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# Perioperative Safety of Gastrectomy for Patients Receiving Antithrombotic Treatment

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**Abstract.** *Background/Aim: 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. Patients and Methods: This single-center retrospective cohort study included 548 patients who underwent gastrectomy for primary gastric adenocarcinoma from January 2011 to December 2019. The surgical outcomes were compared between two groups according to whether they received antithrombotic therapy (n=121) or not (n=427). Results: Among the entire cohort, the patients in the antithrombotic therapy group were significantly older than those who did not receive this therapy and had significantly higher postoperative complication rates than those who did not (33.1% vs. 23.9%; p=0.046). However, after propensity score matching, no significant difference in the postoperative complication rate was observed between the two groups. Conclusion: Despite having a high risk for postoperative complications, patients receiving antithrombotic therapy can safely undergo gastric resection.*

Gastric cancer is the fifth most common malignancy worldwide, especially in 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 an increased risk for cardiovascular disease (2, 3). Despite the growing use of antithrombotic agents for CVD, appropriate perioperative management of those receiving antithrombotic agents still remain 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 has 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 have 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 in patients receiving antithrombotic therapy. The current study therefore sought to investigate the perioperative outcomes of gastrectomy among patients receiving antithrombotic therapy.



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*Key Words:* Antithrombotic treatment, gastrectomy, gastric cancer.

## Patients and 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)], and the 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 considered clinically significant postoperative complications were grade two or more 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 $\chi^2$ 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 I 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 II 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 the groups. Table III details the operative results, incidence of postoperative complications, and postoperative hospital stay. Moreover, no significant difference in operative time, intraoperative blood loss, and transfusion was 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 significant differences in bleeding, thrombosis, SSI, anastomotic leakage, pancreatic leakage, and postoperative pneumonia were noted, significant differences in arrhythmic events were observed between the groups [8 (6.6%) *vs*. 10 (2.3%); $p=0.037$].

After PS matching, no statistically significant difference in age was observed between the 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 IV 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 V 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.

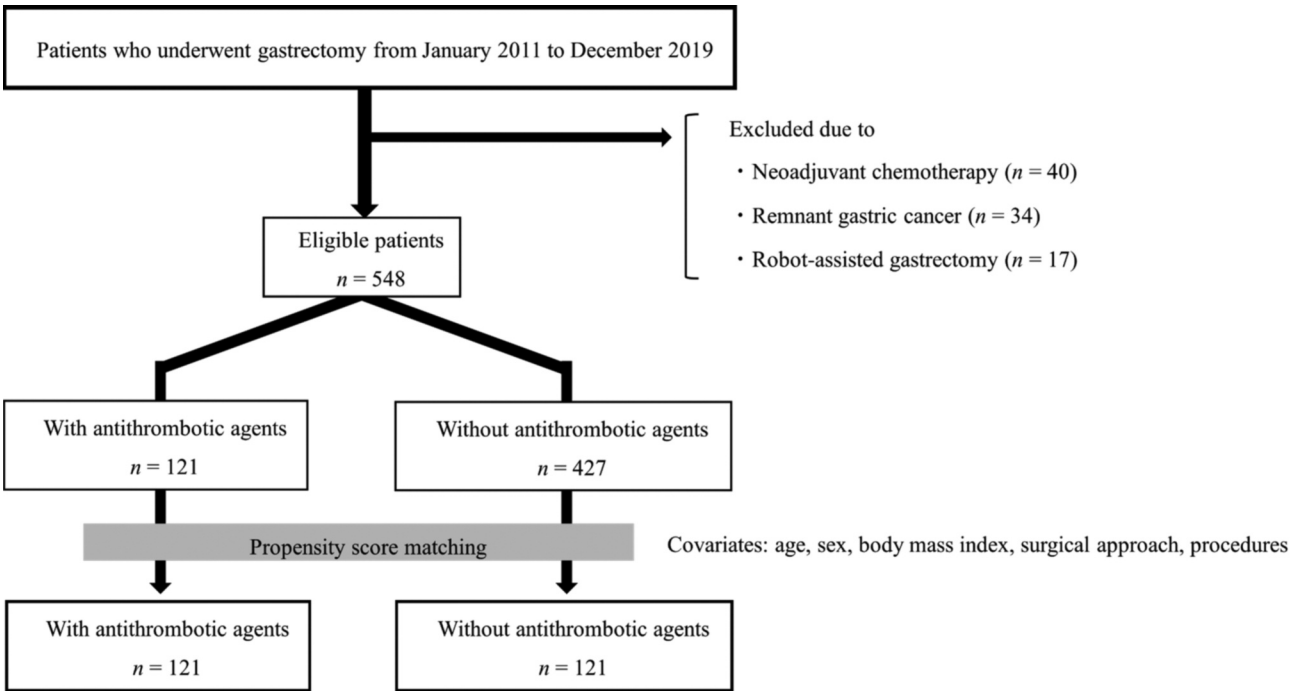


Figure 1. *Flowchart of this study.*

Table I. *Baseline characteristics*.

| | Whole cohort (n=548) | | | Matched cohort (n=242) | | |
|---|---|---|---|---|---|---|
| | Antithrombotic agents (+) (n=121) | Antithrombotic agents (−) (n=427) | *p*-Value | Antithrombotic agents (+) (n=121) | Antithrombotic agents (−) (n=121) | *p*-Value |
| Gender 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. |

BMI: Body mass index; CA19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; COPD: chronic obstructive pulmonary disease; N.S.: not significant. *Median (range).

## 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 were elderly patients who were at risk for postoperative complications, including bleeding and thrombosis. After PS

Table II. *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*-Value | Antithrombotic agents (+) (n=121) | Antithrombotic agents (–) (n=121) | *p*-Value |
| 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 III. *Operative results, incidence of postoperative complications, and postoperative hospital stay.*

| | Whole cohort (n=548) | | | Matched cohort (n=242) | | |
|---|---|---|---|---|---|---|
| | Antithrombotic agents (+) (n=121) | Antithrombotic agents (–) (n=427) | *p*-Value | Antithrombotic agents (+) (n=121) | Antithrombotic agents (–) (n=121) | *p*-Value |
| 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 (0-1,770) | 230.0 (0-3,281) | N.S. | 220.83 (0-1,770) | 252.2 (0-3,281) | N.S. |
| Transfusion | 85.8 (0-1,400) | 60.4 (0-1,680) | N.S. | 85.8 (0-1,400) | 82.8 (0-1,680) | 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. |

*The Clavien–Dindo classification ≥II.

matching to account for the effects of patients' background, no significant difference in postoperative complications was observed between the 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 following gastrectomy, abdominal arterial bleeding and anastomotic bleeding. Abdominal arterial bleeding after gastrectomy, although uncommon, can

Table IV. *Summary of postoperative bleeding cases.*

| Antithrombotic agents | Age | Gender | 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 |

APA: Antiplatelet agents; ASPDA: anterior superior pancreaticoduodenal artery; DG: distal gastrectomy; TG: total gastrectomy; DOAC: direct oral anticoagulant; M: male.

Table V. *Summary of postoperative thrombosis cases.*

| Antithrombotic agents | Age | Gender | 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 |

ACS: Acute coronary syndrome; APA: antiplatelet agents; 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; M: male; F: female.

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 between 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 were observed between the 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 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.

## Conflicts of Interest

The Authors declare no conflicts of interest associated with this study.

## 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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