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Incidence of cancer-associated thromboembolism in Japanese gastric and colorectal cancer patients receiving chemotherapy: a single-institutional retrospective cohort analysis (Sapporo CAT study)

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ABSTRACT

Objective Few data regarding the incidence of cancer-associated thromboembolism (TE) are available for Asian populations. We investigated the incidence of TE (TEi) and its risk factors among gastric and colorectal cancer (GCC) patients received chemotherapy in a daily practice setting.

Design A retrospective cohort study.

Setting A single-institutional study that used data from Sapporo City General Hospital, Japan, on patients treated between January 2008 and May 2015.

Participants Five hundred Japanese GCC patients who started chemotherapy from January 2008 to May 2015.

Primary and secondary outcome measures TE was diagnosed by reviewing all the reports of contrast-enhanced CT performed during the follow-up period. All types of thrombosis detected by CT or additional imaging tests, such as venous TE, arterial TE and cerebral infarction, were defined as TE. Medical records of all identified patients were reviewed and potential risk factors for TE, including clinicopathological backgrounds, were collected. We defined the following patients as 'active cancer'; patients with unresectable advanced GCC, cancer recurrence during or after completing adjuvant chemotherapy and/or presence of other malignant tumours.

Results Of the 500 patients, 70 patients (14.0%) developed TE during the follow-up period. TEi was 9.2% and 17.3% in GCC patients, 18.1% and 3.5% in active and non-active cancer patients, and 24.0% and 12.9% in multiple and single primary, respectively. Multivariate logistic regression analysis showed that colorectal cancer (CRC) (OR 2.371; 95% CI 1.328 to 4.233), active cancer (OR 7.593; 95% CI 2.950 to 19.543) and multiple primary (OR 2.527; 95% CI 1.189 to 5.370) were independently associated with TEi.

Conclusion TEi was 14.0% among Japanese GCC patients received chemotherapy, and was significantly higher among patients with CRC, active cancer and multiple primary than among those with gastric cancer, non-active cancer and single primary, respectively.

Trial registration number UMIN000018912.

Strengths and limitations of this study

- This is the first retrospective cohort study investigating the incidence of thromboembolism (TEi) among gastric and colorectal cancer (GCC) patients received chemotherapy in a Japanese community hospital's daily practice setting.
- There was no selection bias because this study included the entire GCC patients who started chemotherapy from January 2008 to May 2015 in our institution, with the exception of patients who developed TE more than 1 month before starting chemotherapy.
- The uncontrolled design and the small number of cohort limited the power of statistical analyses.
- TEi might be underreported because the diagnosis of TE is mostly based on reviewing CT images, scanned at different time points.
- More prospective studies are warranted to determine the extent of TE more precisely in Asian cancer patients, and to evaluate the thromboembolic potential of different chemotherapeutic agents, treatment combinations and patient-related factors.

INTRODUCTION

Incidence of thromboembolism (TEi) in cancer patients is at least fourfold greater than in patients without cancer,[1–3] and the risk is exacerbated by chemotherapy, up to sevenfold.[1 4 5] The rate of cancer-associated and chemotherapy-associated TEi reportedly ranges from 0.4% to 43%,[2 6 7] but varies widely

between studies, depending on factors, such as cancer types, stage and patient's surgical history. Also, the theory that cancer patients who developed TE have shorter survival than those without TE is supported by many studies and databases.[6 8 9] Several guidelines for the treatment and prophylaxis of cancer-associated TE have been published in Western countries[4 10 11] because of the high rate of TEi and its negative impact on survival in cancer patients, but few data are available regarding cancer-associated TE in Asia, especially in Japanese patients.

Although TE is apparently less common in Asian populations than in Western populations,[12] TEi in Asian populations has reportedly increased because of increased awareness and diagnostic procedures.[13–15] Moreover, although gastric cancer (GC) carries a high risk for TE among cancer types[16] and is more common in Japan than in Western countries,[17] very few studies of TEi in Japanese GC patients have been published.[18 19] Therefore, we conducted a retrospective cohort analysis of TEi in Japanese gastric and colorectal cancer (GCC) patients who received chemotherapy. We also analysed the associations between TEi and several clinicopathological factors, and the prognostic impact of TEi.

PATIENTS AND METHODS

Study design

This was a single-institution retrospective cohort study to evaluate TEi in GCC patients who received chemotherapy in Sapporo City General Hospital, Japan. The protocol was performed in accordance with the Declaration of Helsinki, the Japanese ethical guidelines on clinical research and the Ethical Guidelines for Clinical Studies, and was registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (protocol ID UMIN000018912) .

Participants and data collection

We investigated all patients who started chemotherapy as adjuvant (Adj) or non-Adj treatment for GC and colorectal cancer (CRC) between January 2008 and May 2015 using our hospital data warehouse. We included patients who developed TE within 1 month before starting chemotherapy and excluded patients who developed TE more than 1 month before starting chemotherapy. The cut-off date for follow-up was 31 May 2016. 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 TE, were collected by reviewing electronic medical records. To evaluate Khorana score of each patient, we also collected their haematologic data before initiating chemotherapy. As other diagnostic methods, such as venous ultrasound and venography, were rarely performed in the study population, TE was mostly detected by reviewing reports of contrast-enhanced CT images performed for each patient during follow-up. All types of TE identified on CT, whether symptomatic or not, were recorded as TEi.

Khorana score

Khorana score is a predictive scoring system for venous TE (VTE) risk in patients who receive chemotherapy, and incorporates five parameters: primary cancer site, platelet count, haemoglobin and/or use of erythropoiesis-stimulating agents, leucocyte count and body mass index (BMI).[20 21] In this scoring system, GC and pancreatic cancer are categorised as 'very high risk'; lung, lymphoma, gynaecological and genitourinary cancer as 'high risk'; and breast, CRC, prostate and other cancers as 'others'. Two points are assigned for a 'very high risk' cancer site, and one point each for 'high-risk', platelet count≥350×10^9/L, haemoglobin level<100 g/L, use of erythropoiesis-stimulating agents, leucocyte count>11×10^9/L and BMI≥35 kg/m^2. Finally, patients are divided into three risk categories based on the total score from the risk model: low (score 0), intermediate (score 1–2) and high (score ≥3).

Patients with active cancer

To investigate whether TE is caused by chemotherapy, with or without cancer, we compared the subgroups of patients with 'active cancer' to those with 'non-active cancer'. Patients who received chemotherapy for unresectable advanced GCC suffered cancer recurrences during or after completing Adj chemotherapy, and/or had other unresected malignant tumours were considered to have 'active cancers'. The 'non-active cancer' group included patients who had no cancer recurrence after completing Adj chemotherapy and had no other cancers.

Single and multiple primary

'Single primary' patients were those with only one malignant tumour in a single organ; whereas "multiple primary" patients were those who had two or more cancers, either in the same or different organs in an individual patient (eg, multiple primary carcinomas of the colon or double cancers in the neck and oesophagus).

Outcome assessment

The primary objective of this study was to investigate TEi in GCC patients who received chemotherapy. We subsequently evaluated the association between TEi and several clinicopathological factors, including non-Adj setting, active cancer and multiple primary. To verify whether TEi is associated with poor prognosis in cancer patients, we also assessed the effect of TEi on overall survival (OS).

Statistical analysis

Patient characteristics were summarised using descriptive statistics. The associations between baseline characteristics and TEi were evaluated using Mann-Whitney U test and χ^2 test, and $p<0.05$ was considered significant. All variables were subsequently analysed using a multivariate logistic regression model with a forward-selection procedure (p values for entry=0.05), considering the number

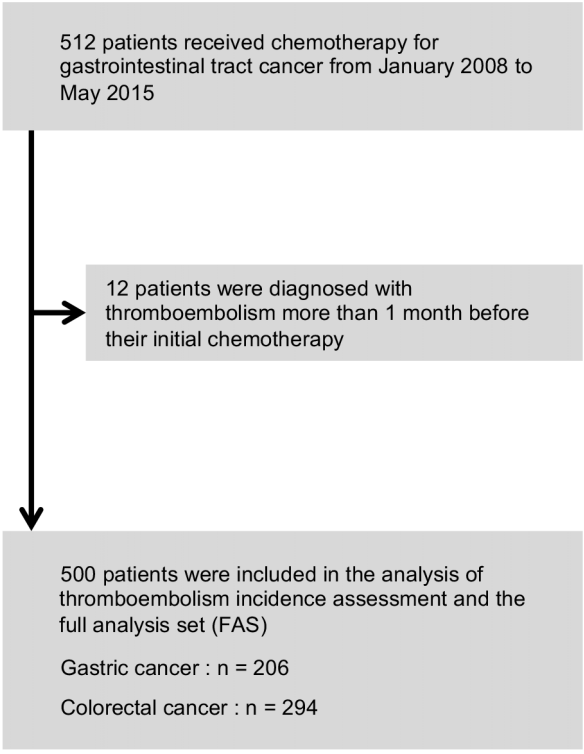

Figure 1 CONSORT diagram.

and similarities of variables. The prognostic impact of TEi was assessed using Kaplan-Meier survival analysis. OS was calculated from the beginning of chemotherapy to the date of death or last news. Survival curves for those with and without TE were compared using the log-rank test. Multivariate Cox regression analysis was used to calculate HRs and 95% CIs, and to estimate the effect of candidate risk factors, including TEi, on OS. All statistical calculations were performed using SPSS V.22.0 for Windows.

Patient and public involvement

The research question and outcome measures were developed from the high frequency of TE in cancer patients in our daily practice, and by the lack of its data among Japanese patients. As we simply extracted the data from medical records, patients and the public were not involved in the design, recruitment or conduct of the study. The results of this study will be disseminated to the public in the form of journal articles, conference presentations and seminars.

RESULTS

Patient characteristics

Overall, 512 patients received chemotherapy for GCC from January 2008 to May 2015 in our institution. Twelve patients were excluded because they developed TE more than 1 month before their initial chemotherapy (figure 1). Our final study cohort included 500 patients; 38.8% (n=194) were women, and 61.2% (n=306) were men, with a median age of 69.0 years (range 21.1–89.1 years). Patients' baseline characteristics are detailed in table 1. Their median follow-up time was 22.0 months.

TE incidence

Among the 500 GCC patients included in this study, TE was detected in 70 (14.0%) patients. The rate of TEi was 9.2% (19/206) in GC patients and 17.3% (51/294) in CRC patients, with a statistically significant difference (p=0.010). TEi did not significantly differ by Khorana risk scores; 10.2% (9/88) developed TE in the high-risk group, 12.8% (28/218) in the intermediate-risk group and 17.0% (33/194) in the low-risk group.

TEi details are described in table 2. TE related to CVC was observed in 34 patients, which was most common. Among the 70 patients who developed TE, only 7.1% (n=5) were symptomatic, and included one patient who died because of mesenteric ischaemia and acute arterial occlusion of lower limbs; two patients were forced to discontinue chemotherapy because they needed intensive treatments for TE; one patient developed hemiplegia resulting from middle cerebral artery infarction, which delayed the start of chemotherapy; and one patient developed exertional dyspnoea, and ended chemotherapy when interstitial pneumonia and pulmonary thrombosis were diagnosed by CT. All patients with TE did not receive treatment because of poor general condition or their primary doctor's decision; only 42.9% (n=30) received therapeutic interventions for TE. The incidence of arterial TE was 2.2% (11/500). The rate of venous-system TE (such as deep vein thrombosis, pulmonary embolism (PE), portal vein TE and CVC-related TE) was 12.0% (60/500; data not shown).

Associations between TEi and variables

Table 1 presents a significantly higher TEi in patients with CRC, non-Adj setting, active cancers, multiple primary and CVC placement than in those with GC, Adj setting, non-active cancers, single primary and no CVC placement, respectively. In multivariate logistic regression analysis, CRC, better ECOG PS, active cancer and multiple primary were significantly associated with high TEi (table 3). No variable was associated with the incidence of arterial TE, and CRC, better ECOG PS and active cancer were significantly associated with high venous TEi (data not shown).

Impact of TEi on survival

Median OS was 31.0 months (95% CI 24.4 to 37.6 months) in cancer patients with TE, and 35.0 months (95% CI 26.9 to 43.1 months) in those without TE, with a statistically significant difference (HR=1.399; 95% CI 1.02 to 1.92; figure 2). Interestingly, however, although ECOG PS (0/1 vs >2), cancer type (GC vs CRC), treatment setting (Adj vs non-Adj), cancer activity status (active vs non-active cancer) and Khorana risk group (high/intermediate vs low) were identified as independent prognostic factors for survival in multivariate Cox regression analysis, TEi

Table 1 Demographic and baseline characteristics and incidence of thromboembolism (TE) associated with each variable in univariate analysis

Variable	All patients (n=500) No. of patients	TE (+), n=70 No. of patients (%)	TE (–), n=430 No. of patients (%)	P values*
Age, years				
Median	69.0	66.1	69.6	0.568
Range	21.1–89.1	27.1–89.1	21.1–89.0	
Sex				
Female	194	20 (10.3)	174 (89.7)	0.058
Male	306	50 (16.3)	256 (83.7)	
ECOG PS				
0–1	449	67 (14.9)	382 (85.1)	0.078
≥2	51	3 (5.9)	48 (94.1)	
Cancer type				
Gastric cancer	206	19 (9.2)	187 (90.8)	0.010
Colorectal cancer	294	51 (17.3)	243 (82.7)	
Histological subtype				
Well and Mod	317	49 (15.5)	268 (84.5)	0.365
Others	169	21 (12.4)	148 (87.6)	
Unknown	14	0 (0)	14 (100.0)	
Resection of primary site				
No	122	18 (14.8)	104 (85.2)	0.782
Yes	378	52 (13.8)	326 (86.2)	
Adj or non-Adj setting				
Non-Adj	306	54 (17.6)	252 (82.4)	0.003
Adj	194	16 (8.2)	178 (91.8)	
Patients with active cancer (AC)				
Non-AC	141	5 (3.5)	136 (96.5)	<0.0001
AC	359	65 (18.1)	294 (81.9)	
Single or multiple primary				
Single	450	58 (12.9)	392 (87.1)	0.032
Multiple	50	12 (24.0)	38 (76.0)	
Khorana score				
High	88	9 (10.2)	79 (89.8)	0.254
Intermediate	218	28 (12.8)	190 (87.2)	
Low	194	33 (17.0)	161 (83.0)	
CVC placement				
No	168	14 (8.3)	154 (91.7)	0.009
Yes	332	56 (16.8)	276 (83.1)	

*P values: Mann-Whitney U test or χ^2 test.
Adj, adjuvant; CVC, central venous catheter; Mod, moderately differentiated adenocarcinoma; ECOG PS, Eastern Cooperative Oncology Group Performance Status; Well, well-differentiated adenocarcinoma.

and OS were not significantly associated (HR=1.031; 95% CI 0.74 to 1.44; table 4).

DISCUSSION

The present study demonstrated that TE incidence was 14.0% among Japanese GCC patients who received chemotherapy, and that CRC, active cancer and multiple primary were independently associated with higher TEi. No significant association was found between TEi and poor prognosis.

To the best of our knowledge, this is the first study to assess TEi and its risk factors among Japanese GCC patients. The TEi in our study was not greatly different from those reported in Western countries,[2 6 7] which implies that cancer-associated and chemotherapy-associated TE is common in both Asians and Caucasians. The

Table 2 Overall TE incidence (n=500)

Variable	No. of patients (%)
All TE	70 (14.0)
Types of TE (n=70)	
VTE alone	49 (70.0)
ATE alone	9 (12.9)
PE alone	6 (8.6)
VTE+PE	3 (4.3)
ATE+PE	1 (1.4)
VTE+ATE	1 (1.4)
Appendage	1 (1.4)
Symptomatic or incidental TE	
Symptomatic	5 (7.1)
Incidental	65 (92.9)
Treatment for TE	
No treatment	40 (57.1)
Warfarin alone	12 (17.1)
Edoxaban alone	5 (7.1)
UFH	3 (4.3)
CV port removal	2 (2.9)
IVC filter+Warfarin+UFH	2 (2.9)
Danaparoid sodium	1 (1.4)
Ozagrel sodium	1 (1.4)
Already receiving oral anticoagulants	4 (5.7)

ATE, arterial thromboembolism; CV, central venous; IVC, inferior vena cava; PE, pulmonary embolism; TE, thromboembolism; UFH, unfractionated heparin; VTE, venous thromboembolism.

Table 3 Multivariate analysis of associations between TE incidence and clinical variables

Variable	OR (95% CI)	P values
ECOG PS		
0–1 (n=449)	1	0.014
≥2 (n=51)	0.217 (0.064 to 0.729)	
Cancer type		
GC (n=206)	1	0.004
CRC (n=294)	2.371 (1.328 to 4.233)	
Presence of active cancer		
Non-AC (n=141)	1	<0.0001
AC (n=359)	7.593 (2.950 to 19.543)	
Single or multiple primary		
Single (n=450)	1	0.016
Multiple (n=50)	2.527 (1.189 to 5.370)	

P values: multivariate logistic regression analyses.
AC, active cancer; CRC, colorectal cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GC, gastric cancer; TE, thromboembolism.

number of symptomatic patients was very small, which may be because most patients had good performance status and/or because most of the TEi were incidentally found by follow-up CT. Also, only 14.3% (n=10) of patients developed PE, which may have been underestimated because screening for PE, such as D-dimer measurement, was not routinely performed.

Various risk factors for cancer-associated TE have been reported, including age, histological subtype, stage and chemotherapy.[5 12 22 23] Certain types of cancer have also been identified as risk factors for VTE, including pancreas, stomach and lung cancer.[5 16 24] However, inconsistent with previous reports, our results showed that TEi was significantly higher in CRC patients compared with GC patients. Several reasons could explain this finding. Compared with the GC group, the CRC group included more patients with high-grade tumours, CVC placement and bevacizumab use, which are common risk factors for cancer-associated TE.[22 25 26] Racial differences may also affect risk factors for cancer-associated and chemotherapy-associated TE between Caucasians and Asians. Previous epidemiological studies of ethnicity and TE have shown that the prevalence of certain genetic risk factors differed somewhat between Caucasians and Asians. For example, factor V Leiden mutation is highly prevalent in Caucasians and almost non-existent in Asians.[27] Differences in blood levels of coagulation factors, such as plasma fibrinogen, factor VIIc and factor VIIIc, have also been reported.[28] Except for these heritable risk factors, according to previous studies, most acquired risk factors for TE, such as cancer and immobility, appear to be similar between

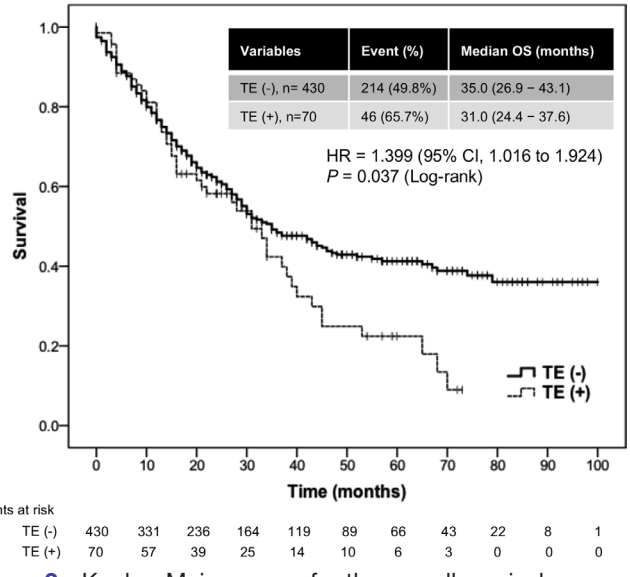

Figure 2 Kaplan-Meier curves for the overall survival (OS). Patients who developed TE had significantly worse OS compared with patients without TE (median OS 31.0 vs 35.0 months, respectively; log-rank p=0.037). TE, thromboembolism.

Caucasians and Asians.[1 29 30] However, Yu *et al*[31] reported that among Taiwanese patients, prostate cancer, lung cancer, sarcoma and metastasis of unknown origin were associated with higher VTE incidence, which differed slightly from the high-risk cancers reported previously in Western countries.[5 24] Chew *et al*[12] also reported that African–Americans with uterine cancer were more likely to develop VTE, whereas those with lung cancer were less likely to develop VTE. Considering these reports, the present study implies that high-risk cancer types for TE may differ among races, especially between Caucasians and Asians. However, this is difficult to conclude, because Asian cancer patients comprised a minority of the subjects in most epidemiological studies[12 32 33]; therefore, the data are limited. Larger data sets for cancer-associated and chemotherapy-associated TE and investigation of the risk factors in Asian populations are necessary.

Cancer patients with distant metastases have a higher risk of TE than those without distant metastases.[3 12 25] Cancer-associated TE and biologic aggressiveness of the tumours are linked, because pathways for coagulation and fibrinolysis intersect with those of tumour growth and metastasis.[34] Aggressive tumours can grow faster and are more likely to develop metastatic dissemination, which results in higher incidence of TE.[12 22] Active cancer was associated with high TEi in the present study, suggesting that tumour aggressiveness is reflected in both distant metastases and early recurrence. To examine whether cancer spread, such as multiple primary cancers and double cancers, is associated with high TEi, we also conducted a subgroup analysis of single/multiple primary and TEi. The results showed that TEi was significantly higher in patients with multiple primary tumours than in those with single primary tumours, which implies that cancer spread is a risk factor for TE. To the best of our knowledge, no previous studies have evaluated the TEi among cancer patients with early recurrence or multiple primary cancers. However, prospective studies are needed to analyse the associations between TEi and early recurrence, and spread of cancer.

Khorana score did not discriminate between patients with and without TE in our study population, even in the subanalysis that focused only on TE originating in the venous system. This may reflect the small sample size. Also, because BMI>35 kg/m^2 is rare among Asian patients, Khorana score may have a limited value in this population. In other words, when considering the added possibility of racial difference in risk factors, a modified scoring system for Asian cancer patients is needed to stratify their TE risk. The Vienna CATS score[21] is the expansion of the original Khorana score with the inclusion of two additional biomarkers, D-dimer and soluble P-selectin, and has been demonstrated to predict cancer patients at a very high risk for VTE more precisely than Khorana score do.[21 35] However, as neither D-dimer and P-selectin were routinely measured at the beginning of chemotherapy in our institution, we were not able to validate the Vienna risk scoring system in the present study. Additional predictors for cancer-associated TE that can be conveniently measured in clinical settings are required.

TE in cancer patients should not be underestimated because of its null impact on survival. TE is a major cause of death in cancer patients[36]; in fact, one of our patients died of acute arterial occlusion of lower limbs and mesenteric ischaemia. Also, cancer patients who develop TE tend to have shorter survival than those who do not develop TE.[6 8 9 12] Both incidental and symptomatic VTE have been significantly associated with high mortality rate in cancer patients.[37 38] In contrast to the previous reports, the Kaplan-Meier curve in our study showed only a trend towards an association between OS and TEi, and the results were not statistically significant in multivariate Cox regression analysis (although for univariate Cox regression analysis: p=0.037 (log-rank) and HR=1.399, 95% CI 1.02 to 1.92). This may reflect the influence of confounding factors. Table 3 shows that CRC, better ECOG PS, active cancer and multiple cancers were independently associated with high TEi. In multivariate Cox regression analysis, worse ECOG PS, GC, non-Adj status, active cancer and Khorana score≥1 were independent prognostic factors (table 4). Therefore, the analysis of TEi and OS might have been confounded by active cancer. In other words, because active cancer was associated with both high TEi and shorter OS, patients

Table 4 Cox multivariate regression model for survival

Variable	HR (95% CI)	P values
TE		
TE (–), n=430	1	0.860
TE (+), n=70	1.031 (0.739 to 1.438)	
ECOG PS		
0–1, n=449	1	<0.0001
≥2, n=51	3.414 (2.392 to 4.873)	
Cancer type		
GC, n=206	1	0.005
CRC, n=294	0.613 (0.436 to 0.863)	
Adj or non-Adj		
Adj, n=194	1	0.008
Non-Adj, n=306	1.779 (1.161 to 2.726)	
Presence of active cancer		
Non-AC, n=141	1	<0.0001
AC, n=359	11.216 (5.527 to 22.759)	
Khorana risk group		
Low, n=194	1	0.027
High/intermediate, n=306	1.492 (1.047 to 2.125)	

P values: multivariate Cox regression model.
AC, active cancer; Adj, adjuvant chemotherapy; CRC, colorectal cancer; GC, gastric cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; TE, thromboembolism;

who developed TE appeared to have a poorer prognosis than those without TE. Another possible explanation is that different cancer types with different prognosis are mixed in this analysis. Khorana score≥1 was also found to be independently associated with poor OS in our study. Several studies have reported the clinical usefulness of Khorana score to predict mortality in cancer patients.[39–41] However, few such studies include Asian patients,[42] and further assessment is necessary to validate the value of Khorana score in predicting TE and mortality among Asian cancer patients.

The pathways of tumour growth, metastasis and hypercoagulation in cancer patients overlap and interact with each other, which leads to TE and reduced survival.[22 34 43] Researchers have hypothesised that preventing and treating TE in cancer patients can inhibit these pathways, and thereby improve patients' prognosis.[44–46] Clinical practice guidelines regarding prophylaxis and treatment of cancer-associated VTE have been published.[4 10 11 47 48] However, whether the management of cancer-associated TE could be equalised across all races remains unclear, because there are differences in genetic, somatometric and dietary backgrounds that may affect the biological mechanisms of TE. Also, racial differences in sensitivity to antithrombotic drugs, such as warfarin,[49] have been reported. Therefore, more large, well-designed and prospective clinical studies are required to evaluate the safety and efficacy of antithrombotic therapy for TE and its effect on survival for Asian cancer patients.

Our study has several limitations. First, the retrospective and uncontrolled design limits the conclusions that can be drawn. We also obtained several results that were contrary to previous reports, such as higher TEi in CRC patients than in GC patients and no significant association between TEi and OS; the reasons for these differences are difficult to conclude. Associations between TEi and treatment characteristics (such as chemotherapy dose, use of vascular endothelial growth factor targeted agents and treatment duration) were also difficult to analyse, because the data size was not large enough to assess each type of chemotherapy separately and accurate information for the onset of TE was unclear. To assess these associations, larger prospective studies which investigate TE by scheduled screening examinations in Asian cancer patients are needed. The second limitation is the possibility of underreporting the TEi rate. Diagnosis of TE was mostly based on reviewing CT images, and most CT images were from chest to pelvis, scanned at different time points. However, it is not practical to perform a universal screening test, such as compression ultrasound or CT venography, for every patient prior to initiating chemotherapy. It is important to develop a screening system that can be easily performed in clinical situations for stratifying cancer patients according to their TE risk. Finally, the sample size was small, and the observation period was very short. However, there are two strengths in this single-institutional small cohort study. First, there was no selection bias; we identified all of the GCC patients who received chemotherapy using our database, and all were included in this study except those who developed TE more than 1 month before starting chemotherapy. Second, we were able to review every patient's record repeatedly, which enabled to collect every patient's follow-up data and assured the data certainty. While our study cannot make strong conclusions and requires larger confirmatory studies, it will provide new research questions and problems which can be used to design future studies.

CONCLUSION

To the best of our knowledge, this is the first study to evaluate the incidence and risk factors for TE among Japanese GCC patients who received chemotherapy. Because data are limited for Asian patients, consensus guidelines published in Western countries may not be entirely applicable to Asian populations. Further data accumulation and large, prospective studies are needed to establish the best management of TE in Asian cancer patients.

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