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Validation of Khorana Risk Score (KRS) in Cancer Patients: An Experience from a Tertiary Care Cancer Centre

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Abstract

Purpose: Venous Thromboembolism is a common and frequent complication seen in active cancer patients. The Khorana Risk Score (KRS) is a simple model which helps to guide selection of high risk VTE cancer patients for thromboprophylaxis. However very little information is available on Khorana score validation in low middle income countries; hence we aimed to evaluate its performance.

Patients and methods: A retrospective single center study utilizing data of 150 cancer patients with either symptomatic deep venous thrombosis (DVT) and/or pulmonary embolism (PE) from January 1, 2012 to Dec 31, 2017. The primary efficacy outcome was to validate Khorana Risk Score in our population.

Results: Overall, 32.7% of these patients had a low Khorana Risk Score of 0 point, 48% of patients had intermediate KRS of 1 or 2 points, and only 19.3% of patients had a high KRS of 3 or more points. We also looked at additional variables i.e. mean difference in albumin (g/dL) in the three Khorana Risk Score category which was statistically significant i.e. 3.88 g/dL ± 0.52 in low risk, 3.58 g/dL ± 0.65 in intermediate risk and 3.15 g/dL ± 0.85 in high risk [p<0.001]. Similarly the mean age difference was also significantly different in intermediate and high risk. We also looked at metastasis status, chemotherapy status and creatinine clearance in these patients but found they were statistically insignificant.

Summary: Our study showed that Khorana Risk Score tool was only able to risk stratify 19.3% of cancer patients in high risk category who would have benefitted from thromboprophylaxis. We recommend the development of a modified risk prediction model best adapted to local needs.

Introduction

VTE which broadly consists of deep vein thrombosis and pulmonary embolism is associated with a poor prognosis in patients with cancer. Around 20-30% of all first venous thromboembolic events are cancer associated and an additional 30% of them will also develop a recurrent VTE [1].

A meta-analysis by Horsted et al described incidence rates of venous thrombosis in cancer patients stratified by background risk of venous thrombosis. Among cohorts with average-risk patients the incidence rate of venous thrombosis was estimated to be 13 per 1000 person-years (95% CI: 7-23) versus 68 per 1000 person-years (95% CI: 48-96) in high risk patients [2]. Venous thromboembolism is the second most leading cause of mortality in cancer patients after cancer progression [3]. Khorana et al reported analysis of 1,824,316 hospitalizations in 1,015,598 cancer patients between 1995 and 2003 at 133 United States medical centers. Mortality was significantly and consistently greater among patients who developed VTE as compared to patients who did not over the duration of study (16.3% versus 6.3%, P<0.0001).

Khorana et al also analyzed patients initiating chemotherapy with VTE (n = 912) and without VTE (n = 2736) to evaluate resource utilization and real-world costs in ambulatory patients and found cancer patients with VTE had approximately three times as many all-cause hospitalizations (mean 1.38 versus 0.55 per patient) and days in hospital (10.19 versus 3.37) versus patients without VTE (all P < 0.0001) [4]. Cancer patients with VTE also incurred higher overall total health care costs (USD 74,959 versus USD 41,691 per patient) than cancer patients without VTE (all P < 0.0001).

This highlights the importance of developing risk stratification models to identify cancer patients at high risk of developing VTE who would benefit from thromboprophylaxis. An ideal risk score would help clinicians identify both patients with a negligible risk as well as those at high risk needing intervention. Several scores for predicting the risk of VTE in ambulatory outpatients with cancer have been developed [5-10]. Among these the Khorana score which was introduced in 2008 is the most popular. It has been validated in large cohorts 2701 patients with cancer undergoing chemotherapy and validated in an independent cohort of 1365 patients with a variety of malignancies who are undergoing chemotherapy [11]. It is even endorsed by latest guideline updates of the American Society of Clinical Oncology and the National Comprehensive Cancer Network to select ambulatory cancer patients for thromboprophylaxis [12].

Many studies have validated Khorana risk score in ambulatory settings with often conflicting data [13]. A clear interpretation of these findings is further hampered by the variation in study designs, cancer type and duration of follow up. Also very little information is available

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for Khorana score validation in low middle income countries. This is important as their demographic and genetic variables vary immensely compared with their rich counterparts. Keeping in mind that ours is a charity run cancer hospital, we wanted to validate Khorana risk prediction model to identify patients who are at highest risk of VTE and would benefit the most from thromboprophylaxis thus best utilizing our resources.

Patients and methods

Design: This study was a single center retrospective chart review study including sample size of 150 patients utilizing data from the Shaukat Khanum Cancer Memorial Hospital and Research Centre [SKMCH] cancer registry between January 1, 2012 to Dec 31, 2017 following the approval by the Institutional Review Board.

Patient Population: Patients were included if they were at least 18 years of age, had a diagnosis of cancer with concurrent diagnosis of DVT or PE in ambulatory setting. Patients were excluded if the diagnosis of PE or DVT was made during inpatient hospitalization.

Outcome: The primary efficacy outcome was to validate and determine if the Khorana Risk Score would have predicted VTE in these patients. The Khorana Risk Score (KRS) is a simple model consisting of five predictive clinical and pre-chemotherapy laboratory parameters including: primary site of cancer (+1 or 2 points), platelet count of $350x10^9$/L or more (+1 point), hemoglobin concentration of 100 g/L or lower or use of erythropoiesis-stimulating agents (+1 point), leukocyte count of $11x10^9$/L or higher (+1 point), and a Body Mass Index of 35 kg/m^2 or higher (+1 point). A sum score of 0 points classifies patients as being at low risk of VTE, 1 or 2 points at intermediate risk, and those with 3 or more points at high risk [11].

Study Procedure: Data extraction was conducted from the charts which included baseline laboratory findings (hemoglobin, platelets, leukocytes, body mass index-BMI, creatinine clearance, albumin), comorbid, risk factors (immobilization, surgery and central line), type and stage of cancer. All patient were divided into three categories of low, intermediate or high risk based on Khorana Risk Score. Wilcox in rank sum test was performed to compare continuous variables. The Fisher exact test was performed to compare categorical variables. All data were analyzed using SAS 9.4 with a significance level of a=0.05.

Results

Patient population: Between January 1,2012 to December 31, 2017, a total of 245 patients were screened and 150 eligible patients diagnosed with VTE in ambulatory setting were included in the study; 99 patients excluded from the study consisted of patients who were diagnosed with VTE in inpatient settings or were absconded.

Our baseline demographics included mean age 50.15 (+/- 14.05 in years) with 1:1 male to female ratio and ethnic backgrounds from all over the country as show in Table 1. Interestingly enough baseline comorbidities which included coronary heart disease, diabetes, hypertension and creatinine clearance were seen in only 44 (29.3%) of cancer patients. Our cohort included 72 (48.05%) patients with metastatic disease and 95 (63.3%) were receiving chemotherapy. GU malignancy was the primary in 43 (28.7%) followed by GI malignancy 41 (27.3%) and breast cancer 26 (17.3%). We also assessed risk factors for thrombosis such as central line 14 (9.3%), immobilization 45 (30%) and major surgery 25 (16.7%) in our cohort.

Pre-chemotherapy baseline laboratory values evaluated in our study showed normal platelet and white blood cell i.e mean 287.85 (+/- 147.13) and 8.96 (+/- 4.51) respectively as shown in Table 2.

Table 1: Baseline patient's characteristics.

Variables	Categories	Total = N° (%)
Sex	Male	76 (50.7%)
	Female	74 (49.3%)
Race	Punjabi	100 (66.7%)
	Balochi	4 (2.7%)
	Pathan	46 (30.7%)
Co-morbidity status	No	106 (70.7%)
	Yes	44 (29.3%)
Coronary Artery Disease	No	148 (98.7%)
	Yes	2 (1.3%)
Hypertension	No	127 (84.7%)
	Yes	23 (15.3%)
Diabetes	No	123 (82.0%)
	Yes	27 (18.0%)
Cancer Type	GI	41 (27.3%)
	Breast	26 (17.3%)
	GU	43 (28.7%)
	Lungs	7 (4.7%)
	Miscellaneous	32 (21.3%)
Khorana Risk Score	0	49 (32.7%)
	1	41 (27.3%)
	2	31 (20.7%)
	3	19 (12.7%)
	4	8 (5.3%)
	5	2 (1.3%)
Khorana Risk	Low Risk	49 (32.7%)
	Medium Risk	72 (48.0%)
	High Risk	29 (19.3%)
Metastatic status	No	78 (52.0%)
	Yes	72 (48.0%)
Chemotherapy administered	No	55 (36.7%)
	Yes	95 (63.3%)
Central line	No	136 (90.7%)
	Yes	14 (9.3%)
Immobilization	No	105 (70.0%)
	Yes	45 (30.0%)
Major surgery	No	125 (83.3%)
	Yes	25 (16.7%)
Age in years	Mean ± standard deviation	50.15 ± 14.05
Creatinine clearance	Mean ± standard deviation	121.61 ± 68.15
Platelets	Mean ± standard deviation	287.85 ± 147.13
Haemoglobin	Mean ± standard deviation	11.81 ± 9.98
White blood cells	Mean ± standard deviation	8.96 ± 4.51
Body mass index	Mean ± standard deviation	24.36 ± 5.10
Albumin	Mean ± standard deviation	3.59 ± 0.70
Creatinine	Mean ± standard deviation	0.77 ± 0.50
Creatinine clearance	< 60	16 (10.7%)
	≥ 60	134 (89.3%)
Albumin	< 4	105 (70.0%)
	≥ 4	45 (30.0%)
Creatinine	< 1	127 (84.7%)
	≥ 1	23 (15.3%)

Hemoglobin was noted to be low i.e mean 11.81 (+/- 9.98). Also noticeable in our cohort were 105 (70%) patients with albumin level less than 4 g/dL and 16 (10.7%) patients with creatinine clearance less than 60 mL/min.

Khorana risk score: We divided our patient cohort based on Khorana risk score and found out 49 (32.7%) scored 0, 41 (27.3%) scored 1, 31 (20.7%) scored 2, 19 (12.7%) scored 3, 8 (5.35%) scored 4 and 2 (1.3%) scored 5. Overall, 49 (32.7%) of these patients had a low

Table 2: Mean difference of baseline patient's characteristics.

Variables	Low Risk	Intermediate Risk	High Risk	p-value
Age in years				
Mean ± SD*	52.69 ± 13.92	46.68 ± 13.64	54.48 ± 13.59	0.01
Creatinine clearance				
Mean ± SD*	115.11 ± 48.98	132.53 ± 84.10	105.51 ± 44.96	0.14
Haemoglobin				
Mean ± SD*	12.16 ± 1.42	12.58 ± 14.07	9.27 ± 2.22	0.30
White blood cells				
Mean ± SD*	6.94 ± 2.21	8.97 ± 3.65	12.35 ± 6.84	0.001
Body mass index				
Mean ± SD*	24.91 ± 4.16	24.20 ± 5.43	23.83 ± 5.57	0.62
Albumin				
Mean ± SD*	3.88 ± 0.52	3.58 ± 0.65	3.15 ± 0.85	0.001
Creatinine				
Mean ± SD*	0.80 ± 0.37	0.70 ± 0.31	0.89 ± 0.91	0.20
*Standard deviation				

Khorana Risk Score of 0 point, 72 (48%) of patients had intermediate KRS of 1 or 2 points, and only 29(19.3%) of patients had a high KRS of 3 or more points.

We also looked at six additional laboratory and clinical parameters popularly used in other risk prediction scorings and are also routinely collected before initiating chemotherapy as shown in Table 2. The mean difference in albumin (g/dL) in the three Khorana Risk Score category was statistically significant i.e 3.88 g/dL ± 0.52 in low risk, 3.58 g/dL ± 0.65 in intermediate risk and 3.15 g/dL ± 0.85 in high risk [p<0.001]. Similarly the mean age difference was also statically different in intermediate risk 46.68 yrs ± 13.64 compared with 54.48yrs ± 13.59 in high risk [p < 0.01]. We also looked at metastasis status, chemotherapy status and creatinine clearance in these patients but found they were statistically insignificant.

Discussion

One of the population based study from Walker European Journal, has shown a steady increase in the absolute rate of venous thrombosis from 10 VTE (per 1000 person-years) to 20 VTE (per 1000 person-years) from 1997 to 2007 in cancer patients; where as it has remained steady i.e 4 VTE (per 1000 person-years) in non-cancer group.[1] This rise in cancer associated VTE poses a serious problem that diminishes the patient's life span and quality of life. Hence identifying patients at high risk of developing VTE will help us in decreasing the complications by initiating thromboprophylaxis early.

In Khorana Risk Score validation cohort, the model had a negative predictive value of 98.5%, a positive predictive value of 6.7%, a sensitivity of 35.7%, and a specificity of 89.6%.[11] While we will need to be careful in interpreting our data as our patient subset included cancer patients with known VTE, it is still surprising to know that retrospectively 80.7% of our cohort was placed in low and intermediate risk category. This meant these patients in real life would not have benefitted from thromboprophylaxis due to scoring low on Khorana risk score. On the contrary only 19.3% of our cancer patients were placed in high risk category with KRS of 3 or more points as shown in Table 1. Which means only this subset of population would had received thromboprophylaxis. Our study stresses on the necessity and importance to evaluate additional risk factors to identify patients at high risk of developing VTE and needing intervention. We strongly believe that risk prediction models should be best adapted to the demographic and genetic needs of the location.

For instance Khorana risk score identifies obesity as an important risk factor for developing VTE and hence scores patients with Body Mass Index of 35 kg/m^2 or higher with +1 point. There is no denying that obesity is a well-known risk factor and can predispose to VTE due to the physical effects of body fat impeding the venous return and/or a proinflammatory/ prothrombotic state [14]. However it is also true that in low middle income countries BMI of 35 kg/m^2 or higher is a rare sight and even so in cancer subset population. Per last national demographic health survey in 2013 less than 15% of women aged 15-49 years are obese (BMI of 30 kg/m^2 or higher) [15]. Hence obesity as a risk factor for risk prediction model might not work for cancer patients in low middle income countries.

Similarly the pre-chemotherapy laboratory parameters including platelet count of 350x10^9/L or more (+1 point), hemoglobin concentration of 100 g/L or lower (+1 point) and leukocyte count of 11x10^9/L or higher (+1 point) were noted to be important risk factors in Khorana Risk Score. Again high platelets and leukocyte counts are well known risk factors as they directly result in proinflammatory/ prothrombotic state [16]. However it is also a well-known fact that laboratory reference values vary with demographics and ethnicity [17]. Hence these laboratory cut off values may not apply to our population and if anything will need a lower threshold.

Our study despite being a retrospective study and patient population selection provides solutions for real world situations especially for low middle income countries. The mean difference in albumin (g/dL) in the three Khorana Risk Score category was statistically significant i.e. 3.88 g/dL ± 0.52 in low risk, 3.58 g/dL ± 0.65 in intermediate risk and 3.15 g/dL ± 0.85 in high risk [p<0.001] as shown in Table 2. Reduced serum albumin has been described as a marker for global declining health and poor prognosis. The underlying causality of VTE risk has been considered to lie in renal loss of albumin in nephrotic syndrome or albumin decrease caused by inflammatory processes [18]. In addition in cancer patients decrease in serum albumin has further been recognized as an expression of the consuming nature of the neoplasm and is associated with poor prognosis in cohorts of different malignancies [19].

Similarly the mean age difference was also statically different in intermediate risk 46.68 yrs ± 13.64 compared with 54.48yrs ± 13.59 in high risk [p < 0.01] as shown in Table 2. It is well established that the risk of VTE increases with age. A large prospective study found that individuals aged 85 years and older have an almost 10-fold higher incidence rate (6.96 per 1000 person-years) compared with those aged

45 to 54 years of age (0.72 per 1000 person-years) [20]. We also looked at additional risk factors i.e. metastasis status, chemotherapy status and creatinine clearance in these patients but found they were statistically insignificant [21, 22]. We believe low middle income countries will have to develop and validate a personalized risk prediction model with risk factors more adapted to their geographic location and needs. This is crucial as utilizing funds on primary prophylaxis will be more cost effective as oppose to treating VTE related complications. This stands especially true for resource limited countries.

Conclusion

Our study shows that Khorana Risk Score tool was only able to risk stratify 19.3% of cancer patients in high risk category who would have received prophylactic anticoagulation. Majority of our patients per Khorana Risk Score would not have derived benefit from thromboprophylaxis. Our data also showed that the age increases and the albumin decreases with each risk category. We recommend the development of a modified and personalized risk prediction model utilizing additional clinical and laboratory variables to implement an effective prophylactic strategy best adapted to the local needs.

Acknowledgement:

Not applicable.

Conflict of Interest:

None to declare.

References

1. Timp JF, Braekkan SK,Versteeg HH, Cannegieter SC (2013) Epidemiology of cancer-associated venous thrombosis. Blood 122(10):1712-1723.
2. Horsted F, West J, Grainge MJ (2012) Risk of venous thromboembolism in patients with cancer: a systematic review and meta-analysis. PLoS Med 9(7):1275.
3. Khorana AA (2010) Venous thromboembolism and prognosis in cancer. Thromb res 125(6):490-493.
4. Khorana AA, Dalal MR, Lin J, Connolly GC (2013) Health care costs associated with venous thromboembolism in selected high-risk ambulatory patients with solid tumors undergoing chemotherapy in the United States. Clinicoecon Outcomes Res 5:101-108.
5. Munoz Martin AJ, Ortega I, Font C, Pachon V, Castellon V, et al. (2018) Multivariable clinical-genetic risk model for predicting venous thromboembolic events in patients with cancer. Br J Cancer 118(8):1056-1061.
6. Gerotziafas GT, Taher A, Abdel-Razeq H, AboElnazar E, Spyropoulos AC, et al. (2017) A predictive score for thrombosis associated with breast, colorectal, lung, or ovarian cancer: the prospective COMPASS-Cancer-Associated thrombosis study. Oncologist 22(10):1222-1231.
7. Ay C, Simanek R, Vormittag R, Dunkler D, Alguel G, et al. (2008) High plasma levels of soluble P-selectin are predictive of venous thromboembolism in cancer patients: results from the Vienna Cancer and Thrombosis Study (CATS). Blood 112(7):2703-2708.
8. Mandala M, Barni S, Prins M, Labianca R, Tondini C, et al. (2010) Acquired and inherited risk factors for developing venous thromboembolism in cancer patients receiving adjuvant chemotherapy: a prospective trial. Ann oncol 21(4):871-876.
9. Ay C, Vormittag R, Dunkler D, Simanek R, Chiriac AL, et al. (2009) D-dimer and prothrombin fragment 1+2 predict venous thromboembolism in patients with cancer: results from the Vienna Cancer and Thrombosis Study. J Clin Oncol 27(25):4124-4129.
10. Kirwan CC, McDowell G, McCollum CN, Kumar S, Byrne GJ (2008) Early changes in the haemostatic and procoagulant systems after chemotherapy for breast cancer. British journal of cancer 99(7):1000-1006.
11. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW (2008) Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood 111(10):4902-4907.
12. Khorana AA (2007) The NCCN Clinical Practice Guidelines on Venous Thromboembolic Disease: strategies for improving VTE prophylaxis in hospitalized cancer patients. Oncologist 12(11):1361-1370.
13. Mulder FI, Candeloro M, Kamphuisen PW, Di Nisio M, Bossuyt PM, et al. (2019) The Khorana score for prediction of venous thromboembolism in cancer patients: a systematic review and meta-analysis. Haematologica 104(6):1277.
14. Ashrani AA, Gullerud RE, Petterson TM, Marks RS, Bailey KR et al. (2016) Risk factors for incident venous thromboembolism in active cancer patients: a population based case–control study. Thromb res 139:29-37.
15. Aslan JE (2021) Platelet proteomes, pathways, and phenotypes as informants of vascular wellness and disease. Arteriosclerosis, thrombosis, and vascular biology 41(3):999-1011.
16. Lee EC, Cameron SJ (2017) Cancer and thrombotic risk: the platelet paradigm. Front Cardiovasc Med 4:67.
17. Kone B, Maiga M, Baya B, Sarro YDS, Coulibaly N, et al. (2017) Establishing reference ranges of hematological parameters from Malian healthy adults. J Blood Lymph 7(1):154.
18. Mahmoodi BK, Gansevoort RT, Næss IA, Lutsey PL, Brækkan SK, et al. (2012) Association of mild to moderate chronic kidney disease with venous thromboembolism: pooled analysis of five prospective general population cohorts. Circulation, 126(16), 1964-1971.
19. Königsbrügge O, Posch F, Riedl J, Reitter EM, Zielinski C, et al. (2016) Association between decreased serum albumin with risk of venous thromboembolism and mortality in cancer patients. Oncologist 21(2):252-257.
20. Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Polak JF, et al. (2002) Cardiovascular risk factors and venous thromboembolism incidence: the longitudinal investigation of thromboembolism etiology. Arch Intern Med 162(10):1182-1189.
21. Zahir MN, Shaikh Q, Shabbir-Moosajee M, Jabbar AA (2017) Incidence of Venous Thromboembolism in cancer patients treated with Cisplatin based chemotherapy-a cohort study. BMC cancer 17(1):1-8.
22. Ferroni P, Guadagni F, Laudisi A, Vergati M, Riondino S, et al. (2014) Estimated glomerular filtration rate is an easy predictor of venous thromboembolism in cancer patients undergoing platinum-based chemotherapy. Oncologist 19(5):562-567.