

Perioperative Safety of Gastrectomy for Patients Receiving Antithrombotic Treatment

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Abstract

Background: With the aging population, more patients are expected to receive antithrombotic treatment. Although many studies have investigated the perioperative management of antithrombotic therapy, few have targeted gastrectomy. Hence, the safety of gastrectomy for patients receiving antithrombotic agents remains unclear. This retrospective cohort study sought to compare outcomes between patients who did and did not receive antithrombotic agents.

Methods: This single-center retrospective cohort study included 548 patients who underwent gastrectomy for primary gastric adenocarcinoma from January 2011 to December 2019. Patients were subsequently classified into two groups according to whether they received antithrombotic therapy (n = 121) or not (n = 427), after which surgical outcomes were compared. Propensity score analysis was performed based on age, sex, body mass index, open versus laparoscopic surgery, and total versus distal gastrectomy. After propensity score matching, 121 patients were included in each group.

Results: Among the entire cohort, receiving antithrombotic therapy group was significantly older than those who did not (age \geq 75 years, 48% vs. 33%; $p \leq 0.0001$). Those receiving antithrombotic therapy had significantly higher postoperative complication rates than those who did not (33.1% vs. 23.9%; $p = 0.046$). After matching, no significant difference in the postoperative complication rate was observed between both groups.

Conclusion: Despite having a high risk for postoperative complications, patients receiving antithrombotic therapy can safely undergo gastric resection.

Introduction

Gastric cancer is one of the fifth most common malignancies globally, especially East Asia [1]. Considering that surgical treatment remains the first choice for localized advanced gastric cancer, gastrectomy has been one of the major gastrointestinal surgeries in Japan.

In general, an aging population, such as that in Japan, exhibits increased risk for cardiovascular disease [2, 3]. Despite the growing use of antithrombotic agents for CVD, appropriate perioperative management of those receive antithrombotic agents still remains controversial. Gotoh et al. [4] reported an association between heparin bridging and postoperative adverse events during surgery or medical procedures. The JCS 2020 guideline [5] describes perioperative management of anticoagulants in detail based on individual risk. However, the aforementioned studies had not focused on gastrectomy. In the current study, 22.8% of the patients who underwent gastrectomy from 2011 to 2019 had received antithrombotic therapy. Moreover, they were older and had more comorbidities, such as hypertension and diabetes mellitus, than patients not receiving antithrombotic therapy. Owing to their age and comorbidities, patients receiving antithrombotic therapy had significantly increased incidence of postoperative complications.

Recently, an updated guideline had provided recommendations for the perioperative management of patients receiving antithrombotic therapy based on their medical history and risk [6]. The antiplatelet therapy for preventing thrombosis in patients with cerebrovascular or cardiovascular disease should not be discontinued for surgery if possible. Anticoagulation therapy for preventing ischemic stroke in patients with arrhythmia or treating deep vein thrombosis (DVT)/pulmonary embolism (PE) is more challenging. Nonetheless, the aforementioned findings had been based on various types of surgery, not particular gastrectomy. Although bleeding risk following gastrectomy can be "high" according to the EHAR guideline, only a few studies have investigated outcomes following gastrectomy for patients receiving antithrombotic therapy. The current study therefore sought to investigate the perioperative outcomes of gastrectomy among patients receiving antithrombotic therapy.

Methods

Study design and patients

This single-center retrospective cohort study enrolled 662 patients who underwent gastrectomy for primary gastric adenocarcinoma from January 2011 to December 2019. All patients preoperatively underwent esophagogastroduodenoscopy, computed tomography and/or positron emission tomography. The diagnosis was based on the Japanese Classification of Gastric Carcinoma [October 2017 (The 15th Edition)], Japanese Gastric Cancer Association [7]. Eligibility criteria included age of 20 years old or older, cT1-4 and cN0/+, and partial or total gastrectomy. Patients who had remnant gastric cancer (n = 34) and underwent preoperative chemotherapy or chemoradiotherapy (n = 40), robot-assisted surgery (n = 17), and composite resection of the lower part of the esophagus (n = 23) were excluded.

This study was approved by the Ethics Committee of Kobe University and the institutional review board (No. B200365). Informed consent was obtained from all patients who satisfied the inclusion criteria.

Anticoagulant and antithrombotic therapy

Patients receiving antithrombotic therapy were defined as those who had received antithrombotic agents for prophylaxis of acute coronary artery disease or brain infarction or treatment of DVT/PE. Antithrombotic agents included anticoagulants, such as warfarin and non-vitamin K antagonist direct oral anticoagulants (DOACs) (e.g., rivaroxaban, apixaban, edoxaban, and betrixaban), and antiplatelets, such as aspirin and others (e.g., clopidogrel, dipyridamole, prasugrel, ticlopidine, cilostazol, and ethyl icosapentate). All patients receiving antithrombotic therapy were referred to cardiologists regarding indications for continuation or discontinuation during surgery. In general, heparin bridging was needed for patients treated with DVT/PE or dual antiplatelet therapy within 6 months after percutaneous coronary intervention for acute coronary syndrome. The use of a single aspirin for prophylaxis of acute coronary artery disease was continued during surgery. Single DOAC or antiplatelet agents, excluding aspirin for prophylaxis, were discontinued during surgery and resumed within 24–72 h after surgery if possible.

Outcomes

Data regarding age, sex, body mass index, comorbidities, laboratory findings, operative data, and postoperative clinical course were extracted from medical records. Operative time, intraoperative blood loss, and transfusion were then compared between patients who did and did not receive antithrombotic therapy. Postoperative complications based on the Clavien–Dindo (C-D) classification were also analyzed. Postoperative complications included postoperative hemorrhage, thrombosis, surgical site infection (SSI), anastomotic leakage, pancreatic leakage, postoperative pneumonia, and arrhythmia. We thought clinically significant postoperative complications were two or more grade of the C-D classification.

Statistical analysis

To remove any bias from all observed covariates, two groups of patients were established using propensity score (PS) matching. PSs for individuals were calculated using age, sex, tumor invasion depth, lymph node metastasis, surgical approach (open or laparoscopic), and procedures as covariates. Accordingly, one group patient was sequentially matched to another group patient using the PSs with a 1:1 nearest neighbor matching algorithm without replacement. To prevent low matches, a caliper equal to 0.20 of the standard deviation of the logit of the PS was used. The χ^2 test, Student's t-test, or Mann–Whitney U test were performed to determine statistical differences between both groups as appropriate, with P values < 0.05 indicating statistical significance.

All statistical computations, including PS matching, were performed using JMP® 14 (SAS Institute, Cary, NC, USA).

Results

A total of 548 patients were eligible for the current study, among whom 121 received antithrombotic therapy (Group A), while the remaining 427 did not (Group B). After PS matching, 242 patients were included in the analysis (Figure 1).

Table 1 compares the clinicopathological features of both groups. Among the entire cohort, Group A was significantly older ($p < 0.0001$) and had significantly higher incidences of hypertension (62.8% vs. 39.3%; $p < 0.0001$), type 2 diabetes mellitus (34.7% vs. 16.4%; $p < 0.0001$), and cardiac comorbidities, including heart failure and history of acute coronary syndrome (78.5% vs. 8.2%, $p < 0.0001$); than B. Table 2 summarizes the TNM and surgical factors. Accordingly, no significant differences in TNM factors, as well as surgical approach, procedures, and lymph dissection, were found between both groups. Table 3 details the operative results, incidence of postoperative complications, and postoperative hospital stay. Moreover, no significant difference in operative time, intraoperative blood loss, and transfusion were noted between both groups. Group A had a significantly higher incidence of postoperative complications than Group B [40 (33.1%) vs. 102 (23.9%); $p = 0.046$]. While no significance differences in bleeding, thrombosis, SSI, anastomotic leakage, pancreatic leakage, and Postoperative pneumonia were noted, significant differences in arrhythmic events were observed between both groups [8 (6.6%) vs. 10 (2.3%); $p = 0.037$].

After PS matching, no statistical difference in age was observed between both groups. However, group A still had significantly higher incidences of hypertension (62.8% vs. 47.1%; $p = 0.02$), type 2 diabetes mellitus (34.7% vs. 20.7%, $p = 0.02$), and cardiac comorbidities, including heart failure and history of acute coronary syndrome (78.5% vs. 10.7%; $p < 0.0001$), than Group B in the matched cohort. No significant difference in the incidence of postoperative complications were observed.

Table 4A shows the cases that developed bleeding postoperatively in the matched cohort group. Accordingly, bleeding occurred in four and three patients who did and did not receive antithrombotic agents, respectively, all of whom were men. One patient with bleeding at the stump of ASPDA underwent angiography and transcatheter arterial embolization. Table 4B shows the cases that developed thrombosis postoperatively in the matched cohort group. Thrombosis included arterial (acute coronary syndrome and stroke) and venous events. Thrombosis occurred in three and two patients who did and did not receive antithrombotic agents, respectively. All three patients who received antithrombotic agent had arterial thrombosis.

Discussion

The current study revealed that patients who received antithrombotic agents had significantly higher incidences of postoperative complications and tended to have longer postoperative hospital stay than those who did not. However, most patients who received antithrombotic agents who were elderly patients who were at risk for postoperative complications, including bleeding and thrombosis. After PS matching to account for the effects of patients' background, no significant difference in postoperative complications had been observed between both groups. As such, the aforementioned findings suggest that gastrectomy can be safely performed for patients with gastric cancer receiving antithrombotic therapy.

Bleeding is an important event during the postoperative period. Two crucial types of bleeding need careful consideration during following gastrectomy, abdominal arterial bleeding and anastomotic bleeding. Abdominal arterial bleeding after gastrectomy, although uncommon, can sometimes be life-threatening. Reported mortality rates among cases with postoperative bleeding have reached up to 26.6% [8]. In the current study, patients receiving antithrombotic therapy exhibited more bleeding events than those who did not, albeit not significantly. Among those who received antithrombotic therapy, the bleeding started around 4 to 14 days after surgery. All cases were over 70 years old and had normal anticoagulant resumption dosages. These events could have therefore been avoided through anticoagulant dose

reduction. None of the patients receiving antithrombotic therapy developed anastomotic bleeding, a surgery-specific complication. Obscure gastrointestinal bleeding occurred in two patients who received DOAC on postoperative day 10. Although the occurrence of anastomotic site bleeding was not frequently observed among those who received antithrombotic therapy, close attention should be given to obscure gastrointestinal bleeding until 1–2 weeks after surgery.

Thrombosis has also been an important postoperative event. In the current study, all thrombotic events among those who received antithrombotic therapy were arterial. Although arterial thrombosis is a potentially crucial complication, no significant differences had been observed between both groups. Elderly patients receiving a combination of antiplatelets and anticoagulants are at high risk for thrombosis. Considering that nutrition status and oral intake are unbalanced during the perioperative period, proper coagulation system monitoring and fluid volume management are important. Among those who received antithrombotic therapy, only 2 (1.65%) developed DVT, a finding consistent with that presented in a previous study showing a 1–2% incidence of postoperative DVT after sleeve gastrectomy [9].

Some limitations of the current study are worth noting. Given the retrospective, single-center design of this study, some selection biases can exist. Throughout the decades, antithrombotic agents have been utilized one after another, while CVD guidelines have been revised successively. Given the unclear individual indications for antithrombotic agents, future research is needed.

Through careful perioperative management, patients receiving antithrombotic therapy can safely undergo gastric resection despite being at high risk for postoperative complications.

Declarations

- Ethics approval and consent to participate:

This study was approved by the Ethics Committee of Kobe University and the institutional review board (No. B200365). Informed consent was obtained from all patients who satisfied the inclusion criteria. This investigation was conducted according to the principles expressed in the Declaration of Helsinki.

- Consent for publication: Not Applicable
- Availability of data and materials: Not applicable
- Competing interests:

The authors declare no conflicts of interest associated with this manuscript.

- Funding:

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Authors' contributions:

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Takuya Kudo. Takuya Kudo wrote the first draft of the manuscript, and all authors commented on previous versions of the document. All authors read and approved the final manuscript.

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Tables

Table 1. Baseline characteristics

	Whole cohort (n = 548)			Matched cohort (n = 242)		
	Antithrombotic agents (+) (n = 121)	Antithrombotic agents (-) (n = 427)	p	Antithrombotic agents (+) (n = 121)	Antithrombotic agents (-) (n = 121)	p
Sex M/F (%)	93/28 (77/23)	304/123 (71/29)	N.S.	93/28 (77/23)	97/24 (80/20)	N.S.
Age ≥ 75 y.o., yes(%)	58 (48)	143 (33)	0.004	58 (48)	68 (56)	N.S.
BMI*	22.3 [15.8-31.0]	22.2 [14.5-34.7]	N.S.	22.3 [15.8-31.0]	22.1 [15.3-28.3]	N.S.
CEA (ng/mL)*	2.8 [0.7-235.4]	2.4 [0.5-562.8]	N.S.	2.8 [0.7-235.4]	2.6 [0.5-562.8]	N.S.
CA19-9 (U/mL)*	14 [0.8-1758]	12 [0.5-3325]	N.S.	14 [0.8-1758]	12 [1.0-3325]	N.S.
Comorbidities (%)						
Hypertension	76 (62.8)	168 (39.3)	<0.0001	76 (62.8)	57 (47.1)	0.020
Diabetes mellitus	42 (34.7)	70 (16.4)	<0.0001	42 (34.7)	25 (20.7)	0.021
Cardiac disease	95 (78.5)	35 (8.2)	<0.0001	95 (78.5)	13 (10.7)	<0.001
COPD	8 (6.6)	19 (4.4)	N.S.	8 (6.6)	7 (5.8)	N.S.
Steroid user	3 (2.5)	16 (3.8)	N.S.	3 (2.5)	3 (2.5)	N.S.
Haemodialysis	3 (2.5)	6 (1.4)	N.S.	3 (2.5)	3 (2.5)	N.S.
Double cancer	10 (8.3)	48 (11.3)	N.S.	10 (8.3)	16 (13.2)	N.S.
History of cancer	26 (21.7)	87 (20.5)	N.S.	26 (21.7)	24 (20.2)	N.S.

Abbreviations: BMI, body mass index; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; COPD, chronic obstructive pulmonary disease; N.S., not significant

* median [range]

Table 2. Clinical characteristics of TNM classification and Surgical factor

	Whole cohort (n = 548)			Matched cohort (n = 242)		
	Antithrombotic agents (+) (n = 121)	Antithrombotic agents (-) (n = 427)	p	Antithrombotic agents (+) (n = 121)	Antithrombotic agents (-) (n = 121)	p
Tumor depth			N.S.			N.S.
T1	55 (45.5)	239 (56.0)		55 (45.5)	56 (46.3)	
T2	24 (19.8)	61 (14.3)		24 (19.8)	24 (19.8)	
T3	33 (27.3)	86 (20.1)		33 (27.3)	34 (28.1)	
T4	9 (7.4)	41 (9.6)		9 (7.4)	7 (5.8)	
LN metastasis			N.S.			N.S.
N0	91 (75.2)	332 (77.8)		91 (75.2)	91 (75.2)	
N+	30 (24.8)	95 (22.2)		30 (24.8)	30 (24.8)	
Distant metastasis			N.S.			N.S.
M0	118 (97.5)	415 (97.2)		118 (97.5)	119 (98.3)	
M1	3 (2.5)	12 (2.8)		3 (2.5)	2 (1.7)	
Approach (%)			N.S.			N.S.
Open	34 (28.9)	110 (25.8)		34 (28.9)	34 (28.9)	
Laparoscopic	86 (71.1)	317 (74.2)		86 (71.1)	86 (71.1)	
Procedure (%)			N.S.			N.S.
Total gastrectomy	32 (26.4)	124 (29.0)		32 (26.4)	35 (28.9)	
Distal gastrectomy	89 (73.5)	303 (71.0)		89 (73.5)	86 (71.1)	
LN dissection (%)			N.S.			N.S.
D1+	60 (49.6)	179 (41.9)		60 (49.6)	56 (46.3)	
D2	61 (50.4)	248 (58.1)		61 (50.4)	65 (53.7)	

Based on the Union for International Cancer Control (UICC) tumor-node-metastasis (TNM) classification 8th edition]

Table 3. Results

* the Clavien-Dindo classification \geq II

Table 4. Summary of postoperative bleeding cases and thrombosis cases

A. Patients who developed bleeding after surgery

Antithrombotic agents	Age	Sex	Procedure	agent	Heparin	Events	C-D Grade	POD
Yes	89	M	TG	DOAC	-	Obscure gastrointestinal bleeding	2	10
	88	M	DG	DOAC	-	Obscure gastrointestinal bleeding	2	10
	80	M	DG	APA+Warfarin	+	Bleeding at trocar site	2	14
	73	M	DG	DOAC	+	Bleeding at the stump of ASPDA	3a	4
No	77	M	DG	-	-	Anastomotic Bleeding	3a	9
	69	M	DG	-	-	Anastomotic Bleeding	3a	0
	53	M	DG	-	-	Anastomotic Bleeding	3a	2

B. Patients developed thrombosis after surgery

	Whole cohort (n = 548)			Matched cohort (n = 242)		
	Antithrombotic agents (+) (n = 121)	Antithrombotic agents (-) (n = 427)	p	Antithrombotic agents (+) (n = 121)	Antithrombotic agents (-) (n = 121)	p
Operative time, min	323.5 [169-986]	345.5 [132-951]	N.S.	323.5 [169-986]	347.1 [146-951]	N.S.
Blood loss	220.8 [0-1770]	230.0 [0-3281]	N.S.	220.83 [0-1770]	252.2 [0-3281]	N.S.
Transfusion	85.8 [0-1400]	60.4 [0-1680]	N.S.	85.8 [0-1400]	82.8 [0-1680]	N.S.
Complications(%)*	40 (33.1)	102 (23.9)	0.046	40 (33.1)	34 (28.1)	N.S.
Bleeding	4 (3.3)	8 (1.9)	N.S.	4 (3.3)	3 (2.5)	N.S.
Thrombosis	3 (2.5)	6 (1.4)	N.S.	3 (2.5)	2 (1.7)	N.S.
Surgical site infection	4 (3.3)	20 (4.7)	N.S.	4 (3.3)	5 (4.1)	N.S.
Anastomotic leakage	2 (1.7)	16 (3.7)	N.S.	2 (1.7)	8 (6.6)	N.S.
Pancreatic leak	14 (11.6)	32 (7.5)	N.S.	14 (11.6)	12 (9.9)	N.S.
Postoperative pneumonia	1 (0.8)	8 (1.9)	N.S.	1 (0.8)	1 (0.8)	N.S.
Arrythmia	8 (6.6)	10 (2.3)	0.037	8 (6.6)	2 (1.7)	0.02
Postoperative hospital stay	26.3 [7-285]	22.8 [8-179]	N.S.	26.27 [7-285]	25.34 [8-142]	N.S.

Antithrombotic agents	Age	Sex	Procedure	Agent	Heparin	Events	C-D Grade	POD
Yes	83	M	DG	APA + Warfarin	+	Stroke	3b	16
	80	M	DG	APA + Warfarin	+	ACS	3a	4
	67	F	DG	DOAC	-	Stroke	2	1
No	79	F	TG			DVT	2	10
	72	F	DG			DVT	2	6

Abbreviations: ACS, acute coronary syndrome; AP, angina pectoris; APA, antiplatelet agents; ASPDA, anterior superior pancreaticoduodenal artery; CAG, coronary angiography; C-D, Clavien-Dindo classification; DG, distal gastrectomy; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; POD, postoperative day; TG, total gastrectomy

Figures

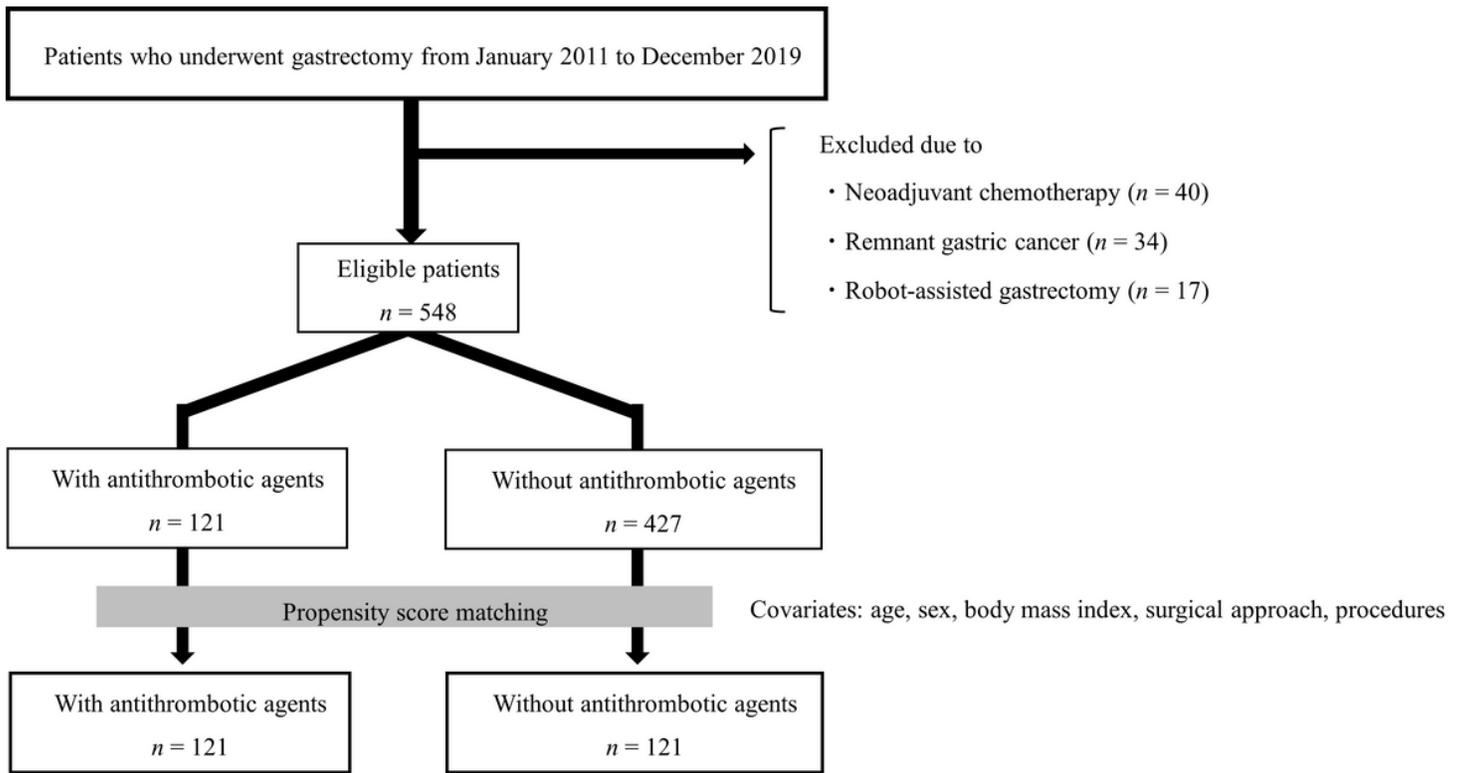


Figure 1

Flowchart