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A multicenter randomized controlled trial comparing administration of antithrombin III after liver resection (HiSCO-05 trial)

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ABSTRACT

Background: Posthepatectomy liver failure is a poor prognostic factor after hepatectomy. Various preventive treatments have been tried; however, there are no clinical trials that use posthepatectomy liver failure as the primary endpoint, and the clinical effects of posthepatectomy liver failure have not been fully verified. The aim of this study was to investigate whether administration of antithrombin III can prevent posthepatectomy liver failure in patients with coagulopathy after hepatectomy. This study also evaluated the safety of AT-III administration after hepatectomy.

Methods: The current study enrolled 141 patients diagnosed with coagulopathy after hepatectomy between October 2015 and September 2018 at 7 hospitals in Hiroshima, Japan (HiSCO group). Patients were randomized to undergo either administration of antithrombin III ($n = 64$) or non-administration ($n = 77$). The primary endpoint was the incidence of posthepatectomy liver failure. This randomized controlled trial was registered with the University Medical Information Network Clinical Trial Registry (UMIN000018852).

Results: Treatment for postoperative coagulopathy was performed safely without adverse events. The incidence of posthepatectomy liver failure was similar in both treatment groups (nonadministration of antithrombin III group, 28.5%, versus administration of antithrombin III group, 28.1%; $P = .953$) The rate of morbidity was higher in the administration group than the non-administrated group (17.2% vs 11.7%, $P = .351$). Following the multivariate analysis of the whole study group, body mass index $\geq$25, total bilirubin $\geq$1.5 mg/dL, and the disseminated intravascular coagulation score $\geq$5 postoperatively were the independent risk factors for posthepatectomy liver failure.

Conclusion: This study showed that the administration of antithrombin III resulted in no significant difference in preventing posthepatectomy liver failure, possibly through suppressing coagulopathy.

Introduction

Liver surgery has a central role in the treatment of hepatocellular carcinoma and colorectal liver metastasis, and it has resulted in an impressive reduction in mortality and morbidity over the last

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decade.[1–3] However, as hepatectomy for liver disease is often performed for patients with insufficient hepatic functional reserve, posthepatectomy liver failure (PHLF) is still an important complication.[4]

The risk factors for PHLF have generally been reported as follows: (1) patient-related risk factors such as old age, fatty liver, hepatitis or liver cirrhosis, obstructive jaundice or cholangitis, and drug-induced liver injury due to chemotherapy; (2) surgery-related risk factors such as small remnant liver volume, prolonged operation, and excessive blood loss; and (3) postoperative risk factors such as hepatic parenchymal congestion, ischemia-reperfusion (IR) injury, and infection.[4] Coagulopathy after hepatectomy is especially noteworthy, as it occurs occasionally and can lead to disseminated intravascular coagulation (DIC) or severe liver failure.[5–7] Although future remnant liver function after hepatectomy is the most important factor for preventing PHLF, there are still few options for specific treatment of hepatic insufficiency. These include goal-directed therapy using human albumin, fresh frozen plasma, and antithrombin III (AT-III) to supplement the liver function.[8] AT-III is a heparin-binding protein and a major inhibitor of coagulation proteases, primarily thrombin and factor Xa.[9] Low levels of AT-III activity have been thought to cause venous thrombosis,[6,10,11] which is also associated with disturbance in liver microcirculation. Various preventive treatments for PHLF after hepatectomy have been tried. However, there are no clinical trials that use PHLF as the primary endpoint, and the clinical effects of PHLF have thus not been fully verified. Previously, we reported that the administration of AT-III after hepatectomy for hepatocellular carcinoma may attenuate PHLF by suppressing coagulopathy.[12] Based on the results of this previous investigation, this study included a multicenter prospective clinical trial to investigate the impact of AT-III administration for PHLF in patients who underwent hepatic resection.

Methods

Trial design

The current study was a multicenter, open, parallel-group, randomized controlled trial (RCT) that compared the incidence of clinically relevant PHLF between patients who had AT-III administered after liver resection and those who had not. The study was conducted at 7 hospitals in Hiroshima, Japan, in compliance with the ethical principles of the Declaration of Helsinki, and the protocol was approved by the institutional review board at each participating institution. All patients provided written, informed consent before enrollment in the study. The study was registered in the University Medical Information Network—Clinical Trial Registry, identification number 000018852.

Participants

Patients eligible for the study were required to meet all the following criteria: (1) underwent hepatectomy for liver diseases; (2) met the Japanese Association for Acute Medicine (JAAM) criteria for acute-phase DIC (Table I) on the day after the operation; (3) aged ≥20 years.

To evaluate coagulopathy after hepatectomy, we use the JAAM DIC criteria, which were the most used criteria in the emergency and surgical fields in Japan, when we began our research. Because the JAAM DIC criteria represent the results of preoperative hepatic reserve and surgical invasion, these criteria were used on the first day postoperatively as inclusion criteria, in order to initiate treatment. Additionally, after the 2005 first report,[13] JAAM's acute DIC criteria were amended to exclude the less sensitive DIC marker fibrinogen, and, since then, fibrinogen-free criteria have been commonly used in Japan.[14,15] DIC was diagnosed when the score was ≥4. These criteria were applied on the first day postoperatively to ensure that the treatment protocol was initiated during the early phase after surgery.

Table I
Japanese Association for Acute Medicine (JAAM) acute-phase DIC diagnosis criteria

Platelet counts	3 points	$<80 \times 10^3/\mu L$ or 50% decrease/24 hours
	1 point	≥ 80, $<120 \times 10^3/\mu L$ or 30% to 50% decrease/24 hours
FDP	3 points	≥25 μg/mL
	1 point	≥10, <25 μg/mL
PT-INR	1 point	≥1.2
SIRS score	1 point	≥3

Four points were required for criteria to be positive.
DIC, disseminated intravascular coagulation; *FDP*, fiblin/fibrinogen degradation products; *PT-INR*, prothrombin time international normalized ratio; *SIRS*, systemic inflammatory response syndrome.

Patients were excluded from participating based on the following exclusion criteria before surgery and until the treatment protocol was completed: (1) severe drug sensitivity; (2) severe liver failure (total bilirubin [T.Bil] ≥5.0 mg/dL); (3) severe postoperative complications classified as Clavien-Dindo Grade ≥IIIB[16] or difficulty continuing treatment protocol, such as surgical site bleeding, gastrointestinal bleeding, or infection that required continuous therapy; (4) severe decline in AT-III level (<30%); (5) simultaneous splenectomy; (6) simultaneous gastrointestinal anastomosis or biliary reconstruction; (7) biliary drainage; (8) anticoagulant therapy; (9) hemodialysis; (10) continuous bacterial infection; or (11) complicating psychiatric disorder.

Treatment protocol

In our Hiroshima Surgical study group of Clinical Oncology (HiSCO), hepatectomy was routinely performed using a unified surgical procedure. The type of hepatectomy selected was based on liver function and the extent of the tumor.[17–19] Liver function was assessed using the Child-Pugh classification[20] and indocyanine green retention rate at 15 minutes (ICG-R15). If liver function was sufficient, anatomic resection (segmentectomy, sectionectomy, or hemihepatectomy) was performed when they are required oncologically. In patients with insufficient hepatic reserve, limited resection was performed according to the ICG-R15 range as previously described.[17] Hepatectomy procedures were performed as previously described by Itamoto et al.[18,19] In addition, the Pringle maneuver was used during hepatectomy when necessary. After hepatectomy, the required number of drains were placed where they are needed. The drains were removed within 1 week but were extended if a bile fistula or intra-abdominal abscess occurred.

Patients assigned to the AT-III administrated group (administrated group) received 1,500 units of AT-III on the first and second postoperative days, whereas those assigned to the non-administrated group were managed postoperatively without AT-III administration. From the first to the fourth postoperative day, all patients received continuous administration of gabexate mesylate (1,500 mg/day) for the basic treatment for coagulopathy (Fig 1). Use of a prostaglandin, thrombomodulin, steroid, or fresh frozen plasma was prohibited until the primary endpoint was reached. However, the use of albumin required for daily medical care was not restricted, as postoperative albumin levels and albumin administration were not considered important factors in the treatment of coagulopathy. Two concentrations of albumin preparations were included a low concentration of albumin for perioperative acute circulatory insufficiency and a high concentration of albumin with diuretics for postoperative hypoalbuminemia, pleural effusion, and ascites. In addition, there were no restrictions on the

Protocol Treatment

Non-administrated group

operation	POD 1	POD 2	POD 3	POD 4	POD 5
gabexate mesylate 1500mg/24hr	+	+	+	+	-
AT-III 1500 units	-	-	-	-	-
					Evaluation of primary endpoint

Administrated group

operation	POD 1	POD 2	POD 3	POD 4	POD 5
gabexate mesylate 1500mg/24hr	+	+	+	+	-
AT-III 1500 units	+	+	-	-	-
					Evaluation of primary endpoint

Fig 1. Treatment protocol for the trial. *AT-III*, antithrombin III; *POD*, postoperative day.

treatment for postoperative complications at the end of the treatment.

Outcome

The primary endpoint was the efficacy of the treatment protocol for preventing PHLF. This was evaluated by the incidence of PHLF as defined by the International Study Group of Liver Surgery criteria.[21] Secondary endpoints included the safety of this protocol (which was evaluated by the incidence of adverse events), major postoperative complications (Clavien–Dindo classification system, grade ≥III),[16] mortality within 30 or 90 days of the operation, and transition of postoperative parameter of blood biochemistry or coagulation system.

Sample size

The sample size for the current study was determined based on the primary endpoint. According to previous data from our institute, the incidence of clinically relevant PHLF after hepatectomy was 44.2%[12] whereby the rate of PHLF improved after AT-III administration by 28%, from 44.2% to 16.3%. Based on these prior data, the assumed rate of clinically relevant PHLF after hepatectomy, with the administration of AT-III, was 20%. To detect such a difference, 122 patients (61 in each group) were required, which was calculated at a power of 80% with a significance level of 0.050 (2-sided). Estimating a 12% perioperative withdrawal rate or exclusion after randomization, a total of 140 patients (70 in each group) were needed to meet the primary endpoint of the study. All analyses were performed using an intention-to-treat approach, in which all randomized patients were analyzed, including those who did not undergo this protocol.

Randomization

After providing written, informed consent, all required sections of a case report form were sent via fax to the Hiroshima Surgical study group of Clinical Oncology data center (HiSCO). Patients were randomly assigned to administrated group or non-administrated group (1:1). Randomization was stratified using the modified permuted block method according to institutions, etiology (hepatitis B virus or hepatitis C virus or non-B and non-C hepatitis), the Liver Cancer Study Group of Japan classification of liver damage A or B,[22] major or minor hepatectomy, and the level of AT-III on the day after surgery (≥60% or <60%). Patients and investigators were aware of each patient's allocated treatment.

Statistical methods

Patient characteristics, intraoperative findings, and postoperative complications were compared between the 2 groups using χ^2 tests or Fisher exact test and Cochran Armitage trend test for categorical variables. For continuous variables, parametric analyses were performed using the Student's *t* test, and the Mann-Whitney *U*-test was used for nonparametric analyses. For significant factors of PHLF, determined using univariate analysis, we performed multivariate analyses using the logistic regression analysis. A difference was considered significant if the *P* value was <.050. Statistical analyses were performed using the JMP Pro 15.0.0 (SAS Institute, Cary, NC).

Definitions

Posthepatectomy coagulopathy was defined according to the JAAM acute-phase DIC diagnosis criteria 1 day postoperatively (Table I). DIC was diagnosed when the DIC score was ≥4. Liver cirrhosis was confirmed by histological examination of resected specimen. Major hepatectomy was defined as a resection of 3 or more Couinaud segments. PHLF was diagnosed based on the International Study Group of Liver Surgery definition. In brief, the International Study Group of Liver Surgery definition of PHLF is an increased prothrombin time international normalized ratio (PT-INR) and hyperbilirubinemia at 5 days after operation or later.[21] PHLF cases were classified from Grade A to C according to the regulations. All postoperative complications were reviewed for at least 30 days postoperatively and were graded as previously

described by Clavien et al.[16] Postoperative mortality was defined as any death that occurred within 30 days of surgery. Hospital death was defined as any death that occurred within 90 days of surgery.

Results

Patient enrollment

Between October 2015 and September 2018, 586 patients were scheduled to undergo hepatectomy and were assessed for eligibility for this trial. Of these, 141 patients with postoperative coagulopathy were registered for the study and randomly assigned to the non-administrated group ($n = 77$) or administrated group ($n = 64$). Although they were divided into groups according to the properties of permuted-block randomization, many stratification factors were included, and cases were thus evenly assigned among each stratification factor. The remaining 445 patients were not enrolled based on inclusion or exclusion criteria. Of the 445 remaining patients, 424 cases did not meet the JAAM's DIC diagnostic criteria. After randomization, 2 patients in the non-administrated group did not complete the treatment protocol due to anticoagulation therapy for paroxysmal atrial fibrillation onset after surgery and severe postoperative respiratory disorder caused by Mendelson's syndrome due to aspiration. Moreover, 1 patient in the administrated group did not complete the treatment protocol because of postoperative bleeding. Including these 3 patients, 141 patients (77 in the non-administrated group and 64 in the administrated group) were included in the intention-to-treat analysis. A CONSORT diagram, which is flow diagram of the progress through the phases of a parallel randomized trial of 2 groups, of the current study is shown in Figure 2.

Patient characteristics

A comparison of patient characteristics, operative statuses, and postoperative courses between the non-administrated group and administrated group is shown in Tables II and III. The postoperative day (POD) 1 laboratory findings are shown in Tables IV and V. The 2 treatment groups were comparable for institute, patient demographic data, primary disease, and preoperative laboratory data. Notably, there were no significant differences between the 2 groups according to the allocation factors. Furthermore, there were no

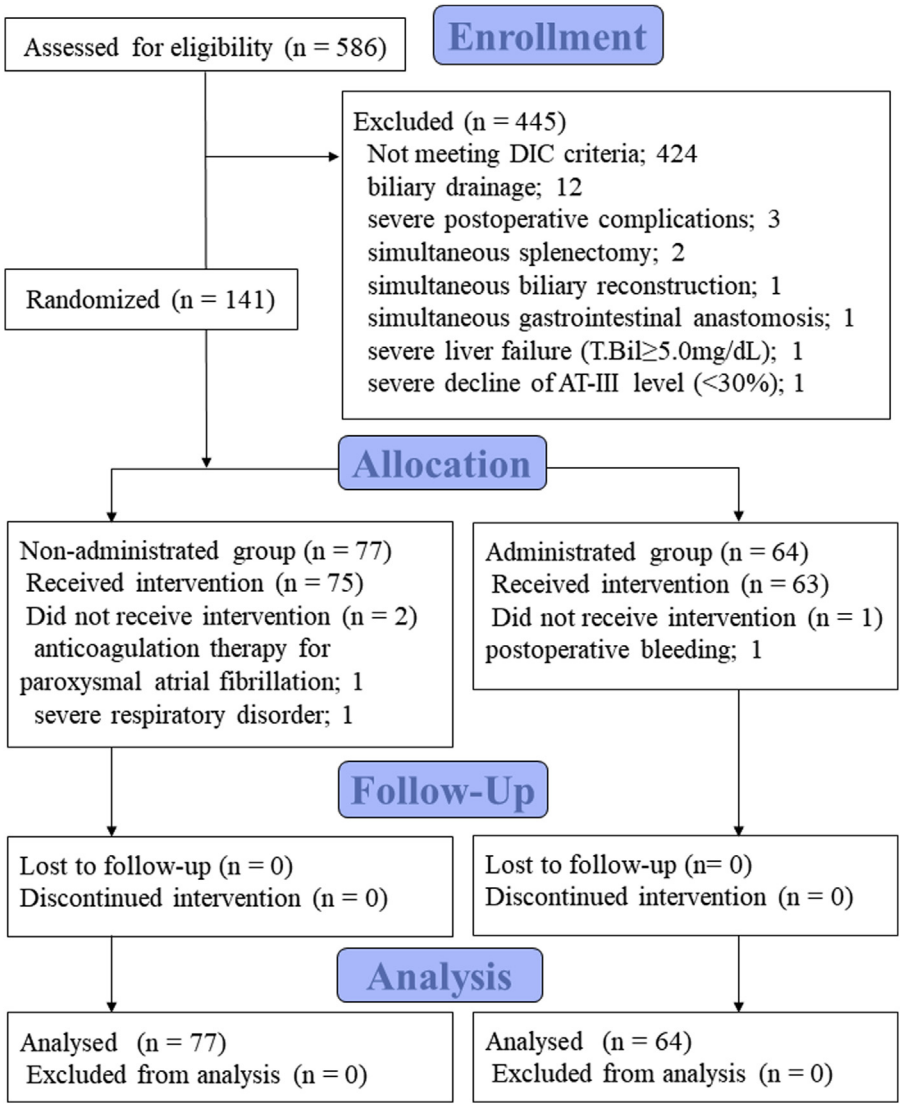

Fig 2. CONSORT diagram for the trial. *T.Bil*, total bilirubin; *AT-III*, antithrombin III.

Table II
Patient characteristics and preoperative status

	Non-administrated group (n = 77)	Administrated group (n = 64)	P value
Institutes* A/B/C/D/E/F/G	36/22/6/5/4/3/1	36/18/1/2/3/2/2	.238†
Age (years old) ‡	72 (41–88)	72 (44–87)	.941
Sex : M/F	54/23	47/17	.664
BMI‡	22.7 (17.1–41.3)	23.0 (15.8–33.1)	.702
HBV/HCV/NBNC*	12/29/36	11/26/27	.600†
Disease HCC/CCC/Meta/Other	56/2/16/3	51/4/9/0	.234†
Number of times hepatectomy:1/2/3/4/5	55/17/5/0/0	43/10/7/3/1	.348†
Liver damage A/B*	60/17	49/15	.848
WBC (/μL) ‡	4500 (1940–10300)	4600 (2300–16000)	.650
Hb (g/dL) ‡	12.3 (8.9–17.1)	12.5 (7.9–16.2)	.402
Plt ($\times 10^3$/μL) ‡	133 (43–377)	130 (41–382)	.464
PT activity (%)‡	87 (56–116)	90 (63–130)	.470
PT-INR‡	1.07 (0.93–1.36)	1.05 (0.88–1.29)	.432
FDP (μg/mL) ‡	3.6 (1.9–96.9)	4.7 (1.2–41.0)	.450
D-dimer (ng/mL) ‡	1.0 (0.3–29.7)	1.0 (0.2–15.8)	.842
TAT (ng/mL) ‡	1.6 (0.5–21.5)	1.6 (0.5–60.1)	.467
SFMC (ng/mL) ‡	3.0 (3.0–150.0)	3.0 (3.0–150.0)	.613
AT-III (%)‡	84 (48–115)	85 (44–119)	.768
T.Bil (mg/dL) ‡	0.8 (0.3–2.5)	0.7 (0.3–2.5)	.832
AST (IU/L) ‡	27 (9–171)	28 (14–102)	.193
Alb (g/dL) ‡	3.9 (2.5–4.8)	3.9 (2.0–4.7)	.371
Cr (mg/dL) ‡	0.83 (0.52–1.65)	0.79 (0.34–2.80)	.600
ICG-R15 (%)‡	11.2 (3.2–58.5)	12.4 (0.5–42.0)	.643
CRP (mg/dL) ‡	0.13 (0.01–6.01)	0.11 (0.01–11.14)	.453

Alb, albumin; *AST*, aspartate aminotransferase; *AT-III*, antithrombin III; *BMI*, body mass index; *CCC*, cholangiocellular carcinoma; *Cr*, creatinine; *CRP*, C-reactive protein; *FDP*, fiblin/fibrinogen degradation products; *Hb*, hemoglobin; *HBV*, hepatitis B virus; *HCC*, hepatocellular carcinoma; *HCV*, hepatitis C virus; *ICG-R15*, indocyanine green retention rate at 15 minutes; *Meta*, metastatic liver tumor; *NBNC*, nonB- nonC; *Plt*, platelet count; *PT*, prothrombin time; *PT-INR*, prothrombin time international normalized ratio; *SFMC*, soluble fibrin/fibrin monomer complex; *TAT*, thrombin antithrombin complex; T.Bil, total bilirubin; *WBC*, white blood cell.
* Allocation factors.
† Using the Cochran Armitage trend test.
‡ Median (range).

significant differences in the open versus laparoscopic approach, use of Pringle maneuver, estimated blood loss, intraoperative blood transfusion, resected liver weight, or postoperative laboratory data. However, there were differences in the pathological results of the liver parenchyma and score of JAAM acute-phase DIC diagnosis criteria (Table I) on POD 1. In the administrated group, there were a few patients with normal liver and many patients with high DIC scores. In the postoperative course, there was no significant deference in the use of diuretics, albumin, drain discharge on POD 1, 2, 3, between both groups. The amount of 20% or 25% albumin use in the AT-III administrated group was significantly larger than the AT-III non-administrated group (median, 200 vs 300 mL; $P = .039$).

Table III
Operative status and postoperative course

	Non-administrated group (n = 77)	Administrated group (n = 64)	P value
Major/minor hepatectomy*	10/67	7/57	.710
Open/laparoscopic surgery	67/10	50/14	.162
Resected liver weight (g)†	137 (7–2442)	114 (5–1170)	.638
Number of tumors†	1 (1–8)	1 (1–15)	.330
Size of tumor (mm)†	20 (8–300)	20 (3–160)	.922
Liver pathology results NL/CH/FL/LC	37/15/3/20	11/28/3/20	.008‡
Use of Pringle maneuver	68 (88.3%)	55 (85.9%)	.801
Pringle time (min)†	63.5 (4–140)	57 (11–152)	.207
Blood loss (g)†	465 (1–2200)	500 (10–1980)	.739
Intraoperative blood transfusion case	7 (9.1%)	9 (14.1%)	.428
Administration of 5% albumin	34 (44.2%)	26 (40.6%)	.673
Amount of 5% albumin administered (mL)†	500 (250–2500)	500 (250–5250)	.951
Administration of 20 or 25% albumin (mL)	30 (39.0%)	22 (34.4%)	.574
Amount of 20 or 25% albumin administered (mL)†	200 (50–2300)	300 (100–800)	.039
Administration of diuretics	37 (48.1%)	37 (57.8%)	.248
Drain discharge volume POD1 (mL)†	201 (21–844)	174.5 (2–1080)	.139
Drain discharge volume POD2 (mL)†	119.5 (29–925)	154 (2–1213)	.488
Drain discharge volume POD3 (mL)†	92 (4–816)	105 (0–1486)	.617

CH, chronic hepatitis; *FL*, fatty liver; *LC*, liver cirrhosis; *NL*, normal liver; *POD*, postoperative day.
* Allocation factors.
† Median (range).
‡ Using the Cochran Armitage trend test.

Table IV
Transition of postoperative parameter of blood cell count and coagulation systems

		Non-administrated group (n = 77)	Administrated group (n = 64)	P value
WBC (/μL)†	POD1	8,330 (3,080–16,300)	9,040 (1,340–23,900)	.199
	POD3	7,400 (1,182–14,430)	8,360 (2,960–16,930)	.083
	POD5	5,495 (2,040–22,100)	6,540 (1,840-16,300)	.028
	POD7	6,545 (2,110–19,600)	6610 (3,160–20,950)	.126
	POD10-14	5,800 (2,370–18,500)	6,390 (2,910–20,150)	.067
Hb (g/dL)†	POD1	10.9 (8.1–15.3)	11.2 (7.3–15.7)	.348
	POD3	10.1 (7.8–14.7)	10.5 (7.6-14.6)	.467
	POD5	10.1 (6.9–14.7)	10.1 (7.1-14.3)	.744
	POD7	10.2 (7.1–14.4)	10.2 (7.1–14.6)	.658
	POD10-14	10.0 (7.1–14.4)	10.3 (6.8–14.3)	.209
Plt ($\times 10^3$/μL)†	POD1	94 (31–240)	79 (31–317)	.589
	POD3	85 (16–219)	70 (19–308)	.419
	POD5	103 (20–262)	101 (32–404)	.263
	POD7	142 (25–343)	124 (53–468)	.142
	POD10-14	173 (29–474)	150 (53–754)	.291
PT (%)†	POD1	57 (37–103)	58 (41–107)	.793
	POD3	69 (45–95)	66 (42–100)	.154
	POD5	77 (51–101)	76 (18–109)	.829
	POD7	75 (52–99)	76 (46–101)	.597
	POD10-14	74 (54–102)	74 (49–102)	.890
PT-INR†	POD1	1.31 (0.99–1.76)	1.32 (0.97–1.64)	.659
	POD3	1.22 (1.03–1.49)	1.25 (1.00–1.62)	.136
	POD5	1.14 (1.00–1.44)	1.16 (0.97–1.50)	.564
	POD7	1.16 (1.01–1.43)	1.16 (1.00–1.48)	.293
	POD10-14	1.16 (0.99–1.39)	1.17 (0.99–1.48)	.923
FDP (μg/mL)†	POD1	27.3 (4.6–248.0)	29.0 (5.8–96.5)	.257
	POD3	19.6 (5.0–428.3)	15.3 (4.5–173.5)	.568
	POD5	29.1 (8.2–133.1)	26.2 (6.8–233.5)	.213
	POD7	35.1 (12.9–147.0)	38.0 (14.2–186.6)	.968
	POD10–14	29.1 (7.7–129.8)	29.8 (8.3–179.7)	.499
D-dimer (ng/mL)†	POD1	14.4 (3.5–69.3)	15.5 (2.9–58.1)	.440
	POD3	11.4 (2.8–92.3)	9.5 (2.5–73.7)	.170
	POD5	19.7 (6.3–107.9)	16.7 (4.9–161.1)	.077
	POD7	25.9 (7.2–107.9)	25.2 (8.5–213.0)	.489
	POD10–14	22.4 (4.7–102.2)	19.7 (5.0–177.6)	.988
TAT (ng/mL)†	POD1	23.2 (5.1–133.4)	21.8 (4.7–53.9)	.847
	POD3	15.9 (3.8–41.3)	18.2 (3.3–54.5)	.027
	POD5	15.8 (2.6–39.6)	17.4 (3.3–82.7)	.118
	POD7	14.4 (3.1–45.1)	16.2 (2.2–46.4)	.169
	POD10–14	10.8 (1.3–39.0)	11.8 (1.4–87.3)	.335
SFMC (ng/mL)†	POD1	49.6 (3.0–150)	39.0 (3.0–150)	.839
	POD3	6.9 (3.0–150)	39.0 (3.0–150)	.585
	POD5	9.7 (3.0–150)	6.35 (3.0–150)	.194
	POD7	11.4 (3.0–77.2)	7.7 (3.0–150)	.259
AT-III ≥60%/<60%*	POD1	21/56	16/48	.760
DIC score 4/5/6/7/8	POD1	33/31/7/5/1	22/19/8/12/3	.038‡

AT-III, antithrombin III; *DIC*, disseminated intravascular coagulation; *FDP*, fiblin/fibrinogen degradation products; *Hb*, hemoglobin; *Plt*, platelet count; *POD*, postoperative day; *PT*, prothrombin time; *PT-INR*, prothrombin time international normalized ratio; *SFMC*, soluble fibrin/fibrin monomer complex; *TAT*, thrombin antithrombin complex; *WBC*, white blood cell.

* Allocation factors.

† Median (range).

‡ Using the Cochran Armitage trend test.

Postoperative changes in serum albumin levels are shown in Table V, and there was no significant deference in both groups. The levels of AT-III activation at POD 1, 3, 5, and 7 were higher in the administrated group than in the non-administrated group (median, POD 1, 54 vs 52; POD 3, 86 vs 49; POD 5, 72 vs 56; and POD 7, 68 vs 64; *P* values, .911, <.001, .022, and .481, respectively) (Fig 3).

Outcome and Estimation

Differences between postoperative laboratory data of the non-administrated group and administrated group are shown in Tables IV and V. The white blood cell count at POD 3, 5, 7, and 10 to 14 was higher in the administrated group than in the non-administrated group (median, 8,360 vs 7,400; 6,540 vs 5,495; 6,610 vs 6,545; and 6,390 vs 5,800 on POD 3, 5, 7, and 10–14, respectively; *P* values, .083, .028, .126, and .067, respectively). The levels of PT-INR at POD 3, 5, 7, and 10 to 14 were higher in the administrated group than in the non-administrated group; however, the differences were not significant (median, 1.25 vs 1.22, 1.16 vs 1.14, 1.16 vs 1.16, and 1.17 vs 1.16 at POD 3, 5, 7, and 10–14, respectively; *P* values, .136, .564, .293, and .923, respectively). In the administrated group, after receiving AT-III for 2 days according to the treatment protocol, the levels of thrombin-antithrombin complex at POD 3 increased in reactivity and was significantly higher than in the non-administrated group; however, the difference narrowed thereafter (median, 18.2 vs 15.9, 17.4 vs 15.8, 16.2 vs 14.4, and 11.8 vs 10.8 at POD 3, 5, 7, and 10–14, respectively; *P* values .027, .118, .169, and .335, respectively). The levels of T.Bil at POD 3, 5, 7, and 10–14 were also slightly higher in the administrated group than in the non-administrated group (median, 1.5 vs 1.3, 1.2 vs 1.1, 1.1 vs 0.8, and 0.9 vs 0.7 at POD 3, 5, 7, and 10–14, respectively; *P* values .238, .069, .013, and .080, respectively). Finally, the levels of

Table V
Transition of postoperative parameter of blood biochemistry

		Non-administrated group (n = 77)	Administrated group (n = 64)	P value
T.Bil (mg/dL)	POD1	1.3 (0.5–3.3)	1.4 (0.5–4.5)	.412
	POD3	1.3 (0.5–4.6)	1.5 (0.5–4.6)	.238
	POD5	1.1 (0.3–3.6)	1.2 (0.4–3.8)	.069
	POD7	0.8 (0.2–2.2)	1.1 (0.4–3.6)	.013
	POD10–14	0.7 (0.3–2.0)	0.9 (0.3–2.3)	.080
AST (IU/L)	POD1	511 (66–2121)	499 (49–1580)	.826
	POD3	160 (46–914)	173 (29–1386)	.497
	POD5	50 (24–336)	58 (20–542)	.211
	POD7	35 (17–114)	39 (13–376)	.203
	POD10–14	27 (12–83)	30 (148–12)	.409
Alb (g/dL)	POD1	2.8 (1.7–3.9)	2.8 (1.8–4.1)	.878
	POD3	3.0 (2.2–3.6)	2.9 (2.1–3.9)	.312
	POD5	3.0 (2.1–3.9)	2.9 (2.0–3.8)	.215
Cr (mg/dL)	POD1	0.89 (0.51–2.50)	0.86 (0.49–3.70)	.740
	POD3	0.78 (0.41–4.12)	0.78 (0.42–3.50)	.874
	POD5	0.78 (0.44–6.04)	0.76 (0.33–3.60)	.655
	POD7	0.80 (0.41–6.57)	0.76 (0.33–3.60)	.664
	POD10-14	0.82 (0.51–8.79)	0.79 (0.34–4.10)	.535
CRP (mg/dL)	POD1	3.95 (0.91–11.35)	4.08 (0.36–15.73)	.947
	POD3	8.99 (1.61–46.00)	11.34 (1.67–87.00)	.007
	POD5	4.96 (0.61–61.00)	7.42 (0.28–65.00)	<.001
	POD7	3.39 (0.24–61.00)	4.71 (0.19–42.00)	<.001
	POD10-14	2.31 (0.06–62.00)	3.34 (0.13–23.03)	.004

All parameters are represented as median (range).
Alb, albumin; *AST*, aspartate aminotransferase; *Cr*, creatinine; *CRP*, C-reactive protein; *POD*, postoperative days; *T.Bil*, total bilirubin.

C-reactive protein at POD 3, 5, 7, and 10 to 14 were significantly higher in the administrated group than in the non-administrated group (median, 11.34 vs 8.99, 7.42 vs 4.96, 4.71 vs 3.39, and 3.34 vs 2.31 at POD 3, 5, 7, and 10–14, respectively; *P* values .007, <.001, <.001, and .004, respectively).

Primary and secondary endpoints

A comparison of postoperative outcomes with intention-to-treat analysis of the 2 treatment groups is shown in Table VI. Of the 141 patients in the intention-to-treat analysis set, PHLF was observed in 39 patients (27.7%), including 22 of 77 in the non-administrated group (28.5%) and 18 of 64 in the administrated group (28.1%). No significant difference in the incidence of PHLF was observed between the 2 treatment groups ($P = .953$). The rate of severe PHLF, grade B and C, was similar in both groups; 18 of 77 in the non-administrated group (23.4%) and 16 of 64 in the administrated group (25.0%) ($P = .822$).

Regarding the secondary endpoints, there was no adverse event due to AT-III administration in the administrated group.

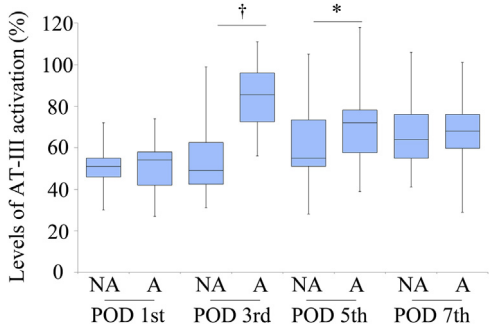

Fig 3. The transition of postoperative levels of antithrombin III activation. The patients in the administrated group received 1500 units of AT-III on postoperative days 1 and 2. Box plots represent the median, range, 25th percentile, and 75th percentile for individual groups. *AT-III*, antithrombin III; *POD*, postoperative day; *NA*, non-administrated group; *A*, administrated group; *$P < .050$ compared to non-administrated group; †$P < .010$ compared to non-administrated group.

Additionally, there was no adverse event due to gabexate mesilate administration in both the treatment groups. Furthermore, there was no significant difference between the 2 treatment groups with regard to 30-day postoperative complications (non-administrated group, 11.7% versus administrated group, 17.2%; $P = .351$), 90-day mortality rate (non-administrated group, 1.3% versus administrated group, 1.6%; $P = 1.000$) and the severity of complications ($P = .387$). Table VII shows the postoperative complications in both groups with intention-to-treat analysis.

A comparison of postoperative outcomes between the 2 treatment groups and postoperative complications in both groups in accordance with protocol analysis are shown in Supplementary Tables S1 and S2. The results of the per-protocol analysis was similar to the intention-to-treat analysis.

Ancillary analysis

As a subanalysis, we determined independent risk factors for PHLF in the 141 patients using univariate and multivariate analysis (Table VIII). According to the univariate analysis, 8 factors had significant differences, whereas from the multivariate analysis, 3 factors were determined as independent risk factors, these included, body mass index (BMI) ≥25 (hazard ratio [HR], 4.08; 95% confidence interval [CI], 1.52–10.93; $P = .005$), T.Bil ≥1.5 mg/dL (HR, 6.06; 95% CI 1.36–26.92; $P = .018$), and DIC score on POD 1 ≥5 (HR, 6.87; 95% CI 1.99–23.73; $P = .002$).

We also performed subgroup analysis for each stratification factor: activity of AT-III on POD 1, institute, liver damage, etiology, hepatectomy type, and liver disease. There was no substantial difference in the incidence of PHLF between the non-administered and the administered groups (Supplementary Table S3). Furthermore, liver condition (chronic hepatitis, liver cirrhosis) was determined as an independent risk factor of PHLF after multivariate analysis and differed in the number of cases, T.Bil levels, BMI, and DIC scores on POD 1 between the non-administered and the administered groups.

Table VI
A comparison of postoperative outcomes between the 2 treatment groups: intention-to-treat analysis

	Non-administrated group (n = 77)	Administrated group (n = 64)	P value
PHLF*	22 (28.5%)	18 (28.1%)	.953
PHLF Grade B or C*	18 (23.4%)	16 (25.0%)	.822
Adverse events due to administration of AT-III†	-	0 (0%)	-
Adverse events due to administration of gabexate mesilate†	0 (0%)	0 (0%)	1.000
30-day Dindo-Clavien <II/IIIa/IIIb/IVa/IVb/V†	68/6/0/2/0/1	53/9/1/1/0/0	.387
30-day Dindo-Clavien ≥III†	9 (11.7%)	11 (17.2%)	.351
90-day mortality†	1 (1.3%)	1 (1.6%)	1.000

AT-III, antithrombin III; *PHLF*, postoperative liver failure.
* Primary endpoint.
† Secondary endpoint.

Harm

Trends in liver enzymes such as aspartate aminotransferase and serum creatinine were similar in both groups, and there were no findings suggestive of drug-induced liver or kidney damage due to treatment protocol. No drug-related allergies were observed in either group.

One patient in the administrated group did not complete the treatment because of reoperation for postoperative bleeding. Intraoperative findings of reoperation performed on POD 2 indicated that the cause of postoperative bleeding was inadequate Glisson's pedicle ligation, which may not have been directly caused by the treatment protocol; however, the effect of AT-III administration for postoperative bleeding on POD 2 after administration of AT-III for 2 days cannot be completely ruled out.

Discussion

The aim of this study was to develop a new treatment for PHLF by improving postoperative coagulopathy using AT-III preparations early after surgery in patients with coagulopathy after hepatectomy. This study compared the changes in PHLF rates in a multicenter RCT. Various preventive treatments for PHLF after hepatectomy have been tried, including prostaglandin E1, and the effect of improving postoperative hepatic function has been partially confirmed.[23] However, there are no clinical trials that use PHLF as the primary endpoint, and the clinical effects of PHLF have not been fully verified. We have previously shown that coagulopathy after hepatectomy is a risk factor for PHLF, and AT-III has the potential to improve PHLF in retrospective studies using single-centered propensity matching. The results of this present prospective study demonstrated the safety of the protocol using the secondary endpoint of systemic antithrombin III; however, a reduction in the PHLF rate was not observed, that is, the efficacy of the primary endpoint.

There are some differences between our previous single-center retrospective study and the current RCT, and they may account for this difference in results. First, although the object of previous study was hepatic resection for hepatocellular carcinoma at a single center, this RCT included cases from multiple centers, with relatively good hepatic function, such as hepatectomy for colorectal liver metastasis. As a result, the administrated group tended to have many injured livers, including cirrhotic livers.

Second, as a subject of the retrospective analysis, AT-III was administered to patients with low levels of AT-III activity, whereas this RCT targeted patients with abnormal blood coagulation, including those with high and low levels of AT-III activity. Therefore, the subjects of the current study may be slightly different from those of the previous retrospective study. In this RCT, all the treatments were covered by the National Health Insurance. Therefore, when administrating AT-III, it was necessary to meet the diagnostic criteria for DIC, to ensure AT-III was covered by the insurance, regardless of the level of AT-III. From 2015, we decided to use the JAAM's DIC criteria, which were the most used in emergency and surgical fields among the multiple DIC criteria in Japan.

To perform the subanalysis, we set the cut-off of the AT-III level at 60% as a stratification factor during the planning of this trial, as we had previously reported that patients with AT-III levels of <60% after hepatectomy had a higher incidence of PHLF in a single-center retrospective analysis.[12] As a subanalysis of the cases with low AT-III values (AT-III, <60%), there was no difference in the incidence of PHLF between both groups (19/56 cases in non-administrated group [33.9%] vs 15/48 cases in administrated group [31.3%]; $P = .940$, Supplementary Table S3).

Third, all patients received continuous administration of gabexate mesilate (1,500 mg/day) from the first to fourth postoperative day, for the basic treatment for coagulopathy. This basic treatment may have reduced the differences between the 2 groups. Our routine management does not involve the use of gabexate mesilate after hepatectomy. However, the use of gabexate mesylate was recommended by the institutional review board (IRB) during the planning of this trial. In addition, the IRB indicated that it is ethically unacceptable not to treat the non-administrated group, who were diagnosed as DIC, even if they were asymptomatic.

Table VII
Postoperative complications in both groups: intention-to-treat analysis

	Non-administrated group (n = 77)	Administrated group (n = 64)
Dindo-Clavien IIIa	Pleural effusion/respiratory failure: 1 Intraperitoneal hematoma: 1 Bile fistula / abdominal abscess: 4	Pleural effusion and respiratory failure: 2 Bile fistula/abdominal abscess: 7
Dindo-Clavien IIIb		Postoperative bleeding: 1
Dindo-Clavien IVa	Pneumonia, respiratory failure: 1 Bile fistula, sepsis: 1	Pneumonia, respiratory failure:1
Dindo-Clavien IVb		
Dindo-Clavien V	Aspiration pneumonia, ARDS: 1	

ARDS, acute respiratory distress syndrome.

Table VIII
Univariate analysis and multivariate analysis of risk factors for PHLF in the whole study group

Variable		PHLF (+) (N = 40)	PHLF (-) (N = 98)	Univariate analysis	Multivariate analysis		
				P value	HR	95% CI	P value
BMI	≥25	15	18	.017	4.08	1.52–10.93	.005
	<25	25	80				
ICG-R15	≥20%	14	17	.031			
	<20%	26	78				
Plt ($\times 10^3/\mu L$)	<100	17	27	.087			
	≥100	23	71				
POD1 Plt ($\times 10^3/\mu L$)	<100	30	47	.004			
	≥100	10	51				
PT	<80%	14	17	.024			
	≥80%	26	81				
POD1 AT-III	<50%	21	33	.040			
	≥50%	19	65				
T.Bil (mg/dL)	≥1.5	7	4	.014	6.06	1.36–26.92	.018
	<1.5	33	94				
POD1 DIC score	≥5	35	49	<.001	6.87	1.99–23.73	.002
	<5	5	49				

95% *CI*, 95% confidence interval; *AT-III*, antithrombin III; *BMI*, body mass index; *DIC*, disseminated intravascular coagulation; *HR*, hazard ratio; *ICG-R15*, indocyanine green retention rate at 15 minutes; *PHLF*, posthepatectomy liver failure; *Plt*, platelet count; *POD*, postoperative days; *PT*, prothrombin time; *T.Bil*, total bilirubin.

Therefore, we decided to treat both groups with gabexate mesylate, which is a relatively inexpensive anti-DIC treatment.[24]

Fourth, because this was a prospective study, 445 patients were excluded from the study because they did not meet certain inclusion criteria, including the treatment protocol that had to be initiated early during postoperative period. Of the 445 patients, 424 cases did not meet the JAAM's DIC diagnostic criteria. However, we could not accurately predict before surgery whether the patient would meet the DIC criteria after hepatectomy. Furthermore, to initiate treatment immediately when coagulopathy was diagnosed, it was necessary to obtain the consent of many patients to participate before surgery. We, therefore, decided to enroll patients who had accepted the request for registration and who met the DIC diagnostic criteria the day after surgery.

After the multivariate analysis of risk factors for PHLF in the study group, postoperative coagulopathy (DIC score on POD 1) was determined. Therefore, overcoming postoperative coagulopathy is still important for the prevention of PHLF. We have previously reported that IR injury is closely related to intrahepatic microcirculation in rat liver.[25,26] In addition to its anticoagulant effects, AT-III also exerts anti-inflammatory effects by limiting the expression of adhesion molecules and cytokines and reducing hepatic IR injury by increasing the production of prostaglandins.[27,28] Notably, in this multivariate analysis, BMI ≥25 and T.Bil ≥1.5 mg/dL were revealed as independent risk factors for PHLF. As Chin et al previously reported, the albumin-bilirubin score and the ratio of pre and postoperative bilirubin levels were one of the risk factors for PHLF.[29] Moreover, T.Bil is an indication of the preoperative hepatic reserve. Regarding BMI, Urdaneta Perez et al stated that obesity (BMI of ≥35) is one of the risk factors for short-term postoperative complications among patients without comorbidities,[30] but the relationship with PHLF was unknown. It is an interesting result that a BMI of ≥25 in Japan, which is relatively lower compared to Western countries, is a risk factor for PHLF. Therefore, not only is BMI a factor of liver etiology, but it may also increase the difficulty of hepatectomy.

AT-III is a natural anticoagulant that regulates the coagulation pathway and is exclusively produced by hepatocytes. Diminished AT-III activity is considered to be central to the pathogenesis of venous embolization,[6,10,11] which is associated with a disturbance in the microcirculation of the liver. Previously, studies have reported the possible effect of AT-III after hepatectomy. Mochida et al reported that AT-III concentrates could prevent massive hepatic necrosis caused by endotoxins after partial hepatectomy in rats.[31] However, Shimada et al reported that the effect of AT-III on liver function was not always positive.[32] There were 2 reasons why the dose of AT-III was set to 1,500 units per day for 2 days in the current study. First, coagulopathy peaks up to the third day after hepatectomy, after which fibrinolytic activity is said to be enhanced.[7] Therefore, it was considered important to administer AT-III during the early postoperative period. Second, the data of our previous retrospective study, where most of cases were administered AT-III for approximately 2 days (median, 2,835 units; range, 1,500–13,500 units), showed the possible improvement in PHLF.[12] In the current study, the 1,500 units/day of AT-III administered for 2 days to the administrated group caused the AT-III values on the third and fifth days to exceed the standard values, and the values were significantly higher than those of the non-administrated group (Fig 3). In this RCT, administration of AT-III could not prevent PHLF by improving postoperative coagulopathy. We thus concluded that the administration of AT-III could not prevent PHLF, and the development of new alternative therapies is required in the future.

However, the number of postoperative complications in the administrated group was higher, although this difference was not significant. Comparing the postoperative complications of both groups, the administrated group tended to experience more postoperative bile fistulas. Biliary fistula may not be a target of AT-III therapy, unlike postoperative bleeding; however, its adverse effects should not be ruled out. Although the causal relationship could not be determined, it is hypothesized that the most probable cause of this difference is the effect of the surgical difficulty and delayed wound healing due to chronic hepatitis and liver cirrhosis, which differed between the 2 groups.

Few prospective trials and large clinical studies have investigated preventive treatments for PHLF, and recommended postoperative treatments are not well established. Among these prospective studies, steroids are reported to have anti-inflammatory activity and may be effective in managing hepatic IR injury in animal models and clinically. Hayashi et al reported that the administration of hydrocortisone during the perioperative period of hepatectomy, decreased serum T.Bil, interleukin-6, and C-reactive protein.[33] Although the improvement in postoperative liver function by branched-chain amino acid treatment has also been reported, the efficacy has not been confirmed by meta-analysis.[34,35] In a RCT, the hepatoprotective effect of the continuous

administration of prostaglandin E1 from the intraoperative period up to 1 day postoperatively was studied. It was reported that the prostaglandin E1 group showed a significant increase in interleukin-6 in liver tissue and improved postoperative liver function.[23] However, the various clinical studies described above have not examined PHLF prevention, and it still remains a problem.

Regarding the secondary endpoints, safety of the administration of AT-III and gabexate mesilate was shown in current RCT. In general, heparin, protease inhibitors, and AT-III preparations have been established and used in clinical practice for the treatment of DIC. The results of current study correspond with the use of AT-III as a treatment for portal vein thrombosis in hepatectomy patients or for prophylaxis in patients with history of thrombosis.

This RCT has some inherent limitations. One was due to its multi-institutional design. Perhaps owing to the influence of the setting, many allocation factors including the backgrounds of both groups did not completely match, and patients in the test group tended to have poorer liver functional reserve. However, as a result, even in the subgroup analysis performed for each stratification factor, there was no notable difference in the incidence of PHLF between the non-administered group and the administered group. Given the fact that liver pathology was significantly different between both groups, disease may not have been an appropriate stratifying factor.

In addition, regarding the selection of many DIC diagnostic criteria, we could not use the latest DIC criteria proposed by the Japanese Society on Thrombosis and Hemostasis, in 2016.[36] However, we used the JAAM's DIC criteria because these were standard in Japan at the time. Additionally, a DIC score of $\geq$5 on day 1 was an independent risk factor for PHLF in this study. As a result, this factor should have been added as a stratification factor, but unfortunately this fact was unpredictable at the time of study planning. The bias of the PHLF scores in both study groups may have influenced the results of the study.

Furthermore, when selecting the cases for this RCT, it was expected that groups with 2 main characteristics would be collected. One was a group with cirrhosis, that would receive a small hepatectomy because of low liver functional reserve, and the other was a group with probable liver reserve function. These 2 major clinical situations affect the pathogenic process and causes. Therefore, to investigate the effect of AT-III on PHLF, it may have been necessary to include patients that were appropriate.

In addition, the sample size in this study may have been small, and although the conditions set in this study are based on the numerical values obtained from our previous retrospective test results, using AT-III to improve the rate of PHLF may have been an optimistic expectation. However, even with the number of cases, results indicated that AT-III does not have the power to improve PHLF.

In conclusion, the current study found no significant difference due to the administration of AT-III (possibly through suppression of coagulopathy) for preventing PHLF.

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Conflict of interest/Disclosure

The authors have no related conflicts of interest to declare.

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Supplementary materials

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