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Development and validation of a risk assessment tool for ischemic stroke in cancer patients

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Cancer patients have an increased risk of ischemic stroke. However, there is no reliable risk prediction model. We aimed to create a risk prediction model for ischemic stroke in cancer patients within the first 2 years after cancer diagnosis. A cohort of 26,717 cancer patients from the University of Osaka Hospital was used to develop the model. A cohort of 31,881 patients from Osaka International Cancer Institute was used for external validation. Data in the development cohort generated an AHANDS score: *A*ge ≥ 75 years, *H*ypertension, *A*trial fibrillation, a high *N*eutrophil-to-lymphocyte ratio, an elevated *D*-dimer level, and cancer *S*tage IV or distant metastasis at the time of cancer diagnosis. Discrimination was assessed using the c-statistic. We compared the AHANDS and Khorana scores in the development cohort. Ischemic stroke occurred within 2 years of diagnosis of cancer in 163 patients (0.61%) in the development cohort and in 99 (0.31%) in the validation cohort. The AHANDS score performed better than the Khorana score (c-statistic 0.703 vs. 0.54; $p < 0.0001$). A similar result was obtained in the external validation cohort (c-statistic 0.75). This score is intended to guide future stroke prevention strategies in patients with cancer.

The risk of ischemic stroke is higher in cancer patients than in the general population[1]. A large US population-based study reported that the cumulative incidence of ischemic stroke in the first 6 months after a diagnosis of cancer was 3.0% in a cancer cohort compared with 1.6% in a control cohort (hazard ratio 1.9)[2]. The risk of ischemic stroke is particularly high at around 6 months before and after a cancer diagnosis[3–5] and then increases gradually year by year[6]. Furthermore, the risks of stroke recurrence and mortality are higher in patients with cancer who sustain an acute ischemic stroke than in the general population[7–9]. Overall, ischemic stroke is a devastating complication in cancer patients. Therefore, it is important to identify patients with a high risk of ischemic stroke at the time of their cancer diagnosis. Primary prevention of ischemic stroke is required in high-risk patients. However, no reliable risk prediction model or prevention strategy has been established.

Venous thromboembolism (VTE) is a common complication in cancer patients[10]. The risk of VTE is assessed in these patients before they start cancer therapy using the Khorana score. This score includes five risk parameters: site of the primary cancer (stomach and pancreas, very high risk; lung, lymphoma, gynecologic, and bladder, high risk); a platelet count of ≥ 350×10^9/L; a hemoglobin concentration of ≤ 100 g/L or use of erythropoiesis-stimulating agents; a leukocyte count of ≥ 11×10^9/L; and a body mass index of ≥ 35[11]. When a cancer patient has a Khorana score of ≥ 3 or is otherwise considered to be at high risk, anticoagulation prophylaxis is prescribed using a direct oral anticoagulant or low-molecular-weight heparin[12–14]. Anticoagulation therapy can reduce the risk of VTE in these patients.

An older age (≥ 75 years)[6,7,15], hypertension[15], atrial fibrillation (Af)[6,16], advanced cancer stage or distant metastasis[2,6,7,17], primary cancer site in the lung, kidney, or pancreas[15,18], and an elevated neutrophil-to-lymphocyte ratio (NLR) at the time of a cancer diagnosis[19] are predictors of ischemic stroke in cancer patients[1]. An elevated D-dimer level and adenocarcinoma histology are also common clinical features in cancer patients with ischemic stroke[9,20–23]. There is a degree of inconsistency between these eight clinical features and the Khorana score, which can be explained by the fact that the Khorana score was developed to predict VTE whereas the above-mentioned clinical features have been associated with the development of ischemic stroke in cancer patients. However, activation of coagulation would contribute to the development of cancer-associated arterial as well as venous thrombosis[1]. Therefore, the Khorana score might be potentially useful for prediction of not only VTE but also ischemic stroke in cancer patients. We hypothesized that a combination of clinical features

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at the time of a cancer diagnosis would be a better tool than the Khorana score for assessment of the risk of ischemic stroke in these patients.

The aims of this study were as follows: to determine the combination of clinical features that has the best discrimination ability; to determine whether the Khorana score can predict ischemic stroke within 2 years of a cancer diagnosis; to identify the score with better discrimination ability; and to assess its usefulness in an independent large-scale validation cohort.

Results

Model development population

Of the 26,717 cancer patients included in the development cohort, 163 (0.61%) had an ischemic stroke within 2 years of their cancer diagnosis. Ischemic strokes were more common in male than female patients. These patients were more likely to have conventional risk factors for ischemic stroke (older age, hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, and a history of ischemic heart disease), stage IV cancer (22.1% versus 14.8%, $p < 0.01$), and increased levels of NLR and D-dimer than those without ischemic stroke. The clinical characteristics are compared between patients who experienced an ischemic stroke and those who did not in Table 1.

	Ischemic stroke ($N = 163$)	No stroke ($N = 26554$)	*P*-value
Age, years	72 [60–78]	66 [53–74]	*< 0.0001*
Male (%)	97 (59.5%)	13,449 (50.7%)	*0.0241*
Past medical history			
Hypertension (%)	87 (53.4)	8144 (30.7%)	*< 0.0001*
Diabetes mellitus (%)	32 (19.6%)	3422 (12.9%)	*0.0105*
Hyperlipidemia (%)	60 (36.8%)	5090 (19.2%)	*< 0.0001*
Atrial fibrillation (%)	33 (20.3%)	1971 (7.4%)	*< 0.0001*
Prior history of ischemic heart disease	62 (38.0%)	5091 (19.2%)	*< 0.0001*
Cancer status			
Cancer stage IV (%)	36 (22.1%)	3939 (14.8%)	*0.0095*
Adenocarcinoma (%)	72 (44.2%)	14,236 (53.6%)	*0.0160*
Cancer site			*< 0.0001*
Bladder (%)	2 (1.2%)	539 (2.0%)	
Bone (%)	1 (0.6%)	354 (1.3%)	
Breast (%)	7 (4.3%)	2881 (10.9%)	
Colon and rectum (%)	15 (9.2%)	2373 (8.9%)	
Esophagus (%)	12 (7.4%)	1848 (7.0%)	
Gallbladder (%)	2 (1.2%)	352 (1.3%)	
Hematopoietic (%)	14 (8.6%)	2317 (8.7%)	
Larynx (%)	8 (17%)	292 (1.1%)	
Liver (%)	6 (3.7%)	1045 (3.9%)	
Lung (%)	20 (12.3%)	1807 (6.8%)	
Oral (%)	10 (6.1%)	1075 (4.1%)	
Ovary (%)	6 (3.7%)	556 (2.1%)	
Pancreas (%)	13 (8.0%)	917 (3.5%)	
Prostate (%)	4 (2.5%)	1310 (4.9%)	
Renal (%)	4 (2.5%)	908 (3.4%)	
Skin (%)	3 (1.8%)	598 (2.3%)	
Stomach (%)	8 (4.9%)	2251 (8.5%)	
Thyroid (%)	22 (13.5%)	1240 (4.7%)	
Uterus (%)	8 (4.9%)	2504 (9.4%)	
Other (%)	5 (3.1%)	1387 (5.2%)	
Lab			
NLR	2.64 [1.74–4.50]	2.42 [1.72–3.53]	*0.00484*
D-dimer (μg/ml)	1.18 [0.45–3.83]	0.58 [0.29–1.51]	*< 0.0001*

Table 1. Baseline clinical characteristics of cancer patients with and without ischemic stroke in the University of Osaka Hospital cancer registry (development cohort). Data are shown as the median (interquartile range) or count (percentage). NLR, neutrophil-to-lymphocyte ratio.

Predictors of ischemic stroke within 2 years of a cancer diagnosis

Previous research has found that older age (≥ 75 years), hypertension, atrial fibrillation, stage IV cancer, adenocarcinoma histology, cancer in the lung, kidney, or pancreas, a higher NLR, and an elevated D-dimer level are associated with occurrence of ischemic stroke in cancer patients[1]. To develop the prediction model, we obtained cutoff values for the NLR (4.28) and D-dimer level (1.52 μg/ml) by receiver-operating characteristic curve analysis. Our univariate analysis confirmed that all the above-mentioned factors, except for adenocarcinoma histology, were independent predictors of ischemic stroke in the development cohort (Table S1).

Ischemic stroke prediction model

Next, we developed ischemic stroke prediction models by combining these parameters (Table 2). Figure 1 shows that model 3 (Fig. 1C), which included six parameters (*A*ge ≥ 75 years, *H*ypertension, *A*trial fibrillation, a higher *N*LR, an elevated *D*-dimer level, and *S*tage IV cancer) had the highest c-statistic (0.703), suggesting that this model had a moderate and acceptable discrimination ability. The optimal cutoff point for model 3 was 2. Therefore, we focused on model 3 for designation of the AHANDS score.

The khorana score could not accurately predict ischemic stroke in cancer patients

Next, we assessed the ability of the Khorana score to predict ischemic stroke in cancer patients. Based on the Khorana score[11], we divided the patients into a low-risk group (score 0, $n = 13{,}872$), an intermediate-risk group (score 1–2, $n = 11{,}820$), and a high-risk group (score ≥ 3, $n = 1025$). Table S2 showed the patients' clinical characteristics according to risk group. The proportions of patients with lung, renal, or pancreatic cancer, adenocarcinoma histology, and stage IV cancer were higher in the high-risk group than in the low-risk group. The high-risk group also had significantly higher NLR and D-dimer values. We then compared the discrimination ability of the Khorana score with that of the AHANDS score. As shown in Fig. 2, the performance of the AHANDS score was significantly superior to that of the Khorana score in the development cohort (c-statistic 0.703 vs. 0.54; $P < 0.0001$).

Validation test

We also assessed the discrimination ability of the AHANDS score in the external validation cohort, which included 31,881 cancer patients. The median age was 65 years (IQR 44, 73), and 17,249 (54.1%) of the patients were male. Ninety-nine of these patients had experienced an ischemic stroke within 2 years of their cancer diagnosis, indicating that the stroke rate was lower in the validation cohort than in the development cohort (0.31% vs. 0.61%, $p < 0.0001$) (Table S3). However, conventional risk factors for stroke, with the exception of atrial fibrillation, were more common in the validation cohort than in the development cohort. The clinical characteristics of the patients in the validation cohort are shown in Table S3. Figure 3A shows that the AHANDS score also had acceptable performance in the validation cohort (c-statistic 0.75).

Prediction performance of the AHANDS score in the development and validation cohorts

Next, we examined the ability of the AHANDS score to predict ischemic stroke. The patients were stratified into tertiles of risk according to the AHANDS score (low risk, 0–2; moderate risk, 3–4; and high risk, 5–6). In the development cohort, ischemic stroke occurred within 2 years of diagnosis of cancer in 0.57% of low-risk patients, 2.32% of moderate-risk patients, and 3.57% of high-risk patients (Fig. 4). In the external validation cohort, ischemic stroke occurred within 2 years of diagnosis of cancer in 0.21% of low-risk patients, 1.09% of moderate-risk patients, and 5.88% of high-risk patients (Fig. 4). These data indicated that a higher AHANDS score predicted a higher risk of future ischemic stroke in cancer patients.

Discrimination ability and performance of four clinical parameters

Overall, the AHANDS score had a moderate ability to identify high-risk patients. However, the AHANDS score includes not only clinical parameters but also the results of blood tests, including the NLR and D-dimer level.

Parameters	Model 1	Model 2	Model 3	Model 4	Model 5
Age > = 75 y	+ 1	+ 1	+ 1	+ 1	
Hypertension	+ 1	+ 1	+ 1	+ 1	
Atrial fibrillation	+ 1	+ 1	+ 1	+ 1	+ 1
Lung, renal, or pancreas cancers		+ 1		+ 1	
Adenocarcinoma histology		+ 1		+ 1	
NLR > = 4.28			+ 1	+ 1	
D-dimer > = 1.52			+ 1	+ 1	+ 1
Cancer stage IV	+ 1	+ 1	+ 1	+ 1	
Maximum score	4	6	6	8	2
C statics	0.673	0.628	0.703	0.676	0.648

Table 2. Development of prediction models. A point-based risk stratification model was created whereby + 1 point was allocated for each parameter for calculation of the risk of ischemic stroke. NLR, neutrophil-to-lymphocyte ratio.

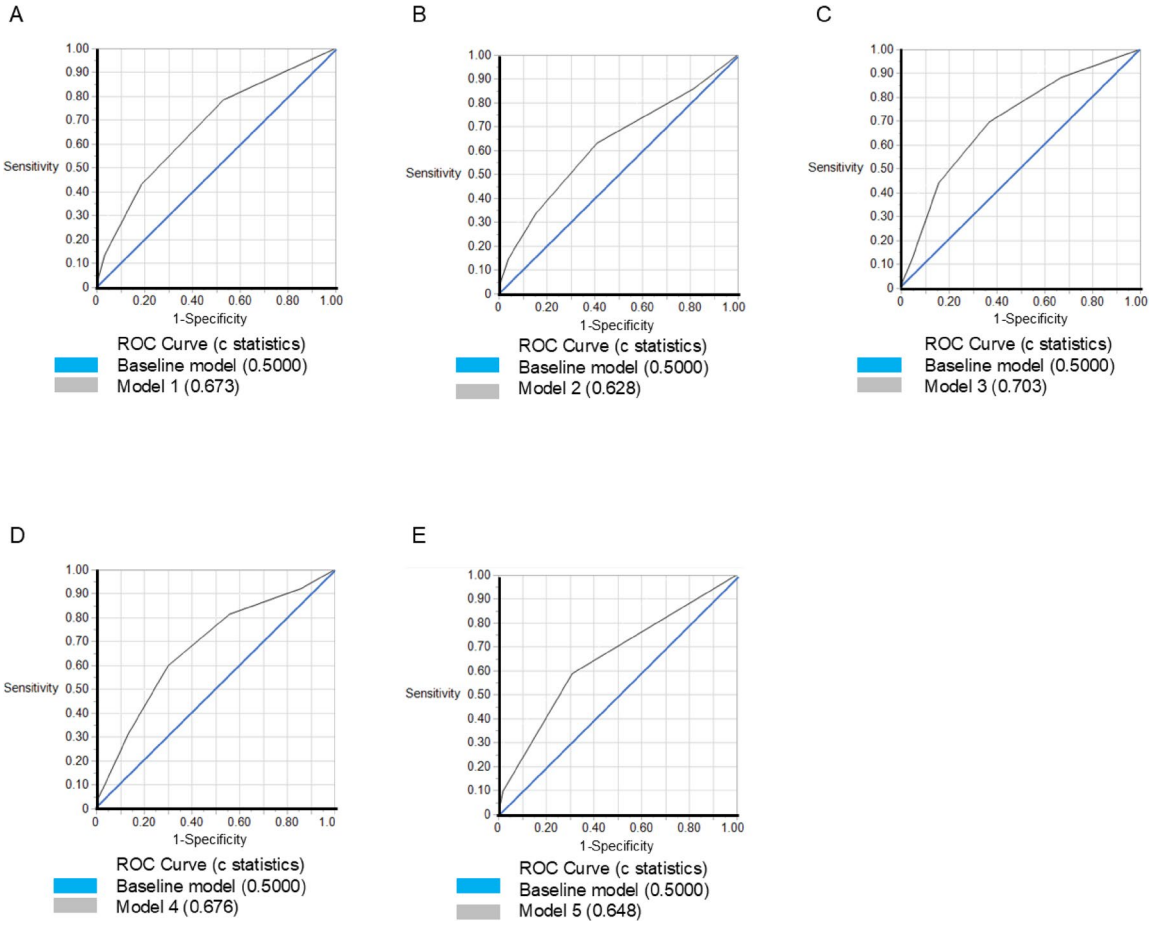

Fig. 1. Results of ROC curve analysis for each model in the development cohort. (**A**) Model 1 included four parameters (age ≥ 75 years, hypertension, atrial fibrillation, and stage IV cancer). (**B**) Model 2 included six parameters (the parameters in model 1 plus cancer site [lung, kidney, or pancreas] and adenocarcinoma). (**C**) Model 3 included the parameters in model 1 plus an NLR of ≥ 4.2 and a D-dimer level of ≥ 1.52 μg/ml. (**D**) Model 4 included the parameters in model 1 plus cancer site (lung, kidney, or pancreas), adenocarcinoma, an NLR of ≥ 4.28, and a D-dimer level of ≥ 1.52 μg/ml. (**E**) After stepwise logistic regression analysis, model 5 included atrial fibrillation and a D-dimer level of ≥ 1.52 μg/ml. In these all models, the total risk score was calculated by adding 1 point for each factor present. AUC, area under the curve; NLR, neutrophil-to-lymphocyte ratio; ROC, receiver-operating characteristic.

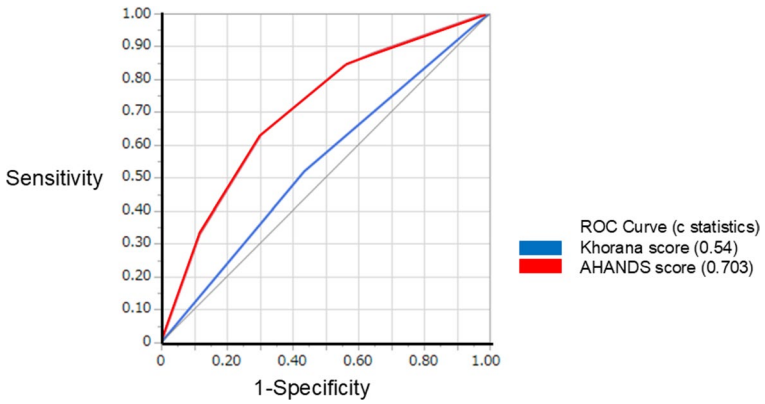

Fig. 2. Comparison of the AHANDS and Khorana score in the development cohort. The performance of the AHANDS score (red) was significantly superior to that of the Khorana score (blue) in the development cohort (c-statistic 0.703 vs. 0.54; p for difference < 0.0001).

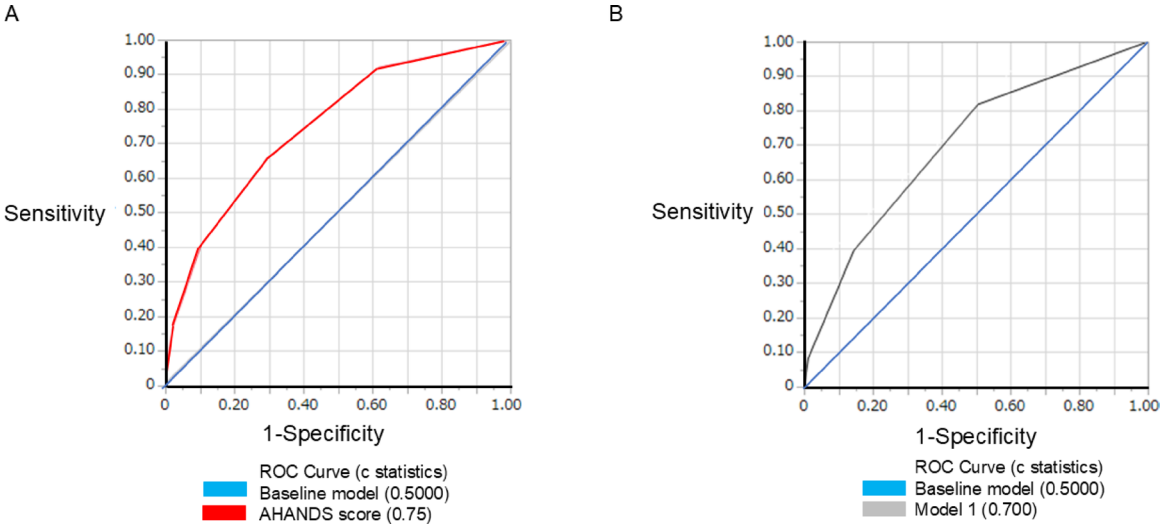

Fig. 3. Results of ROC curve analysis in the validation cohort. (**A**) The c-statistic for the AHANDS score (red) was 0.75. (**B**) Model 1 showed moderate discrimination (c-statistic 0.70).

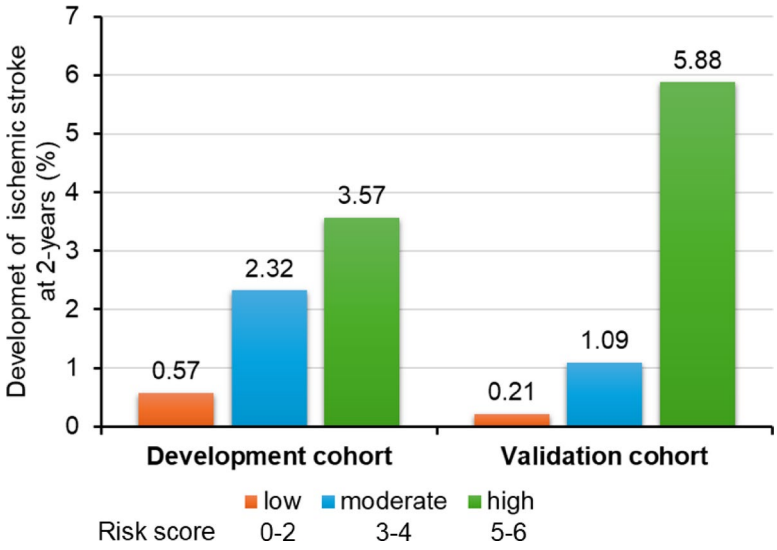

Fig. 4. Performance of the AHANDS score in the development and validation cohorts. Risk was categorized as low (0–2 points), moderate (3–4 points), or high (5–6 points). A higher score indicates a higher risk of developing ischemic stroke in cancer patients.

We examined the discrimination ability of model 1 in the validation cohort. Model 1 included only four clinical parameters (older age, hypertension, atrial fibrillation, and stage IV disease or distant metastasis at the time of cancer diagnosis) and had mild discrimination ability (c-statistic 0.673) (Fig. 1 and Table 1), indicating that it would be easy to use in practice.

Next, we examined the discrimination ability of model 1 in the validation cohort and its performance in predicting ischemic stroke. Interestingly, Fig. 3B shows that model 1 also had moderate discrimination ability in the validation cohort (c-statistic 0.700). However, compared with the AHANDS score, the patients who were considered high-risk using model 1 were less likely to develop ischemic stroke (AHANDS score vs. model 1; 3.57% vs. 2.40% for the development cohort and 5.88% vs. 2.88% for the validation cohort) (Fig. 4 and Fig. S1). These results suggested that the AHANDS score would be a superior risk prediction model.

Discussion

We have developed the AHANDS score, which is a novel risk assessment tool that can stratify the risk of ischemic stroke in cancer patients. The AHANDS score showed moderate and acceptable discrimination in both the development cohort (c-statistic 0.703) and the validation cohort (c-statistic 0.75) (Figs. 2 and 3A). Furthermore, the AHANDS score outperformed the Khorana score (c-statistic 0.54) in the development cohort (Fig. 2). When

cancer patients had an AHANDS score of ≥5 at the time of cancer diagnosis, which is considered high risk for ischemic stroke, 3.57%–5.88% had ischemic stroke within 2 years of their cancer diagnosis (Fig. 4). To our knowledge, this is the first clinical scoring system for ischemic stroke to be developed and validated in cancer patients.

Ischemic stroke is a serious event that is associated with increased morbidity and mortality in cancer patients[8]. Major barriers to improving clinical outcomes in these patients has been the inability to identify those at high-risk and an absence of prevention strategies. The exact pathophysiology of ischemic stroke in cancer patients remains unknown. However, activation of coagulation induced by cancer cells is suspected to play a key role in the development of ischemic stroke in these patients[1]. D-dimer is released during plasmin-mediated degradation of fibrin and is often secondary to activation of the coagulation system. Cancer patients with elevated D-dimer levels who develop ischemic stroke have more systemic metastasis[24], and an elevated D-dimer level is more likely in those with metastasis than in those without metastasis[25]. We speculate that an elevated D-dimer level and an advanced cancer stage are associated with activation of coagulation in cancer patients. It has been reported that patients with both an elevated D-dimer level and distant metastasis have a poorer prognosis than those without these features[25]. The post-treatment D-dimer level after anticoagulation therapy is an independent predictor of a poor prognosis in cancer patients with ischemic stroke[24,26]. These data suggest that reduction of the D-dimer level using anticoagulation therapy might help to improve outcomes.

The question arises regarding what type of primary prevention should be started if the AHANDS score can identify patients at high risk for ischemic stroke. Cancer patients with a Khorana score ≥ 3 are considered to be at high risk for VTE and are prescribed a direct oral anticoagulant or low-molecular-weight heparin for prevention. We consider that a direct oral anticoagulant or low-molecular-weight heparin would also be a useful choice for primary prevention of ischemic stroke in cancer patients. These anticoagulation therapies may be able to stabilize activation of coagulation, thereby decreasing the risk of ischemic stroke. However, cancer patients also have an increased the risk of bleeding complications[27]. Research in mouse models of human pancreatic cancer found that tumor-bearing mice had fewer platelet receptors and poorer platelet function, resulting in prolongation of bleeding time[28]. The mechanism of the increased bleeding risk in cancer patients is not fully understood. Further studies are needed to be able to prevent ischemic stroke and minimize the risk of bleeding. In addition, closer monitoring D-dimer levels and brain imaging might also be helpful to reduce the stroke events.

Contrary to expectations, adenocarcinoma histology showed a protective effect (OR 0.68, 95% CI 0.50–0.95, $p = 0.0166$). (Table S1) Then, we compared cancer sites between non-adenocarcinoma and adenocarcinoma in the development cohort. We found that adenocarcinoma group had a higher percentage of low-risk cancers (breast (19%), colorectal (16%), and prostate (9.1%) (data not shown). These differences in cancer sites might affect the results.

This study has several limitations. First, we could not obtain a medication history, including antithrombotic agents and chemotherapy, for inclusion in the statistical analysis. Some types of chemotherapy might increase the risk of thrombosis[29]. This possibility should be investigated in the future. Agents that increase the risk of stroke should be added to the prediction model. Second, our study cohorts comprised mainly Japanese patients, thereby restricting the generalizability of our findings to other groups of cancer patients. In particular, the generalizability of the AHANDS score to other populations awaits validation. Third, the incidences of ischemic stroke in the development cohort (0.61% per 2 years) and the validation cohort (0.31% per 2 years) are lower than in other studies (3.0% and 0.87% per 6 months)[2,17]. There is a possibility that some stroke patients were taken to other hospitals, resulting in missing data. We are now constructing a patient data network system linking hospitals in Osaka (Osaka Clinical Research network: OCR-net; https://www.hosp.med.osaka-u.ac.jp/home/chukaku/ocr_net/). Even if stroke patients are taken to other hospitals, OCR-net will be able to detect them and avoid missing data. We will cope with this problem using the OCR-net in future research.

On the other hand, the major strength of this study is the inclusion of a large cohort of patients for both the development cohort (26,717 patients) and an independent external validation cohort (31,881 patients). In addition, these cancer registries had a wide variety of cancer sites. We believe these advantages could increase the generalizability of AHANDS score.

In conclusion, we have developed and validated a novel risk assessment tool called the AHANDS score that can predict ischemic stroke in cancer patients. The AHANDS score would assist clinicians to assess the risk of ischemic stroke in cancer patients and allow us to guide future preventive intervention.

Methods

The study was approved by the Institutional Review Board of the University of Osaka Hospital (approval number 24049) and the Osaka International Cancer Institute (approval number 24051) and was performed in accordance with the Declaration of Helsinki. The need for informed consent was waived due to the retrospective nature of the study and an opt-out opportunity on the institutional website.

Study population

Development cohort

The risk prediction models were initially developed in the development cohort using information from the University of Osaka Hospital cancer registry, which includes data for patients diagnosed with cancer at the hospital and patients with cancer who came to the hospital after being diagnosed elsewhere. This registry includes data for 47,331 patients who were newly diagnosed with cancer between 2007 and 2020. The following exclusion criteria were applied: not followed up at the University of Osaka Hospital; diagnosis of a brain tumor because brain tumor is sometimes difficult to differentiate from ischemic stroke; incomplete cancer staging records; and no blood tests within the month following diagnosis of cancer. Data for a total of 26,717 patients were analyzed.

External validation cohort
An independent external validation cohort included patient data from the hospital-based cancer registry at Osaka International Cancer Institute, which includes data for 34,086 patients with a new diagnosis of cancer between 2011 and 2019. There is no overlap between development cohort and validation cohort. Data for a total of 31,881 patients were included in the analysis.

Predictors
The development cohort included the following data obtained from the electric medical records: sex, age at time of diagnosis of cancer, body mass index, a previous history of ischemic heart disease, cancer site, stage at time of diagnosis of cancer, tumor histology, and conventional risk factors for stroke using ICD-10 codes (hypertension (I10-I15), dyslipidemia (E78), diabetes mellitus (E10-E14), and atrial fibrillation (I48)). Blood test values, including D-dimer levels and NLR, were obtained within 1 month after diagnosis of cancer or registration. The NLR was calculated by dividing the number of neutrophils by the number of lymphocytes[19]. We could not obtain data on cancer stage from the Osaka International Cancer Institute for the validation cohort. Therefore, patients with distant metastasis at the time of their cancer diagnosis were considered to have stage IV disease.

Outcomes
The primary outcome measure was newly diagnosed ischemic stroke within 2 years of diagnosis of cancer. The date of occurrence of stroke was identified according to the algorithm[30]. Briefly, the algorithm indicates a stroke event when the diagnostic code is registered and a brain imaging has been performed within a day of diagnosis. Follow-up was terminated at the time of death, the last hospital visit, or 2 years after the cancer diagnosis, whichever came first.

Prediction model development
Five prediction models were constructed through discussion with study investigators. For models 1 to 4, we selected only clinical variables (Table 1). In model 5, we identified atrial fibrillation and an increased D-dimer level as possible clinical parameters by stepwise logistic regression analysis of the eight clinical items. To allow for calculation of the risk of ischemic stroke, we created a point-based risk stratification model in which + 1 point was allocated for each parameter (Table 1). Missing data was given o point.

Statistical analysis
The patient characteristics are shown as the count (percentage) or as the median (interquartile range [IQR]). Categorical variables were compared between the cohorts using the chi-squared test, and continuous variables were compared using the Wilcoxon test or Kruskal–Wallis test with the post hoc Dunn test. Laboratory test cutoff values, including for the NLR and D-dimer level, were calculated using receiver-operating characteristic curve analyses. Univariate logistic regression was performed to obtain an overall understanding of the predictive capacity of each variable. Model discrimination was assessed using the c-statistic. Previous work has suggested that a c-statistic of > 0.9 indicates high accuracy, 0.7–0.9 indicates moderate accuracy, 0.5–0.7 indicates low accuracy, and 0.5 indicates a chance result[31]. We defined a c-statistic of > 0.7 as an acceptable threshold. We also calculated the Youden's J index to determine the optimal probability cutoff. The individual scores were categorized into low-risk, moderate-risk, and high-risk groups to facilitate clinical interpretation. All statistical analyses were performed using JMP Pro 17.0.0 software (SAS Institute Inc., Inc., Cary, NC, USA). A p-value of < 0.05 was considered statistically significant.

Data availability
The data that support the findings of this study are available from the corresponding author on reasonable request.

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Author contributions

T.K. designed the study, the main conceptual ideas, and the proof outline. T.K. and Y.G. collected the data. Y.G., T.M., and I.M. were involved in gaining ethical approval and data analysis. T.M., J.K., H.K., T.S., and I.M. aided in interpreting the results and worked on the manuscript. H.M. supervised the project. T.K. wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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