STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	Association between the Khorana Risk Score and all-cause mortality in Japanese patients with gastric and colorectal cancer: A restrospective cohort study Page 1
		Men and patients with Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≥2 displayed a higher 2-year risk of death than women and those with ECOG PS 0–1 in the intermediate/high risk group for KRS. The higher the score, the higher the risk of early death; however, the relevance of this independent prediction decreased with longer survival. The overall survival (OS) of each patient was recorded via real-world follow-up and retrospective observations, and this study yielded the overall relationship between KRS and all-cause mortality. The prechemotherapy baseline of KRS was independently associated with all-cause mortality within 2 years; however, this independent predictive relationship weakened as survival time increased. Page 2-3
Introduction		
Background/rationale	2	The Khorana risk score (KRS) has poor predictive value for cancer-associated thrombosis in a single tumor type but is associated with early all-cause mortality from cancer. Evidence for the association between KRS and all-cause mortality in Japanese patients with gastric and colorectal cancer is limited. Page 1 lines 19-22
Objectives	3	To investigate whether KRS was independently related to all-cause mortality in Japanese patients with gastric and colorectal cancer after adjusting for other covariates and to shed light on its temporal validity. Page 2 lines 24-26
Methods		
Study design	4	The incidence of and mortality associated with gastric and colorectal cancers have reached the top five positions in Japan. Cancer-associated thrombosis (CAT) is one of the most dangerous complications and is directly related to patient prognosis. The Khorana risk score (KRS) is a risk scoring tool and has been internally and externally validated for stratifying thrombotic risks in patients with cancer. Studies on the relationship between KRS and all-cause mortality are limited. In addition, investigations in Asian populations are especially lacking, and the follow-up observation time for predicting early mortality is not long, which does not exclude the possibility that KRS possesses the ability to predict long-term survival. Page 3-4
Setting	5	Patients in the Gastroenterology Department of Sapporo General Hospital, Sapporo, Japan, were enrolled. The starting and ending dates of the enrollment were January 1, 2008 and January 5, 2015, respectively. The cutoff date for follow-up was May 31, 2016. Complete inclusion/exclusion criteria, collection of patient history, and diagnostic methods for CAT have been described in the study by Aonuma et al. The flowchart for the selection of the study cohort is depicted in Figure 1. The requirement for informed consent was waived owing to the retrospective nature of the study. The institutional review board of Affiliated Hospital of Jiaxing University approved this study. Page 4-5 lines 81-90, Figure 1
Participants	6	From January 2008 to May 2015, 512 patients received chemotherapy for

		gastrointestinal tumors in a hospital in Japan. Twelve patients were excluded because they had a CAT more than 1 month before their first chemotherapy. The cutoff date for follow-up was May 31, 2016. Regular hospital and telephone follow-up reviews were used. Page 4-5, Figure 1
		Complete inclusion/exclusion criteria, collection of patient history, and diagnostic methods for CAT have been described in the study by Aonuma et al. Page 4
Variables	7	The following were selected as covariates: (1) demographic data; (2) variables affecting the KRS or all-cause mortality have been reported in previous studies; and (3) variables based on our clinical experience. The full adjustment model was constructed using the following variables: (1) continuous variables: age (obtained at baseline); (2) categorical variables: sex, CAT, arterial thromboembolism (ATE), Eastern Cooperative Oncology Group Performance Status (ECOG PS), cancer type (GC: gastric cancer; CRC: colorectal cancer), pathological type, primary site surgery, adjuvant chemotherapy, single or multiple primary tumor, active cancer (AC), opportunity for diagnosis, central venous catheter (CVC) placement. Active cancer (AC) was defined as unresectable advanced gastric and colorectal tumors that recur during or after the completion of adjuvant chemotherapy and/or other unrelated malignancies. The opportunity for diagnosis was defined as the final clinical diagnosis of a patient based on the presentation of symptoms associated with CAT. Patients diagnosed with GC and CRC were treated according to the then-current ASCO or National Comprehensive Cancer Network guidelines, and who developed CAT were administered anticoagulation therapy. Page 5-6
Data sources/ measurement	8*	All the clinical data, including age, sex, cancer type, Eastern Cooperative Oncology Group Performance Status (ECOG PS) scale, histological subtypes, resection of primary site, Adj or non-Adj setting, single or multiple primary, central venous catheter (CVC) placement and interventions for CAT, were collected by reviewing electronic medical records. Khorana score of each patient, we also collected their haematologic data before initiating chemotherapy. CAT was mostly detected by reviewing reports of contrast-enhanced CT images performed for each patient during follow-up. Page 4 lines 89
Bias	9	There was no selection bias because this study included the entire GCC patients who started chemotherapy from January 2008 to May 2015 in a research institute in Japan, with the exception of patients who developed CAT more than 1 month before starting chemotherapy. Page 4, Figure 1
Study size	10	This retrospective study was conducted using data from the Dryad database. Patients in the Gastroenterology Department of Sapporo General Hospital, Sapporo, Japan, were enrolled. The starting and ending dates of the enrollment were January 1, 2008 and January 5, 2015, respectively. The cutoff date for follow-up was May 31, 2016. Page 4 lines 81-84
Quantitative variables	11	Step 1: To examine the association between KRS and all-cause mortality, univariate and multivariate Cox proportional hazards models were employed. Four models were constructed: crude model, no covariates were adjusted; model 1: only adjusted for

		sociodemographic data; model 2: model 1+ those considerable covariates ($p < 0.10$ or having significant clinical significance); model 3: all covariates. To ensure the robustness of the experimental results, a sensitivity analysis was simultaneously performed by converting the KRS to categorical variables and calculating the trend in p value. Step 2: Subgroup analyses were performed using the hierarchical Cox proportional hazards model. Continuous variables were initially converted to categorical variables according to the clinical cut point, and subsequently, an interaction test was performed. Tests for effect modification of subgroup indicators were followed by the likelihood ratio test. Step 3: The OS time of each group was recorded, and Kaplan–Meier (KM) survival curves were plotted to compare the median survival time of each group. Step 4: The multivariate Cox proportional hazards model was employed to calculate the risk ratios over a given number of years, and a trend graph was plotted. Page 6-7
Statistical methods	12	(a) Categorical variables were expressed as frequency or percentage. Chi-squared (categorical variables, normal distribution) or Krusckal-Wallis H test (skewed distribution) were used to test for differences among different KRS groups (clinical cut point). Single-factor and multi-factor tests, trend tests, and multi-model analysis were used.All analyses were performed using the statistical software packages R 3.3.2 (http://www.R-project.org, The R Foundation) and Free Statistics software version 1.7. A two-tailed test was performed and $p < 0.05$was considered statistically significant. Page 6-7
		(b) Subgroup analyses were performed using the hierarchical Cox proportional hazards model. Continuous variables were initially converted to categorical variables according to the clinical cut point, and subsequently, an interaction test was performed. Tests for effect modification of subgroup indicators were followed by the likelihood ratio test. Page 6-7
		(c) Data from the Dryad database were used in this study. No missing data. N/A
		(d) Data from the Dryad database were used in this study. No missing data. N/A
		(e) model 3: all covariates. To ensure the robustness of the experimental results, a sensitivity analysis was simultaneously performed by converting the KRS to categorical variables and calculating the trend in p value. Page 6 lines 129-132
Results		
Participants	13*	(a) A total of 500 participants were selected for the final data analysis (Figure 1 for the flow chart). Their median follow-up time was 22.0 months (Figure 3). Page 7 lines 146-147
		(b) According to the inclusion and exclusion criteria of this study, all the 500 patients included had completed the data statistics at various stages. Page 7
		(c) Figure 1 for the flow chart Figure 1
Descriptive data	14*	(a) The baseline characteristics of these participants are listed in table 1 based on the clinical grouping of the KRS. Their average age was 68.9 (62.5 ± 75.9) years, and 38.8% were women. There were 194 participants in the KRS low-risk group, 218 in the moderate-risk group, and 88 in the high-risk group. There were group differences

		among the three KRS groups in terms of cancer type, pathological type, primary site surgery, and CVC placement ($p < 0.001$); however, there were no statistically significant differences in terms of additional covariates (all p values > 0.05). Page 7 lines 147-154
		(b) Data from the Dryad database were used in this study. No missing data. N/A
		(c) Their median follow-up time was 22.0 months (Figure 3). Page 7 lines 147
Outcome data	15*	The overall survival (OS) time of each patient was recorded as of May 31, 2016. Page 4
Main results	16	(a) The univariate Cox proportional hazards model, revealed that sex, CAT, ATE, single or multiple primary tumor, thrombosis treatment, and opportunity for diagnosis were not associated with all-cause mortality. Moreover, cancer type, primary site surgery, and adjuvant chemotherapy were negatively associated with all-cause mortality ($p < 0.001$). In contrast, univariate analysis indicated that age ($p = 0.034$), KRS intermediate/high-risk group, ECOG PS, pathological type (others vs. well and mod), AC and CVC placement were positively correlated with all-cause mortality ($p < 0.001$). In this study, four models were constructed to analyze the independent effects of KRS on all-cause mortality within 2 years (univariate and multivariate Cox proportional hazards model). Multivariable-Adjusted Model 1: Adjusted for Age and Sex. Multivariable-Adjusted Model 2: Adjusted for Age, Sex, CAT, ECOG PS, Cancer type, Primary site surgery, Adjuvant chemotherapy, Active cancer and CVC. Multivariable-Adjusted Model 3: Adjusted for Age, Sex, CAT, ECOG PS, Cancer type, Pathological *type,* Primary site surgery, Adjuvant chemotherapy, Active cancer, Single or multiple primary, CVC, *Thrombosis t*reatment, Opportunity for Diagnosis Multiple factors that need to be adjusted include: single factor analysis $p < 0.1$, covariates with effect size changes of more than 10% after addition to the model and previously reported clinical significance. Page 8, Figure 2
		(b) Patients were classified into three risk categories based on the total risk model: low-risk group (score = 0), intermediate-risk group (score = 1-2), and high-risk group (score = ≥3). The remaining continuous variables are not classified. Page 5, Figure 1
		(c) Similar results were obtained for Model 2 (adjusted for significant covariates) and Model 3 (fully adjusted), showing a 45% increased risk of 2-year death in the moderate-risk group compared to the low-risk group (95%CI: 1.02 -- 2.06; $p = 0.041$). In contrast, there was a two-fold increase in high-risk groups (95%CI: 1.26-3.24; $p = 0.004$). Page 9
Other analyses	17	Age, sex, cancer type, primary site surgery, ECOG PS, CVC placement, CAT were used as stratification variables to examine the trend of effect sizes in these variables (Figure 2). No interactions were seen in these variables based on our a priori specification (all P values for interaction < 0.05). The p value of the trend test for the different models was < 0.05, which suggesting the same trend effect and stable study results (Table 3).

		Page 9
Discussion		
Key results	18	The findings from this study indicated that the KRS was independently associated with all-cause mortality within 2 years in Japanese patients with GC and CRC before receiving chemotherapy. Subgroup analysis aided in better understanding the trend of KRS and all-cause mortality in different populations. Men and patients with ECOG PS ≥2 displayed a higher 2-year risk of death than women and those with ECOG PS 0–1 in the intermediate/high risk group for KRS. Hence, the higher the score, the higher the risk of early death; however, the relevance of this independent prediction decreased with longer survival. The OS of each patient was recorded via real-world follow-up and retrospective observations, and this study yielded the overall relationship between KRS and all-cause mortality. Page 11 lines 228-237
Limitations	19	There are certain limitations in this study: (1) This research was a retrospective observational cohort study with selection bias and bias for unknown confounders, which might have affected the findings. (2) The study population comprised Japanese patients with gastrointestinal tract tumors. Therefore, generalizability and extrapolation of the results are somewhat lacking. (3) Regarding the time effect of KRS in predicting mortality, only the approximate period could be derived and not the exact time. (4) As patients in whom CAT occurred > 1 month before the start of chemotherapy were excluded, the results cannot be applied to these individuals. Page 15
Interpretation	20	This study has several advantages: (1) The sample size was larger compared with previous similar studies. (2) This study observed and recorded the OS of each patient with GC and CRC in Japan and analyzed it entirely as well as by time period. (3) This study is the first to explain the temporal validity of KRS at the baseline in predicting cancer-related mortality. (4) The effect modifier factor analysis enhanced the use of data and yielded stable conclusions in different models and subgroups. Page 15
Generalisability	21	The study population comprised Japanese patients with gastrointestinal tract tumors. Therefore, generalizability and extrapolation of the results are somewhat lacking Page 15
Other information		
Funding	22	We are grateful to Dr. Jie Liu of Department of Vascular and Endovascular Surgery, Chinese PLA General Hospital for his contribution to the statistical support, study design consultations, and comments regarding the manuscript. This study was supported by key medical disciplines jointly established by the Zhejiang province and Jiaxing City: Oncology(2023-SSGJ-001) and Jiaxing Key Laboratory of Tumor Radiotherapy (2021-zlzdsys). Aonuma AO, Nakamura M, Sakamaki K, Murai T, Matsuda C, Itaya K, Sone T, Yagisawa M, Koike Y, Endo A, Tsukuda Y, Ono Y, Nagasaka A, Nishikawa S, Yamanaka T, Sakamoto N. (2019), Data from: Incidence of cancer-associated thromboembolism in Japanese gastric and colorectal cancer patients receiving chemotherapy: a single-institutional retrospective cohort analysis (Sapporo CAT study), Dryad, Dataset, https://doi.org/10.5061/dryad.84s01sv Page 16-18

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.