellular neutrophil traps (NETs) were possible explanations. A high platelet count may indicate potential inflammation in addition to a direct role in thrombus formation. This is because several inflammatory mediators (such as the pro-inflammatory cytokines IL-6 and TNF-α) stimulate platelet proliferation and cause reactive thrombocytosis. This suggests that the value of PLR for platelet count may be related to the importance of inflammation encompassed by this index [21].

In the present study VTE showed a statistically significant association with high D dimer (ng/ml), sP-selectin (ng/ml), Khorana score, and Vienna CATS score. This is in similarity to **Li *et al.*** [22] who reported that VTE showed a statistically significant association with high D dimer ($P<0.05$), but contrary to **Hayashida *et al.*** [23] who found that D-dimer levels were not associated with VTE in the multivariate analysis, likely because they are affected by many risk factors, such as cancer and aging.

Following the findings of the current investigation, a different study found that sP-selectin levels were higher in VTE cancer cases than in cases of non-VTE cancer [24]. Additionally, **Khorana and Connolly,** [25] discovered that s P-selectin has been touted as a promising biomarker that could predict VTE in cancer.

Mulder *et al.* [26] discovered that the Khorana score can be used to select cancer cases at high risk of VTE, and **Ay *et al.*** [27] demonstrated that the Vienna CATS Score was an improvement to the Khorana risk score and both can predict VTE in cancer cases.

In the current study, cases with VTE, extremely high-risk tumors, high-risk tumors, and cases receiving chemotherapy all had statistically significant increases in their Vienna CATS scores. Due to the small number of cases with BMIs below 35 kg/m^2, it did not have a statistically meaningful correlation with BMI.

In the same vein**, Giaccherini *et al.*** [28] concluded that the Vienna-CATS score distinguished cases with low and high VTE risk in a meaningful way. A promising method for developing accurate and practically usable risk assessment models for VTE prediction in these common malignancies appears to be the inclusion of D-dimer, a circulating coagulation biomarker.

According to the AUC of the ROC curve in the current study, D dimer, sP-selectin, Khorana score, Vienna CATS, and modified Vienna CATS are all very accurate predictors of VTE. The AUC of the modified Vienna CATS score differed statistically significantly from that of the Khorana score ($P=0.013$). These findings are consistent with those of **van Es *et al.*** [29] who showed that the Vienna CATS score appears to differentiate between cases at low and high risk for VTE more accurately. Furthermore, **Ay *et al.*** [27] concluded that by using more parameters in Khorana's risk model, it is possible to forecast the likelihood of VTE with greater accuracy.

In the current study, a statistically significant relationship between an increase in Vienna CATS score or modified Vienna CATS score and a decline in the cumulative proportion of survival without VTE and a decline in the duration of survival without VTE was found (p 0.001). **Ay *et al.*** [30] observed that the cumulative VTE probability after six months was thirty-five percent in cases with the highest score of more than or equal to five and ten percent in individuals with an intermediate level score of three, compared to just one percent in cases with score zero.

CONCLUSION

In conclusion, as compared to the Khorana score, the modified Vienna CATS score was more sensitive in the detection of cancer cases at risk for VTE. The use of modified Vienna CATS in the clinical evaluation of cancer cases may enable clinicians to better customize anticoagulant medication and increase the use of thromboprophylaxis.

REFERENCES

1. **Adrián S, de Castro E, Olmos V *et al.* (2016):** PO-05 - Incidence of venous thromboembolism (VTE) in bile duct tumors (BDT) treated with chemotherapy in the ambulatory setting. Thrombosis Research, 140 (1): S178.
2. **Streiff M, Holmstrom B, Ashrani A *et al.* (2015):** Cancer-Associated Venous Thromboembolic Disease, Version 1.2015. Journal of the National Comprehensive Cancer Network, 13(9):1079-95.
3. **Mulder F, Candeloro M, Kamphuisen P *et al.* (2019):** The Khorana score for prediction of venous thromboembolism in cancer cases: a systematic review and meta-analysis. Haematologica, 104(6):1277-87.
4. **Riondino S, Ferroni P, Zanzotto F, Roselli M, Guadagni F (2019):** Predicting VTE in Cancer Cases: Candidate Biomarkers and Risk Assessment Models. Cancers (Basel), 11(1).
5. **Ahmed G, Nasir H, Hall K, Weissmann L (2020):** Validation of the Khorana Score to assess venous thromboembolism and its association with mortality in

cancer cases: a retrospective community-based observational experience Cureus. https://pubmed.ncbi.nlm.nih.gov/32489737

6. **Samuel S, Gomez L, Savarraj J, Bajgur S, Choi H (2017):** Assessment of the relationship between body mass index and incidence of venous thromboembolism in hospitalized overweight and obese cases. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 37(8):893-9.
7. **Hotoleanu C. (2020):** Association between obesity and venous thromboembolism. Medicine and pharmacy reports, 93(2):162.
8. **El-Menyar A, Asim M, Al-Thani H. (2018):** Obesity paradox in cases with deep venous thrombosis. Clinical and Applied Thrombosis/Hemostasis, 24(6):986-92.
9. **Group E, Eichinger S, Evers J *et al.* (2013):** Venous thromboembolism in women: a specific reproductive health risk. Human Reproduction Update, 19(5):471-82.
10. **Khorana A, Francis C, Culakova E, Kuderer N, Lyman G (2007):** Frequency, risk factors, and trends for venous thromboembolism among hospitalized cancer cases. Cancer: Interdisciplinary International Journal of the American Cancer Society, 110(10):2339-46.
11. **Ohashi Y, Ikeda M, Kunitoh H *et al.* (2020):** Venous thromboembolism in cancer cases: report of baseline data from the multicentre, prospective Cancer-VTE Registry. Japanese journal of clinical oncology, 50(11):1246-53.
12. **Ades S, Pulluri B, Holmes C, Lal I, Kumar S, Littenberg B (2022):** Risk factors for venous thromboembolism in metastatic colorectal cancer with contemporary treatment: A SEER-Medicare analysis. Cancer Medicine, 11(8):1817-26.
13. **Matsuo K, Hom M, Yabuno A *et al.* (2019):** Association of statins, aspirin, and venous thromboembolism in women with endometrial cancer. Gynecologic oncology, 152(3):605-11.
14. **King R, Schaefer J, Sahai V, Griffith K, Sood S (2022):** Retrospective Cohort Analysis of Aspirin Use and Venous Thromboembolism in Cases with Pancreatic Cancer and an Indwelling Central Venous Catheter. TH Open, 6(03):e221-e9.
15. **Ahmed G, Hall K, Weissmann L (2019):** Validation of the Khorana Score to assess venous thromboembolism and its association with mortality. Blood, 134:2119.
16. **Rothwell P, Cook N, Gaziano J *et al.* (2018):** Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: analysis of individual case data from randomized trials. The Lancet, 392(10145):387-99.
17. **Connolly G, Khorana A, Kuderer N, Culakova E, Francis C, Lyman G (2010):** Leukocytosis, thrombosis and early mortality in cancer cases initiating chemotherapy. Thrombosis Research, 126(2):113-8.
18. **Simanek R, Vormittag R, Ay C *et al.* (2010):** High platelet count associated with venous thromboembolism in cancer cases: results from the Vienna Cancer and Thrombosis Study (CATS). Journal of Thrombosis and Haemostasis, 8(1):114-20.
19. **Chi G, Gibson C, Hernandez A *et al.* (2018):** Association of anemia with venous thromboembolism in acutely ill hospitalized cases: an APEX trial substudy. The American journal of medicine, 131(8):972. e1-. e7.
20. **Wu G, Yao Y, Bai C*et al.* (2015):** Combination of platelet to lymphocyte ratio and neutrophil to lymphocyte ratio is a useful prognostic factor in advanced non-small cell lung cancer cases. Thoracic cancer, 6(3):275-87.
21. **Ferroni P, Riondino S, Formica V *et al.* (2015):** Venous thromboembolism risk prediction in ambulatory cancer cases: clinical significance of neutrophil/lymphocyte ratio and platelet/lymphocyte ratio. International journal of cancer, 136(5):1234-40.
22. **Li J, Yan S, Zhang X *et al.* (2022):** Circulating D-Dimers Increase the Risk of Mortality and Venous Thromboembolism in Cases With Lung Cancer: A Systematic Analysis Combined With External Validation. DOI:10.3389/fmed.2022.853941.
23. **Hayashida K, Kawabata Y, Saito K *et al.* (2022):** Prevalence and risk factors of preoperative venous thromboembolism in cases with malignant musculoskeletal tumors: an analysis based on D-dimer screening and imaging. Thrombosis Journal, 20(1):1-8.
24. **Barbour F, Fregnani J, Strunz C, Nogueira A, Longatto-Filho A (2018):** Role of P-selectin in thromboembolic events in cases with cancer. Molecular and clinical oncology, 8(1):188-96.
25. **Khorana A, Connolly G (2009):** Assessing risk of venous thromboembolism in the case with cancer. Journal of Clinical Oncology, 27(29):4839.
26. **Mulder F, Candeloro M, Kamphuisen P, Di Nisio M, Bossuyt P, Guman N *et al.* (2019):** The Khorana score for prediction of venous thromboembolism in cancer cases: a systematic review and meta-analysis. Haematologica, 104(6):1277.
27. **Ay C, Dunkler D, Marosi C *et al.* (2010):** Prediction of venous thromboembolism in cancer cases. Blood, The Journal of the American Society of Hematology, 116(24):5377-82.
28. **Giaccherini C, Marchetti M, Verzeroli C *et al.* (2022):** TEMPORARY REMOVAL: PO-04: Thrombin generation and D-dimer significantly predict for early disease progression and mortality in cases with gastrointestinal cancer. Thrombosis research, 213:S12-S3.
29. **van Es N, Di Nisio M, Cesarman G *et al.* (2017):** Comparison of risk prediction scores for venous thromboembolism in cancer cases: a prospective cohort study. Haematologica, 102(9):1494.
30. **Ay C, Vormittag R, Dunkler D J *et al.* (2009):** D-dimer and prothrombin fragment 1+ 2 predict venous thromboembolism in cases with cancer: results from the Vienna Cancer and Thrombosis Study. Journal of Clinical Oncology, 27(25):4124-9.