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Original Article

Microparticles and D-dimers improve prediction of chemotherapy-associated thrombosis in cancer patients

Chekkal Mohamed[1,2*], Bennaoum Mohamed Nazim[1,2], Adda Affaf [1,2], Zmouli Noujoum[1,2], Yafour Nabil[2,3], Arabi Abdessamad[2,3], Elhorri Mohamed[2], Badsi Dounia[4], Seghier Fatima[2,5]

Abstract

Background: The cancer is associated with a state of hypercoagulability, which may be the cause of venous thromboembolism (VTE), representing an undeniable cause of morbidity and mortality. Our study aimed to investigate the role of hypercoagulability markers (D-dimers, microparticles, and V Leiden mutation) in predicting cancer-associated VTE.

Methods: A prospective cohort study was conducted among cancer patients who will receive chemotherapy in the Medical Oncology and Hematology departments of the EHU of Oran, Algeria from February 2013 to May 2015, followed by an observation period of two years. First, we evaluated the risk of cancer-related VTE by hypercoagulability parameters (D-dimers, microparticles, V Leiden mutation). In the second step, we tested the predictive value of the Khorana risk score (KRS) of cancer-related VTE. Then, we developed and tested the predictive value of an expanded score based on the addition of predictive biomarkers to the KRS parameters.

Results: A total of 165 patients were included in our study whose median age was 62 years. More than half were males (52.7%). After an observation period of 2 years, ten patients (6.0%) developed a VTE. Among the criteria studied, only the D-dimers and the microparticles were predictive of VTE in cancer. The positive predictive value (PPV) of the KRS was 13.6%, and the negative predictive value (NPV) was 97.9%. After adding two predictive biomarkers (D-dimers and microparticles), the expanded score had a better predictive value with a PPV of 23.5% and a VPN of 98.6%.

Conclusion: The addition of hypercoagulability biomarkers (microparticles and D-dimers) to the routine clinical and biological parameters of the KRS enhances the predictive potential of VTE risk in cancer.

Keywords: Thrombosis, Cancer, D-Dimers, Microparticles, Khorana Risk Score, Algeria

Background

Venous thromboembolism (VTE) is strongly linked to cancer. The association between cancer and VTE had been previously established in different settings and populations. Nevertheless, the pathophysiology of thrombi formation has not yet been fully elucidated. Many studies have shown increased mortality in the case of VTE in cancer patients [1]. Also, there was a considerable variation in the incidence of cancer-related VTE between the different studies. This phenomenon is aggravated by the use of chemotherapy and many other factors related to the patients or the treatments they receive [2,3]. Accurate population-based data are needed on the incidence of VTE in patients with different cancers in order to inform guidelines on which hospitalized and ambulatory cancer patients should receive VTE prophylaxis. Several risk factors have been identified as contributing to VTE, such as site and stage of cancer [4,5], age, comorbidities, obesity, acquired prothrombotic states, congenital prothrombotic states such as prothrombotic gene mutation factor V G1691A (factor V Leiden), and prothrombin G20210A [6]. Multivariable analyses showed that coagulation activation and fibrinolysis biomarkers predict the occurrence of VTE in patients with cancer. Elevated D-dimers, prothrombin fragment 1+2 (F 1+2), and microparticles were independently associated with an increased risk for occurrence of VTE [7,8]. It has been suggested that the risk score of Khorana et al. [9] can identify cancer patients at high risk for VTE. This study aimed to investigate the role of hypercoagulability markers (D-dimers, microparticles, and V Leiden mutation) in predicting cancer-associated VTE.

*Correspondence: chekkal.mohamed@univ-oran1.dz
[1]Department of Hemobiology and blood transfusion, Faculty of Medicine, Oran University Hospital Establishment (EHUO), Oran1 university, Oran, Algeria.

A full list of author information is available at the end of the article

Methods

Study design and sample selection

This prospective cohort study was carried out in the Hemobiology and blood transfusion department of the Oran University hospital "EHU 1er Novembre 1954" (West Algeria). The universal sampling technique was recruited to collect data from all patients attending the medical oncology and hematology departments of the Oran University hospital from February 2013 to May 2015, followed by an observation period of two years. The study protocol was approved by the ethical scientific committee of the Oran faculty of medicine. Written informed consent was obtained from all patients.

Inclusion and exclusion criteria

All patients aged 16 years and older with newly diagnosed cancer or disease progression after complete remission, both gender and willing to participate are included in the study. Discharge letters from participating patients with cancer who participated in the full study were collected. Exclusion criteria for participation were overt venous or arterial thromboembolism within the last three months, continuous anticoagulation with vitamin K antagonists or low molecular-weight heparin (LMWH), surgery or radiotherapy within the past two weeks, pregnancy and chemotherapy within the past three months.

Procedure of study

At study inclusion, patients underwent a structured interview; data on the tumor site, histologic confirmation diagnosis, and stage were documented. Patients received detailed information on symptoms of VTE and were asked to report immediately to our department if symptoms developed. Patients were observed for two years until VTE occurrence, death, loss of follow-up, or withdrawal of consent, whichever came first.

Blood collection and laboratory analysis

Three tubes of venous blood (approximately 15 mL) were collected from our patients. One on a tube containing EDTA which was used to do a complete blood count (CBC) on an ADVIA 2120i hematology system (Siemens Healthcare Diagnotics®. USA) and for a DNA extraction when two others were collected on tubes containing anticoagulant citrate complying with recommendations for hemostasis which were used for the assay of hypercoagulability biomarkers (D dimers, microparticles, and activated protein C) on a coagulation system (STA Compact. Stago®. France).

Thus, the D-dimers were dosed by immuno- turbidimetric method (STA- Latest Ddi. Stago®) and the microparticles by the functional test based on the detection of procoagulant phospholipids (STA- Procoag- PPL. Stago®). We measured in the presence of calcium; the clotting time after addition of activated clotting factor X (CTXa) of a platelet depleted plasma (obtained by double centrifugation 2500g for 15 minutes and intermediate decantation) where the addition of the substrate plasma depleted in procoagulant phospholipids makes the test dependent on the procoagulant phospholipids contained in the tested sample. The initiation of coagulation with a reagent containing FXa eliminates the interaction of all upstream factors. The V Leiden mutation was detected by the APCR test (STA-Staclot APC-R. Stago®). The heterozygous or homozygous state of positive cases was looked for for FRET-PCR (Fluorescence Resonance Energy Transfer- Polymerase Chain Reaction).

Confirmation of the thrombosis diagnosis

Objective imaging methods were performed to confirm or exclude the diagnosis only when a patient developed symptoms of VTE. Duplex sonography was applied to diagnose deep vein thrombosis (DVT), and computed tomography was applied to diagnose pulmonary embolism (PE). Accidentally detected thrombotic events were considered events when clinicians confirmed the diagnosis and proved the clinical significance of these events.

Definition of risk scores

Firstly, we used the Khorana Risk Score for predicting chemotherapy-associated VTE in ambulatory cancer patients using baseline clinical and laboratory variables: site of cancer (2 points for very high-risk site, 1 point for high-risk site), platelet count of 350 X 109/L or more, hemoglobin less than 10 g/dL (and/or use of erythropoiesis-stimulating agents), leukocyte count more than 11x109/L, and BMI of 35 kg/m2 or more (1 point each). A sum score of 0 points classifies patients as at low risk of VTE, 1 or 2 points at intermediate risk, and those with three or more points at high risk. Then we expanded the KRS by assigning 1 point to each predictive hypercoagulability biomarker. A hypercoagulability biomarker was considered predictive when a significant statistical relationship was found with VTE, and the hazard ratio with its confidence interval was strictly greater than 1.

Statistical analysis

The patients were categorized into low-risk (0 points), intermediate-risk (1–2 points), and high-risk (≥ 3 points) groups when we used the KRS, then into two groups when we used our expanded risk score based on a threshold value defined by a ROC curve (receiver operating characteristic curve). The quantitative variables were described by the median and the interquartile range (IQR). In contrast, the qualitative variables were described by percentage. The Chi-square test and Fisher's exact test sought the statistical relationship between these variables. The probabilities of survival without VTE were estimated via the Kaplan-Meier Survival Curve and the log-rank test was used to compare the survival distributions of groups. The Cox proportional hazards model was fitted to estimate the effect of the analyzed factors on the outcome. In this model, the hazard ratio (HR) for each independent variable was determined with a 95% CI. A P-value < 0.05 was regarded as statistically significant. The sensitivity, specificity, negative predictive value, and positive predictive value of occurrence of VTE for KRS and extended KRS were calculated after two years of observation from the date of recruitment of each patient. The statistical analyses were performed with SPSS Statistics 17.0.

Results

Characteristics of the participants

One hundred and sixty-eight patients were considered eligible. Three women were excluded because of their pregnancies. Our study population consisted of 165 patients whose basic characteristics clinical and therapeutic data are shown in Table

1. More than fifty percent (52.7%) of patients were males, with localized tumor (60.0%) in colorectal (21.2%), lung (20.0%) and breast (17.6%), respectively. All patients received chemotherapy, combined with radiotherapy or surgery in about 74.2% and 24.2%, respectively (Table 1).

Ten patients (6.0 %) developed VTE in a median follow-up period of 188.5 days (25th–75th percentile: 183–346.25) day (Table 2). Six of them were males, and five were having metastases mainly in the stomach and colorectal sites. All of them received chemotherapy combined with surgery in five and radiotherapy in four patients, respectively.

Table 1 Baseline characteristics of the total study population (n=165 patients)

Characteristics of patients	Categories	Value
Median age at inclusion, (25th_75th percentile)		62 (53-73)
Sex, n (%)	Male	87 (52.7)
	Female	78 (47.3)
Classification of the tumour at inclusion, n (%)	Localized	100 (60.6)
	Metastasis	54 (32.7)
	Unclassifiable	11 (6.7)
Cancer site, n (%)	Lung	33 (20.0)
	Breast	29 (17.6)
	Ovary	12 (7.3)
	Cervix	7 (4.3)
	Colorectal	35 (21.2)
	Stomach	11 (6.7)
	Pancreas	03 (1.8)
	Undifferentiated nasopharyngeal cancer	08 (4.8)
	Bladder	07 (4.3)
	Prostate	06 (3.6)
	Brain	04 (2.4)
	Multiple Myeloma	03 (1.8)
	Lymphoma	04 (2.4)
	Melanoma skin cancer	2 (1.2)
	Larynx	1 (0.6)
Treatment during observation, n (%)	Chemotherapy	165 (100)
	Surgery	40 (24.2)
	Radiotherapy	78 (47.2)
	Hormonotherapy	18 (11)
Median laboratory values (25th-75th percentile)	Platelet count, ×109/L	276 (229-351)
	Leukocyte count, ×109/L	7.9 (5.8-9.2)
	Hemoglobin, g/L	127 (114-143)
	D-dimers, µg/mL	0.72 (0.47-1.53)
	Microparticles (CTXa), sec	41.1 (33.6 - 60.1)
V Leiden mutation, n (%)		5 (3.0)

Table 2: Characteristics of the patients with VTE (n =10)

Characteristics of patients	Catégories	Value
Median age at inclusion, (25th_75th percentile)		66 (58-73)
Sex, n (%)	Male	6 (60)
	Female	4 (40)
Classification of the tumor at inclusion, n (%)	Localized	3 (30)
	Metastasis	5 (50)
	Unclassifiable	2 (20)
Cancer site, n (%)	Lung	1 (10)
	Breast	1 (10)
	Ovary	1 (10)
	Cervix	0 (00)
	Colorectal	2 (20)
	Stomach	2 (20)
	Pancreas	0 (00)
	Undifferentiated nasopharyngeal cancer	0 (00)
	Bladder	0 (00)
	Prostate	1 (10)
	Brain	0 (00)
	Multiple Myeloma	2 (20)
	Lymphoma	0 (00)
	Melanoma skin cancer	0 (00)
	Larynx	0 (00)
Treatment during observation, n (%)	Chemotherapy	10 (100)
	Surgery	5 (50)
	Radiotherapy	4 (40)
	Hormonotherapy	1 (10)
Median laboratory values (25th-75th percentile)		
	Platelet count, ×109/L	312 (235-408)
	Leukocyte count, ×109/L	7.4 (6.3-9.0)
	Hemoglobin, g/L	123 (105-136)
	D-dimers, µg/mL	1.52 (1.01-4.12)
	Microparticles (CTXa), sec	36.2 (21.2-48.2)
V Leiden mutation, n (%)		1 (10)

In Kaplan Meier analysis, the Log Rank test demonstrated a statistically significant difference between the groups defined by the Khorana score (P = 0.025) (Figure 1). In univariate Cox regression analysis, the Hazard Ratio (HR) of VTE was 3.514, 95% CI [1.133-10.900] between one group and another of higher risk. Incidence of VTE did not present a statistically significant difference between intermediate-risk and low-risk patients (p=0.447) with an HR of 2.539, 95% CI [0.230-27.998].

After two years and at the cut-off point for the high-risk category (score ≥ 3), we calculated the sensitivity (probability of high risk in those patients experiencing VTE), specificity (probability of high risk in those patients not experiencing VTE), positive predictive value (PPV, probability of high risk in those patients identified to be at high risk) and negative

predictive value (NPV, probability of no VTE in those patients identified to be at low risk) for VTE development. The sensitivity was 50%, specificity was 88.0%, PPV was 13.6%, and NPV was 97.9%. Among the hypercoagulability markers, D-dimers were predictive of cancer-related VTE when their level was more significant than 1.53 (75th percentile) with an HR of 4.449, 95% CI [1.194-16.573. An elevated microparticles count was also predictive of cancer-related VTE with an HR of 5.678, 95% CI [1.523- 21.163]. Microparticles elevation was defined as a shortening of clotting time after the addition of activated clotting factor X (CTXa) to values ≤ the 25th percentile. We did not find a statistical relationship between the heterozygous V Leiden mutation and the VTE when Fisher's exact test was applied (P=0.268). Adding these two biomarkers (D dimers and microparticles) to the Khorana score improved its predictive power. At the cut-off point for the high-risk category (score ≥ 4) and using the Kaplan Meier analysis, the Log Rank test demonstrated a statistically significant difference between the two groups defined by the expanded Khorana score (P = 0.000) (Figure 2). In univariate Cox regression analysis, the Hazard Ratio (HR) of VTE was 17.987, 95% CI [3.291-98.294] between the low-risk group and the high-risk one. The sensitivity was 66.7%, specificity was 91.8%, PPV was 23.5%, and NPV was 98.6%.

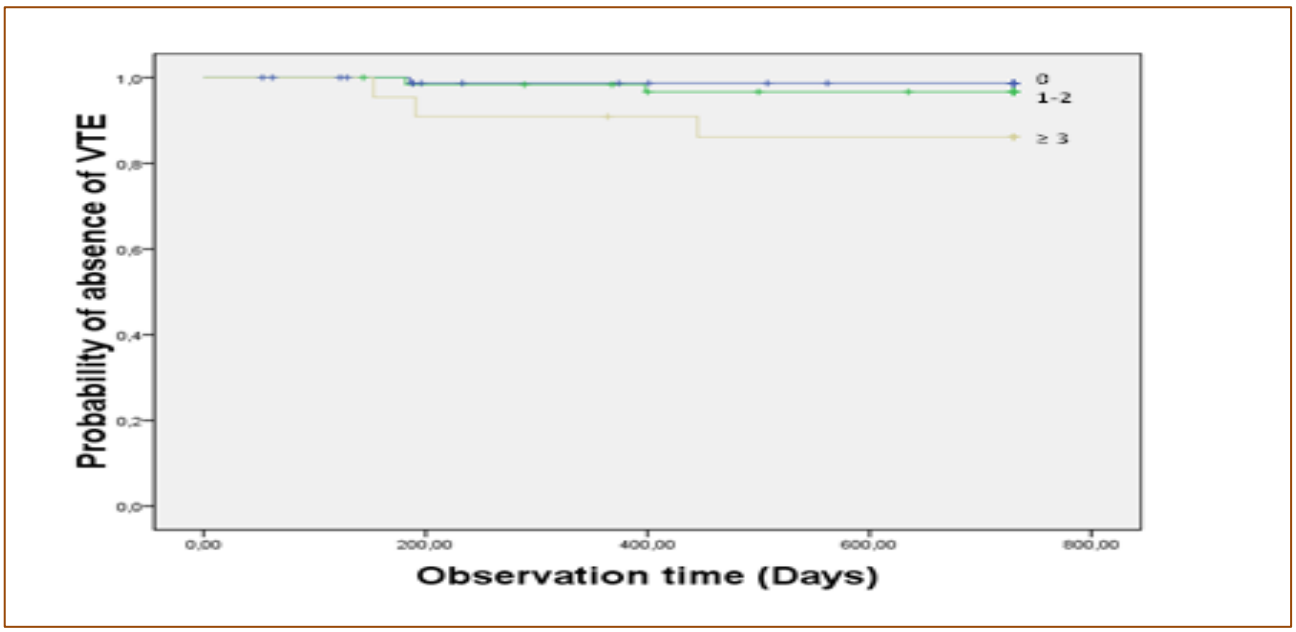

Figure1: Kaplan Meier estimates of risk of VTE among patients with cancer according to the Khorana score. There is a statistically significant difference between the groups defined by the Khorana score (Log Rank=0.025)

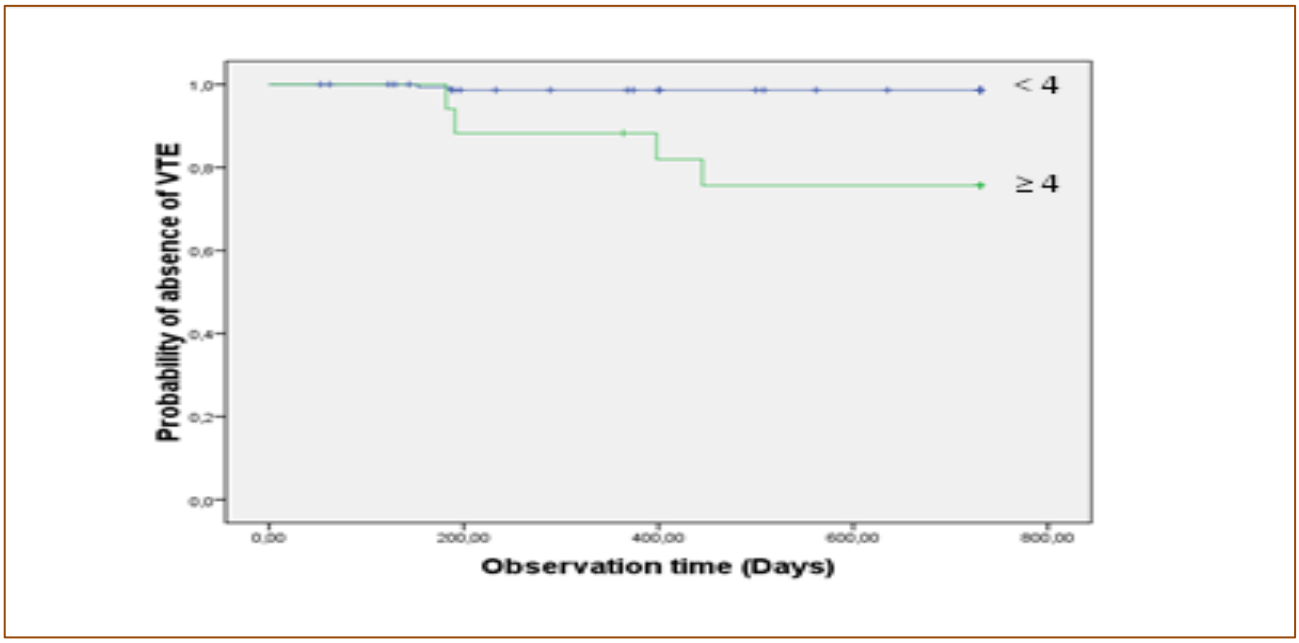

Figure 2: Kaplan Meier estimates of risk of VTE among patients with cancer according to the expanded Khorana score. There is a statistically significant difference between the low risk (<4) group and the high risk one (>4) defined by the expanded Khorana score (Log Rank=0.000)

Discussion

This cohort study tested the Khorana predictive model in patients from western Algeria using five clinical and biological parameters before chemotherapy. The sensitivity and specificity of the Khorana Predictive Model for VTE were comparable between the original study and our own. However, the two studies differed in predicting VTE using this score. The rate of VTE was also higher in our study than the original one (6.0% vs. 2.1%). Such finding is most likely due to the observation time of these two studies (2.5 months in the original study and 24 months in ours). Moreover, while Khorana's study only concerned patients on chemotherapy, ours was more heterogeneous with the addition of chemotherapy other treatments received during the observation period of 24 months, which may increase the risk of VTE, such as radiation therapy and surgery. It has been reported that cancer patients undergoing a surgical procedure have twice the risk of postoperative VTE, which remains a long time after surgery [10,11]. In similar KRS validation studies, the incidence of thrombotic events ranged from 4 to 18% [12,13]. During our KRS study, we found that patients considered to be at intermediate risk (score=1 or 2) had the same risk of VTE as those considered to be at low risk (score=0). We thus concluded that for our population, only the cut-off value of a score ≥3 should be considered to determine the risk of VTE. At the end of our study, we find that in addition to KRS parameters, two other biomarkers have good predictive values: D-dimers and microparticles. In contrast, no statistical relationship was found between the V Leiden mutation and cancer-related VTE. Such a result is most probably because 100% of the cases observed were heterozygous, knowing that there is a significant difference between the heterozygous and homozygous state of the mutation varying from 3.5 and 24 depending on the LITE study (Longitudinal Investigation Thromboembolism Etiology) [14]. In their guidance for the prevention of cancer-related VTE, Khorana et al. [15] clarified that in addition to the biomarkers of their score (platelet count, leukocytes count, and hemoglobin rate), others are associated with MTEV in cancer and cited D-dimers, prothrombin activation products, soluble P selectin, thrombin generation and microparticles [15]. Visuddho V, et al. [16] found that elderly patients (>59 years) with d-dimer of >440 ng/ml experienced lower survival during hospitalization. By integrating D-dimers and microparticles into the KRS with the determination of the cut-off value by ROC curve, we succeeded in increasing the positive predictive value from 13.6% using the original Khorana score to 23.5% using the expanded score. We found that the risk of VTE in the high-risk stratified group was much higher than that of surgery or prolonged hospitalization in which thromboprophylaxis was nevertheless well indicated with many benefits [17,18]. In the recommendations of the guidelines of the American Society of Clinical Oncology and those of the European Society of Medical Oncology on VTE in cancer, it is clarified that prophylaxis in cancer patients receiving outpatient chemotherapy is not routinely recommended except for high-risk patients where it may be considered [19, 20].

Conclusion

In conclusion, the Khorana score is a simple score, reproducible, and validated on our population of western Algeria. Its use will allow better stratification of patients according to the risk of VTE for a better benefit-risk ratio of thromboprophylaxis in them. Clinical trials should be encouraged in our population to demonstrate the efficacy and safety of thromboprophylaxis in high-risk patients defined by this score.

Abbreviation

VTE: venous thromboembolism; CBC: Complete Blood Count; KRS: Khorana Risk Score; LMWH: Low Molecular-Weight Heparin; HR: Hazard Ratio; PPV: Positive Predictive Value: NPV: Negative Predictive Value; ROC curve: Receiver Operating Characteristic Curve; IQR: Interquartile Range

Declaration

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Availability of data and materials

Data will be available by emailing chekkal.mohamed@univ-oran1.dz

Authors' contributions

All authors equally contributed to the concept, design, literature search, data analysis, and data acquisition, manuscript writing, editing, and reviewing. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

We conducted the research following the Declaration of Helsinki. The ethical protocol was approved by the Scientific Council of the Faculty of Medicine of the University of Oran1, Algeria. Certificate issued on November 11, 2012 under the reference/315/V.D.G.P.R.R.RXT/2012.

Consent for publication

Not applicable

Competing interest

The authors declare that they have no competing interests.

Author Details

[1]Department of Hemobiology and blood transfusion. Oran University Hospital Establishment (EHUO), Oran, Algeria. [2]Oran1 university. Medicine faculty, Oran, Algeria. [3]Department of Hematology and cellular therapy, Oran University Hospital Establishment (EHUO), Oran, Algeria. [4]Department of vascular neurology, Oran University Hospital Establishment (EHUO), Oran, Algeria.

[5]Department of Hemobiology and blood transfusion, Oran University Hospital Center, Algeria.

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