ORIGINAL RESEARCH

Validation of the Khorana Venous Thromboembolism Risk Score in Japanese Cancer Patients

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ABSTRACT

BACKGROUND Although the Khorana venous thromboembolism (VTE) risk score (KRS) is well recognized as a simple VTE risk assessment method in patients with cancer, whether it is suitable for Asian populations is unclear.

OBJECTIVES This study validated KRS for the prediction of VTE and investigated the value of the KRS in predicting mortality in Japanese patients with cancer.

METHODS A body mass index value of 25 kg/m^2 or more was defined as obesity according to World Health Organization consensus. A total of 27,687 patients with cancer were subdivided into low- (0), intermediate- (1-2), and high-score (3) groups by the KRS. The primary and secondary endpoints were VTE and all-cause mortality, respectively.

RESULTS The prevalence of VTE was 1.7%, 7.3%, and 11.0% for low-, intermediate-, and high-score patients, respectively. Receiver operating characteristic (ROC) analysis showed that the KRS significantly predicted VTE (area under the curve, 0.679; 95% confidence interval [CI] 0.666-0.692; $P < 0.001$). The cutoff value for the KRS was 1.0. Logistic regression analysis demonstrated that the KRS was an independent predictor of VTE (odds ratio 1.766; 95% CI 1.673-1.865; $P < 0.01$). The cutoff value of the KRS for all-cause mortality determined by ROC analysis was 2.0. Kaplan–Meier analysis demonstrated a significantly higher incidence of mortality in the KRS ≥2 group than in the KRS 0-1 group (log-rank: $P < 0.01$).

CONCLUSIONS The KRS was useful in Japanese patients with cancer and might be a potentially useful marker for the prediction of mortality. Establishing optimal scores for Japanese subjects is mandatory because of its low diagnostic ability. (KUMAMON Cancer registry; UMIN000047554) (JACC: Asia 2021;1:259–270) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

ABBREVIATIONS AND ACRONYMS

AUC = area under the curve

BMI = body mass index

CAT = cancer-associated thrombosis

CI = confidence interval

CKD = chronic kidney disease

DL = dyslipidemia

DM = diabetes mellitus

HT = hypertension

ICD = International Classification of Diseases

KRS = Khorana venous thromboembolism risk score

ROC = receiver-operating characteristic

VTE = venous thromboembolism

Thromboembolism is one of the diseases that affects the prognosis of patients with cancer (1). Thromboembolism that accompanies cancer is called cancer-associated thrombosis (CAT) (2), and new anticancer agents such as molecular targeted therapies have been developed. It is expected that the prognosis of patients with cancer will improve and the frequency of CAT will increase.

Because it is difficult to predict the onset time of CAT associated with cancer treatment and because it may be difficult to treat, the Khorana risk assessment score (KRS) can be used to determine the risk of developing thromboembolism in advance when administering anticancer drugs (**Table 1**) (3). The score obtained by adding 2 factors, D-dimer level and soluble P-selectin level, t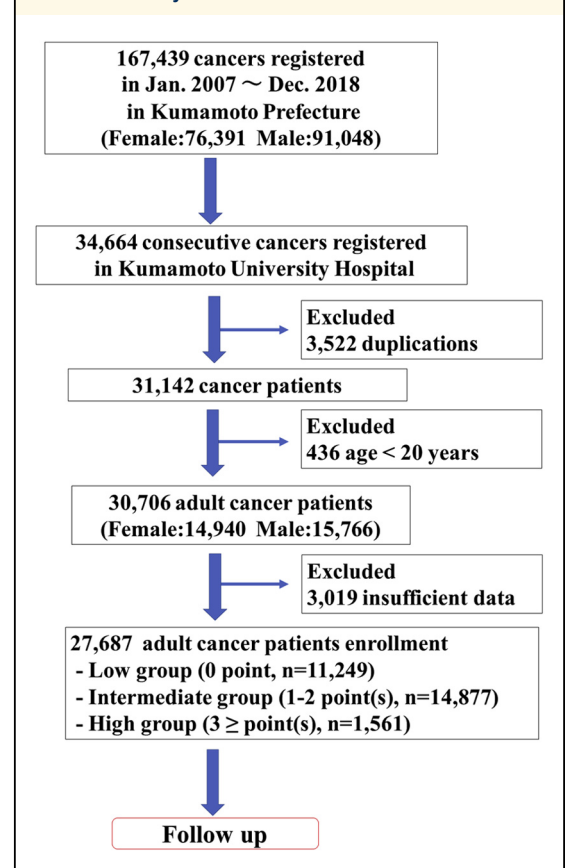o the KRS is the Vienna venous thromboembolism (VTE) risk assessment score (4). Moreover, the Myeloma Working Group suggested a specific algorithm for the prevention of thalidomide- and lenalidomide-associated thrombosis in patients with myeloma patients (5). The KRS could be improved by adding gemcitabine or platinum compounds (PROTECHT score) (6), by replacing body mass index (BMI) with functional status (CONKO score) (7), and by adding metastatic disease, vascular compression, and previous VTE to the dichotomized KRS (ONKOTEV score) (8). Recently, the COMPASS-CAT score (9) and ROADMAP-CAT score (10) were reported to be well validated for the prediction of VTE. The Ottawa scores (original [11] and modified [12]) are useful tools to stratify the risk of recurrence of CAT. Thus, these risk assessment models should be used to screen patients with cancer at high CAT risk, which would lead to an appropriate approach to VTE screening. Although the validity of these risk assessment models has been verified (13,14), there are few studies including mortalities. However, in Japan, soluble P-selectin levels cannot be easily measured in daily clinical practice; thus, it is considered that evaluation by the KRS is realistic at present. In addition, because these scoring reports are from studies using Western populations, it is doubtful that they can provide effective and accurate scoring evaluations for Asian individuals, including Japanese individuals. Cancer is reported to be a leading cause of VTE in Japan (15,16), and Yamashita et al. (17) recently reported the actual situation of VTE in Japan. Although previous studies have demonstrated the prediction of VTE in East Asian individuals (18-21), these previous studies were relatively small cohorts and specialized for particular cancer sites. We used the community-based

TABLE 1   Khorana VTE Risk Score for Prediction of VTE in Patients With Cancer

	Points
Site of cancer	
Very high-risk cancer (stomach, pancreas)	2
High-risk cancer (lung, lymphoma, gynecological, bladder, or testicular)	1
Prechemotherapy platelet count $\geq 350 \times 10^9$/L	1
Prechemotherapy hemoglobin level < 10.0 g/dL or use of red cell growth factors	1
Prechemotherapy leukocyte count $> 11 \times 10^9$/L	1
Body mass index ≥ 35 kg/m^{2a}	1
Traditional risk categories	
High	≥ 3
Intermediate	1-2
Low	0

This table is modified from Khorana et al. (3). [a]According to the World Health Organization Asian classification defined by expert consultation (24) based on the typical body shape of the Asian populations, a body mass index value 25 kg/m^2 or more was defined as obesity.

VTE = venous thromboembolism.

FIGURE 1   Study Flowchart

FIGURE 2 Distributions of Malignant Diseases of 30,706 Adult Patients With Cancer

(A) Female patients. (B) Male patients. CNS = central nervus system; MM = malignant lymphoma; VTE = venous thromboembolism.
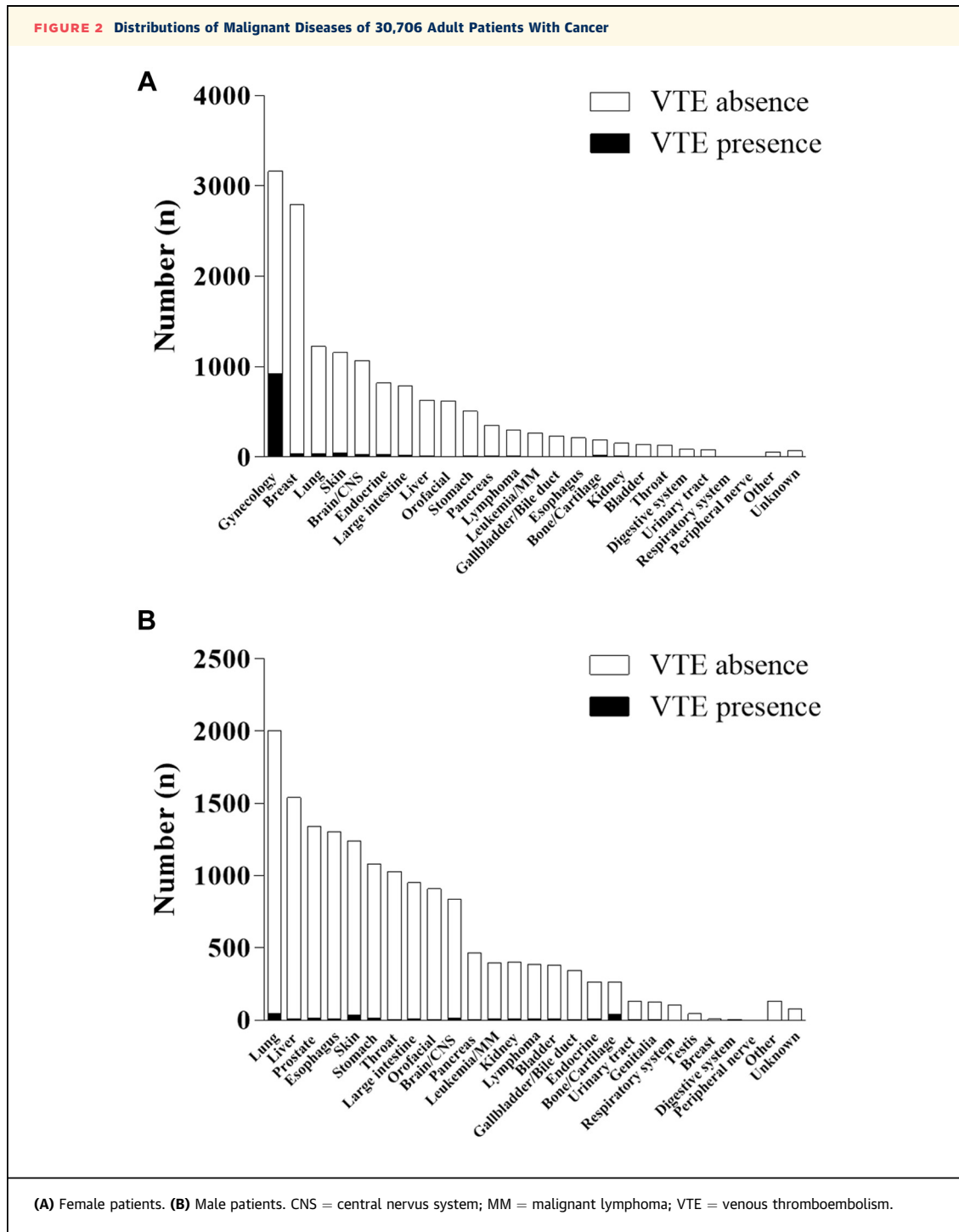
registry of Japanese patients with cancer to verify the validity of the KRS in predicting VTE in Japanese patients with cancer.

METHODS

The current study was a prospective, single-center, observational study that explored clinical outcomes in patients with cancer or with a history of cancer.

ETHICAL CONSIDERATION. All procedures were conducted in accordance with the Declaration of Helsinki and its amendments. The study protocol was approved by the institutional review board of Kumamoto University (Approval number, Rinri 1858). This

FIGURE 3 Distribution of the KRS in Enrolled Patients

Black, blue, and red columns indicate low, intermediate, and high risks of Khorana risk score (KRS), respectively.
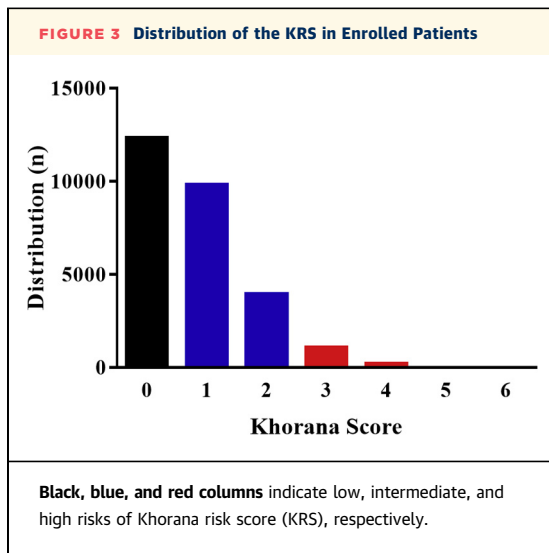
study is registered at the University Hospital Medical Information Network Clinical Trials Registry (UMIN000047554).

STUDY SUBJECTS. The Kumamoto Malignancy Mortality and Morbidity (KUMAMON) registry was a multicenter, prospective, community-based observational registry study conducted throughout Kumamoto Prefecture. The Kumamoto Prefecture is located southwest of Tokyo and has a population of approximately 1.8 million people (22,23). The KUMAMON registry included 167,439 cancers in the Kumamoto Prefecture (21 hospitals [details are described in the Supplemental Appendix]) between January 2007 and December 2018. The present study included 34,664 consecutive cancer registrations at Kumamoto University Hospital from the KUMAMON registry. We excluded 3,522 duplicated patients. Of 31,142 patients with cancer, 436 patients younger than 20 years were excluded. Moreover, we excluded subjects with insufficient explanatory data (missing the data of the components of KRS, n = 3,019). The remaining 27,687 adult patients with cancer were enrolled (Figure 1). The exact observational end date was August 31, 2020. All data were collected and aggregated by a trained research team at the Division of Cardiovascular Disease of Kumamoto University.

CALCULATION OF THE KHORANA VTE RISK ASSESSMENT SCORE (KRS). The KRS was calculated as previously described (Table 1) (3). In brief, the KRS consisted of the following 5 clinical items: tumor site (stomach and pancreatic cancers, classified as "very-high-risk"; lung, lymphoma, gynecological, bladder,

or testicular cancer, classified as "high-risk"), a prechemotherapy platelet count of $\geq 350 \times 10^9$/L, a prechemotherapy hemoglobin concentration of <10 g/dL and/or the use of erythropoiesis-stimulating agents, a prechemotherapy leukocyte count of $>11 \times 10^9$/L, and a BMI value of >35 kg/m^2. According to the World Health Organization Asian classification defined by expert consultation (24) based on the typical body shape of Asian populations, a BMI value of 25 kg/m^2 or more was defined as obesity. The methodology was widely applied in clinical studies (21,25).

CLINICAL PARAMETERS. Baseline demographic data, cardiovascular risk factors, and medications on enrollment were documented. Hypertension (HT) was defined as blood pressure $>140/90$ mm Hg or taking antihypertensive medication, as previously described (26-28). Diabetes mellitus (DM) was defined as the presence of the symptoms of DM and a casual plasma glucose concentration ≥ 200 mg/dL, fasting plasma glucose concentration ≥ 126 mg/dL, and 2-hour plasma glucose concentration ≥ 200 mg/dL from an oral glucose tolerance test (75 g) or taking medication for DM. Dyslipidemia (DL) was defined as low-density lipoprotein cholesterol concentration ≥ 140 mg/dL (≥ 3.63 mmol/L), high-density lipoprotein cholesterol concentration <40 mg/dL (1.04 mmol/L), or triglyceride concentration ≥ 150 mg/dL (≥ 1.7 mmol/L). The estimated glomerular filtration rate (eGFR) was calculated using the Japanese Society of Nephrology formula (29). Chronic kidney disease (CKD) was defined as an eGFR level ≤ 60 mL/min/1.73 m^2.

THE DIAGNOSIS OF VTE. We determined a diagnosis of VTE based on the International Classification of Diseases-10th Revision (ICD-10) code. The diagnosis of VTE was confirmed to meet the following conditions:

1) VTE codes: I260, I269, I800, I801, I802, I803, I809, I822, I823, I828, I829, O222, O223, O229, O870, O870, and O879 (details in Supplemental Table 1), and

2) the practice of enhanced computed tomography or lower extremity ultrasound.

FOLLOW-UP AND ENDPOINTS. After enrollment, the patients were followed up prospectively at the outpatient clinics until August 2020 or the occurrence of endpoints. The primary and secondary endpoints were the incidence of VTE and all-cause mortality, respectively. The endpoints were ascertained from a review of the medical records and confirmed by direct contact with the patients, their families, their physicians, or an annual telephone interview conducted with each patient.

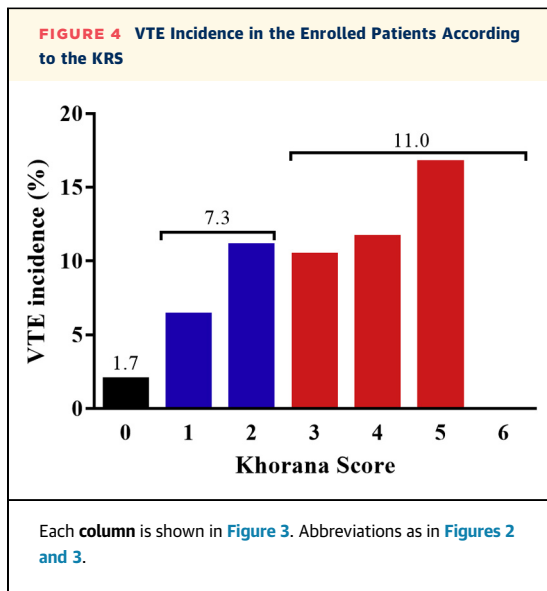**TABLE 2** Baseline Characteristics of Enrolled Patients With Cancer

	All Patients (N = 27,687)	Low Group (n = 11,249)	Intermediate Group (n = 14,877)	High Group (n = 1,561)	P Value
Age, y	67 (57-75)	68 (59-76)	66 (56-75)[a]	66 (55-75)[a]	<0.01
Male (%)	14,493 (52.3)	6,181 (52.6)	7,477 (51.8)[a]	835 (48.4)[b]	<0.01
BMI, kg/m^2	22.51 (20.21-24.99)	21.63 (19.72-23.23)	23.56 (20.66-26.42)[a]	25.22 (20.73-27.05)[a,c]	<0.01
BSA, m^2	1.574 (1.454-1.702)	1.541 (1.427-1.651)	1.599 (1.475-1.734)[a]	1.626 (1.486-1.764)[a,c]	<0.01
Cancer stage					
0-II (%)	15,071 (54.4)	6,102 (54.2)	8,239 (55.4)	730 (46.8)[a,c]	<0.01
III-IV (%)	6,517 (23.5)	2,406 (21.4)	3,506 (23.6)[a]	605 (38.8)[a,c]	<0.01
Procedure(s)[d] (%)	17,882 (64.6)	7,531 (66.9)	9,457 (63.6)[a]	894 (57.3)[a,c]	<0.01
Surgery (%)	13,208 (47.7)	5,899 (52.4)	6,748 (45.4)[a]	561 (35.9)[a,c]	<0.01
Endoscopic surgery (%)	1,518 (5.5)	424 (3.8)	884 (5.9)[a]	210 (13.5)[a,c]	<0.01
Video-assisted surgery (%)	3,327 (12.0)	1,267 (11.3)	1,926 (12.9)[a]	134 (8.6)[a,c]	<0.01
Radiation therapy (%)	4,187 (15.1)	2,012 (17.9)	2,021 (13.6)[a]	154 (9.9)[a,c]	<0.01
Chemotherapy (%)	8,824 (31.9)	3,180 (28.3)	4,937 (33.2)[a]	707 (45.3)[a,c]	<0.01
Endocrine therapy (%)	1,679 (6.1)	1,009 (9.0)	658 (4.4)[a]	12 (0.8)[a,c]	<0.01
Hypertension (%)	14,727 (53.2)	5,659 (50.3)	8,158 (54.8)[a]	910 (58.3)[a,b]	<0.01
Diabetes (%)	3,558 (12.9)	1,178 (10.5)	2,108 (14.2)[a]	272 (17.4)[a,c]	<0.01
Dyslipidemia (%)	5,145 (18.6)	1,853 (16.5)	2,933 (19.7)[a]	359 (23.0)[a,c]	<0.01
CKD (%)	6,240 (23.1)	2,215 (20.0)	3,579 (24.7)[a]	446 (28.9)[a,c]	<0.01
WBC, /µL	6.1 (4.8-7.7)	5.7 (4.6-7.0)	6.3 (5.0-8.0)[a]	8.2 (5.85-12.10)[a,c]	<0.01
RBC, /µL	4.24 (3.80-4.61)	4.26 (3.90-4.60)	4.24 (3.76-4.63)[a]	3.83 (3.14-4.51)[a,c]	<0.01
Hemoglobin, g/dL	13.1 (11.7-14.2)	13.3 (12.2-14.3)	13.0 (11.4-14.2)[a]	10.7 (9.15-13.5)[a,c]	<0.01
Platelet, 10$^{3/}$/µL	213 (170-263)	207 (167-248)	216 (171-268)[a]	271 (187-380)[a,c]	<0.01
TP, g/L	7.0 (6.5-7.4)	7.1 (6.7-7.4)	7.0 (6.5-7.4)[a]	6.6 (6.0-7.2)[a,c]	<0.01
Albumin, g/dL	4.1 (3.6-4.4)	4.1 (3.8-4.4)	4.0 (3.5-4.4)[a]	3.5 (2.8-4.1)[a,b]	<0.01
AST, U/L	22 (17-29)	22 (17-29)	21 (17-29)[a]	21 (16-30)[a,b]	<0.01
ALT, U/L	17 (12-26)	17 (12-25)	17 (12-27)	17 (11-29)	0.64
BUN, g/dL	14.1 (11.3-17.7)	14.0 (11.4-17.3)	14.1 (11.2-17.9)	13.8 (10.8-19.0)	0.28
Cr, mg/dL	0.72 (0.59-0.88)	0.72 (0.60-0.86)	0.72 (0.59-0.89)[a]	0.74 (0.59-0.95)[a,c]	0.02
eGFR, mL/min/1.73m^2	74.35 (61.31-88.12)	75.03 (62.91-87.53)	73.95 (60.15-88.41)[a]	72.86 (56.49-90.12)[a]	<0.01
UA, mg/dL	5.1 (4.1-6.2)	5.1 (4.1-6.1)	5.1 (4.1-6.3)	5.1 (3.9-6.4)	<0.01
T-chol, mg/dL	188 (161-215)	110 (88-134)	187 (161-215)[a]	173 (146-207)[a,c]	<0.01
LDL, mg/dL	109 (88-133)	109 (88-133)	110 (88-134)	103 (81-130)[a,c]	<0.01
HDL, mg/dL	58 (46-72)	61 (49-75)	56 (45-69)[a]	49 (39-64)[a,c]	<0.01
TG, mg/dL	101 (73-144)	94 (69-134)	106 (76-152)[a]	107 (80-151)[a]	<0.01
CRP, mg/dL	0.13 (0.05-0.70)	0.09 (0.04-0.36)	0.17 (0.05-0.90)[a]	0.73 (0.11-4.43)[a,c]	<0.01
HbA1c, %	5.8 (5.5-6.2)	5.7 (5.4-6.1)	5.8 (5.5-6.3)[a]	5.9 (5.5-6.4)[a,c]	<0.01
F/U periods, mo	53 (27-94)	58 (32-99)	52 (26-91)[a]	34 (13.5-64)[a,c]	<0.01
KRS, points	1 (0-1)	0 (0-0)	1 (1-2)[a]	3 (3-3)[a,c]	<0.01

Values are median (interquartile range) or n (%). [a]P < 0.01 vs Low group. [b]P < 0.05. [c]P < 0.01 vs Intermediate group. [d]Overlaps possible. *P<0.05

Albumin = serum albumin concentration; ALT = alanine aminotransferase concentration; AST = aspartate aminotransferase concentration; BMI = body mass index; BSA = body surface area; BUN = blood urea nitrogen; CKD = chronic kidney disease; Cr = serum creatinine concentration; CRP = plasma C-reactive protein concentration; eGFR = estimated glomerular filtration rate; F/U = follow-up; HbA1c = hemoglobin A1c level; HDL = serum high-density lipoprotein cholesterol concentration; Hemoglobin = blood hemoglobin level; KRS = Khorana venous thromboembolism risk assessment score; LDL = serum low-density lipoprotein cholesterol concentration; Platelet = blood platelet count; RBC = red blood cell count; T-chol = serum total cholesterol concentration; TG = serum triglyceride concentration; TP = serum total protein concentration; UA = serum uric acid concentration; WBC = white blood cell count.

STATISTICAL ANALYSIS. Continuous variables are expressed as the median (interquartile range). Categorical data are presented as numbers or percentages. The data were analyzed with the chi-square test for categorical variables and the Kruskal-Wallis test followed by post hoc Dunn's multiple comparison test for continuous variables among comparison groups, as appropriate. We used the Kaplan-Meier method to estimate the secondary endpoint probabilities and the log-rank test to compare the distributions of survival times among groups. Logistic regression and Cox proportional hazards models were used to calculate the odds ratios and hazard ratios, respectively. Receiver operating characteristic (ROC) curves were generated, and their 95% confidence intervals (CIs) were calculated to assess the predictive ability of the KRS. We used a method that may be used to determine the optimal cutoff point for a test is the

FIGURE 4 **VTE Incidence in the Enrolled Patients According to the KRS**

Each **column** is shown in **Figure 3**. Abbreviations as in **Figures 2 and 3**.

Youden index (30). The Youden index is defined as the maximum vertical distance between the ROC curve and the diagonal or chance line and is calculated as Youden index = maximum {sensitivity + specificity − 1}. Using this measure, the cutoff point on the ROC curve that corresponds to the Youden index, that is, at which (sensitivity + specificity − 1) is maximized, is taken to be the optimal cutoff point. An intuitive interpretation of the Youden index is that it corresponds to the point on the curve farthest from chance (31). A *P* value <0.05 was considered to denote statistical significance. Statistical analyses were performed using SPSS version 26 (IBM Inc).

RESULTS

PATIENT CHARACTERISTICS. The top 3 most common malignant diseases in female patients were gynecological, breast, and lung cancers (**Figure 2A**), and the top 3 in male patients were lung, liver, and prostate cancers (**Figure 2B**). **Figure 3** shows the distribution of the enrolled patients according to the KRS. **Table 2** shows the baseline characteristics of the enrolled patients in the low (n = 11,249), intermediate (n = 14,877), and high (n = 1,561) groups according to traditional risk categories. The results are demonstrated in **Table 2**.

THE PREVALENCE OF VTE IN PATIENTS WITH CANCER. Patients were followed for 53 [27-94] months (median [interquartile range]). Of the 27,687 enrolled patients, 1,455 patients (5.26%) experienced VTE in the observation period. **Figure 4** shows the VTE incidence according to the KRS, which was 1.7%, 7.3%, and

11.0% for the low, intermediate. and high groups, respectively.

ROC ANALYSIS OF THE KRS FOR VTE INCIDENCE AND PREDICTORS OF VTE INCIDENCE. A ROC curve was constructed to assess the ability of the KRS to predict VTE incidence (**Central Illustration A**). The area under the curve (AUC) of the KRS for the detection of VTE incidence was 0.679 (95% CI: 0.666-0.692; *P* < 0.001). Using the cutoff value obtained from ROC analysis for the KRS (0.5), the sensitivity and specificity were 86.7% and 42.1%, respectively. As the KRS can only take integer values from 0 to 6, the optimal cutoff value for VTE was 1.0.
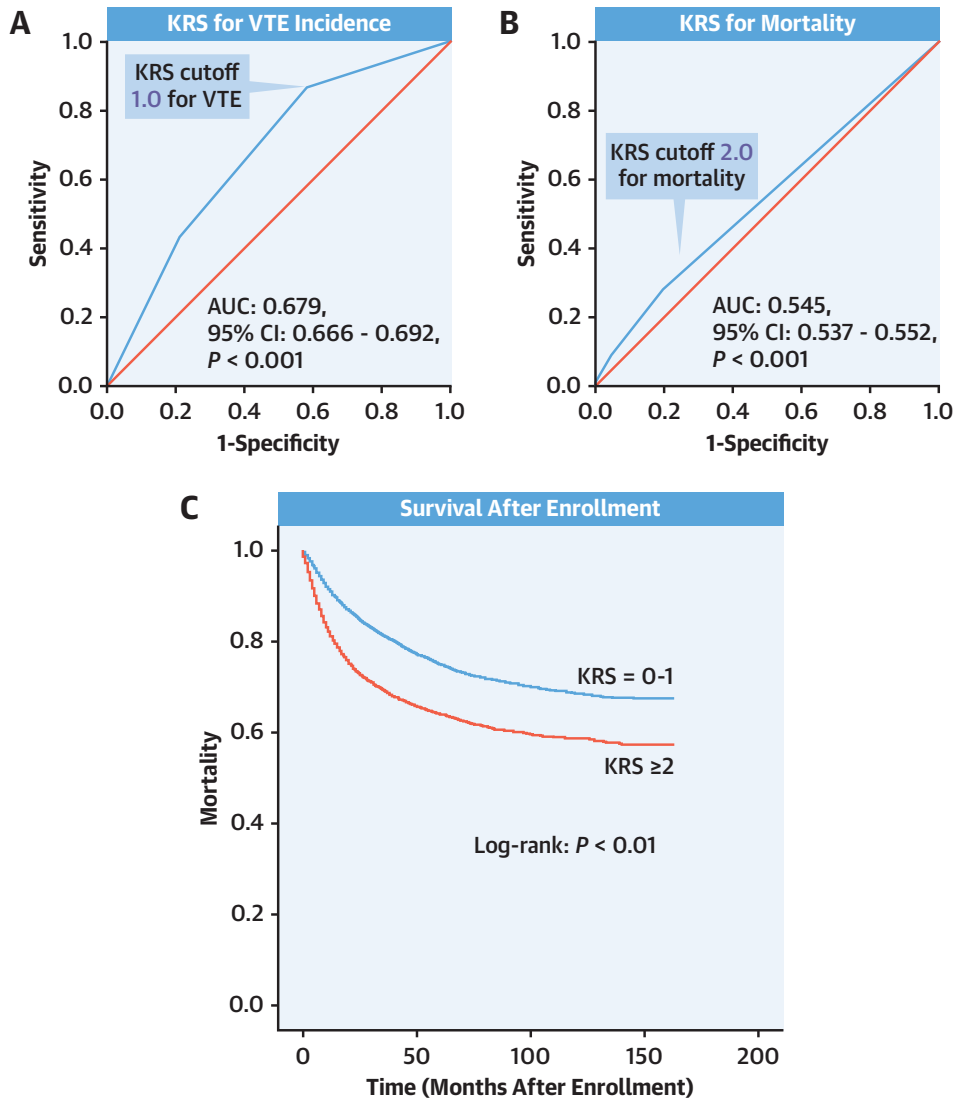
In univariable logistic regression analyses of VTE incidence, age; sex; body surface area; cancer stage 0-II; practice of procedure(s); surgery, endoscopic surgery, video-assisted surgery; chemotherapy and endocrine therapy; prevalence of HT, DM, and CKD; KRS; cancer site (2 points), cancer site (1 point), cancer site (0 point); platelet count >350 × 10^9/L; prevalence of anemia; white blood cell count >11 × 10^9/L; BMI ≥25 kg/m^2; KRS category; and KRS ≥1 were used to examine the potential significant determinants of VTE in patients with cancer (**Table 3**). In multivariable logistic regression analysis of VTE incidence, young age, female sex, cancer stage (0-II), practice of procedure(s), and chemotherapy, and KRS were independent and significant predictors of VTE incidence. Practice of endocrine therapy was associated with a risk of VTE incidence (**Table 3**).

ALL-CAUSE MORTALITY IN PATIENTS WITH CANCER. Of the 27,687 enrolled patients, 7,832 patients (28.3%) died within the follow-up period. **Figure 5** shows the all-cause mortality rates in the observation period according to the KRS, which were 26.1%, 28.4%, and 43.0% in the low, intermediate, and high groups, respectively.

ROC ANALYSIS OF THE KRS FOR ALL-CAUSE MORTALITY AND PREDICTORS OF ALL-CAUSE MORTALITY. A ROC curve was constructed to assess the ability of the KRS to predict mortality (**Central Illustration B**). The AUC of the KRS for the prediction of mortality was 0.545 (95% CI: 0.537-0.552; *P* < 0.001). Using the cutoff value obtained from ROC analysis for the KRS (1.5), the sensitivity and specificity were 28.1% and 80.3%, respectively. As the KRS can only take integer values from 0 to 6, the optimal cutoff value for mortality was 2.0.

In univariate Cox regression analyses of mortality; age; sex; body surface area; cancer stage 0-II; cancer stage III-IV; practice of procedure(s); surgery, endoscopic surgery, video-assisted surgery; radiation therapy, chemotherapy, and endocrine therapy;

CENTRAL ILLUSTRATION The Current Proposed Risk Categories of Venous Thromboembolism and Mortality for Asian Patients With Cancer

A KRS for VTE Incidence

KRS cutoff 1.0 for VTE

AUC: 0.679, 95% CI: 0.666 - 0.692, *P* < 0.001

Sensitivity / 1-Specificity

B KRS for Mortality

KRS cutoff 2.0 for mortality

AUC: 0.545, 95% CI: 0.537 - 0.552, *P* < 0.001

Sensitivity / 1-Specificity

C Survival After Enrollment

KRS = 0-1

KRS ≥2

Log-rank: *P* < 0.01

Mortality / Time (Months After Enrollment)

D

Khorana Score for Prediction in Cancer Patients	Points
Currently proposed risk categories for VTE	
-Intermediate to high	≥1
-Low	0
Currently proposed risk categories for mortality	
-Intermediate to high	≥2
-Low	<2

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ROC curves of the KRS for the prediction of VTE incidence **(A)** and all-cause mortality **(B)**, Kaplan-Meier analysis of all-cause mortality in the follow-up period according to the KRS **(C)**. The 0 time point on the x-axis indicates the day of enrollment. The current proposed risk categories for VTE and mortality **(D)**. AUC = area under the curve; CI = confidence interval; KRS = Khorana risk score; ROC = receiver operating characteristic; VTE = venous thromboembolism.

TABLE 3 Logistic Regression for Prediction of VTE

	Univariable Regression			Multivariable Regression Stepwise Backward		
	OR	95% CI	P Value	OR	95% CI	P Value
Age, y	0.976	0.972-0.979	<0.01	0.987	0.983-0.991	<0.01
Male	0.185	0.162-0.212	<0.01	0.194	0.168-0.224	<0.01
BSA, m^2	0.481	0.360-0.645	<0.01		Not selected	
Cancer stage						
0-II	1.359	1.220-1.515	<0.01	1.330	1.172-1.509	<0.01
III-IV	1.022	0.903-1.157	0.726			
Procedure(s)[a]	1.546	1.372-1.741	<0.01	1.392	1.212-1.598	<0.01
Surgery	2.384	2.132-2.666	<0.01		Not selected	
Endoscopic surgery	0.289	0.194-0.431	<0.01		Not selected	
Video-assisted surgery	0.307	0.237-0.397	<0.01		Not selected	
Radiation therapy	1.603	0.921-1.227	0.405			
Chemotherapy	1.510	1.356-1.681	<0.01	1.591	1.411-1.795	<0.01
Endocrine therapy	0.522	0.391-0.696	<0.01	0.457	0.337-0.619	<0.01
Hypertension	0.784	0.705-0.871	<0.01	1.035	0.914-1.171	0.589
Diabetes	0.711	0.595-0.849	<0.01	0.857	0.706-1.039	0.116
Dyslipidemia	1.013	0.885-1.159	0.856			
Chronic kidney disease	0.698	0.607-0.803	<0.01	0.945	0.809-1.103	0.471
KRS	1.790	1.704-1.880	<0.01	1.766	1.673-1.865	<0.01
Cancer Site						
2 points	0.287	0.260-0.399	<0.01		Not selected	
1 point	8.484	7.555-9.528	<0.01		Not selected	
0 point	0.161	0.143-0.182	<0.01		Not selected	
Platelet count ≥350 × 10^9/L	2.356	1.999-2.776	<0.01		Not selected	
Anemia[b]	1.908	1.658-2.196	<0.01		Not selected	
Leukocyte count >11 × 10^9/L	1.427	1.182-1.722	<0.01		Not selected	
Body mass index ≥25 kg/m^2	1.328	1.183-1.490	<0.01		Not selected	
KRS categories	1.591	1.517-1.668	<0.01		Not selected	
KRS≥1	4.764	4.086-5.554	<0.01		Not selected	

[a]Overlaps possible. [b]Anemia was defined as hemoglobin level <10.0 g/dL or use of red cell growth factors.

CI = confidence interval; OR = odds ratio; other abbreviations as in **Tables 1 and 2**.

prevalence of HT, DM, DL, and CKD; VTE; serum total protein concentration; serum albumin concentration; C-reactive protein level; KRS; cancer site (2 points), cancer site (1 point), cancer site (0 point); platelet count >350 × 10^9/L; prevalence of anemia; white blood cell count >11 × 10^9/L; BMI >25 kg/m^2; KRS category high; and KRS≥2 were used to examine the potential significant determinants of mortality in patients with cancer (**Table 4**). In multivariate Cox regression analyses of mortality, age, male sex, cancer stage (III-IV), practice of chemotherapy, prevalence of HT, CRP level, and KRS ≥2 were independent and significant positive predictors of mortality. Practice of procedure(s) and endocrine therapy, prevalence of DL, and serum albumin concentration were significant negative predictors of all-cause mortality (**Table 4**).

KAPLAN-MEIER CURVES FOR ALL-CAUSE MORTALITY. We performed Kaplan-Meier analysis and observed
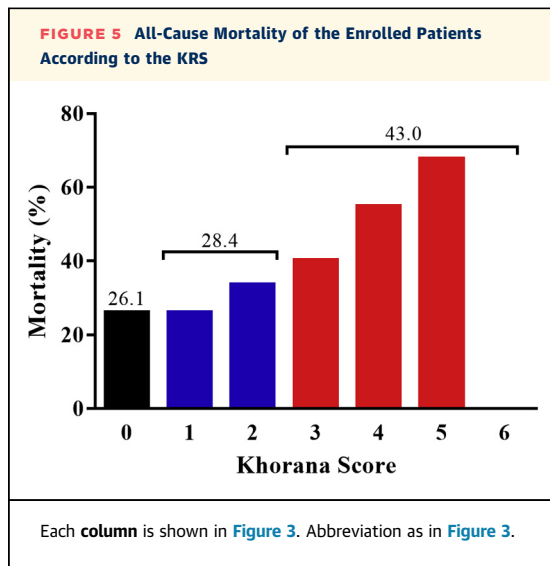
that the KRS ≥2 group was at higher risk of mortality than the KRS 0-1 group (**Central Illustration C**) (log-rank: P < 0.01).

DISCUSSION

The main feature of this study is the validation of VTE and mortality in patients with cancer, and the main findings of this study were as follows

1) The higher the KRS is, the higher the incidence of VTE and all-cause mortality.
2) Multivariable logistic proportional hazards and multivariate Cox regression analyses revealed that the KRS was an independent and significant predictor of VTE and mortality in patients with cancer, respectively.
3) The optimal cutoff levels of the KRS for VTE and mortality were 1.0 and 2.0, respectively.

FIGURE 5 All-Cause Mortality of the Enrolled Patients According to the KRS

Each **column** is shown in **Figure 3**. Abbreviation as in **Figure 3**.

4) Kaplan-Meier analysis revealed that KRS ≥2 was associated with significantly higher mortality than KRS 0-1.

Although there is a close relationship between cancer and thromboembolism, cardiovascular adverse effects that appear with cancer treatment, especially thromboembolism caused by anticancer drugs, have different pathological conditions; thus, it is necessary to take appropriate measures for the drugs. There are many unclear points about the pathophysiology of thromboembolism induced by anticancer drugs; however, angiogenesis inhibitors are one of the most frequently used drugs and have a clear mechanism of action. Angiogenesis inhibitors target vascular endothelial cells and lead to the development of thrombosis along with vascular endothelial impairment (32). Bevacizumab, a typical angiogenesis inhibitor, is used in many cancers, and the incidences of VTE and atrial thromboembolism are high at 11.9% and 3.3%, respectively (33). These findings have been comprehensively reviewed (34). In fact, the practice of chemotherapy was an independent and significant prognostic predictor of VTE in this study.

Khorana et al. (3) divided the VTE risk category into high (KRS ≥3), intermediate (KRS = 1-2), and low (KRS = 0). Recently, a meta-analysis revealed that among ambulatory patients with cancer with an intermediate to high-risk KRS of >2, thromboprophylaxis significantly reduces the risk of VTE without a significantly increased risk of major bleeding (35). Based on the findings of this study, we suggest that the current proposed risk categories for VTE should be intermediate to high (KRS ≥1) and low (KRS = 0),

and for all-cause mortality, they should be intermediate to high (KRS ≥2) and low (KRS <2) (**Central Illustration D**).

In the present study, the KRS was an independent and significant predictor of VTE and all-cause mortality in patients with cancer, including surgical cases, although it was originally developed for the prediction of symptomatic VTE in patients with cancer initiating a new chemotherapy. However, the AUCs of the KRS for the detection of VTE incidence and all-cause mortality were as low as 0.679 and 0.545, respectively. Hence, the diagnostic ability in Japanese subjects might be low. Therefore, it is essential to establish optimal score for Japanese subjects. Interestingly, the higher the KRS was, the higher the prevalence of cardiovascular risk factors such as HT, DM, DL, and CKD, which may be associated with a high BMI value (**Table 4**). This may be related not only to all-cause mortality but also to VTE.

It is well known that Westerners are more likely than Asians to develop thromboembolism due to their differences in genetic backgrounds (eg, coagulation factor V Leiden [36]). Moreover, the recent reviews have suggested the marked differences in other thrombogenic profiles (37,38). Therefore, it was necessary to verify the validity of KRS specialized for Asians. There is no report that examined the prognosis by KRS even in Westerners, and the novelty of this study demonstrated the patient prognosis (mortality rate). Hence, future clinical studies in Westerners are also essential to enhance the clinical significance of the present study. Moreover, although it would be very interesting if this study could evaluate the relationship between KRS and bleeding events, this study could not consider bleeding events because we conducted a study based on ICD-10. Hence, future clinical studies for investigating bleeding events are warranted.

To the best of our knowledge, this study is the first to investigate the association of the novel marker KRS with future VTE and all-cause mortality in Japanese patients with cancer. Associations between elevated levels and the development of VTE in patients with cancer have been shown for D-dimer (18,39-41), D-dimer and prothrombin fragment 1+ 2 (42), soluble P-selectin (43), clotting factor VIII (44), thrombin generation potential (45), and D-dimer and extracellular vesicles (46). In contrast, each component of the KRS is simple, and the calculation is not only easy in clinical practice but also well validated, with a low cost, which indicates that the score can be widely applied. If this score further predicts subsequent clinical events in patients with cancer, it could also serve as a useful indicator for oncologists and

TABLE 4   Cox Regression for Prediction of Mortality

	Univariate Regression			Multivariate Regression Stepwise Backward		
	HR	95% CI	P Value	HR	95% CI	P Value
Age, y	1.031	1.029-1.033	<0.01	1.030	1.028-1.032	<0.01
Male	1.847	1.763-1.934	<0.01	1.382	1.318-1.449	<0.01
BSA, m^2	0.423	0.374-0.479	<0.01		Not selected	
Cancer stage						
0-II	0.327	0.312-0.343	<0.01		Not selected	
III-IV	3.130	2.992-3.275	<0.01	1.956	1.859-2.059	<0.01
Procedure(s)[a]	0.305	0.291-0.319	<0.01	0.421	0.401-0.442	<0.01
Surgery	0.490	0.468-0.513	<0.01		Not selected	
Endoscopic surgery	0.592	0.525-0.667	<0.01		Not selected	
Video-assisted surgery	0.304	0.272-0.339	<0.01		Not selected	
Radiation therapy	1.526	1.445-1.612	<0.01	0.921	0.869-0.977	0.006
Chemotherapy	2.477	2.370-2.588	<0.01	1.631	1.548-1.718	<0.01
Endocrine therapy	0.419	0.368-0.477	<0.01	0.519	0.454-0.593	<0.01
Hypertension	1.406	1.344-1.472	<0.01	1.089	1.036-1.144	0.001
Diabetes	1.264	1.188-1.345	<0.01	1.015	0.950-1.085	0.658
Dyslipidemia	0.837	0.788-0.889	<0.01	0.732	0.687-0.779	<0.01
Chronic kidney disease	1.523	1.450-1.600	<0.01	1.097	1.041-1.156	0.001
VTE	0.739	0.658-0.829	<0.01		Not selected	
TP	0.685	0.667-0.704	<0.01		Not selected	
Alb	0.376	0.365-0.387	<0.01	0.476	0.458-0.495	<0.01
CRP	1.109	1.104-1.114	<0.01	1.013	1.007-1.020	<0.01
KRS	1.258	1.229-1.287	<0.01		Not selected	
Cancer site						
2 points	1.817	1.696-1.946	<0.01		Not selected	
1 point	0.843	0.799-0.890	<0.01		Not selected	
0 point	0.917	0.875-0.961	<0.01		Not selected	
Platelet count $\geq$350 $\times$ 10^9 /L	1.628	1.500-1.767	<0.01		Not selected	
Anemia[b]	2.874	2.719-3.038	<0.01		Not selected	
Leukocyte count >11 $\times$ 10^9 /L	1.891	1.751-2.041	<0.01		Not selected	
Body mass index $\geq$25 kg/m^2	0.677	0.640-0.717	<0.01		Not selected	
KRS categories	1.267	1.232-1.303	<0.01		Not selected	
KRS $\geq$2	1.604	1.527-1.685	<0.01	1.489	1.415-1.567	<0.01

[a]Overlaps possible. [b]Anemia was defined as hemoglobin level <10.0 g/dL or use of red cell growth factors.

HR = hazard ratio; other abbreviations as in **Tables 1 to 3**.

cardiologists in clinical situations. Although the KRS is highly expected to have clinical value, multi-centered clinical studies are needed to confirm its value. Therefore, additional detailed, prospective, multicenter studies are warranted to verify its precise usefulness.

It is highly possible that the incidence of thromboembolism due to a new mechanism by a new anti-cancer drug will continue to increase with the progress of cancer treatment. If cardiologists actively participate in cancer treatment and gain clinical experience, which is lacking in thrombotic treatment from a wide range of perspectives, cancer treatment can be optimized as onco-cardiology treatment, and it is expected that the prognosis of patients with cancer will be improved.

STUDY LIMITATIONS. The present study has some limitations. First, it was a single-center study. Therefore, a multicenter study is needed. Second, because the primary endpoint in the present study is based on the insurance disease name according to ICD-10, it is unclear whether it accurately represents the actual disease. Third, for the reasons mentioned previously, the possibility of having already developed VTE at the time of enrollment cannot be ruled out. Fourth, we assumed that BMI >35 kg/m^2 was not applicable to Japanese patients and changed this parameter to 25 kg/m^2. Based on derivation studies, we should first confirm that the statistical model with a BMI value >35 kg/m^2 does not fit the population and then change the model cutoff. Finally, we could not analyze prognostic implication

of biomarkers in this cohort; thus, it is unclear which factors contribute, and the extent of their contribution, to the development of VTE and mortality. Thus, further pathophysiological and molecular physiological studies, including animal experiments, are warranted. Additional detailed, large-scale clinical studies may be needed to verify our results.

CONCLUSIONS

The KRS, which can be easily and accurately calculated, is well validated in Japanese subjects and might be a potentially useful marker for the prediction of mortality. Establishing optimal scores for Japanese subjects is mandatory, and multicenter large-scale studies are needed to confirm the prognostic value of KRS and optimal scores for patients with cancer.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: This large, cohort study first demonstrated a prognostic value of the KRS in patients with cancer for predicting VTE.

TRANSLATIONAL OUTLOOK: The KRS is simple, widely applicable, well validated, and has a low cost, and it would be a useful tool for oncologists, as well as cardiologists to identify patients with cancer with a high risk of VTE for the optimization of risk-reducing treatments.

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KEY WORDS cancer, Khorana VTE risk score, mortality, risk stratification, venous thromboembolism

APPENDIX For a list of the hospitals participating in the KUMAMON registry, please see the online version of this paper.