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ORIGINAL ARTICLE
Epidemiology

The Kagoshima-DVT Score Is a Useful Predictive Model for Cancer-Associated Thrombosis in Patients With Gastrointestinal Cancer

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Background: Cancer-associated thrombosis (CAT) is a common complication of cancer and has received increasing attention; the Khorana Risk Score (KRS) is a recommended but insufficient risk assessment model for CAT. We propose a novel Kagoshima-DVT score (KDS) to predict preoperative deep vein thrombosis (DVT). This scoring method scores D-dimer ≥1.5 μg/mL, age ≥60 years, female sex, ongoing glucocorticoids, cancer with high risk of DVT, and prolonged immobility. The purpose of this study was to compare the performance of the KDS and KRS in predicting CAT in patients with gastrointestinal cancer.

Methods and Results: In all, 250 patients without a history of thrombosis who received their first chemotherapy for gastrointestinal cancer were divided into low- (48.0%), intermediate- (38.8%), and high-risk (13.2%) groups for CAT development by the KDS. The patients' median age was 67 years and 63.2% were men. In all, 61 (27.1%) patients developed CAT (17.6%, 35.3%, and 36.4% of patients in the low-, intermediate, and high-risk groups, respectively; log-rank P=0.006). The area under the time-dependent receiver operating characteristic curve for CAT occurrence within 1 year was larger for the KDS than KRS (0.653 vs. 0.494).

Conclusions: A high KDS at the start of first chemotherapy is a risk indicator for CAT development during chemotherapy. Moreover, the KDS is more useful than the KRS in predicting CAT risk.

Key Words: Cancer-associated thrombosis; Kagoshima-DVT score; Khorana risk score

The formation of a venous thromboembolism (VTE) is a significant risk factor for deep vein thrombosis (DVT) and pulmonary artery thromboembolism (PTE), which can be painful and lead to death.[1] The early detection of and interventions for VTE in the perioperative period are imperative because PTE has a high in-hospital mortality rate of 14% and a high 30-day mortality rate when it occurs in the perioperative period.[2,3] Therefore, Hamamoto et al recently proposed a new preoperative DVT probability score, the Kagoshima-DVT score (KDS), which scores patients according to D-dimer ≥1.5 μg/mL, age ≥60 years, female sex, ongoing glucocorticoids, active cancer with a high risk of DVT, and prolonged immobility.[4] Patients with a KDS of 0–2, 3–4, and 5–7 are classified into low-, intermediate-, and high-risk groups for developing DVT, respectively (**Table 1**).[4] The KDS is a simple and easy-to-use objective measure. However, the first study investigating the use of the KDS was a preoperative cross-sectional study, and no studies that have evaluated the KDS longitudinally in other clinical conditions.

VTE is particularly concerning in cancer patients. Patients with cancer have a 4- to 7-fold higher risk of developing thrombosis, termed cancer-associated thrombosis (CAT), than those without cancer.[5] CAT is the second leading cause of death in patients with cancer undergoing chemotherapy and is associated with prognosis.[6] With an aging population, the incidence of cancer continues to increase, despite advances in cancer research and prevention strategies. However, due to limited testing resources, there is a need for more efficient detection of CAT. The American Society of Clinical Oncology (ASCO) guidelines on thrombosis recommend the Khorana Risk Score (KRS) to assess the risk of thrombosis at the start of chemotherapy for solid tumors.[7] The KRS uses cancer location, blood count

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Table 1. Comparison of the Khorana Risk Score and Kagoshima-DVT Score

Variable	Points
Khorana risk score	
Site of cancer	
Very high risk (stomach and pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, and testicular)	1
Prechemotherapy platelet count ≥350×10^9/L	1
Hemoglobin level ≤100 g/L or the use of RBC growth factors	1
Prechemotherapy leukocyte count ≥11×10^9/L	1
BMI ≥35 kg/m^2	1
Total score range	0–6
Risk group	
Low	0
Intermediate	1–2
High	3–6
Kagoshima-DVT score	
D-dimer ≥1.5 μg/mL	2
Age ≥60 years	1
Female sex	1
Ongoing glucocorticoids	1
Cancer with a high risk of DVT	1
Prolonged immobility	1
Total score range	0–7
Risk group	
Low	0–2
Intermediate	3–4
High	5–7

BMI, body mass index; DVT, deep venous thrombosis; RBC, red blood cell.

(white blood cell [WBC] count, hemoglobin level, and platelet count), and body mass index (BMI) to produce a risk score (**Table 1**).[8] The Vienna score, which adds P-selectin and D-dimer levels to the KRS parameters, is also used to predict CAT.[9] However, some reports suggest that the KRS is not useful for predicting CAT.[10–12] This may be due to racial differences in the prevalence of CAT by the primary site of cancer, which is unaccounted for in the KRS.[13,14] In addition, the KRS considers very obese patients (BMI ≥35 kg/m^2) to be at risk of CAT, but few patients with cancer are very obese, especially in Asia. Therefore, the KRS may not be an accurate predictor of DVT in Asian patients. Moreover, we have previously reported that a high KRS at the start of chemotherapy for gastrointestinal cancer failed to predict CAT during chemotherapy.[15] A useful CAT prediction assessment model for the Asian population is needed.

The study of Hamamoto et al had a relatively high percentage of cancer patients (29.2% [284/973]).[4] In addition, cancer patients are often older and are known to have elevated D-dimer concentrations.[9] Patients with cancer are more likely to meet 3 of the 6 criteria of the KDS. The KDS is a probability score for DVT, and a high KDS may be used as a risk score for CAT. Therefore, the aim of the present study was to evaluate the usefulness of the KDS for predicting CAT in gastrointestinal cancer patients undergoing initial chemotherapy.

Methods

Study Design and Subjects

We retrospectively enrolled 280 consecutive patients who received their first cycle of chemotherapy for gastrointestinal cancer between January 1, 2017 and December 31, 2018, at Kagoshima Nanpuh Hospital (a referral hospital with 288 beds), with the observation period ending on December 31, 2019.

Of these 280 patients, 20 had a history of VTE and were

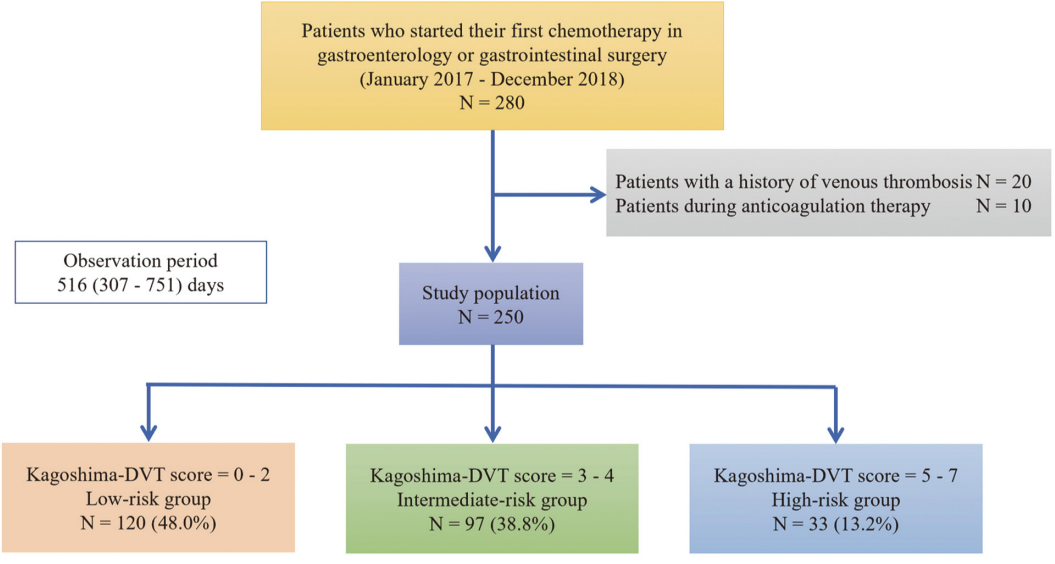


Figure 1. Study flowchart. The median observation period, with interquartile range, is indicated.

excluded because patients with a history of VTE tend to require anticoagulation therapy and have been reported to have a high recurrence rate.[16] Thus, the characteristics of patients with a history of VTE are significantly different from those of patients without a history of VTE. Another 10 patients receiving anticoagulation therapy at the start of chemotherapy were also excluded because this treatment would have a strong effect on preventing VTE. Finally, 250 patients were enrolled in this study, and were further classified according to their KDS into low-risk (n=120; 48.0%), intermediate-risk (n=97; 38.8%), and high-risk (n=33; 13.2%) groups for developing CAT (**Figure 1**).

Clinical Data Collection

Basic information was collected from patients' medical charts and included age, sex, height, weight, BMI, smoking history, cancer-related items (e.g., site, clinical stage, Eastern Cooperative Oncology Group Performance Status [ECOG PS]),[17] data on comorbidities (diabetes, hypertension, dyslipidemia, metabolic syndrome, chronic kidney disease [CKD]), history of surgery, medications (anticoagulants, antiplatelet drugs), and laboratory data (WBC count, hemoglobin level, platelet count, albumin, total bilirubin, blood urea nitrogen [BUN], creatinine [Cr], estimated glomerular filtration rate [eGFR], total cholesterol, blood sugar, C-reactive protein [CRP], D-dimer) before starting chemotherapy.

The psoas muscle volume, lumbar L3-level psoas muscle area, psoas muscle index (PMI), subcutaneous fat area at the umbilical level, and internal fat area at the umbilical level on computed tomography (CT) before the start of chemotherapy were measured using SYNAPSE VINCENT ver. 4.6 (FUJIFILM Medical Co., Tokyo, Japan) image analysis software (**Figure 2**).

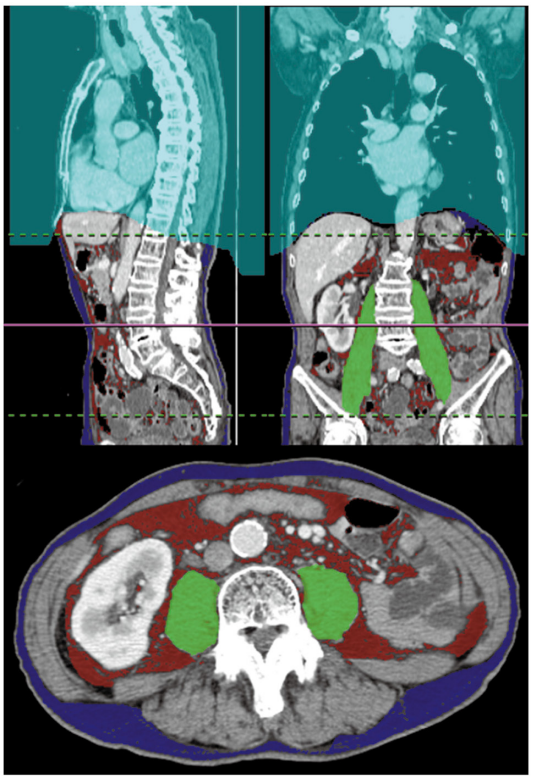


Figure 2. Computed tomography measurement before the start of chemotherapy of psoas muscle volume, L3-level psoas muscle area, the psoas muscle index (PMI), subcutaneous fat area at the umbilical level, and internal fat area at the umbilical level using image analysis software (SYNAPSE VINCENT, ver. 4.6; FUJIFILM Medical Co., Tokyo, Japan). The psoas muscle is shown in green, visceral fat in red, and subcutaneous fat in blue.

Definitions

Complications were assessed at the start of chemotherapy. Hypertension was defined as consuming antihypertensive medication or having a systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg. Diabetes was defined as the requirement for medication (regular subcutaneous injections of insulin or glucagon-like peptide-1 inhibitors, or consuming oral hypoglycemic agents), HbA1c ≥6.5%, random blood glucose ≥200 mg/dL, or fasting blood glucose ≥126 mg/dL. Dyslipidemia was defined as the requirement for medication (regular subcutaneous injections of proprotein convertase subtilisin/kexin type 9 inhibitors or oral medication) or having total cholesterol ≥220 mg/dL, triglycerides ≥150 mg/dL, low-density lipoprotein cholesterol ≥140 mg/dL, or high-density lipoprotein cholesterol ≤40 mg/dL. CKD was defined as eGFR <60 mL/min/1.73 m^2. Surgery was defined as surgery under general anesthesia for cancer performed 1 year before the start of chemotherapy. BMI was calculated as weight (kg) divided by height squared (m^2), and obesity was defined as BMI ≥25 kg/m^2. PMI is an index of skeletal muscle mass and was calculated by dividing the L3-level psoas muscle area (cm^2) by height squared (m^2). Low muscle mass was defined as PMI <6.36 cm^2/m^2 in men and <3.92 cm^2/m^2 in women.[18]

Outcome Measures

The primary outcome was the occurrence of CAT during the observation period. Data were collected retrospectively from medical records. Thrombosis was classified as symptomatic (swelling, pain etc.) or asymptomatic. Asymptomatic thrombosis was diagnosed incidentally on contrast-enhanced CT during follow-up cancer treatment or on whole-leg ultrasound (WLUS) performed after close examination of high D-dimer concentrations. Kagoshima Nanpuh Hospital has adopted an in-hospital manual that recommends measuring D-dimer concentrations before administering general anesthesia, before chemotherapy, and every 3 months after the start of chemotherapy, and recommends WLUS if D-dimer concentrations are ≥2.0 μg/mL. However, the decision to perform the test is at the discretion of individual physicians. CAT sites were categorized as PTE, DVT, or others investigated retrospectively by chart review.

Statistical Analysis

The KDS risk groups were compared using the Chi-squared test for nominal variables and the Kruskal-Wallis test for continuous variables. Nominal variables are presented as numbers and percentages, and continuous variables are presented as the median with interquartile range (IQR). Cumulative incidence was estimated by the Kaplan-Meier method, and differences were evaluated using a log-rank test.

A time-dependent receiver operating characteristic (ROC) curve was generated for the diagnostic ability of the throm-

Table 2. Baseline Characteristics in All Patients and According to Kagoshima-DVT Score Risk Category

	All (n=250)	Low-risk group (n=120)	Intermediate-risk group (n=97)	High-risk group (n=33)	P value
Age (years)	67 [59–74]	65 [54–72]	68 [63–76]	74 [66–80]	<0.0001
Male sex	158 (63.2)	103 (85.8)	55 (56.7)	0 (0.0)	<0.0001
Smoking	66 (26.4)	48 (40.0)	16 (16.5)	2 (6.1)	<0.0001
Comorbidities					
Diabetes	78 (31.2)	48 (40.0)	24 (24.7)	6 (18.2)	0.011
Hypertension	105 (42.0)	45 (37.5)	43 (44.3)	17 (51.5)	0.3
Dyslipidemia	58 (23.2)	22 (18.3)	26 (26.8)	10 (30.3)	0.2
Metabolic syndrome	39 (15.6)	20 (16.7)	17 (17.5)	2 (6.1)	0.3
Chronic kidney disease	35 (14.2)	11 (9.2)	18 (19.0)	6 (18.8)	0.1
Medication					
Antiplatelet	16 (6.4)	8 (6.7)	6 (6.2)	2 (6.1)	0.99
Primary cancer site					0.4
Colorectal	110 (44.0)	58 (48.3)	38 (39.2)	14 (42.4)	
Pancreatic	54 (21.6)	22 (18.3)	23 (23.7)	9 (27.3)	
Stomach	52 (20.8)	24 (20.0)	22 (22.7)	6 (18.2)	
Biliary tract	19 (7.6)	8 (6.7)	7 (7.2)	4 (12.1)	
Esophageal	12 (4.8)	8 (6.7)	4 (4.1)	0 (0.0)	
Cancer of unknown primary	3 (1.2)	0 (0.0)	3 (3.1)	0 (0.0)	
Surgery	149 (86.1)	72 (82.8)	61 (91.0)	16 (84.2)	0.3
Stage III–IV	186 (81.2)	89 (80.9)	69 (79.3)	28 (87.5)	0.6
ECOG-PS 2–4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–
Baseline laboratory values					
White blood cell count (/μL)	5,700 [4,800–7,010]	5,870 [4,820–6,890]	5,530 [4,830–7,480]	5,380 [4,250–6,450]	0.4
Hemoglobin (g/dL)	12.5 [11.2–13.7]	13.2 [11.6–14.2]	12.2 [11.1–13.1]	11.7 [10.8–12.7]	<0.0001
Platelet count ($10^3/\mu$L)	24.4 [19.5–30.4]	24.1 [19.4–28.8]	24.4 [19.6–31.3]	25.9 [20.2–34.0]	0.5
D-dimer (μg/mL)	1.0 [0.5–2.4]	0.6 [0.3–0.9]	1.9 [0.8–3.5]	2.9 [1.9–5.8]	<0.0001
Total bilirubin (mg/dL)	0.7 [0.5–0.9]	0.6 [0.5–0.9]	0.7 [0.5–0.9]	0.7 [0.5–1.2]	0.3
BUN (mg/dL)	12.6 [10.3–15.5]	12.5 [9.9–15.3]	13.2 [10.7–16.3]	11.8 [10.2–13.6]	0.2
Cr (mg/dL)	0.72 [0.61–0.85]	0.79 [0.68–0.87]	0.71 [0.59–0.84]	0.59 [0.51–0.70]	<0.0001
eGFR (mL/min/1.73 m^2)	74.4 [63.8–87.2]	75.1 [66.3–88.1]	73.7 [62.5–85.6]	73.0 [62.3–87.2]	0.4
Albumin (g/dL)	4.0 [3.6–4.3]	4.1 [3.8–4.3]	3.9 [3.4–4.2]	3.7 [3.2–4.0]	0.0010
Total cholesterol (mg/dL)	175 [151–203]	176 [155–213]	164 [137–188]	195 [172–215]	0.012
Blood glucose (mg/dL)	109 [97–136]	114 [97–143]	107 [96–131]	107 [96–136]	0.3
CRP (mg/dL)	0.25 [0.09–1.38]	0.16 [0.07–0.67]	0.45 [0.09–5.20]	0.46 [0.12–1.69]	0.03
Body height (cm)	161 [154–167]	164 [159–168]	161 [153–166]	151 [146–154]	<0.0001
Body weight (kg)	54.3 [47.9–62.3]	57.2 [51.6–64.4]	52.9 [46.0–61.4]	47.3 [44.2–52.8]	<0.0001
BMI (kg/m^2)	21.3 [19.4–23.6]	21.6 [19.7–24.0]	20.9 [18.7–23.4]	21.0 [19.7–23.7]	0.2
Obesity (BMI ≥25 kg/m^2)	36 (14.4)	22 (18.3)	11 (11.3)	3 (9.1)	0.2
Psoas muscle area at L3 (cm^2)	15.2 [11.3–18.8]	17.3 [14.8–20.7]	14.4 [11.1–17.4]	9.8 [9.1–11.0]	<0.0001
Psoas muscle volume (cm^3)	268.6 [202.7–357.3]	321.9 [266.3–390.0]	250.7 [190.2–305.2]	171.1 [142.7–202.7]	<0.0001
PMI (cm^3/m^2)	5.82 [4.75–6.93]	6.55 [5.55–7.33]	5.43 [4.41–6.53]	4.24 [4.04–4.81]	<0.0001
Sarcopenia by PMI	109 (44.3)	52 (44.1)	47 (49.5)	10 (30.3)	0.2
Internal fat area (cm^2)	77.6 [42.8–119.6]	75.8 [50.4–119.8]	76.2 [38.3–121.4]	84.4 [61.1–107.1]	0.7
Subcutaneous fat area (cm^2)	98.3 [65.2–146.7]	91.9 [61.8–137.8]	94.9 [64.1–143.0]	123.1 [107.8–166.6]	0.004

Unless indicated otherwise, data are given as the median [interquartile range] or n (%). BMI, body mass index; BUN, blood urea nitrogen; Cr, creatinine; CRP, C-reactive protein; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; eGFR, estimated glomerular filtration rate; PMI, psoas muscle index.

bosis score and evaluated by the area under curve (AUC). A comparison test of the time-dependent AUCs of the KDS and KRS was performed with the null hypothesis that "the AUCs of both scores are equal at time "t"".[19]

In all cases, 2-sided P<0.05 was considered statistically significant. Statistical analyses were performed using JMP version 15.0 (SAS Institute, Cary, NC, USA) and R version 4.0.2 (The R Foundation for Statistical Computing, Vienna, Austria).

Ethical Considerations

To protect patient confidentiality, medical information was anonymized. This study was approved by the Clinical Research Ethics Committee of the Kagoshima Nanpuh

Hospital (Registration no. R2019029) and was conducted in accordance with the Ethical Guidelines for Clinical Research of the Ministry of Health, Labor and Welfare, Japan, and the Declaration of Helsinki. Informed consent was obtained from participants using an opt-out approach.

Results

Patient Characteristics: All Subjects

The median observation period for the participants was 516 days (IQR 307–751 days), the median age was 67 years (IQR 59–74 years), and 158 (63.2%) were men. Comorbidities at the start of chemotherapy were diabetes (n=78; 31.2%), hypertension (n=105; 42.0%), dyslipidemia (n=58; 23.2%), and CKD (n=39; 15.6%). No patient had an ECOG-PS of 2 or higher, and 186 (81.2%) had clinical stage III–IV cancer. Primary cancer sites were the colorectum (n=110; 44.0%), pancreas (n=54; 21.6%), stomach (n=52; 20.8%), biliary tract (n=19; 7.6%), esophagus (n=12; 4.8%), and unknown (n=3; 1.2%).

Anthropometric indices at the start of chemotherapy were

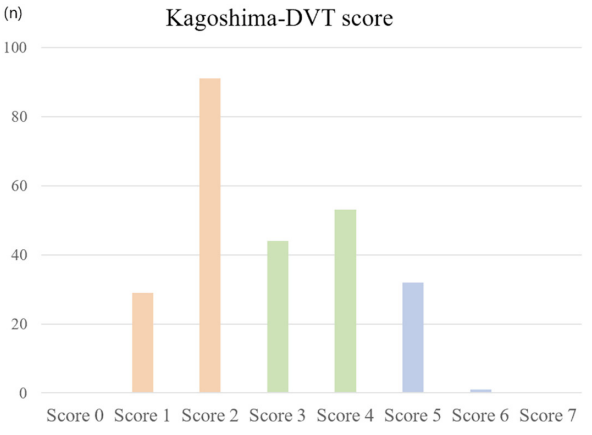
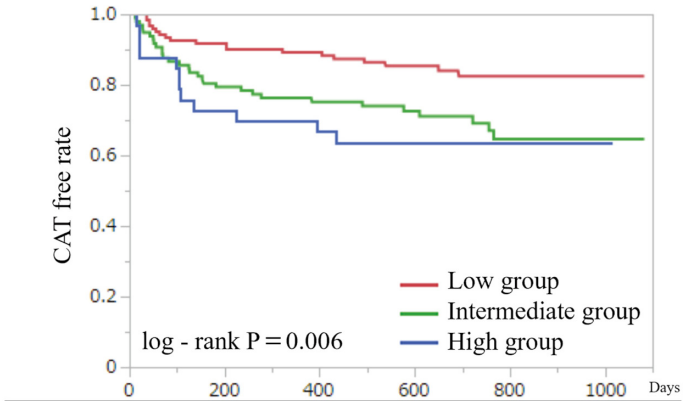


Figure 3. Distribution of Kagoshima-DVT scores (KDS). Patients were divided into low-, intermediate-, and high-risk groups for developing deep venous thrombosis (DVT) based on KDS of 0–2, 3–4, and 5–7, respectively.

Table 3. Overall Incidence of Death and Thromboembolic Events in All Patients and According to Kagoshima-DVT Score Risk Category

Events	All (n=250)	Low-risk group (n=120)	Intermediate-risk group (n=97)	High-risk group (n=33)	Log-rank P value
Thrombosis	61 (27.1)	19 (17.6)	30 (35.3)	12 (36.4)	0.006
Site					
DVT	51 (23.4)	16 (15.2)	25 (30.9)	10 (30.8)	0.02
PTE	7 (3.7)	2 (1.7)	5 (7.5)	0 (0.0)	0.2
Other sites	9 (5.0)	2 (2.0)	4 (6.9)	3 (10.8)	0.08
Opportunity for diagnosis					
Asymptomatic	53 (24.2)	18 (16.8)	25 (31.2)	10 (30.3)	0.04
Symptomatic	8 (3.8)	1 (1.0)	5 (6.0)	2 (8.7)	0.08

DVT, deep venous thrombosis; PTE, pulmonary thromboembolism.



	Baseline	200 days	400 days	600 days	800 days	1000 days
Low risk						
Incidence		8.3%	10.8%	14.6%	17.6%	17.6%
Number at risk	120	110	103	73	37	12
Intermediate risk						
Incidence		20.6%	24.8%	27.4%	35.3%	35.3%
Number at risk	97	77	68	49	25	6
High risk						
Incidence		27.3%	33.3%	36.4%	36.4%	36.4%
Number at risk	33	24	22	13	6	1

Figure 4. Kaplan-Meier curves showing the cancer-associated thrombosis (CAT)-free rate over time in patients in the low-, intermediate-, and high-risk groups based on the Kagoshima-DVT score (KDS). The KDS is evaluated considering D-dimer ≥1.5 μg/mL, age ≥60 years, female sex, ongoing glucocorticoids, cancer with a high risk of deep venous thrombosis (DVT), and prolonged immobility. A KDS of 0–2 is defined as low risk, a KDS of 3–4 is defined as intermediate risk, and a KDS of 5–7 is defined as high risk.

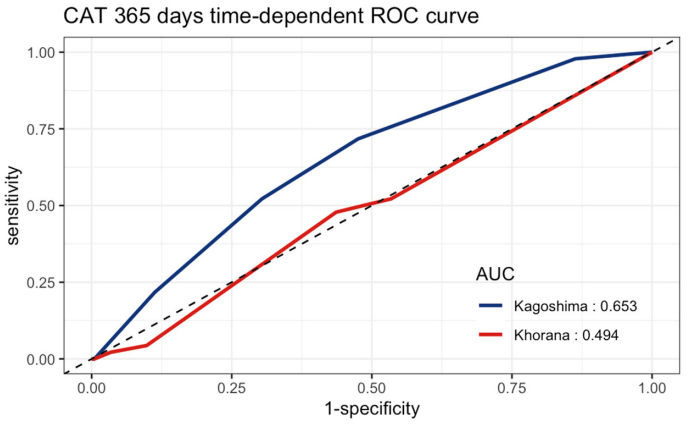


Figure 5. Time-dependent receiver operating characteristic curves for cancer-associated thrombosis (CAT) events within 1 year for the Khorana risk score (KRS) and Kagoshima-DVT score (KDS). AUC, area under curve.

as follows: median BMI 21.3 kg/m^2 (IQR 19.3–23.6 kg/m^2), median L3-level psoas muscle area 15.2 cm^2 (IQR 11.3–18.8 cm^2), median psoas muscle volume 268.6 cm^3 (IQR 202.7–357.3 cm^3), and median PMI 5.82 cm^2/m^2 (IQR 4.75–6.93 cm^2/m^2); 137 (55.7%) patients had a PMI above the threshold (**Table 2**).

At the start of chemotherapy, patients were classified according to the KDS into low-risk (0–2 points), intermediate-risk (3–4 points), and high-risk (5–7 points) groups. There were 120 (48.0%), 97 (38.8%), and 33 (13.2%) patients in the low-, intermediate-, and high-risk groups, respectively. Among the patients, 29 (11.6%) scored 1 point, 91 (36.4%) scored 2 points, 44 (17.6%) scored 3 points, 53 (21.2%) scored 4 points, 32 (12.8%) scored 5 points, 1 (0.4%) scored 6 points, and 0 (0.0%) scored 7 points (**Figure 3**).

Patient Characteristics in the KDS Low-, Intermediate-, and High-Risk Groups

Patients in the high-risk KDS group were significantly older, more likely to be women, and smoked less than those in the intermediate- and low-risk groups. There were no differences between the groups in the incidence of comorbidities, such as dyslipidemia, hypertension, metabolic syndrome, and CKD. The complication rate of diabetes was associated with higher KDS (P=0.011). There were no differences in primary cancer site, stage, ECOG-PS, and use of antithrombotic drugs between the 3 groups.

Blood tests showed no group differences in the WBC count, platelet count, and eGFR between the groups. Low hemoglobin, high D-dimer, and low Cr (all P<0.0001) were noted in the group with a high KDS.

In terms of anthropometric indices, there were no between-group differences in BMI, subcutaneous fat area, internal fat area, and percentage of low muscle mass by PMI. Height, weight, psoas muscle volume, L3-level psoas muscle area, and PMI were significantly lower in the high-risk KDS group than in the other 2 groups (**Table 2**).

Outcomes

CAT During the follow-up period, 61 (27.1%) patients developed CAT. Of these, 51 (23.4%) had DVT and 7 (3.7%) had PTE. Only 8 (3.8%) patients with CAT were symptomatic; patients in the low-risk KDS group were significantly less likely to develop CAT than those in the other 2 groups (log-rank test, P=0.006; **Table 3**; **Figure 4**). Overall, 126 (48.5%) patients had WLUS after chemotherapy (48 [38.1%], 54 [54.5%], and 24 [68.6%] in the low-, intermediate-, and high-risk groups, respectively; P=0.04).

Efficacy of the KRS vs. KDS In a time-dependent ROC curve analysis, the AUC for the KDS was higher than that for the KRS when comparing CAT onset within 1 year (0.653 vs. 0.494; **Figure 5**). Comparing the AUCs for the KDS and KRS, the AUC for the KDS was significantly higher (P=0.0039).

Discussion

This study suggests that the KDS, a preoperative thrombosis probability score, may predict the occurrence of future thrombosis, with higher scores possibly associated with a greater likelihood of thrombosis in cancer patients undergoing chemotherapy. Because the present study is a retrospective observational study of usual care, not all patients were investigated for thrombosis before starting chemotherapy. However, many patients underwent contrast-enhanced CT during the course of cancer treatment evaluation. In addition, Kagoshima Nanpuh Hospital has adopted an in-hospital manual that measures D-dimer concentrations before chemotherapy and every 3 months after the start of chemotherapy, and recommends WLUS if the D-dimer concentration is 2.0 μg/mL or higher. Thus, in the present patient cohort, even if the D-dimer concentration was high at the start of chemotherapy, this was a group of patients in whom no thrombus was detected by CT or WLUS. Nevertheless, the KDS at the start of chemotherapy was useful in assessing the risk of CAT during chemotherapy. Thus, to clarify the reason for this, we have focused the discussion on muscle mass and D-dimer.

Muscle Mass

Low muscle mass may be a risk factor for DVT due to impaired pump functions related to venous return in the lower extremities. A study on the relationship between the muscle mass measured by CT and the development of venous thrombosis in patients undergoing knee arthroplasty suggested that the risk for DVT increased by 2.97-fold in patients with reduced vastus lateralis muscle mass.[20] In the present study, the KDS high-risk group had significantly lower PMI, measure of skeletal muscle mass

(**Supplementary Figure 1**). The psoas muscle mass was evaluated by CT in 229 patients. A comparison of the group with incident CAT (53 patients; 21.2%) with the group without incident CAT (174 patients; 69.6%) suggested no significant differences in BMI, internal fat area, and subcutaneous fat area between the 2 groups, but indicated significantly lower L3-level psoas muscle area, psoas muscle volume, and PMI in the group with than without incident CAT (**Supplementary Table**).

Of the parameters taken into account by the KDS, women, elderly patients, and patients who are immobile for a prolonged period of time are the subgroups that are most likely to have low muscle mass. Thus, a high KDS is associated with lower muscle mass, which may reflect a loss of pump function in the lower extremities and be a factor for increased CAT risk, even if no thrombus is detected at the start of chemotherapy. Therefore, high KDS may be a risk factor for thrombosis in other underlying diseases, and we would like to consider expanding its use in various settings, such as using it with patients hospitalized for internal medicine-related diseases and rehabilitation. In addition, we think that patients with a high KDS should be observed more carefully for the possibility of thrombosis, even if thrombosis is not initially observed.

D-Dimer

The KDS considers D-dimer ≥1.5 μg/mL as the highest risk factor, with a score of 2. It has been established that patients with cancer often have abnormalities in coagulation/fibrinolytic systems. It has been reported that 50% of all cancer patients and 95% of patients with metastatic cancer have abnormal blood and coagulation.[21,22] D-dimer is a product of the degradation of stabilized fibrin by plasmin, and increases in D-dimer suggest an increased fibrinolytic system and the presence of thrombi; indeed, 75% of patients with cancer have D-dimer ≥1.44 μg/mL.[9] Therefore, the Vienna score, a risk assessment model for CAT, also considers D-dimer ≥1.44 μg/mL and high serum selectin concentrations as risk factors.[9] There are differences in cut-off values, but a high D-dimer concentration is considered a high risk for CAT. High D-dimer concentrations have also been found to be associated with vascular invasion in colorectal cancer, and cancer progression has been reported to increase the occurrence of CAT in various cancer types.[23,24] This means that high D-dimer concentrations may reflect cancer progression and may be associated with an increased risk of incident CAT.

Clinical Implications

Compared with the KRS, the KDS had a higher AUC in the time-dependent ROC analysis for the development of CAT within 1 year of starting chemotherapy. Comparing the AUCs for the KDS and KRS, the AUC for the KDS was significantly higher (P=0.0039). We think that adding cancer-related factors to the KDS may allow us to more accurately examine the risk of CAT. For example, the primary cancer site is likely to be affected by racial differences. KRS gives gastric and pancreatic cancers 2 points and a higher risk of CAT than other cancer sites. But, in the present cohort, there was a low incidence of CAT among those with gastric cancer, which is considered the highest risk factor in the KRS (**Supplementary Figure 2**). Therefore, we would like to develop a risk assessment model for CAT suitable for Asians through further study.

Study Limitations

This study has some limitations. First, it was a single-center retrospective study, and thus may have associated potential bias. However, this setting also has some advantages, such as uniform testing and treatment regimens, and accurate data collection. In addition, because this study has a small sample size, the results may not be generalizable. Second, the study failed to examine immobility, which is a parameter of the KDS and may therefore have decreased the score. However, only 1 (0.4%) patient showed a decrease in activity beyond PS2, and thus the effect was considered to be small. Finally, this study did not include any male patients with a score of 5 or higher, because only 4 (1.6%) patients were on steroids, and 2 (immobility and steroid) of the 6 KDS parameters were present in very few patient groups.

Conclusions

In this study we longitudinally investigated the utility of the newly proposed DVT probability score, the KDS, by comparing it to the KRS. The study suggests that a high KDS at the start of the first chemotherapy cycle for gastrointestinal cancer is predictive of CAT during chemotherapy and is more accurately predictive than the KRS. In addition, if used for screening of CAT, the KDS may contribute to early DVT or PTE detection and treatment.

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Disclosures

The authors have no conflicts of interest directly relevant to the contents of this study to declare. M.O. is a member of *Circulation Reports*' Editorial Team.

IRB Information

This study was approved by the Institutional Review Board of Kagoshima Nanpuh Hospital (Registration no. R2019029).

Data Availability

The deidentified participant data will not be shared.

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Supplementary Files

Please find supplementary file(s);
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