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ORIGINAL ARTICLE

The incidence of cardiovascular thrombotic complications after laparoscopic resection in colorectal cancer in Japanese hospitals: A large-scale clinical study

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Abstract

Aim: The aim of this retrospective study was to investigate the incidence of cardiovascular thrombotic complications after laparoscopic resection in colorectal cancer.

Methods: This study involved 2017 patients with stages 0-III colorectal cancer who underwent laparoscopic surgery at 17 Japanese hospitals between January 2010 and December 2013. We assessed the incidence of postoperative cardiovascular thrombotic and haemorrhagic complications.

Results: Laparoscopic surgeries were performed in 1152 men and 865 women with 1405 colon and 612 rectal cancers, respectively. Overall, 3%, 38%, 17%, 8%, and 9% of patients had comorbidities of heart failure, high blood pressure, diabetes, history of stroke, and vascular disease, respectively. Antithrombotic agents were being consumed by 17% of patients. The types (and perioperative rest periods) of the antithrombotic agents were aspirin in 58% (18.6 days), clopidogrel in 19% (21.1 days), cilostazol in 13% (13.3 days), and warfarin potassium in 21% (14.6 days) of cases with antithrombotic agents. Surgical time and blood loss in the total cohort were 234 minutes and 56 mL. Four cases (0.2%) had cardiovascular thrombotic complications, including one severe cardiac infarction and one stroke with major sequelae (CHADS2 scores were 2 points in both cases). Hemorrhagic complications occurred in 19 cases (0.9%). In particular, the incidence of the major gastroduodenal haemorrhagic ulcer was higher in cases with antithrombotic agents than without them (0.05% vs 0%, $P = .02$).

Conclusion: The incidence of cardiovascular thrombotic complications was rare, although severe cardiac infarction and stroke could occur even after minimally invasive surgery in colorectal cancer.

KEYWORDS
colorectal neoplasms, ischemic heart disease, laparoscopy, stroke, thrombosis

See Appendix 1 for all members of Hokkaido Colorectal Surgical Research Group Collaborative.

1 | INTRODUCTION

An aging society and the increase in lifestyle-related diseases have increased the number of patients on anticoagulant medications. There are over 1 million patients with each of ischemic heart disease and cerebral infarction in Japan,[1] and over 1 million and 3 million patients consume the anticoagulant and antiplatelet drugs, respectively, for cardiovascular disease.[2] Anticoagulants such as warfarin potassium are useful in deep venous thrombosis, pulmonary embolism, and thrombosis related to atrial fibrillation (AF), and antiplatelet drugs such as aspirin are used in cerebral and cardiac infarctions, which develop as a sequelae to arteriosclerosis.[3,4] These drugs are prescribed once or multiple times for the treatment or prevention of disease-relapse according to the disease state. On the other hand, these anticoagulant and antiplatelet therapies induce haemorrhagic diathesis, and the appropriate cessation of medication is needed during the perioperative period.[5,6] However, the cessation has been reported to increase the risk of thrombotic complications. For instance, the cessation of aspirin increased the risks of cardiovascular events such as cerebral infarction by three times,[7] and 70% of the infarction occurred within 10 days after the cessation.[8] The drug-eluting stent in the coronary artery within 1 year after its insertion had risks of clogging after the cessation of antiplatelet medication.[9,10] The withdrawal of warfarin potassium restituted the patients to the original hyper-coagulated condition.[11] One hundred warfarin potassium withdrawals contribute to one cardiovascular thrombosis. The thrombotic event after the withdrawal of medication often results in poor outcomes with increase in the severity of the condition.[7,12] Therefore, surgeons should consider the risk of both haemorrhage and thrombosis during surgery in patients on anticoagulant/antiplatelet medications.

Owing to the superior short-term results and non-inferior long-term oncological outcomes of laparoscopic colon resection compared with those of laparotomy, laparoscopic surgery is becoming a standard treatment for colon cancer worldwide as it has less risk of haemorrhage than laparotomy.[13,14]

Postoperative bleeding after laparoscopic colon resection occurred in approximately 1.1% of cases in a Japanese randomized trial that compared the outcomes of laparoscopic colectomy and laparotomy in colon cancer.[15] Some investigators have reported that the administration of aspirin without cessation during the perioperative period does not increase the haemorrhagic events during and after laparoscopic colorectal surgery.[16–18] However, the risks of thrombotic events after laparoscopic colorectal surgery remain unclear. We, therefore, aimed to determine the incidence of cardiac and cerebral infarctions after laparoscopic colorectal resection.

2 | METHODS

In this study, we retrospectively assessed the outcomes of 2017 laparoscopic colorectal resections for adenocarcinoma of pathological stages 0-III performed between January 2010 and December 2013 in Hokkaido University Hospital and 17 collaborative hospitals. Patients who had other synchronous or metachronous cancers (excluding in situ cancer) within 5 years and received chemotherapy/radiotherapy prior to surgery were excluded. The endpoint evaluated in this study was the incidence of cardiac and cerebral infarctions after laparoscopic colorectal resection within 30 days after surgery. Further, the incidence of haemorrhage after laparoscopic colorectal resection was evaluated, and this was compared between the patients who were on antithrombotic agents (AT group) and those who were not (non-AT group; Figure 1). Postoperative complications were assessed according to the Clavien-Dindo classification.[19] To assess the potential risk of cardiovascular attack in individual cases, congestive heart failure, hypertension, age of 75 years, diabetes mellitus, and stroke (CHADS2) scoring criteria (total point of each value: chronic heart failure, 1; hypertension, 1; over 75 years, 1; diabetes mellitus, 1; and history of cerebral infarction or transient ischemic attack, 2) were evaluated. This score was originally introduced as the risk score for stroke in cases with AF,[20] and it has been reported to be useful in predicting the adverse cardiovascular events in coronary artery disease in patients without AF[21] and prognostic stratification of patients with coronary artery disease.[22]

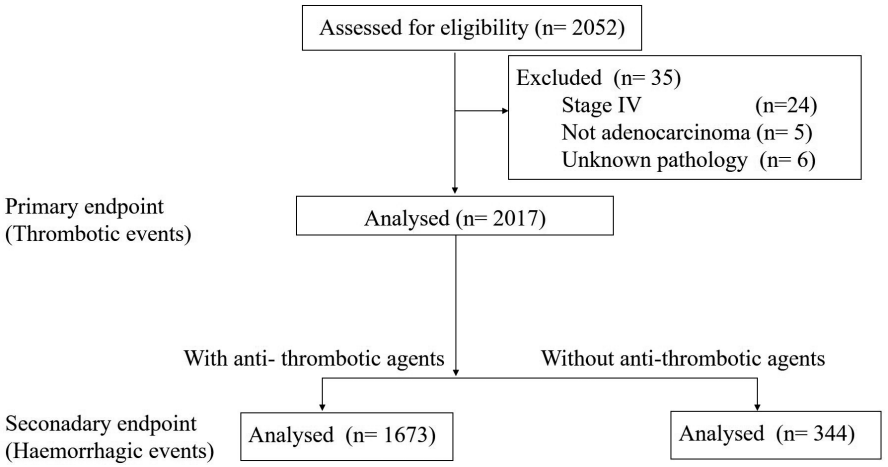

FIGURE 1 Patient flow diagram

2.1 | Statistical analysis

Continuous data were reported as mean and minimum and maximum values. All statistical tests were performed using an alpha level of 0.05 (two-sided). Chi-squared and Student's *t* tests were used for categorical and non-normal continuous data, respectively. The incidence of postoperative cardiovascular thrombotic and haemorrhagic complications was calculated and estimated with 95% confidence intervals (CIs). All statistical analyses were performed using JMP Pro version 14.0 software (SAS Institute, Inc).

3 | RESULTS

3.1 | Patient characteristics and procedures

Laparoscopic surgeries were performed in 1152 male and 865 female patients with 1405 colon and 612 rectal cancers, respectively. Pathologically, the average tumour size was 36 mm and tumour stages were 0, I, II, and III in 131, 681, 624, and 581 patients, respectively. The patients' average age and body mass index were 68.9 years and 23.1 kg/m^2, respectively. Of 2017 patients, 15% had preoperative comorbidity (American Society of Anesthesiologists [ASA] class III) and 30% had a history of smoking. Overall, 3%, 38%, 17%, 8%, and 9% of patients had comorbidities of heart failure, high blood pressure, diabetes, history of stroke, and vascular diseases, respectively. Antithrombotic agents were consumed by 17% of the patients (Table 1).

TABLE 1 Patient characteristics

Characteristic	Value
Age, y	68.9 (25-96)
Sex	
Male	1152 (57%)
Female	865 (43%)
Body mass index, kg/m^2	23.1 (12.9-48.4)
Tumor location	
Colon	1405 (70%)
Rectum	612 (30%)
Pathological stage	
0	131 (6%)
I	681 (34%)
II	624 (31%)
III	581 (29%)
ASA	
Class 3 or 4	295 (15%)
Previous laparotomy	435 (22%)
Smoking history	613 (30%)
Preoperative comorbidity	
Chronic heart failure	51 (3%)
Hypertension	761 (38%)
Diabetes mellitus	344 (17%)
History of stroke or TIA	160 (8%)
Cardiovascular disease	185 (9%)
CHADS2 score	1.17 (0-5)
Medication of antithrombotic agents	344 (17%)

3.2 | Anti-thrombotic agents

The types (and perioperative rest periods) of the included antithrombotic agents were aspirin in 58% (18.6 days), clopidogrel in 19% (21.1 days), cilostazol in 13% (13.3 days), and warfarin potassium in 21% (14.6 days) of the cases with antithrombotic agents. Single, double, and triple usage occurred in 70%, 20%, and 5% of cases, respectively, and heparin bridge was performed in 31% of the cases with antithrombotic agents. The mean CHADS2 score was 1.17 (Table 2).

3.3 | Short-term outcomes

Of the 2017 cases, 31%, 19%, 16%, and 18% of the cases underwent laparoscopic right colectomy, sigmoidectomy, high and low anterior rectal resections, respectively. Surgical time and blood loss in the total cohort were 234 minutes and 56 mL, respectively, and 7.7% had postoperative complications (Clavien-Dindo grade III or over). Four cases (0.2% with 95% Confidence Interval [CI], 0.08%-0.5%) had cardiovascular thrombotic complications (all grades). On the other hand, haemorrhagic complications (all grades) occurred in 19 cases (0.9% with 95% CI, 0.6%-1.5%; Table 3). Among them, only one case without antithrombotic agents experienced severe bleeding that needed re-surgery; 10, six, and three cases experienced anastomotic bleeding, intraperitoneal bleeding, and haemorrhagic ulcer, respectively.

3.4 | Details of thrombotic incidences

Of 2017 patients who underwent laparoscopic colorectal resection, one patient experienced cardiac, one experienced mesenteric infarction that needed surgical intervention, and two experienced cerebral infarction that was treated without surgical intervention. Among them, one patient who was on warfarin potassium since previous stroke and had withdrawn 6 days before the surgery with alternative usage of heparin experienced stroke with major sequelae. There were two (0.34%) thrombotic complications in CHADS $\geqq$ 2 and two (0.14%) in CHADS < 2, respectively (P = .39). However, the CHADS2 score was 2 in the case with severe cardiac infarction and in the case with stroke with sequelae (Table 4).

TABLE 2 Antithrombotic agent usage

Characteristic	Number (%)	Cessation period
Types of antithrombotic agents		
Aspirin	194 (58%)	18.6 (1-180)
Clopidogrel	63 (19%)	21.1 (1-100)
Cilostazol	43 (13%)	13.3 (5-26)
Warfarin potassium	73 (21%)	14.6 (4-78)
Others	66 (20%)	
Heparinization during the withdrawal	105 (31%)	
Number of antithrombotic agents		
1	241 (70%)	
2	70 (20%)	
3 or more	18 (5%)	
Unknown	15 (4%)	

3.5 | Comparison of the cases with and without anti-thrombotic agents in haemorrhage events

A total of 243 men and 101 women with a mean age of 73.7 years were assigned to the AT group, whereas 909 men and 764 women with a mean age of 67.9 years were allocated to the non-AT group. More cases with rectal cancer were included in the AT group than in the non-AT group. No differences in body mass index, pathological stages, and history of previous abdominal surgery were observed between the two groups. The frequency of preoperative comorbidities with ASA class greater than 3 (35.8% vs 10.3%, $P < .0001$) and smoking history (37.2% vs 29.0%, $P = .001$) were higher in the AT group than in the non-AT group. Furthermore, the frequency of preoperative medical history with heart failure, hypertension, stroke, and cardiovascular disease was significantly higher in the AT group. CHADS2 score was significantly higher in the AT group than in the non-AT group (Table 5). There were no significant differences between the two groups in surgical procedures, types of anastomosis, and extent of lymph node dissection. Surgical time (225 vs 235 minutes, $P = .98$), rate of conversion to open surgery (2.3% vs 3.1%, $P = .43$), and rate of major postoperative complications (8.1% vs 7.7%, $P = .76$) were similar between the groups. The thrombotic incidence after laparoscopic colorectal resection was not significantly different between the two groups (0.2% vs 0.4%, $P = .78$). However, the incidence of postoperative haemorrhage (2.3% vs 0.7%, $P = .01$) and intraoperative blood loss (64.9 vs 53.8 mL, $P = .09$) were higher in the AT group than in the non-AT group. The incidence of major postoperative haemorrhage (Clavien-Dindo grade III) was also higher in the AT group than in the non-AT group (1.2% vs 0.2%, $P = .04$). The rate of major (Clavien-Dindo grade III) surgical site (intraperitoneal and anastomotic) bleeding was not significantly different; however, the incidence of major (Clavien-Dindo grade III) gastroduodenal haemorrhagic ulcer was higher in the AT group than in the non-AT group (0.6% vs 0%, $P = .02$; Table 6). Details of gastroduodenal haemorrhagic incidences are shown in Table 7.

TABLE 3 Surgical outcomes

Procedures	Right colectomy	633 (31%)
	Transverse colectomy	86 (4%)
	Left colectomy	118 (6%)
	Sigmoidectomy	391 (19%)
	High anterior resection	328 (16%)
	Low anterior resection	364 (18%)
	APR	56 (3%)
	Others	40 (2%)
Anastomosis	FEEA	766 (38%)
	Triangular anastomosis	213 (11%)
	DST	783 (39%)
	Others	157(8%)
Lymph node dissection	D0/1	70 (4%)
	D2	617 (30%)
	D3	1329 (66%)
Operative time (min)		234 (55-663)
Blood loss (mL)		56 (0-3300)
Conversion		60 (3.0%)
Postoperative complication (Grade ≥ III)[a]		155 (7.7%)
Postoperative thrombotic complication (All grades)[a]		4 (0.2%)
Postoperative bleeding (All grades)†		19 (1.2%)

Abbreviations: APR, abdominoperineal resection; DST, double stapling technique; FEEA, functional end-to-end anastomosis.
[a]Clavien-Dindo classification.

4 | DISCUSSION

Here, we reported the incidence of postoperative cardiovascular thrombotic complications after laparoscopic colorectal resection in the Japanese real-world large cohort for the first time; such complications were rare compared to other postoperative complications, with 0.2% incidence in 2017 cases. However, if complications occurred, they were critical, including severe cardiac infarction and stroke with major sequelae.

We evaluated the potential risks of cardiovascular thrombosis in each case by using CHADS2 score in which 2 points or more were considered high risks for cardiovascular thrombotic events both in the cases with and without AF.[20–22] For instance, when the CHADS2 score was 2 points, the occurrence of thrombotic attacks was 3.6% annually in AF cases[20] and 3.3% in non-AF cases.[21] In the current cohort, the mean CHADS2 score was 1.17, and 29% of the cases gained 2 points or more. There was no significant difference between the cases with CHADS $\geqq 2$ and CHADS < 2 in terms of the incidence of thrombotic attack. However, the score was 2 points in both two cases who suffered severe thrombotic attack (one case

TABLE 4 Postoperative thrombotic events

Age /sex	Date	Complication	Grade[a]	Risk Score[b]	AT	Comorbidity	Procedure	Operation time	Blood loss
72/F	2	Cardiac Infarction	IIIb	2	No	HT DM	LAR Conversion	480	40
67/F	1	SMA thrombosis	IIIb	1	No		RC	242	600
64/F	5	TIA	II	0	No		LAR	330	330
70/M	2	Stroke	IId[c]	2	Warfarin (heparin)	AF Stroke	HAR	215	215

Abbreviations: AT, medication of antithrombotic agents; DM, diabetes mellitus; DVT, deep venous thrombosis; HAR, high anterior resection; HT, hypertension; LAR, low anterior resection; RC, right colectomy; SMA, superior mesenteric artery; TIA, transient ischemic attack.

[a]Clavien-Dindo classification.

[b]CHADS2 score.

[c]Sequelae of hemiplegia.

TABLE 5 Comparison of patient characteristics between non-AT and AT groups

	Non-AT	AT	*P*-value
Age, y	67.9 (25-96)	73.7 (41-95)	<.001
Sex			
Male	909 (54%)	243 (71%)	<.001
Female	764 (46%)	101 (29%)	
Body mass index, kg/m^2	23.1 (14.6-34.7)	23.2 (12.9-48.4)	.19
Tumor location			
Colon	1138 (68%)	266 (77%)	.002
Rectum	535 (32%)	78 (23%)	
Pathological stage			
0	107 (6%)	24 (7%)	.33
I	560 (34%)	121 (35%)	
II	510 (31%)	114 (33%)	
III	496 (30%)	85 (25%)	
ASA			
Class 3 or 4	172 (10%)	123 (36%)	<.001
Previous laparotomy	370 (22%)	65 (19%)	.16
Smoking history	485 (29%)	128 (37%)	.01
Preoperative comorbidity			
Chronic heart failure	17 (1%)	34 (10%)	<.001
Hypertension	584 (35%)	177 (52%)	<.001
Diabetes mellitus	233 (14%)	111 (32%)	<.001
History of stroke or TIA	39 (2%)	121 (35%)	<.001
Cardiovascular disease	63 (4%)	122 (36%)	<.001
CHADS2 score	0.93 (0-5)	2.32 (0-5)	<.001

Abbreviations: ASA, American Society of Anesthesiologists physical status classification; AT, cases with antithrombotic agents; non-AT, cases without antithrombotic agents; TIA, transient ischemic attack.

with postoperative cardiac infarction and one case with stroke with sequelae). Therefore, the surgeons need to consider that this critical complication could occur especially in cases with CHADS ≧ 2 and it directly leads to the crisis of loss of physical function once they occur.

The risks of thrombotic events after laparoscopic colorectal surgery compared to open procedures remain unclear in the literature. However, laparoscopic surgery has shown to be minimally invasive, with a significant reduction in the mortality risk in colorectal surgery.[23] Rajeev-Kumar et al reported the incidence of ischemic stroke, assessed using the US national database, as 0.084% and 0.2% in 30 and 90 days, respectively, after colectomy (36% of the procedure was laparoscopic surgery). They reported a significantly lower risk of ischemic stroke with laparoscopic vs open colectomy (hazard ratio 0.59).[24] A retrospective analysis of the Nationwide Inpatient

TABLE 6 Comparison of the surgical outcomes between non-AT and AT groups

		Non-AT	AT	*P*-value
Procedures[§]	Right colectomy	513 (31%)	120 (36%)	.15
	Transverse colectomy	70 (4%)	16 (5%)	
	Left colectomy	92 (5%)	26 (8%)	
	Sigmoidectomy	321 (19%)	70 (21%)	
	High anterior resection	275 (16%)	53 (16%)	
	Low anterior resection	318 (19%)	46 (14%)	
	APR	49 (3%)	7 (2%)	
	Others	35 (2%)	5 (2%)	
Anastomosis[§]	FEEA	653 (39%)	132 (40%)	.61
	Triangular anastomosis	628 (38%)	137 (40%)	
	DST	183 (11%)	30 (9%)	
	Others	129 (8%)	27 (8%)	
Lymph node dissection	D0/1	59 (4%)	11 (3%)	.07
	D2	501 (30%)	116 (34%)	
	D3	1113 (67%)	216 (63%)	
Operative time (min)		235 (55-663)	225 (70-600)	.98
Blood loss (mL)		53.8 (0-3300)	64.9 (0-1310)	.09
Conversion		52 (3.1%)	8 (2.3%)	.43
Postoperative complication (Grade ≥III)[a]		128 (7.7%)	28 (8.1%)	.76
Postoperative cardiovascular thrombotic complication (all grades)[a]		6 (0.4%)	1 (0.2%)	.78
Postoperative bleeding (all grades)[a]		11 (0.7%)	8 (2.3%)	.01
Postoperative bleeding (Grade ≥III)[a]		4 (0.2%)	4 (1.2%)	.04
Anastomosis and intraperitoneal bleeding		4 (0.2%)	2 (0.6%)	.27
Bleeding from ulcer		0 (0%)	2 (0.6%)	.02

Abbreviations: APR, abdominoperineal resection; AT, cases with antithrombotic agents; DST, double stapling technique; FEEA, functional end-to-end anastomosis; non-AT, cases without antithrombotic agents.

[a]Clavien-Dindo classification.

Sample in the United States revealed that out of total 230 006 elective admissions for open colectomy, 1.0% experienced myocardial infarction, and 0.41% cardiac arrest.[25] A meta-analysis showed that the laparoscopic right colectomy procedures had favourable outcomes in terms of cardiac complications, including acute coronary syndrome.[26] In the current study, we have shown that the incidence of cardiovascular thrombotic complications after laparoscopic colorectal resection in cancer patients was 0.2%, which was lower than previous reports. The laparoscopic approach might have contributed to the lower incidence.

According to the Japanese guidelines, discontinuing aspirin, clopidogrel, cilostazol, and warfarin potassium was recommended from 7, 14, 3, and 5 days before surgery to several days after surgery. However, the withdrawal periods of aspirin, clopidogrel, cilostazol, and warfarin potassium in our study were 18, 21, 13, and 14 days, respectively, which were longer than those recommended. Nevertheless, the incidence of cardiovascular thrombotic complications in cases with anti-thrombotic agents was 0.4%, and the prolonged cessation of anti-thrombotic medication might not increase the rate of thrombotic event. This might be related to racial factors. Asians are not prone to coagulation, unlike other races,[27] and the incidence of thrombotic attacks might be lower than assumed. Most of the reports that showed increased risk of thrombotic attack after cessation of anti-thrombotic agents were not from Asia.[7–12]

Further, the incidence of haemorrhage in cases with anti-thrombotic agents after laparoscopic colorectal resection was evaluated. We observed postoperative haemorrhagic events in 1.2% of the total cohort; this was comparable to the results of the Japan Clinical Oncology Group 0404, which is the Japanese classical randomized controlled trial comparing surgical outcomes between open and laparoscopic colectomies, in which the postoperative haemorrhage was 0.8% and 1.1% in open and laparoscopic procedures ($P = .75$), respectively.[15] When we compared cases with and without anti-thrombotic agents, the incidence of major haemorrhagic complications was significantly higher in the AT group than in the non-AT group despite sufficiently long period of medication discontinuation. Based on the literature, the haemorrhagic complications did not increase after abdominal surgery without withdrawal of aspirin,[15–18] whereas it could increase after the procedure with heparin bridge.[28,29] In the current study, the assessment by haemorrhagic site showed that the rate of

TABLE 7 Postoperative incidences of gastroduodenal haemorrhage

Sex/Age	Procedure	Operation time	Blood loss	Other complication	Date of bleeding (Grade)	AT agent	Withdrawal (heparin)	Medical history
Male/82	HAR	143	20	None	3¶ (IIIa)	Aspirin (heparin bridge)	7 days before op	HT
Male/84	HAR	225	10	None	5¶ (II)	Aspirin Clopidogrel Warfarin (heparin bridge)	14 days before op 14 days before op 14 days before op	ACS after PCI AF
Male/82	APR	292	20	None	7¶ (IIIa)	Aspirin	6 days before op	ACS after PCI AAA after EVAR

Abbreviations: AAA, abdominal aortic aneurysm; ACS, acute coronary syndrome; AF, atrial fibrillation; APR, abdominoperineal resection; AT, cases with antithrombotic agents; EVAR, endovascular aortic repair; HAR, high anterior resection; PCI, percutaneous coronary intervention; ¶, before resuming the AT medication.

severe haemorrhage from surgical site (anastomosis and peritoneal cavity) was similar in both groups. Instead, the rate of haemorrhagic gastric ulcer was higher in AT group than in the non-AT group. All three patients who experienced gastric haemorrhage were on aspirin. It is well-known that aspirin itself could induce gastric ulcer.[30,31] Therefore, surgeons should attend more carefully to haemorrhagic ulcer and screen patients to determine whether they have ulcers preoperatively, especially in patients on antithrombotic agents. Two out of three patients who had gastric ulcers had heparinization before and after the surgery in the present study; therefore, it is possible that the heparinization encouraged the haemorrhagic diathesis. Surgeons may therefore need to take gastric bleeding into careful consideration when they perform laparoscopic colorectal surgery in a patient on antithrombotic medication.

One limitation of this study is the low incidence rate of the evaluated endpoints. To confirm the result of the current study, studies with more cases are needed in the future. Moreover, we could not accurately assess the relationship between the types and duration of the withdrawn medications and the incidence of thrombotic events because of its low rate of incidence. We investigated the outcomes in patients who underwent surgery between 2010 and 2013, and there were only few patients using direct oral anticoagulants such as dabigatran, edoxaban, and rivaroxaban, which are novel alternative agents to warfarin that were introduced in 2011. Their anticoagulation effects are similar or superior to those of warfarin,[32] their dose adjustment is easier, and their incidence of cerebral bleeding is lower than that of warfarin.

Nevertheless, we reported here, for the first time, the incidence of postoperative cardiovascular thrombotic complications after laparoscopic colorectal resection in a Japanese real-world large cohort. In the future, we will investigate this topic in a larger nationwide cohort to confirm the results of this study. Our study implies that thrombotic events after laparoscopic colorectal cancer resection are rare but may lead to poor outcomes requiring heavy intervention or resulting in sequelae. Therefore, surgeons should consider the potential risk of thrombosis during surgery. Based on our data from the current study, there is not enough evidence for deriving the implication of the aggressive intervention to avoid thrombotic complications during the perioperative period, such as continuing the anticoagulant/antiplatelet medication or additional anticoagulant/antiplatelet medication. However, surgeons should dedicate efforts to lessen the surgical stress and consider more straightforward procedures when possible, especially in cases with higher CHADS2 scores. For patients receiving anticoagulant/antiplatelet medications, medication withdrawal should be limited sufficiently to the crucial period.

5 | CONCLUSIONS

The incidence of the cardiovascular thrombotic complications after laparoscopic colorectal resection in cancer patients was 0.2%. Cardiovascular thrombotic complications were rare compared

to other postoperative complications. However, critical cardiovascular complications could occur even after minimally invasive surgery. Therefore, surgeons should take more care regarding these complications, given the aging population on antithrombotic medication.

ETHICAL STATEMENT

The protocol for this research project has been approved by a suitably constituted Ethics Committee of the institution and it conforms to the provisions of the Declaration of Helsinki. Committee of Hokkaido University Hospital and all participating hospitals, Approval No. 019-0265. Informed consent was obtained from all patients for being included in the study by opt-out method.

DISCLOSURE

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Author Contributions: Ichikawa N, Homma S and Taketomi A conceived the idea for this study. Funakoshi T, Obuchi K, Ohshima T, Uemura K, Kon H, Ohno Y, Yokota, Kazui K, Ishikawa T, Mizukami T, Mino K, Maeda Y, Yoshida T, Shimokuni T, Aiyama T, Ono H, and Morita T contributed to the data collection. Ichikawa N performed statistical analyses and prepared the manuscript. All authors participated in the interpretation and analysis of the data, revised the manuscript, and read and approved the final version.

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REFERENCES

1. Statistics and Information Department, Ministry of Health, Labour and Welfare, Japanese Government. Abridged Tables for Japanese patients of major disease in 2017 [cited 9 Jul 2021]. Available from: https://www.mhlw.go.jp/toukei/saikin/hw/kanja/17/dl/01.pdf
2. Yamazaki T, Goto S, Shigematsu H, Shimada K, Uchiyama S, Nagai R, et al. Prevalence, awareness and treatment of cardiovascular risk factors in patients at high risk of atherothrombosis in Japan. Circ J. 2007;71(7):995–1003.
3. Albertson M, Sharma J. Stroke: current concepts. S D J Med. 2014;67(11):455–65.
4. Gelbenegger G, Erari-Canyurt U, Grafeneder J, Jilma B, Lesiak M, Komosa A, et al. Optimal duration and combination of antiplatelet therapies following percutaneous coronary intervention: a meta-analysis. Vascul Pharmacol. 2021;138:106858.
5. Fujimoto K, Fujishiro M, Kato M, Higuchi K, Iwakiri R, Sakamoto C, et al. Guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment. Dig Endosc. 2014;26(1):1–14.
6. Vivas D, Roldán I, Ferrandis R, Marín F, Roldán V, Tello-Montoliu A, et al. Perioperative and Periprocedural Management of Antithrombotic Therapy: Consensus Document of SEC, SEDAR, SEACV, SECTCV, AEC, SECPRE, SEPD, SEGO, SEHH, SETH, SEMERGEN, SEMFYC, SEMG, SEMICYUC, SEMI, SEMES, SEPAR, SENEC, SEO, SEPA, SERVEI, SECOT and AEU. Rev Esp Cardiol (Engl Ed). 2018;71(7):553–64.
7. Maulaz AB, Bezerra DC, Michel P, Bogousslavsky J. Effect of discontinuing aspirin therapy on the risk of brain ischemic stroke. Arch Neurol. 2005;62(8):1217–20.
8. Sibon I, Orgogozo JM. Antiplatelet drug discontinuation is a risk factor for ischemic stroke. Neurology. 2004;62(7):1187–9.
9. Ferrari E, Benhamou M, Cerboni P, Marcel B. Coronary syndromes following aspirin withdrawal: a special risk for late stent thrombosis. J Am Coll Cardiol. 2005;45(3):456–9.
10. Rhee SJ, Yun KH, Lee SR, Chae J-K, Nam C-W, Jun D-H, et al. Drug-eluting stent thrombosis during perioperative period. Int Heart J. 2008;49(2):135–42.
11. Palareti G, Legnani C, Guazzaloca G, Frascaro M, Grauso F, De Rosa F, et al. Activation of blood coagulation after abrupt or stepwise withdrawal of oral anticoagulants–a prospective study. Thromb Haemost. 1994;72(2):222–6.
12. Garcia DA, Regan S, Henault LE, Upadhyay A, Baker J, Othman M, et al. Risk of thromboembolism with short-term interruption of warfarin therapy. Arch Intern Med. 2008;168(1):63–9.
13. Lacy AM, García-Valdecasas JC, Delgado S, Castells A, Taurá P, Piqué JM, et al. Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomised trial. Lancet. 2002;359(9325):2224–9.
14. van der Pas MH, Haglind E, Cuesta MA, Fürst A, Lacy AM, Hop WCJ, et al. Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. Lancet Oncol. 2013;14(3):210–8.
15. Yamamoto S, Inomata M, Katayama H, Mizusawa J, Etoh T, Konishi F, et al. Short-term surgical outcomes from a randomized controlled trial to evaluate laparoscopic and open D3 dissection for stage II/III colon cancer: Japan Clinical Oncology Group Study JCOG 0404. Ann Surg. 2014;260(1):23–30.
16. Ohya H, Watanabe J, Suwa Y, Nakagawa K, Suwa H, Ozawa M, et al. Comparison of the continuation and discontinuation of perioperative antiplatelet therapy in laparoscopic surgery for colorectal cancer: A retrospective, multicenter, observational study (YCOG 1603). Ann Gastroenterol Surg. 2020;5(1):67–74.
17. Yoshimoto Y, Fujikawa T, Tanaka A, Hayashi H, Shimoike N, Kawamoto H, et al. Optimal use of antiplatelet agents, especially aspirin, in the perioperative management of colorectal cancer patients undergoing laparoscopic colorectal resection. World J Surg Oncol. 2019;17(1):92.
18. Taguchi K, Shimomura M, Egi H, Hattori M, Mukai S, Kochi M, et al. Is laparoscopic colorectal surgery with continuation of antiplatelet therapy safe without increasing bleeding complications? Surg Today. 2019;49(11):948–57.
19. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205–13.
20. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA. 2001;285(22):2864–70.
21. Tabata N, Yamamoto E, Hokimoto S, Yamashita T, Sueta D, Takashio S, et al. Prognostic value of the $CHADS_2$ score for adverse cardiovascular events in coronary artery disease patients without atrial fibrillation-a multi-center observational cohort study. J Am Heart Assoc. 2017;6(8):e006355.
22. Zhou X, Cao K, Kou S, Qu S, Li H, Yu Y, et al. Usefulness of $CHADS_2$ score for prognostic stratification of patients with coronary artery

disease: a systematic review and meta-analysis of cohort studies. Int J Cardiol. 2017;1(228):906–11.
23. van den Bosch T, Warps AK, de Nerée tot Babberich MPM, Stamm C, Geerts BF, Vermeulen L, et al. Predictors of 30-day mortality among Dutch patients undergoing colorectal cancer surgery, 2011-2016. JAMA Netw Open. 2021;4(4):e217737. Erratum in: JAMA Netw Open. 2021 Aug 2;4(8):e2127694.
24. Rajeev-Kumar G, Sarpel U, Dhamoon MS. Risk of stroke after colorectal surgery for cancerous versus benign conditions. J Stroke Cerebrovasc Dis. 2018;27(11):3311–9.
25. Sanaiha Y, Juo YY, Aguayo E, Seo Y-J, Dobaria V, Ziaeian B, et al. Incidence and trends of cardiac complications in major abdominal surgery. Surgery. 2018;164(3):539–45.
26. Li YS, Meng FC, Lin JK. Procedural and postoperative complications associated with laparoscopic versus open abdominal surgery for right-sided colonic cancer resection: a systematic review and meta-analysis. Medicine (Baltimore). 2020;99(40):e22431.
27. Bassand JP, Accetta G, Al Mahmeed W, Corbalan R, Eikelboom J, Fitzmaurice DA, et al. Risk factors for death, stroke, and bleeding in 28,628 patients from the GARFIELD-AF registry: rationale for comprehensive management of atrial fibrillation. PLoS One. 2018;13(1):e0191592.
28. Douketis JD, Spyropoulos AC, Kaatz S, Becker RC, Caprini JA, Dunn AS, et al. Perioperative bridging anticoagulation in patients with atrial fibrillation. N Engl J Med. 2015;373(9):823–33.
29. Yong JW, Yang LX, Ohene BE, Zhou YJ, Wang ZJ. Periprocedural heparin bridging in patients receiving oral anticoagulation: a systematic review and meta-analysis. BMC Cardiovasc Disord. 2017;17(1):295.
30. Hawkey CJ. Review article: aspirin and gastrointestinal bleeding. Aliment Pharmacol Ther. 1994;8(2):141–6.
31. Iwamoto J, Saito Y, Honda A, Matsuzaki Y. Clinical features of gastroduodenal injury associated with long-term low-dose aspirin therapy. World J Gastroenterol. 2013;19(11):1673–82.
32. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369(22):2093–104.

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APPENDIX 1

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