Risk of thromboembolism in patients with gastric cancer

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Directed by Professor Eun-Cheol Park

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This certifies that the Doctoral Dissertation of Ji Sung Yoo is approved.

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ABSTRACT

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Purpose: The aim of our study was to define epidemiological relationships and evaluate the risk of thromboembolism (TE) in patients with new diagnoses of gastric cancers in South Korea using population-based cohort data.

Methods: This cohort study used population-based data from the Korean National Health Insurance Service between 2005 and 2015. The study included 4,093 patients with a new primary diagnosis of gastric cancer who had undergone treatment and were aged 20 years and older. To determine the effect of treatment modality on gastric cancer, we divided the patients into five groups: only endoscopic submucosal dissection (ESD), only subtotal gastrectomy, only total gastrectomy, surgery with other treatment (chemotherapy or chemo-radiation) and other treatment (palliative chemotherapy or chemo-radiotherapy). The occurrence of venous thromboembolism (VTE), defined as deep vein thrombosis, or pulmonary thromboembolism and arterial thromboembolism (ATE), defined as diagnosis of ischemic stroke or myocardial infarction, was measured. To identify the

effect of specified risk factors on the development of TE, VTE or ATE after treatment in gastric cancer patients, we used the Cox proportional hazard model to perform a survival analysis. Kaplan-Meier survival curves with log-rank tests were used to compare the incidence of TE between patient groups according to treatment. Subgroup analyses were performed based on treatment modalities and follow-up duration after diagnosis.

Results: The development of TE was associated with only subtotal gastrectomy (HR, 1.456; p=0.0154), only total gastrectomy (HR, 1.676; p=0.0062), surgery with other treatment (HR, 2.336; p=0.0002) and other treatment (chemotherapy or chemo-radiotherapy) (HR, 1.888; p=0.0016) compared with only ESD. The development of TE was associated with the age groups of 60~69 years (HR, 2.852; p=0.0014), 70-79 years (HR, 3.864; p<0.0001) and 80 years or older (HR, 6.262; p<0.0001) compared with under 40 years; in addition, the development of TE was associated with high Charlson Comorbidity Index (CCI) (4 or more) (HR, 1.542; p=0.0001) compared with low CCI (2 or less). When TE was divided into VTE and ATE, only subtotal gastrectomy (HR, 3.124; p=0.0159), only total gastrectomy (HR, 4.272; p=0.0022), surgery with other treatment (HR, 10.178; p<0.0001) and other treatment (HR, 12.215; p<0.0001) modality were significantly associated with VTE compared with only ESD. However, risk factors for the development of ATE were not significantly associated with the group of treatment modality. With respect to the association between the development of TE and treatment modality by follow-up duration, the significant greatest excess risk was seen at six months in the only subtotal gastrectomy, only total gastrectomy and other treatment groups in VTE. In surgery with other treatment, the hazard of VTE increased over time. The increased risk of VTE

incidence was sustained until five years in all treatment modalities. The risk of ATE occurrence was significantly increased within one year after diagnosis for only subtotal gastrectomy group and two years after diagnosis for only total gastrectomy group, whereas the occurrence of ATE was not associated with surgery with other treatment and other treatment groups.

Conclusions: In gastric cancer patients who have undergone treatment, the development of TE was associated with the treatment modality. The occurrence of VTE was more commonly associated with the treatment modalities than that of ATE. In gastric cancer patients who underwent gastrectomy, surgery with other treatment, and other treatment (compared to ESD), old age and high comorbidity were independent risk factors. The patients faced a substantially increased short-term and long-term risk of VTE, while for ATE, the patients faced only a short-term risk in the only gastrectomy group.

Key words: risk factor, arterial thrombosis, venous thrombosis, gastric cancer

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I. INTRODUCTION

In South Korea, more than 200,000 patients were newly diagnosed with cancer in 2017. The 5-year survival rate for all cancers had increased from 42.9% for patients diagnosed between 1993 and 1995 to 70.4% for those diagnosed between 2013 and 2017 due to improvements in early detection and treatment.[1] Cancer often induces a hypercoagulable state. This is due to various intrinsic and extrinsic mechanisms, including the secretion of procoagulant substances by tumor cells, endothelial dysfunction caused by the release of inflammatory cytokines from native immune cells, and complications of cancer therapy.[2] As a result, patients with cancer frequently experience arterial and venous thromboembolic (TE) events.

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE), is a common complication and leading cause of death in cancer patients.[3] Patients with cancer have an increased risk of venous thrombosis, especially in the first few months after diagnosis and in the presence of distant metastases.[4] Among the risk factors identified as contributors to VTE in cancer patients, the primary tumor site strongly affects the occurrence of VTE.[4,5] Gastric

cancer is associated with a high incidence of TE events.[5-7] Recent studies have shown that VTE is an independent predictor of mortality among patients with gastric cancer,[8,9] and thus, western guidelines for the treatment and prophylaxis of cancer-associated TE have been published.[10,11]

Arterial thromboembolism (ATE)-related events such as ischemic heart disease and stroke are the leading causes of death and disability worldwide.[12] Clinical series have suggested that ATE events may be common in patients with cancer.[13-16] Recent studies using population-based data have shown that patients with incident cancer face a substantially increased short-term risk of ATE. The 6-month cumulative incidence of ATE was 4.7% in patients with cancer compared with 2.2% in control patients using American population-based data.[17] In this study, excess risk varied by cancer type and gastric cancer had a high risk of 6.5%.[17] In a Taiwan population-based study, lung cancer was shown to be associated with an increased risk of subsequent stroke within one year after diagnosis for men and two years after diagnosis for women.[18] Several review studies have shown that the characteristics of cancer-related stroke are very distinct from those of conventional stroke.[19,20] Embolism caused by cancer-related coagulopathy is the important mechanism underlying cancer-related stroke.[19-21] Nevertheless, incident cancer has not been established as an independent risk factor for ATE, and patients with cancer do not routinely receive therapies to prevent myocardial infarction (MI) and stroke.[17]

Coupled with the clear association between metastatic disease and the development of TE, this finding suggested that the biological aggressiveness of the cancer may be the risk factor associated with the development of TE.[5,17] However, it is also possible that cancer treatment such as major surgery, chemotherapy, or radiation treatment, may contribute to the high incidence of TE in the early months following the diagnosis of cancer.[5]

Despite gastric cancer showing a high risk for VTE or ATE among cancer types[5,17] and being the most common type of cancer in South Korea,[1] there have been few studies on the incidence of TE in patients with gastric cancer, especially ATE, and population-based data are particularly scarce. The aim of our study was to define epidemiological relationships and evaluate the risk of TE in patients with new diagnoses of gastric cancers in South Korea using population-based cohort data.

II. MATERIALS AND METHODS

1. Study population

The National Health Insurance Service-National Sample Cohort (NHIS-NSC) is a population-based cohort established by the NHIS in South Korea. From the target population a representative sample cohort of 1,025,340 participants was randomly selected, comprising 2.2% of the total eligible Korean population in 2002.[22] These participants were followed for 13 years until 2015 unless the participants' eligibility was disqualified due to death or emigration.[22] The cohort comprised four databases; participants' insurance eligibility, medical treatments, medical care institutions and general health examinations.[22] The insurance eligibility database contained 14 variables including information on the participant's identity and socioeconomic variables such as gender, residential area, type of health insurance, level of income, disability registered, birth and death.[22]

This study was a retrospective cohort study using the NHIS-NSC 2005–2015 in South Korea. Our study population included all patients aged 20 years and older with a gastric cancer diagnosis and who had undergone treatment from January 1, 2005 to December 31, 2015. This study received institutional review board approval (National Cancer Center, Korea; NCC2018-0140).

2. Gastric cancer study group

Cancer cases consisted of all patients aged 20 years and older who were diagnosed with gastric cancer and treated for gastric cancer from January 1, 2005 to December 31, 2015. A diagnosis of gastric cancer was determined by the International Classification of Diseases 10th Revision (ICD-10) code and ICD-10 codes are as follows: gastric (C16.0 to C16.9). C codes are carefully reviewed by the NHIS

because they have implications for additional insurance benefit for patients in South Korea.[23] We excluded patients who were diagnosed with gastric cancer but did not receive treatment and patients who were diagnosed with other cancers within five years of being diagnosed with gastric cancer. To minimize ascertainment bias and restrict our evaluation to first-ever VTE and ATE cases, we excluded patients who were diagnosed with DVT, PTE, MI or ischemic stroke in the year before cancer diagnosis. After applying the exclusion criteria, a total 4,093 patients were eligible for this study.

Because we wanted to analyze about the effect of treatment modality on TE and there are no stages information of cancer in NHIS-NSC, we divided gastric cancer patients into five groups according to treatment method referring to Korean Practice Guideline for Gastric Cancer.[24] According to the Korean Practice Guideline for Gastric Cancer, "endoscopic submucosal dissection (ESD) had been used as a minimally invasive treatment modality for early gastric cancer, considered as the first-line treatment modality for early gastric cancer with well or moderately differentiated tubular adenocarcinoma or papillary adenocarcinoma with tumor size ≤2 cm, confined to the mucosal layer, and without ulcers in the tumor since lesions were found to have had a very low-risk of lymph node (LN) metastasis. Surgical resection was recommended if the tumor was outside of the endoscopic resection indications. Standard surgery was defined as a total or subtotal gastrectomy with D2 lymph node dissection (LND). Adjuvant chemotherapy (S-1 or capecitabine plus oxaliplatin) was recommended in patients with pathological stage II or III gastric cancer after curative surgery with D2 LND. Adjuvant chemoradiation could be considered in patients with incomplete resection. Palliative first-line platinum/fluoropyrimidine combination was recommended in patients with locally advanced unresectable or metastatic gastric cancer if the patient's performance status and major organ functions were preserved. Palliative radiotherapy (RT) could be considered for the alleviation of tumor-related symptoms or to improve survival."

Therefore, we divided patient into 5 groups: only ESD, only subtotal gastrectomy, only total gastrectomy, surgery with other therapy (chemotherapy or chemo-radiotherapy), and other therapy (palliative chemotherapy or chemo-radiotherapy)

For the selection of ESD, total or subtotal gastrectomy patients, we used the NHIS reimbursement codes. NHIS reimbursement codes for ESD were removal or ablation (Q7651), mucosal resection and submucosal resection (Q7652), and endoscopic submucosal dissection (QZ933). The NHIS reimbursement codes that refer to gastric resection are shown in Table 1. For the selection of chemotherapy, we used adjuvant chemotherapy drug code (including S-1 or capecitabine plus oxaliplatin) and palliative first-line chemotherapy drug code, platinum/fluoropyrimidine combination (including fluorouracil and oxaliplatin, capecitabine and oxaliplatin, fluorouracil and cisplatin, capecitabine and cisplatin).

Table 1. Korean National Health Insurance Service reimbursement codes for surgery in gastric cancer

Reimbursement code		**Surgery type**
LND (+)	LND (-)	
Q2533	Q2536	Total gastrectomy (abdominal approach)
Q2534	Q2537	Total gastrectomy (thoracic and abdominal approach)
Q2594	Q0251	Subtotal gastrectomy (partial)
Q0252	Q0253	Subtotal gastrectomy (distal)
Q0254	Q0255	Subtotal gastrectomy (pylous preserving)
Q0258	Q2598	Subtotal gastrectomy (proximal resection)

LND, lymph node dissection

3. **Outcome measurements**

The follow-up duration started on the index date and lasted until VTE, ATE, withdrawal from NHIS, death, or December 31, 2015, whichever came first. VTE was defined as presence of DVT or PTE and ATE was defined as diagnosis of ischemic stroke or MI. DVT was identified using the ICD-10 codes I80.1–2, I81, and I82.2–I82.9, and PTE was identified using the ICD-10 code I26. MI was identified using the ICD-10 codes I21.0, I21,1, I21,2, I21,3, I21,4, and I21,9 (acute MI) and I22.0, I22.1, I22.8, and I22.9 (subsequent MI). We did not include angina. Ischemic stroke was identified using the ICD-10 codes I63.0-I63.9. The NHIS reimbursement codes used to search for VTE and ATE are shown in Table 2.

Table 2. International Classification of Diseases codes used for defining thromboembolism

	ICD-10
Venous thromboembolism	
Deep vein thromboembolism	I80.1-I80.2, I81, I82.2-I82.9
Pulmonary thromboembolism	I26
Arterial thromboembolism	
Myocardial infarction (acute MI and subsequent MI)	I21.0, I21,1, I21,2, I21,3, I21,4, I21,9 & I22.0, I22.1, I22.8, I22.9
Ischemic stroke	I63.0 to 63.9

ICD, International Classification of Diseases; MI, myocardial infarction

Other independent variables included the Charlson comorbidity index (CCI), sex, age (10-year interval), residential area (capital, metropolitan, or other regions), household income (four categories), and disability. The income level was classified as less than 30% (low income), 31–60%, 61–90%, and more than 91% (high income). The year of study entry referred to the year corresponding to the date of the cohort entry. CCI was calculated by scoring the comorbid conditions that could affect

patients' health outcomes, and by categorizing them into four groups, from 1 (low risk) to 4 or more (high risk).

4. Statistical analysis

Descriptive statistics were used to evaluate baseline characteristics. To identify the effect of the specified risk factors on the development of TE, VTE or ATE after treatment in gastric cancer patients, we used the Cox proportional hazards model to perform survival analysis. After adjusting for other independent variables, we performed subgroup analyses to identify the associations of DVT, PTE, MI, and ischemic stroke with the treatment modality using the Cox proportional hazards model. And these analyses were performed by follow-up duration after diagnosis (six months, one year, two years, three years and five years). We used log-rank test and Kaplan-Meier survival curve to compare incidence of TE between patient groups according to treatment. A significance level of 0.05 was selected.

III. RESULTS

1. General characteristics of study population

In total, 4,093 patients met the eligibility criteria; 66.7% were male. Table 3, Table 3-1 and Table 3-2 show the characteristics of patients. The classification of patients according to the treatment modality was as follows: ESD (17.6%), only subtotal gastrectomy (50.7%), only total gastrectomy (13.8%), gastrectomy with other (10.7%), and other treatment (7.3%). Age distribution was as follows: under 39 years old (5.0%), 40–49 years old (15.3%), 50–59 years old (27.2), 60–69 years old (29.3%), 79–79 years old (19.3%), and over 80 years old (4.0%).

Table 3. General characteristics of study population for total, venous and arterial thromboembolism

Variables	TE event				*p*-value	Venous TE				*p*-value	Arterial TE				*p*-value
	Yes		No			Yes		No			Yes		No		
	N	%	N	%		N	%	N	%		N	%	N	%	
Patient classification															
ESD	52	7.2	668	92.8	0.0154	5	0.7	715	99.3	<.0001	47	6.5	673	93.5	0.0008
Only subtotal gastrectomy	244	11.8	1,830	88.2		50	2.4	2,024	97.6		194	9.4	1,880	90.6	
Only total gastrectomy	66	11.7	498	88.3		19	3.4	545	96.6		47	8.3	517	91.7	
Surgery with other treatment	51	10.8	387	89.2		30	6.8	408	93.2		21	4.8	417	95.2	
Other treatment	32	11.8	265	88.2		19	6.4	278	93.6		13	4.4	284	95.6	
Sex															
Male	303	11.1	2,425	88.9	0.4951	80	2.9	2,648	97.1	0.7006	223	8.2	2,505	91.8	0.3018
Female	142	10.4	1,223	89.6		43	3.2	1,322	96.8		99	7.3	1,266	92.7	
Age (years)															
≤39	10	4.9	194	95.1	<.0001	5	2.5	199	97.5	0.1903	5	2.5	199	97.5	<.0001
40-49	35	5.6	591	94.4		11	1.8	615	98.2		24	3.8	602	96.2	
50-59	95	8.5	1,019	91.5		35	3.1	1,079	96.9		60	5.4	1,054	94.6	
60-69	154	12.9	1,044	87.1		39	3.3	1,159	96.7		115	9.6	1,083	90.4	
70-79	121	15.4	667	84.6		24	3.0	764	97.0		97	12.3	691	87.7	
≥80	30	18.4	133	81.6		9	5.5	154	94.5		21	12.9	142	87.1	
Income level															
≤30th percentile	100	11.8	744	88.2	0.0374	28	3.3	816	96.7	0.1991	72	8.5	772	91.5	0.1068
31-60th percentile	99	10.0	890	90.0		22	2.2	967	97.8		77	7.8	912	92.2	
61-80th percentile	82	9.1	823	90.9		28	3.1	877	96.9		54	6.0	851	94.0	
81-90th percentile	57	10.2	500	89.8		13	2.3	544	97.7		44	7.9	513	92.1	
≥91st percentile	107	13.4	691	86.6		32	4.0	766	96.0		75	9.4	723	90.6	

Types of insurance coverage															
Medical-aid	35	21.3	129	78.7	<.0001	6	3.7	158	96.3	0.7495	29	17.7	135	82.3	<.0001
NHI, self-employed	138	10.0	1,236	90.0		38	2.8	1,336	97.2		100	7.3	1,274	92.7	
NHI, employee	272	10.6	2,283	89.4		79	3.1	2,476	96.9		193	7.6	2,362	92.4	
Disability															
With	52	14.7	302	85.3	0.0158	15	4.2	339	95.8	0.1554	37	10.5	317	89.5	0.0588
Without	393	10.5	3,346	89.5		108	2.9	3,631	97.1		285	7.6	3,454	92.4	
Charlson Comorbidity Index (excluded cancer)															
≤2	187	9.0	1,886	91.0	<.0001	50	2.4	2,023	97.6	0.0005	137	6.6	1,936	93.4	0.0025
3	109	10.6	919	89.4		25	2.4	1,003	97.6		84	8.2	944	91.8	
≥4	149	15.0	843	85.0		48	4.8	944	95.2		101	10.2	891	89.8	
Residence area															
Capital area	148	9.7	1,381	90.3	0.0043	43	2.8	1,486	97.2	0.2335	105	6.9	1,424	93.1	0.0203
Metropolitan	101	9.6	952	90.4		26	2.5	1,027	97.5		75	7.1	978	92.9	
Others	196	13.0	1,315	87.0		54	3.6	1,457	96.4		142	9.4	1,369	90.6	
Location of medical institution at first treatment															
Capital area	245	10.4	2,121	89.6	0.3400	76	3.2	2,290	96.8	0.1764	169	7.1	2,197	92.9	0.1304
Metropolitan	125	11.2	996	88.8		25	2.2	1,096	97.8		100	8.9	1,021	91.1	
Others	75	12.4	531	87.6		22	3.6	584	96.4		53	8.7	553	91.3	
Types of medical institution at first treatment															
Tertiary hospital	284	10.0	2,542	90.0	0.0353	83	2.9	2,743	97.1	0.9019	201	7.1	2,625	92.9	0.0246
General hospital	157	12.8	1,070	87.2		39	3.2	1,188	96.8		118	9.6	1,109	90.4	
Others	4	10.0	36	90.0		1	2.5	39	97.5		3	7.5	37	92.5	
Total	445	10.9	3,648	89.1		123	3.0	3,970	97.0		322	7.9	3,771	92.1	

TE, thromboembolism; ESD, endoscopic submucosal dissection; N, number; NHI, national health insurance

Table 3-1. General characteristics of study population for deep vein thrombosis and pulmonary thromboembolism

Variables	DVT				*p*-value	PTE				*p*-value
	Yes		No			Yes		No		
	N	%	N	%		N	%	N	%	
Patient classification										
ESD	2	0.3	718	99.7	<.0001	3	0.4	717	99.6	<.0001
Only total gastrectomy	36	1.7	2,038	98.3		14	0.7	2,060	99.3	
Only subtotal gastrectomy	12	2.1	552	97.9		7	1.2	557	98.8	
Surgery with other treatment	17	3.9	421	96.1		13	3.0	425	97.0	
Other treatment	11	3.7	286	96.3		8	2.7	289	97.3	
Sex										
Male	49	1.8	2,679	98.2	0.4688	31	1.1	2,697	98.9	0.7488
Female	29	2.1	1,336	97.9		14	1.0	1,351	99.0	
Age (years)										
≤39	3	1.5	201	98.5	0.5022	2	1.0	202	99.0	0.4991
40-49	7	1.1	619	98.9		4	0.6	622	99.4	
50-59	22	2.0	1,092	98.0		13	1.2	1,101	98.8	
60-69	27	2.3	1,171	97.7		12	1.0	1,186	99.0	
70-79	14	1.8	774	98.2		10	1.3	778	98.7	
≥80	5	3.1	158	96.9		4	2.5	159	97.5	
Income level										
≤30th percentile	19	2.3	825	97.7	0.8625	9	1.1	835	98.9	0.0082
31-60th percentile	16	1.6	973	98.4		6	0.6	983	99.4	
61-80th percentile	19	2.1	886	97.9		9	1.0	896	99.0	
81-90th percentile	10	1.8	547	98.2		3	0.5	554	99.5	
≥91st percentile	14	1.8	784	98.2		18	2.3	780	97.7	

Types of insurance coverage										
Medical aid	2	1.2	162	98.8	0.8021	4	2.4	160	97.6	0.1376
NHI, self-employed	27	2.0	1,347	98.0		11	0.8	1,363	99.2	
NHI, employee	49	1.9	2,506	98.1		30	1.2	2,525	98.8	
Disability										
With	8	2.3	346	97.7	0.6101	7	2.0	347	98.0	0.0974
Without	70	1.9	3,669	98.1		38	1.0	3,701	99.0	
Charlson Comorbidity Index (excluded cancer)										
≤2	30	1.4	2,043	98.6	0.0506	20	1.0	2,053	99.0	0.0007
3	21	2.0	1,007	98.0		4	0.4	1,024	99.6	
≥4	27	2.7	965	97.3		21	2.1	971	97.9	
Residence area										
Capital area	25	1.6	1,504	98.4	0.0226	18	1.2	1,511	98.8	0.7127
Metropolitan	13	1.2	1,040	98.8		13	1.2	1,040	98.8	
Others	40	2.6	1,471	97.4		14	0.9	1,497	99.1	
Location of medical institution at first treatment										
Capital area	48	2.0	2,318	98.0	0.1039	28	1.2	2,338	98.8	0.8336
Metropolitan	14	1.2	1,107	98.8		11	1.0	1,110	99.0	
Others	16	2.6	590	97.4		6	1.0	600	99.0	
Types of medical institution at first treatment										
Tertiary hospital	56	2.0	2,770	98.0	0.6226	27	1.0	2,799	99.0	0.3355
General hospital	22	1.8	1,205	98.2		17	1.4	1,210	98.6	
Others	0	0.0	40	100.0		1	2.5	39	97.5	
Total	78	1.9	4,015	98.1		45	1.1	4,048	98.9	

DVT, deep vein thrombosis; PTE, pulmonary thromboembolism; ESD, endoscopic submucosal dissection; N, number; NHI, national health insurance

Table 3-2. General characteristics of study population for myocardial infarction and ischemic stroke

Variables	MI				*p*-value	Ischemic stroke				*p*-value
	Yes		No			Yes		No		
	N	%	N	%		N	%	N	%	
Patient classification										
ESD	17	2.4	703	97.6	0.0787	30	4.2	690	95.8	0.028
Only subtotal gastrectomy	81	3.9	1,993	96.1		113	5.4	1,961	94.6	
Only total gastrectomy	20	3.5	544	96.5		27	4.8	537	95.2	
Surgery with other treatment	8	1.8	430	98.2		13	3.0	425	97.0	
Other treatment	7	2.4	290	97.6		6	2.0	291	98.0	
Sex										
Male	94	3.4	2,634	96.6	0.3167	129	4.7	2,599	95.3	0.6321
Female	39	2.9	1,326	97.1		60	4.4	1,305	95.6	
Age (years)										
≤39	3	1.5	201	98.5	0.0072	2	1.0	202	99.0	<.0001
40-49	14	2.2	612	97.8		10	1.6	616	98.4	
50-59	24	2.2	1,090	97.8		36	3.2	1,078	96.8	
60-69	50	4.2	1,148	95.8		65	5.4	1,133	94.6	
70-79	34	4.3	754	95.7		63	8.0	725	92.0	
≥80	8	4.9	155	95.1		13	8.0	150	92.0	
Income level										
≤30th percentile	30	3.6	814	96.4	0.5359	42	5.0	802	95.0	0.0003
31-60th percentile	36	3.6	953	96.4		41	4.1	948	95.9	
61-80th percentile	32	3.5	873	96.5		22	2.4	883	97.6	
81-90th percentile	16	2.9	541	97.1		28	5.0	529	95.0	
≥91st percentile	19	2.4	779	97.6		56	7.0	742	93.0	

Types of insurance coverage										
Medical-aid	7	4.3	157	95.7	0.7542	22	13.4	142	86.6	<.0001
NHI, self-employed	44	3.2	1,330	96.8		56	4.1	1,318	95.9	
NHI, employee	82	3.2	2,473	96.8		111	4.3	2,444	95.7	
Disability										
With	15	4.2	339	95.8	0.2728	22	6.2	332	93.8	0.1341
Without	118	3.2	3,621	96.8		167	4.5	3,572	95.5	
Charlson Comorbidity Index (excluded cancer)										
≤2	54	2.6	2,019	97.4	0.0185	83	4.0	1,990	96.0	0.1169
3	34	3.3	994	96.7		50	4.9	978	95.1	
≥4	45	4.5	947	95.5		56	5.6	936	94.4	
Residence area										
Capital area	41	2.7	1,488	97.3	0.1423	64	4.2	1,465	95.8	0.0006
Metropolitan	43	4.1	1,010	95.9		32	3.0	1,021	97.0	
Others	49	3.2	1,462	96.8		93	6.2	1,418	93.8	
Location of medical institution at first treatment										
Capital area	61	2.6	2,305	97.4	0.0086	108	4.6	2,258	95.4	0.679
Metropolitan	51	4.5	1,070	95.5		49	4.4	1,072	95.6	
Others	21	3.5	585	96.5		32	5.3	574	94.7	
Types of medical institution at first treatment										
Tertiary hospital	81	2.9	2,745	97.1	0.1125	120	4.2	2,706	95.8	0.1594
General hospital	50	4.1	1,177	95.9		68	5.5	1,159	94.5	
Others	2	5.0	38	95.0		1	2.5	39	97.5	
Total	133	3.2	3,960	96.8		189	4.6	3,904	95.4	

MI, myocardial infarction; ESD, endoscopic submucosal dissection; N, number; NHI, national health insurance

2. Incidence of thromboembolism by follow-up duration

Table 4 shows the incidence of TE by follow-up duration. The 2-year incidence was 5.6%, 2.1%, and 3.5% for TE, VTE, and ATE, respectively. The 5-year incidence was 9.0%, 2.7%, and 6.3% for TE, VTE, and ATE, respectively.

Table 4. Incidence of thromboembolism by follow-up duration

	Incidence (%)				
	6 months	**1 year**	**2 years**	**3 years**	**5 years**
Total TE	2.8	4.0	5.6	7.1	9.0
Venous TE	1.0	1.7	2.1	2.4	2.7
DVT	0.8	1.2	1.4	1.6	1.7
PTE	0.2	0.4	0.7	0.8	1.0
Arterial TE	1.8	2.3	3.5	4.7	6.3
MI	1.1	1.3	1.7	2.2	2.6
Ischemic stroke	0.7	1.0	1.8	2.5	3.7

TE: thromboembolism; DVT: deep vein thrombosis; PTE, pulmonary thromboembolism; MI: myocardial infarction

Figure 1–3 shows the Kaplan-Meier survival curve to compare incidence of TE between patient groups according to treatment. Vertical lines indicate incidence of TE, and horizontal lines indicate observation years. The incidence of TE and VTE was significantly associated with treatment modality (p=0.0031 and p<0.0001). The association between incidence of ATE and treatment modality was not significant (p =0.5532).

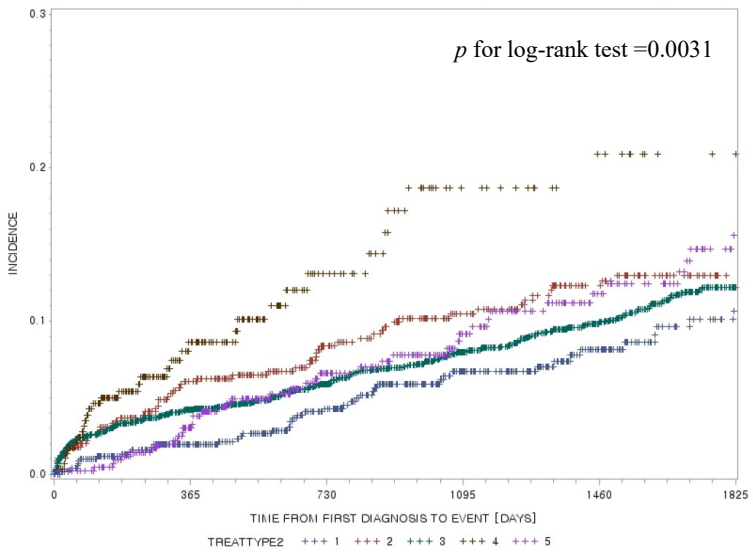

Figure 1. Kaplan-Meier survival curves for total thromboembolism

1, endoscopic submucosal dissection; 2, only total gastrectomy; 3, only subtotal gastrectomy; 4, other treatment; 5, surgery with other treatment

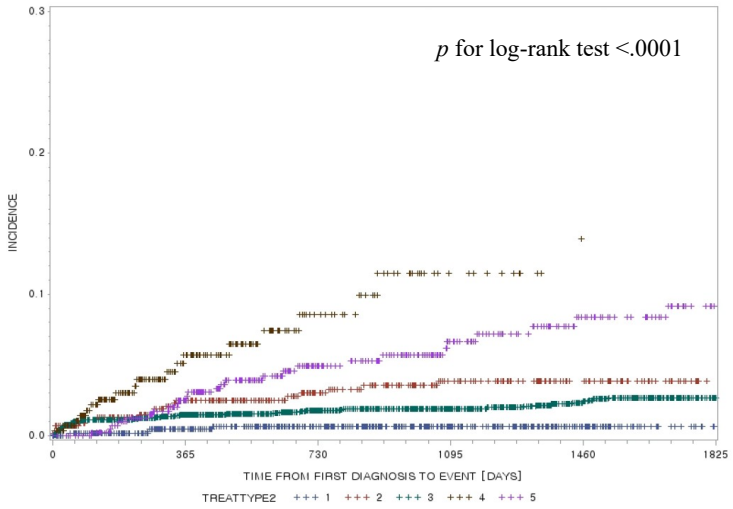

Figure 2. Kaplan-Meier survival curves for venous thromboembolism

1, endoscopic submucosal dissection; 2, only total gastrectomy; 3, only subtotal gastrectomy; 4, other treatment; 5, surgery with other treatment

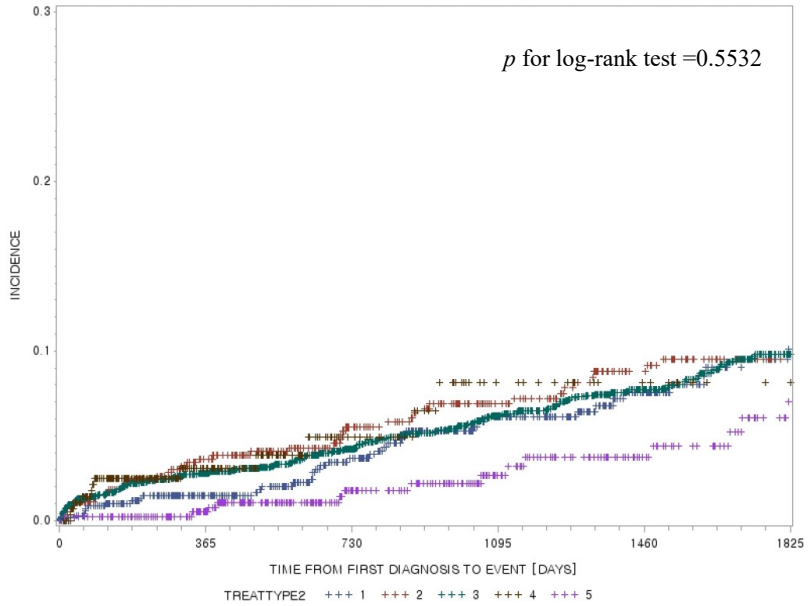

Figure 3. Kaplan-Meier survival curves for arterial thromboembolism

1, endoscopic submucosal dissection; 2, only total gastrectomy; 3, only subtotal gastrectomy; 4, other treatment; 5, surgery with other treatment

3. Risk factors for thromboembolism development

The results from the multivariate analyses are shown in Table 5. The development of TE were associated with only subtotal gastrectomy (HR, 1.456; 95% CI, 1.074 to 1.974, p=0.0154), only total gastrectomy (HR, 1.676; 95% CI, 1.158 to 2.425, p=0.0062), surgery with other treatment (HR, 1.888; 95% CI, 1.274 to 2.800, p=0.0016) and other treatment (chemotherapy or chemo-radiotherapy) (HR, 2.336; 95% CI, 1.484 to 3.678, p=0.0002) compared with only ESD. The development of TE was associated with ages 60-69 years (HR, 2.852; 95% CI, 1.500 to 5.424, p=0.0014), 70-79 years (HR, 3.864; 95% CI, 2.015 to 7.411, p<0.0001) and 80 years or older (HR, 6.262; 95% CI, 3.008 to 13.037, p<0.0001). TE development was also associated with high CCI (4 or more) (HR, 1.542; 95% CI, 1.234 to 1.927, p=0.0001).

We then divided TE into VTE and ATE and analyzed the risk factors. Risk factors for the development of VTE, DVT and PTE were significantly associated with treatment modality (Table 5-1, Table 5-1-1, Table 5-1-2). There was a significant association between development of VTE and DVT and subtotal gastrectomy, only total gastrectomy, surgery with other treatment, and other treatment modalities compared to only ESD group. A significant association was observed between surgery with other treatment and other treatment modalities with PTE development. However, risk factors for the development of ATE were not significantly associated with any group of treatment modalities (Table 5-2, Table 5-2-1, Table 5-2-2).

Table 5. Results of survival analysis using Cox proportional hazard model for the development of total thromboembolism in gastric cancer patients

Variables	TE event			*p*-value
	HR	LCL	UCL	
Patient classification				
ESD	1.000	-	-	-
Only subtotal gastrectomy	1.456	1.074	1.974	0.0154
Only total gastrectomy	1.676	1.158	2.425	0.0062
Surgery with other treatment	1.888	1.274	2.800	0.0016
Other treatment	2.336	1.484	3.678	0.0002
Sex				
Male	1.063	0.869	1.300	0.5540
Female	1.000	-	-	-
Age (years)				
≤39	1.000	-	-	-
40–49	1.142	0.565	2.309	0.7122
50–59	1.813	0.942	3.488	0.0747
60–69	2.852	1.500	5.424	0.0014
70–79	3.864	2.015	7.411	<.0001
≥80	6.262	3.008	13.037	<.0001

Income level				
≤30th percentile	1.113	0.816	1.516	0.4994
31~60th percentile	0.932	0.683	1.271	0.6556
61~80th percentile	0.774	0.562	1.067	0.1185
81~90th percentile	0.887	0.624	1.260	0.5033
≥91th percentile ~	1.000	-	-	-
Types of insurance coverage				
Medical-aid	1.429	0.933	2.189	0.1009
NHI, self-employed	0.894	0.726	1.101	0.2927
NHI, employee	1.000	-	-	-
Disability				
With	1.115	0.829	1.499	0.4732
Without	1.000	-	-	-
Charlson Comorbidity Index (excluded cancer)				
≤2	1.000	-	-	-
3	1.050	0.826	1.335	0.6905
≥4	1.542	1.234	1.927	0.0001
Residence area				
Capital area	1.000	-	-	-
Metropolitan	1.051	0.763	1.447	0.7612
Others	1.284	0.996	1.654	0.0533
Location of medical institution at first treatment				
Capital area	1.000	-	-	-
Metropolitan	1.021	0.776	1.342	0.8827
Others	0.948	0.701	1.282	0.7285
Types of medical institution at first treatment				
Tertiary hospital	1.000	-	-	-
General hospital	1.168	0.955	1.427	0.1302
Others	0.791	0.293	2.137	0.6438

ESD, Endoscopic submucosal dissection; TE, thromboembolism; HR, hazard ratio; UCL, upper confidence limit; LCL, lower confidence limit

Table 5-1 Results of survival analysis using Cox proportional hazard model for the development of venous thromboembolism in gastric cancer patients

Variables	Venous thromboembolism			*p*-value
	HR	LCL	UCL	
Details of treatment				
ESD	1.000	-	-	-
Only subtotal gastrectomy	3.124	1.238	7.884	0.0159
Only total gastrectomy	4.727	1.749	12.774	0.0022
Surgery with other treatment	10.178	3.900	26.566	<.0001
Other treatment	12.215	4.450	33.529	<.0001

*Adjusted other independent variables

ESD, endoscopic submucosal dissection; HR, hazard ratio; UCL, upper confidence limit; LCL, lower confidence limit

Table 5-1-1 Results of survival analysis using Cox proportional hazard model for the development of deep vein thrombosis in gastric cancer patients

Variables	Deep vein thrombosis			*p*-value
	HR	LCL	UCL	
Details of treatment				
ESD	1.000	-	-	-
Only subtotal gastrectomy	5.882	1.408	24.577	0.0151
Only total gastrectomy	7.832	1.737	35.324	0.0074
Surgery with other treatment	14.004	3.198	61.322	0.0005
Other treatment	18.435	3.975	85.486	0.0002

*Adjusted other independent variables

ESD, endoscopic submucosal dissection; HR, hazard ratio; UCL, upper confidence limit; LCL, lower confidence limit

Table 5-1-2 Results of survival analysis using Cox proportional hazard model for the development of pulmonary thromboembolism in gastric cancer patients

Variables	Pulmonary thromboembolism			*p*-value
	HR	LCL	UCL	
Details of treatment				
ESD	1.000	-	-	-
Only subtotal gastrectomy	1.295	0.367	4.572	0.6883
Only total gastrectomy	2.686	0.681	10.583	0.1580
Surgery with other treatment	8.043	2.215	29.203	0.0015
Other treatment	8.107	2.056	31.959	0.0028

*Adjusted other independent variables

ESD, endoscopic submucosal dissection; HR, hazard ratio; UCL, upper confidence limit; LCL, lower confidence limit

Table 5-2 Results of survival analysis using Cox proportional hazard model for the development of arterial thromboembolism in gastric cancer patients

Variables	Arterial thromboembolism			*p*-value
	HR	LCL	UCL	
Details of treatment				
ESD	1.000	-	-	-
Only subtotal gastrectomy	1.282	0.927	1.774	0.1334
Only total gastrectomy	1.360	0.901	2.054	0.1435
Surgery with other treatment	0.903	0.536	1.522	0.1473
Other treatment	1.138	0.608	2.132	0.6854

*Adjusted other independent variables

ESD, endoscopic submucosal dissection; HR, hazard ratio; UCL, upper confidence limit; LCL, lower confidence limit

Table 5-2-1 Results of survival analysis using Cox proportional hazard model for the development of myocardial infarction in gastric cancer patients

Variables	Myocardial infarction				*p*-value
	HR	LCL	UCL		
Details of treatment					
ESD	1.000	-	-	-	1.000
Only subtotal gastrectomy	1.519	0.893	2.583	0.1232	1.519
Only total gastrectomy	1.631	0.845	3.149	0.1450	1.631
Surgery with other treatment	0.904	0.386	2.117	0.8169	0.904
Other treatment	1.481	0.599	3.659	0.3948	1.481

*Adjusted other independent variables

ESD, endoscopic submucosal dissection; HR, hazard ratio; UCL, upper confidence limit; LCL, lower confidence limit

Table 5-2-2 Results of survival analysis using Cox proportional hazard model for the development of ischemic stroke in gastric cancer patients

Variables	Ischemic stroke			*p*-value
	HR	LCL	UCL	
Details of treatment				
ESD	1.000	-	-	-
Only subtotal gastrectomy	1.161	0.770	1.751	0.4760
Only total gastrectomy	1.222	0.719	2.078	0.4589
Surgery with other treatment	0.911	0.470	1.768	0.7839
Other treatment	0.911	0.374	2.222	0.8380

*Adjusted other independent variables

ESD, endoscopic submucosal dissection; HR, hazard ratio; UCL, upper confidence limit; LCL, lower confidence limit

4. Hazard ratios for thromboembolism development by follow-up duration after diagnosis

We performed a subgroup analysis to determine the association of development of TE and treatment modality with follow-up duration after diagnosis. The results of the subgroup analysis for total TE occurrence are shown in Table 6. The development of TE was associated with only subtotal gastrectomy, only total gastrectomy, and other treatment during 5 years of follow-up. The greatest excess risk was seen at the 6 months or 1 year follow-up. At 6 months, the hazard ratio for TE in patients with gastric cancer was 3.038 (95% CI: 1.450 to 6.365) for patients with only subtotal gastrectomy, 3.401 (95% CI: 1.483 to 7.798) for patients with only gastrectomy, and 3.418 (95% CI: 1.297 to 7.640) for patients with other treatment. At 1 year, the hazard ratio for TE in patients with gastric cancer was 2.435 (95% CI: 1.349 to 4.393) for patients with only subtotal gastrectomy, 3.594 (95% CI: 1.869 to 6.909) for patients with only gastrectomy, and 3.442 (95% CI: 1.682 to 7.047) for patients with other treatment.

Subsequently, we conducted an analysis after dividing TE into VTE and ATE (Table 6-1, Table 6-2). For VTE, the greatest excess risk was seen at 6 months, which attenuated over time until 2 years in only subtotal gastrectomy (HR at 6 months 8.382; 95% CI 1.124 to 62.509, HR at 2 years 2.860; 95% CI 1.007 to 8.124), only total gastrectomy (HR at 6 months 9.549; 95% CI 1.159 to 78.659, HR at 2years 4.778; 95% CI 1.568 to 14.560), and other treatment (HR at 6 months 15.349; 95% CI 1.841 to 127.942, HR at 2 years 8.925; 95% CI 2.885 to 27.613) groups. In surgery with other treatment group, the hazard ratio for VTE increased over time (HR at 1 year 5.407; 95% CI 1.460 to

20.023, HR at 5 years 10.560; 95% CI 3.641 to 30.628). The increased risk of VTE incidence was sustained until 5 years at all treatment modalities.

The incidence of ATE increased in only subtotal gastrectomy and only total gastrectomy groups at 6 months and 1 year. The increased risk of ATE incidence persisted for longer in the only total gastrectomy group until 2 years. The hazard ratio for occurrence of ATE in only subtotal gastrectomy group was 2.283 (95% CI: 1.018 to 5.120) at 6 months and 2.158 (95% CI: 1.091 to 4.270) at 1 year. The hazard ratio for occurrence of ATE in only total gastrectomy group was 2.548 (95% CI: 1.003 to 6.477) at 6 months, 2.955 (95% CI: 1.356 to 6.436) at 1 year, and 2.058 (95% CI: 1.150 to 3.682) at 2 years; no association was observed in the surgery with other treatment and other treatment groups.

Since surgery with other treatment group represented thrombosis occurrence after chemotherapy or chemo-radiotherapy, we repeated the analysis by dividing only subtotal gastrectomy and only total gastrectomy into a surgery group and surgery with other treatment, other treatment into the other therapies group in order to determine the effects of surgery and other treatments. The results of the multivariate analyses are shown in Table 7. For VTE, the greatest excess risk was seen at 6 months and the increased risk sustained until 5 years in the surgery group (HR at 6 month 8.530; 95% CI 1.154 to 63.059, HR at 5 years 3.977; 95% CI 1.438 to 10.998) and the excess risk sustained for 5 years at the other therapies group (HR at 6 month 8.986; 95% CI 1.134 to 71.212, HR at 2 years 7.631; 95% CI 2.654 to 21.944, HR at 5 years 11.444; 95% CI 4.062 to 32.245). The ATE occurrence was increased in the only surgery group at 6 months and 1 year. The hazard ratio for

occurrence of ATE in the surgery group were 2.334 (95% CI: 1.053 to 5.170) at 6 months and 2.308 (95% CI: 1.181 to 4.507) at 1 year.

Table 6. Hazard ratios for total thromboembolism occurrence by follow-up duration after diagnosis

Variables	6 months	1 year	2 year	3 year	5 year
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Total TE					
Only subtotal gastrectomy	3.038(1.450-6.365)	2.435(1.349-4.393)	1.666(1.074-2.584)	1.475(1.015-2.145)	1.443(1.036-2.010)
Only total gastrectomy	3.401(1.483-7.798)	3.594(1.869-6.909)	2.460(1.487-4.070)	2.070(1.333-3.212)	1.765(1.185-2.629)
Surgery with other treatment	0.769(0.237-2.673)	1.604(0.723-3.555)	1.704(0.963-3.016)	1.577(0.960-2.591)	1.657(1.071-2.562)
Other treatment	3.148(1.297-7.640)	3.442(1.682-7.047)	2.709(1.531-4.796)	2.554(1.538-4.241)	2.309(1.436-3.712)

*Adjusted other independent variables

TE, thromboembolism; HR, hazard ratio; CI, confidence interval

Table 6-1. Hazard ratios for venous thromboembolism occurrence by follow-up duration after diagnosis

Variables	6 months	1 year	2 year	3 year	5 year
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Venous TE					
Only subtotal gastrectomy	8.382(1.124-62.509)	3.505(1.058-11.609)	2.860(1.007-8.124)	2.975(1.052-8.413)	3.577(1.279-10.006)
Only total gastrectomy	9.549(1.159-78.659)	5.847(1.645-20.779)	4.778(1.568-14.560)	5.699(1.909-17.008)	5.600(1.879-16.690)
Surgery with other treatment	4.563(0.467-1.597)	5.407(1.460-20.023)	6.911(2.298-20.783)	8.581(2.914-25.265)	10.560(3.641-30.628)
Other treatment	15.349(1.841-127.942)	9.520(2.610-34.732)	8.925(2.885-27.613)	11.150(3.666-33.910)	13.271(4.406-39.974)

*Adjusted other independent variables

TE, thromboembolism; HR, hazard ratio; CI, confidence interval

Table 6-2. Hazard ratios for arterial thromboembolism occurrence by follow-up duration after diagnosis

Variables	6 months	1 year	2 year	3 year	5 year
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Arterial TE					
Only subtotal gastrectomy	2.283(1.018-5.120)	2.158(1.091-4.270)	1.476(0.905-2.408)	1.306(0.871-1.959)	1.237(0.868-1.763)
Only total gastrectomy	2.548(1.003-6.477)	2.955(1.356-6.436)	2.058(1.150-3.682)	1.610(0.973-2.665)	1.395(0.892-2.180)
Surgery with other treatment	0.239(0.029-1.965)	0.375(0.081-1.726)	0.558(0.223-1.397)	0.517(0.236-1.134)	0.671(0.362-1.243)
Other treatment	1.600(0.543-4.713)	1.697(0.651-4.427)	1.371(0.630-2.984)	1.273(0.640-2.531)	1.064(0.550-2.058)

*Adjusted other independent variables

TE, thromboembolism; HR, hazard ratio; CI, confidence interval

Table 7. Hazard ratios for thromboembolism occurrence in surgery and other therapies by follow-up duration after diagnosis

Variables	6 months	1 year	2 year	3 year	5 year
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Total TE					
Surgery	3.100(1.492-6.440)	2.656(1.488-4.743)	1.818(1.184-2.791)	1.588(1.102-2.288)	1.505(1.087-2.083)
Other therapies	1.906(0.819-4.432)	2.392(1.240-4.616)	2.089(1.275-3.423)	1.931(1.259-2.962)	1.881(1.280-2.764)
Venous TE					
Surgery	8.530(1.154-63.059)	3.967(1.218-12.922)	3.242(1.160-9.059)	3.516(1.264-9.779)	3.977(1.438-10.998)
Other therapies	8.986(1.134-71.212)	6.997(2.052-23.858)	7.631(2.654-21.944)	9.436(3.321-29.809)	11.444(4.062-32.245)
Arterial TE					
Surgery	2.334(1.053-5.170)	2.308(1.181-4.507)	1.585(0.984-2.553)	1.362(0.917-2.024)	1.267(0.895-1.793)
Other therapies	0.925(0.328-2.607)	0.982(0.401-2.403)	0.878(0.452-1.708)	0.797(0.449-1.414)	0.807(0.488-1.333)

*Adjusted other independent variables

TE, thromboembolism; HR, hazard ratio; CI, confidence interval

IV. DISCUSSION

In this population-based cohort study, we focused on TE in gastric cancer patients treated using different modalities. In our study, the 2-year incidence of TE, VTE, and ATE was 5.6%, 2.1%, and 3.5%, respectively. We found that the incidence of total incidence of TE was 10.8% and 11.8% for gastrectomy with other treatments (chemotherapy or chemo-radiotherapy) and other treatments only (chemotherapy or chemo-radiotherapy), respectively. Several studies have examined the incidence of TE, VTE, and ATE in gastric cancer. In previous studies from western countries, the incidence of TE before and during chemotherapy has been reported to be 13.6% in cases of advanced gastroesophageal cancer[25]; in studies from Asia, the reported value is 9.2% in patients with advanced gastric cancer receiving chemotherapy.[26] In several studies, the incidence of VTE has been reported in various ranges. One study showed cumulative incidences of VTE in gastric cancer patients with localized, regional and remote stages were 2.3%, 3.4% and 4.4% respectively[5] and another study showed VTE occurred in 12.6% of the cancer cohort over 12 months after the initiation of chemotherapy.[27] At the Korean studies, one study showed the 2-year incidences of VTE were 0.5%, 3.5%, 24.4% in stages I, II-IV(M0), IV(M1), respectively[9] and other study showed 3.5% 1-year cumulative incidence in patients with inoperative advanced gastric cancer.[28] Regarding ATE, a recent study showed that the 1-year cumulative incidence of ATE, MI, and ischemic stroke was 7.9%, 3.1%, and 3.7%, respectively.[17] There are few studies on the incidence of ATE in cases of gastric cancer in Asia. It was difficult to directly compare our results with those of previous studies due to differences in study populations and definitions of embolic events. Nevertheless, our reported incidence of VTE was lower than that in previous western studies. A previous study showed that Asian–Pacific patients have a significantly lower risk of developing VTE than Caucasian patients,[5]

suggesting that our findings may be the result of racial differences. Previous studies have also shown that the highest incidence of VTE occurs during the first year,[4] and the risk of ATE is substantially higher during the first few months after the diagnosis of cancer,[17,29] with excess risks of TE becoming attenuated over time.[4,17,29] One study showed that the HR for MI was consistently higher than for ischemic stroke among ATE.[17] We had not been able to analyze the HR for DVT, PTE, MI and ischemic stroke due to each number being too small to analyze statistically.

In our study, TE risk was associated with treatment modality (subtotal gastrectomy, total gastrectomy, gastrectomy with other treatment and other treatment), older age, and high comorbidity. These results are consistent with previous reports.[5,9,27] When TE divided into VTE and ATE, development of VTE was also significantly associated with treatment modality, however the development of ATE was not significantly associated with treatment modality. In gastric cancer patients, development TE is affected by treatment modality, which may be more affected in VTE than ATE. In association with development of TE and treatment modality by follow-up duration, the greatest excess risk was seen with a 6 month and attenuated over time until 2 years at the subtotal gastrectomy, total gastrectomy, others treatment in the VTE. In surgery with other treatment, the hazard of VTE increased over time. The VTE incidence was sustained of increased risk thereafter until 5 years at all treatment modalities. The ATE occurrence was increased with only subtotal gastrectomy and only total gastrectomy at the period of 6 month and 1~2 year. Whereas it was not associated with surgery with other treatment and other treatment groups. The previous studies finding showed risk of VTE occurrence sustained more than 5 years[4,30] and excess risk of ATE occurrence generally had resolved by 1 year[17] and is similar to out result. We suggested

the increased risk of VTE persisted for longer than ATE occurrence in gastric cancer patients.

The risk factors of VTE are cancer type, cancer surgery, comorbidities and chemotherapy and so on.[27,31] The major risk factors of ATE are considered to tobacco smoking, blood pressure and cholesterol than cancer treatment.[32] In contrast to VTE, little is known about arterial thromboembolism about association with cancer surgery. In this study showed risk of ATE occurrence may be association with gastrectomy in short-term period. In previous study showed that the risk of coronary heart disease and ischemic stroke were decreased in gastric cancer survivors who followed-up for more than 2 years after gastrectomy because of weight loss and metabolic changes.[33] The weight loss and metabolic change after gastrectomy may affected to decreased risk of ATE in patients with gastrectomy. In TE event in patients with chemotherapy, some studies showed the high incidence of TE (VTE and ATE) in gastric cancer patients especially of cisplatin-based chemotherapy,[34,35] but there was a study showed that no associated between TE and the type of chemotherapy type.[25,36] In our study showed the high risk of VTE and no association with ATE occurrence in chemotherapy or chemo-radiotherapy group. Previous studies analyzed about the risk of total TE. The results of our study showed that chemotherapy or chemo-radiotherapy may be more relevant in VTE than in ATE. As a result of our study, we thought the effect of treatment modality on ATE is not certain because of small sample size. Therefore, further study is needed ATE occurrence according to the cancer treatment. Besides, the previous review study suggested the interrelationship between stroke and cancer is complex.[20] Cancer and stroke may occur independently in a given patient, or cancer may directly or indirectly lead to stroke.[20] And the most frequent causes of stroke in cancer patients are traditional cerebrovascular risk factors such as hypertension, hyperlipidemia, diabetes, atrial fibrillation and

tobacco use.[20,21] We suggest that the diversity of the mechanisms of occurrence of ATE in these cancer patients may also have influenced these results. And we presume that these results may be related to the limitations of our study. In this study, events of ATE were confirmed by NHIS claim data and there were some discrepancies occur between diagnoses entered in the data and diseases that a patient has in reality.[37,38] In previous Korean studies on the validation of the data showed the validity of acute MI was about 71-73%[39] and that of cerebrovascular disease was 83.0%.[40] However, validity study of subsequent MI has not yet been reported and hemorrhagic infarction was included on cerebrovascular disease in previous validation study. Therefore, we thought that measurement errors for the outcome may still exist. In this study, it should be considered that little association between development of ATE and treatment modality for gastric cancer may be associated with this error.

Western guidelines for treatment and prophylaxis of recommend of cancer-associated VTE have been pulished.[10,11] There was the controversy associated with prophylactic anticoagulation in patients with chemotherapy and the optimal antithrombotic strategy to prophylaxis for ATE in cancer patients is uncertain. And previous studies showed race influenced the incidence of VTE and Asian-Pacific Islanders had a lower risk than Caucasians,[5,9,28] but the there are no studies about ATE rates by racial differences. Therefore, further studies are needed in this specific cancer population treated with chemotherapy or prophylaxis for ATE and ATE rates by racial differences.

To the best of our knowledge, this is the first nationwide cohort study about risk of venous and arterial thromboembolism in gastric cancer patients who have undergone treatment. on South Korea. And study subjects represented

the general population of South Korea because we used samples from the NHIS claim data for the entire population. However, our study has several limitations because of the use of a claim data. The most important limitation is the lack of information on behavioral factors and lifestyle variables including smoking history. Smoking is an important cardiovascular risk factor, but we were unable to adjust for the confounding effect of these factors. However, result of this study showed that TE risk affected considerably according to treatment modality, especially of VTE. Second, there were no information about the histology of tumor, laboratory values and imaging data in the claims data. Further studies will be needed to identify relationships between histology of tumor and risk of TE. Third, we divided gastric cancer patients into five groups according to treatment method because there were no stages information of cancer. However, surgery with other treatment group included patients with stage II or stage III as well as patients with recurrence. Therefore, to define the impact on the occurrence of TE of stage is difficult with this study. Finally, there were some discrepancies occur between diagnoses entered in the data and diseases that a patient has in reality as mentioned earlier.

V. CONCLUSION

In gastric cancer patients who have undergone treatment, the development of TE was associated with the treatment modality used. The treatment modalities had a greater effect on VTE risk than on ATE risk. In gastric cancer patients who underwent gastrectomy, surgery with other treatments, and other treatments only (compared to ESD), old age and high comorbidities were independent risk factors for TE. Patients with these risk factors faced a substantially higher short- and long-term risk of VTE, while the risk of ATE was only higher in the short term in the gastrectomy alone group.

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ABSTRACT (IN KOREAN)

위암 환자에서 혈전 색전증의 위험에 대한 분석

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유 지 성

목적: 이 연구의 목적은 인구기반 코호트를 이용하여 치료를 받는 위암환자에서 혈전색전증 발생에 관련된 위험인자를 확인하고, 혈전색전증의 발생에 위암의 치료방법에 따른 연관성을 확인하고자 한다.

방법: 본 연구는 2005년에서 2015년까지의 국민건강보험공단 표본 코호트 자료를 이용하여 이루어졌다. 이 기간 동안 새롭게 위암으로 진단받고 치료를 시작한 20세이상의 성인 4,093명이 연구에 포함되었다. 위암의 치료방법이 혈전색전증의 발생에 영향을 주는지 확인하기 위해 치료방법에 따라 5군으로 나누어서 확인하였다; 5군은 내시경적점막하박리술만 시행한 경우, 아전위절제만 시행한 경우, 전위절제만 시행한 경우, 수술과 항암치료(또는 항암방사선치료)를 시행한 경우, 항암치료나 항암방사선 치료만 시행한 경우로 나누었다. 정맥혈전색전증의 발생은 심부정맥혈전증 또는 폐색전증의 발생

으로 정의하였고 동맥 혈전색전증은 심근경색증 또는 허혈성 뇌졸중의 발생으로 정의하였다. 통계 분석은 Cox 비례위험모형과 카플란-마이어 (Kaplan-Meier) 생존 분석을 이용하였다. 치료방법과 진단 후 시간에 따른 하위그룹분석을 시행하였다.

결과: 혈전색전증의 발생은 내시경적점막하박리술만 시행한 그룹에 비해 아전위절제만 시행한 경우(HR, 1.456; p=0.0154), 전위절제만 시행한 경우(HR, 1.676; p=0.0062), 수술 및 항암치료(또는 항암방사선치료)를 시행한 경우(HR, 2.336; p=0.0002) 및 항암이나 항암방사선치료만 시행한 경우(HR, 1.888; p=0.0016), 39세 미만에 비해 60-69세(HR, 2.852; p=0.0014), 70-79세(HR, 3.864; p<0.0001), 80세 이상(HR, 6.262; p<0.0001)인 경우, 동반질환 지수 2이하인 경우에 비해 4이상인경우(HR, 1.542; p=0.0001)에 통계적으로 유의한 연관성이 관찰되었다. 혈전색전증을 동맥 혈전색전증보다 정맥 혈전색전증으로 나누어 치료방법과의 관련성을 확인하였을때 정맥 혈전색전증의 발생에는 내시경적점막하박리술만 시행한 그룹에 비해 아전위절제만 시행한 경우(HR, 3.124; p=0.0159), 전위절제만 시행한 경우(HR, 4.272; p=0.0022), 수술 및 항암치료(또는 항암방사선치료)를 시행한 경우(HR, 12.215; p<0.0001) 및 항암이나 항암방사선치료만 시행한 경우(HR, 10.178; p<0.0001)에서 통계적으로 유의한 연관성이 확인되었으나, 동맥 혈전색전증의 발생에서는 치료 방법에 따른 통계적

인 연관성이 없었다. 진단이후 시간에 따른 정맥 혈전색전증의 발생의 위험은 아전위절제만 시행한 경우, 전위절제를 시행한 및 항암치료나 항암방사선 치료만 시행한 경우에서 치료시작 6개월 시점에서 가장 높았다. 그리고 모든 치료방법에서 5년 시점까지 높은 발생 위험이 관찰되었다. 동맥 혈전색전증의 발생의 위험은 아전위절제만 시행한 군에서는 1년시점까지 및 전위절제를 시행한 그룹에서 2년시점까지 높게 관찰되었다.

결론: 치료를 받은 위암환자에서 혈전색전증의 발생은 치료방법과 유의한 관련성이 있었으며, 이는 동맥 혈전색전증보다 정맥 혈전색전증에서 뚜렷한 연관성이 관찰되었다. 혈전색전증의 발생과 통계적으로 유의한 위험인자는 내시경적점막하박리술만 시행한 그룹에 비해 아전위절제, 전위절제행, 수술 및 항암치료, 항암이나 항암방사선치료만 시행한 경우, 고령과 동반질환이 많은 경우였다. 정맥 혈전색전증의 발생은 모든 치료방법에서 단기 및 장기 위험이 모두 높고 동맥 혈전색전증의 경우는 위 절제군에서 단기적인 위험이 높은 것으로 확인하였다.

핵심되는 말: 위암, 혈전 색전증, 위험인자