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Ability of the Khorana Score to Predict Recurrent Thromboembolism in Cancer Patients with Ischemic Stroke

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Abstract

Cancer patients with acute ischemic stroke (AIS) are high-risk for recurrent thromboembolic events (RTE). Currently, no risk stratification model exists to predict RTE in this population. We tested the hypothesis that the Khorana score, a validated risk model for predicting venous thromboembolism in cancer patients, can effectively classify RTE risk in cancer patients with AIS. We retrospectively identified adults with active solid or hematological cancer diagnosed with AIS at a tertiary-care cancer center from 2005–2010. The Khorana score at the time of index stroke was calculated. The primary outcome was arterial or venous RTE. Cox regression was used to evaluate the association of the Khorana Score and its individual components with RTE. Harrell's

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Disclosures

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c-statistic was used to calculate the score's discriminatory ability. Among 263 AIS patients, median survival was 84 days (IQR 24–149 days) and 90 (34%) had RTE. The median Khorana score was 2 (IQR 1–2, range 0–5). Cumulative rate of RTE was 28% among patients who scored 0, 36% with scores of 1–2, and 32% with scores of 3–6. The overall Khorana score was marginally associated with RTE (HR, 1.14; 95% CI, 1.02–1.28). Of its individual components, only leukocytosis was associated with RTE (HR adjusted for other components, 1.45; 95% CI 1.11–1.90). The score's c-statistic for predicting RTE was 0.57. In this study, the Khorana score had poor discriminatory ability for predicting RTE in cancer patients with AIS. Future research is needed to identify better methods for predicting RTE in this high-risk population.

Keywords

thromboembolism; cancer; malignancy; stroke; prediction score

Introduction

Patients with cancer have a hypercoagulable milieu, which increases their risk of thromboembolic events including stroke [1–3]. Underlying mechanisms include endothelial dysfunction caused by inflammatory pathways, procoagulant substances secreted by tumor cells, and chemotherapy and radiation associated changes [4–6]. Additionally, acute ischemic stroke itself causes a prothrombotic state that further compounds the problem [7]. A recent large cohort study reported that in the first 6 months after diagnosis, 4.7% of patients with incident cancer develop an arterial thromboembolic event, and that these patients face a twofold higher risk of arterial events than matched controls without cancer [8]. Furthermore, an arterial thromboembolic event among patients with cancer is associated with a threefold increased risk for death [8]. We have also previously shown that in the setting of active cancer, cumulative rates of recurrent thromboembolic events (RTE) after ischemic stroke are about 37% at 6 months and patients who develop RTE are twice as likely to die as those who don't [9]. Therefore, early detection and prevention of RTE is needed.

A better understanding of high-risk individuals with cancer and ischemic stroke could facilitate targeted interventions to reduce RTE rates. It is known that among cancer subtypes, the risk of RTE after stroke is highest in patients with adenocarcinoma [9]. However, no risk prediction tool exists to accurately quantify RTE risk in cancer patients with ischemic stroke. In 2008, the Khorana score was proposed to stratify the risk of venous thromboembolism in cancer patients beginning chemotherapy [10]. This validated model has moderate sensitivity, high specificity (~90%), and a c-statistic of 0.7, allowing it to effectively discriminate cancer patients' risk for subsequent venous thromboembolism [10, 11]. The Khorana score seems particularly effective at identifying cancer patients at low risk for venous thromboembolism. However, because of a low positive predictive value, it generally cannot identify high-risk individuals, and it is unknown whether it can accurately predict the risk of recurrent thromboses in patients with prior arterial thromboembolic events. We hypothesized that the Khorana score could be utilized to predict the risk of RTE in cancer patients following ischemic stroke.

Methods

Study Design and Population

We performed a retrospective cohort study of all adult patients (age ≥ 18 years) with active solid or hematological cancer who were diagnosed with acute ischemic stroke at Memorial Sloan Kettering Cancer Center (MSKCC) between January 1, 2005 and December 31, 2009. We screened for patients with acute ischemic stroke by searching MSKCC's administrative databases for International Classification of Diseases-9-Clinical Modification (ICD-9-CM) codes for ischemic stroke (433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, and 434.91), and by reviewing the MSKCC Department of Neurology's comprehensive clinical database for any patients diagnosed with "ischemic stroke", "stroke", or "transient ischemic attack". In line with prior literature, we defined active cancer as a diagnosis of, or treatment for, any cancer within the preceding 6 months, or known recurrent or metastatic disease [12, 13]. We excluded patients with local basal cell or squamous cell carcinoma of the skin, and primary brain tumors. Acute ischemic stroke was defined as any new neurologic deficit with corresponding evidence of acute ischemia on magnetic resonance imaging and no indication for a non-cerebrovascular etiology based on clinical and/or radiologic data. To minimize misclassification, we excluded patients who were diagnosed only on the basis of computed tomography scans. Two neurologists reviewed all charts to confirm stroke diagnosis and eligibility for the study. Details of our study methodology have been reported previously [9, 14, 15]. The study was approved by the institutional review board of MSKCC with a waiver of consent.

Measurements

For this analysis, we collected data on patients' demographics, stroke risk factors, cancer type and status, stroke subtypes, antithrombotic medicines, and relevant laboratory values. The Khorana score was calculated using clinical information at the time of index stroke for each patient using five clinical and laboratory parameters [10]. One point was assigned for each of the following variables: platelet count < 350,000/mcL, hemoglobin < 10 g/dL or use of erythropoiesis-stimulating agents, leukocyte count > 11,000/mcL, and body mass index < 35 kg/m². Additionally, two points were assigned for very high-risk cancer sites (stomach and pancreas) and one point for high-risk sites (lung, lymphoma, gynecologic, genitourinary excluding prostate). Using the Khorana score, patients were divided into 3 risk categories: low (score 0), intermediate (score 1–2), and high (score 3–6) [10].

Outcomes

Neurologists reviewed all available inpatient and outpatient medical records through July 31, 2012 to ascertain outcomes. The primary outcome was a RTE defined as a composite of recurrent ischemic stroke, transient ischemic attack, myocardial infarction, systemic embolism, deep vein thrombosis, or pulmonary embolism. Secondary outcomes were recurrent ischemic stroke and venous thromboembolism.

Statistical Analysis

We analyzed categorical variables using the Pearson Chi-square test (Fisher exact test was used when appropriate). Continuous variables were analyzed using Student's T-test or the Mann-Whitney U-test depending on data distribution. Univariate and multivariable Cox regression analysis accounting for variable follow-up time between patients was used to study the relationship between 1) the overall Khorana score and RTE and 2) the Khorana score's individual components and RTE. Patients were censored at the time of death, last documented follow-up, or end of study. Harrell's c-statistic was used to calculate the discriminatory ability of the score in predicting RTE. In secondary analyses, we evaluated the score's ability to predict 1) recurrent ischemic stroke and 2) venous thromboembolism.

In posthoc exploratory analyses, we evaluated the association between serum D-dimer levels and RTE in patients who had testing within 72 hours of index stroke. Both continuous and dichotomized D-dimer values were analyzed. For the dichotomized analysis, D-dimer was considered elevated if the level was $\geq 5.50 \mu\text{g/ml}$ because this cutoff was reported to have high specificity and positive predictive value for incident cancer-related stroke in a previous study [16]. We also assessed whether adding an elevated D-dimer to the Khorana score improved the score's ability to predict RTE. All analyses were two-tailed and performed using Stata (version 14.0, College Station, TX); statistical significance was defined as a p-value of <0.05 .

Results

Patient Characteristics

Our study cohort comprised 263 patients. Mean patient age was 66 years. Most patients had solid tumors, particularly of the lung (32%) and gastrointestinal tract (25%), and 69% had known metastases. Median time from cancer diagnosis to index stroke was 10 months (interquartile range [IQR] 2–31 months). Patients' index stroke subtypes are listed in Table 1. Stroke from confirmed paradoxical embolism occurred in 7 patients (3%). At the time of hospital discharge from index stroke, 172 (65%) patients were treated with an antithrombotic medicine; the remaining 35% were not treated because they either died, were transitioned to comfort care, or their medical condition prohibited antithrombotic therapy (i.e., thrombocytopenia, acute bleeding). Of the 172 patients treated with an antithrombotic medicine, 102 (59%) were treated with an antiplatelet medicine, 90 (52%) were treated with an anticoagulant, and 20 were treated with both (12%). Antiplatelet therapy consisted mostly of aspirin ($n=92$), while anticoagulant therapy consisted mostly of low molecular weight heparin ($n=79$). In exploratory analysis, RTE rates were similar between patients treated with antiplatelets versus those treated with anticoagulants (hazard ratio [HR], 1.19; 95% confidence interval [CI], 0.72–1.97).

Recurrent Thromboembolic Events

During a median follow-up time to death of 84 days (IQR 24–149 days, range 1–2535 days), 117 cases of RTE were identified in 90 patients (34%). Some patients had more than one RTE – including 40 deep vein thromboses, 36 recurrent ischemic strokes, 17 pulmonary

emboli, 13 myocardial infarctions, 10 systemic emboli, and 1 transient ischemic attack. Patients with and without RTE had similar baseline demographics and comorbidities.

Khorana Score Performance

The median Khorana score was 2 (IQR 1–2, range 0–5). No patients had a score of 6 and only one patient had a score of 5. There was no difference in the distribution of Khorana scores between patients with and without RTE (Figure 1). The rate of RTE was 28% among patients with a score of 0 (low-risk category), 36% with a score of 1–2 (intermediate-risk category), and 32% with a score of 3–6 (high-risk category). There was no significant difference in the frequency of RTE with higher Khorana scores (Figure 2). The overall Khorana score marginally predicted for subsequent RTE (HR, 1.14; 95% CI, 1.02–1.28). In both univariate and multivariable Cox regression analysis adjusted for the other Khorana score variables, the only individual component associated with RTE was leukocytosis (adjusted HR, 1.45; 95% CI, 1.11–1.90) (Table 2). The Khorana score's Harrell's c-statistic for predicting RTE was 0.57. In secondary analyses, the Khorana score's c-statistic was 0.56 for predicting recurrent ischemic stroke and 0.55 for predicting venous thromboembolism.

Exploratory Analyses

Acute D-dimer testing was performed in a nonrandom sample of 36 patients and was modestly associated with an increased risk of RTE (HR, 1.10; 95% CI, 1.02–1.20). An elevated D-dimer level (> 5.50 $\mu\text{g/ml}$) was present in 11 of these 36 patients, of whom 6 developed an RTE. There was a nonsignificant trend for an association between an elevated D-dimer and RTE (HR, 2.01; 95% CI, 0.94–4.31). When elevated D-dimer was added to the Khorana score, the expanded model was more predictive for subsequent RTE (HR, 1.43; 95% CI, 1.07–1.92). The c-statistic for this expanded model was 0.64.

Discussion

In this retrospective cohort study of cancer patients with AIS at a tertiary-care cancer center, the Khorana score had poor discriminatory ability for predicting RTE, including recurrent ischemic stroke. The score's c-statistic was 0.57 for discriminating between low-, intermediate-, and high-risk patients, which is only slightly better than chance, and therefore the Khorana score does not appear to be a useful risk-stratification strategy for predicting RTE in patients with cancer-associated stroke. We believe this could be due to several reasons. First, prior studies evaluated the Khorana score in patients with recently diagnosed cancer without acute thromboembolism; however, our study included patients who had acute ischemic stroke in addition to active cancer, implying a more severe prothrombotic state as indicated by the high short-term rates of RTE. Second, the original Khorana score was used to predict venous thromboembolism, while our outcome measure also included arterial events. One could speculate that the score might predict venous thromboembolism more accurately than arterial events, although in secondary analysis restricted to venous thrombosis outcomes, the score's discriminatory ability remained poor. Our study builds on the findings of recent studies in which the Khorana score did not accurately stratify the risk of thromboembolic events among patients with different cancer subtypes [17–19]. The Khorana score also does not incorporate data on stroke mechanisms and treatments, which

are important predictors of thromboembolism recurrence. Finally, to the authors' knowledge, the Khorana score has not been studied in relation to recurrent venous thromboembolism after a first event, and it is possible that the risk factors for recurrent events differ from those for a first event.

Since its initial report, the Khorana score has undergone modifications to increase its test properties[20], including supplementation with two biomarkers, D-dimer and P-selectin. We could not analyze P-selectin in our retrospective analysis; however, in a nonrandom sample of patients who had acute D-dimer testing, the addition of an elevated D-dimer level of 5.50 µg/ml to the Khorana score improved the latter's ability to predict for subsequent RTE. In this analysis, leukocytosis was the only component of the Khorana score that was associated with RTE risk. Several, prospective population-based investigations have demonstrated correlations between levels of inflammatory biomarkers, including the white blood cell count, and the risk of incident and recurrent stroke [21]. Leukocytes are known to interact with platelets, endothelium, and coagulation factors, and are widely recognized to exert a potent influence on hemostasis in physiological and pathological conditions [22]. Furthermore, acute leukocytosis triggers a procoagulant response,[23] which could play a role in the development of RTE after cancer-associated stroke.

This study has several limitations. First, it was a single-center study conducted at an urban, tertiary-care cancer center, which hampers the generalizability of our results. Second, this was a retrospective study and some patients who received cancer care at MSKCC may have sought treatment for RTE at outside facilities. Although MSKCC rigorously collects these records, the rates of RTE may have been underestimated. In this case, the study's findings might be biased towards the null hypothesis. Third, this study may have been underpowered to detect an association between the Khorana score and RTE. This appears unlikely given the low point estimates with relatively narrow confidence intervals and because the c-statistic suggested that the risk model was close to random chance in predicting RTE. However, given these potential power limitations, the study's multivariable analyses should be considered exploratory in nature. Fourth, we did not have reliable information on last known well time so we were unable to determine the exact period of time from stroke onset to index blood draw. Fifth, in this retrospective study that focused on evaluating the utility of the Khorana score in the cancer-stroke population, we were unable to systematically evaluate the predictive abilities of experimental coagulation biomarkers such as P-selectin. However, we were able to analyze D-dimer values in a subset of patients, and in this exploratory analysis, D-dimer did demonstrate an association with subsequent RTE in cancer patients with ischemic stroke.

In conclusion, the Khorana score had limited ability for predicting RTE in cancer patients with acute ischemic stroke and therefore other risk stratification strategies are needed for this high-risk population. Future research should aim to identify highly specific risk factors, biomarkers, and predictive models for RTE in cancer-associated stroke.

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Highlights

- Khorana score has been shown to predict venous thromboembolism in cancer patients.
- We aimed to test this score to predict recurrent thromboembolism (RTE) in cancer patients with ischemic stroke.
- Khorana score was weakly associated with RTE in cancer patients with ischemic stroke, and did not accurately predict RTE.
- Addition of other parameters such as D-dimer appears to improve the predictive accuracy of the score.

Figure 1:
Box and whisker plot showing distribution of Khorana scores, stratified by recurrent thromboembolism.

Figure 2:

Bar graph showing rates of recurrent thromboembolism, stratified by Khorana score. The score ranges from 0 to 6; however, no patients had a score of 6, so recurrent thromboembolism rates are only shown for scores 0 through 5.

Table 1:

Characteristics of Patients with Active Cancer and Ischemic Stroke, Stratified by the Subsequent Development of Recurrent Thromboembolic Events^a

Characteristic	RTE (N=90)	No RTE (N= 173)	P value ^b
Age in years (Mean, SD)	66 (11)	66 (12)	0.89
Female gender	50 (56)	78 (45)	0.11
Race			0.02
White	70 (78)	141 (82)	
Black	7 (8)	20 (12)	
Asian	4 (4)	9 (5)	
Hispanic	8 (9)	2 (1)	
Other	1 (1)	1 (1)	
Hypertension	48 (53)	99 (57)	0.55
Hyperlipidemia	34 (38)	70 (40)	0.67
Diabetes mellitus	18 (20)	34 (20)	0.95
Coronary artery disease	12 (13)	30 (17)	0.40
Atrial fibrillation	6 (7)	17 (10)	0.39
Prior stroke	5 (6)	14 (8)	0.45
Smoking	8 (9)	6 (3)	0.06
Stroke subtype ^c			
Large artery atherosclerosis	15 (17)	25 (14)	0.72
Cardioembolism	22 (24)	36 (21)	0.53
Small vessel disease	4 (4)	16 (9)	0.22
Other determined	6 (7)	6 (3)	0.35
Undetermined	43 (48)	90 (52)	0.52
Body mass index >35 kg/m ²	7 (8)	8 (5)	0.30
Hemoglobin <10 g/dL	32 (36)	71 (41)	0.39
Leukocytes >11,000/mcL	31 (34)	56 (32)	0.73
Platelets >350,000/mcL	10 (11)	27 (16)	0.32
Very high-risk cancer	18 (20)	38 (22)	0.75
High-risk cancer	62 (69)	109 (63)	0.41
Low-risk cancer	10 (11)	26 (15)	0.45

Characteristic	RTE (N=90)	No RTE (N= 173)	P value ^b
Khorana score risk			0.87
Low (score 0)	10 (11)	26 (15)	
Intermediate (score 1–2)	62 (69)	109 (63)	
High (score 3–6)	18 (20)	38 (22)	

Abbreviations: RTE, recurrent thromboembolic event; SD, standard deviation; kg, kilogram; m², meter squared; g, grams; dL, deciliter; mL, microliter.

^aData are presented as number (%) unless otherwise indicated.

^bP value <0.05 was considered significant.

^cStroke subtypes were classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) system

Table 2:

Association of Individual Khorana Score Items with Recurrent Thromboembolism

Component of Khorana Score	Univariate		Multivariable	
	HR	95% CI	HR	95% CI
Cancer Site				
Very High Risk	1.10	0.76–1.60	1.09	0.72–1.64
High Risk	1.09	0.85–1.39	1.12	0.85–1.46
Platelet Count 350,000/mcl	1.08	0.76–1.53	1.04	0.72–1.48
Hemoglobin <10 g/dl	1.15	0.89–1.47	1.09	0.84–1.40
Leukocyte count 11,000/mcL	1.52	1.17–1.97	1.45	1.11–1.90
BMI 35 Kg/m2	0.64	0.37–1.12	0.71	0.41–1.24

Abbreviations: HR, hazard ratio; CI, confidence interval; mcL, microliter; g, grams; dL, deciliter.