Peer Review File

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Reviewer A

Major points:

1. In the Introduction section, the authors stated that there is insufficient evidence for antithrombin administration in critically ill patients, but what exactly is the patient background of critically ill patients? Does this study target critically ill patients?

-Answer to comment:

We agree with the reviewer about that.

We would like to thank you for your kind consideration.

We have corrected the sentence in the revised manuscript as the reviewer pointed out as follows: (page 10, lines 229-232)

"However, despite these favorable reports regarding the effect of antithrombin therapy on patients' outcomes, there are still several conflicting reports on the utility of antithrombin supplementation in the critical conditions such as DIC and DIC associated with trauma or sepsis."

2. It seems that the contents of the Introduction section do not match the background and purpose of this study. For example, the authors stated that there is no evidence for antithrombin supplementation for DIC in the pediatric population, but this study focused on adults, which is a different subject. The content should be consistent with the patient background of this study.

-Answer to comment:

We agree with the reviewer about that.

We would like to thank you for your kind consideration.

This study focused on adults, and it was consistently complied with in whole manuscript.

We have corrected the sentence in the revised manuscript as the reviewer pointed out as follows:

(page 10, lines 236, to page 11, lines 244)

“In an observational study 2019, Kim et al. reported high-dose antithrombin (AT) supplementation significantly improved 28-day mortality in septic shock patients with DIC [4], and Akahoshi et al. addressed targeted AT activity should be at least 70%, and ideally 80%, and sufficient AT doses to maintain this activity should be required to achieve better outcomes for DIC patients in Japan [5]. In most recent systematic review, meta-analysis and trial sequential analysis, the improvement of AT level in perioperative cardiopulmonary bypass surgery showed no significant effect on blood conservation, contrary to expectations this might increase in hospital mortality and the incidence of acute kidney injury [6].”

3. There appears to be no information regarding the administration period or amount of antithrombin III.

-Answer to comment:

We agree with the reviewer about that.

We would like to thank you for your kind consideration.

We have corrected the sentence in the revised manuscript as the reviewer pointed out as follows:

(page 07, lines 162-164)

(page 12, lines 282, to page 13, lines 285)

“The total administration period of antithrombin III was limited to within 3 days in most cases, and the total administration dose was below 7,000 IU (loading dose, 1,000 IU in 1 hour: maintenance dose, 500 IU every 6 hours for 3 days) following the MFDS guidelines [8].”

4. In the Discussion section, the authors stated that antithrombin administration should aim for antithrombin III activity of 80-120%, and that the duration and dosage of the current guidelines may be insufficient. In this study, both the non-survivor group and the survivor group were able to achieve this goal on the 1st and 2nd day, and both groups were below the target value on the 7th day. Why was there a difference in outcome? This does not seem to be explained by changes in antithrombin III activity.

-Answer to comment:

We agree with the reviewer about that.

We would like to thank you for your kind consideration.

As the final outcome, the clinical improvement and situation of patients' conditions would be most important framework, however the antithrombin only has a biological half-life from 2 to 3 days (55-70 hours), therefore we would like to suggest a little longer and/or more antithrombin administration would be helpful to overcome this drawback, a relatively short half-life. We think that further larger studies are essential and needed to conclusively confirm these findings.

5. The authors state that antithrombin III supplementation increased hemoglobin levels in the survivor group, but the effects of DIC treatment are generally evaluated using FDP, platelet count, fibrinogen, and PT. There appears to be no significant difference in these points after treatment, and it seems difficult to conclude that antithrombin III supplementation improved DIC.

-Answer to comment:

We agree with the reviewer about that.

We would like to thank you for your kind consideration.

We carefully tried to perform a variety of statistical verifications, and found significant results only in antithrombin III on the day just before the administration (p=0.016), aPTT (sec) on 1st day (p=0.032), Hemoglobin (g/dL) on 2nd day (p=0.017), Hemoglobin (g/dL) on 7th day (p=0.006), and BUN (mg/dL) on 7th day (p=0.004). (Table 1, 2 & Figure 1, 2). We carried out multiple logistic regression analysis by stepwise backward regressions, these efforts demonstrated significant odds ratio (OR) only on anti-thrombin III (%) on the day just before the administration day and SAPS II for the difference between the non-survivor and survivor groups (P=0.0483; OR, 1.0447; SE, 0.022; 95% CI of difference, 1.0003 to 1.0911 vs. P=0.0361; OR, 0.9370; SE, 0.031; 95% CI of difference, 0.8817 to 0.9958) (Table 3 & Figure 3). In these statistical verifications, hemoglobin level in the 2nd day showed insignificant difference between the non-survivor and survivor groups (P=0.0525; OR, 1.3165; SE, 0.141; 95% CI of difference, 0.9971 to 1.7382) (Table 3 & Figure 3).

We have corrected the sentence in the revised manuscript as the reviewer pointed out as follows:

(page 16, lines 365-369

“Multiple logistic regression analysis by stepwise backward regression demonstrated significant odds ratio (OR) on anti-thrombin III (%) on the day just before the administration, hemoglobin level in the 2nd day and SAPS II for the difference between the non-survivor and survivor groups (P=0.0483; OR, 1.0447; SE, 0.022; 95% CI of difference, 1.0003 to 1.0911 vs. P=0.0361; OR, 0.9370; SE, 0.031; 95% CI of difference, 0.8817 to 0.9958) (Table 3 & Figure 3).”

Minor points:

1. The abstract is too long, so please consider making it more concise.

-Answer to comment:

We agree with the reviewer about that.

We would like to thank you for your kind consideration.

The abstract was shortened and was made more concise as follows:

Pages 2, Words 479, and Characters (no spaces) 2,824 or (with spaces) 3,301.

(page 7, lines 145, to page 8, lines 190)

“Background and Objective:

Antithrombin is a small plasma glycoprotein synthesized in the liver that belongs to the serpin family of serine protease inhibitors and inactivates several enzymes in the coagulation pathway. It plays a leading major factor on coagulation pathway, therefore administration of antithrombin is essential to treat serious clinical conditions such as disseminated intravascular coagulation (DIC). Despite the theoretical benefits of antithrombin supplementation, the optimal antithrombin activity for heparin efficacy and the benefits of antithrombin supplementation in various disease entities are not yet fully understood.

Methods:

In a single medical center, single investigator and single arm on the DIC program was first initiated from January 2010, and active DIC treatment using antithrombin was consistently carried out on adult patients between January 1, 2010 and October 31, 2021. The strict administration guidelines on antithrombin III in cases of DIC by the National Health Insurance Service and the Ministry of Food and Drug Safety complied as follows: antithrombin levels below 20 mg/dL in adults; antithrombin activity below 70% of normal in adults; total administration period of antithrombin

must be carefully limited to within maximum 3 days, and the total administration dose must be below 7,000 IU (loading dose, 1,000 IU in 1 hour: maintenance dose, 500 IU every 6 hours for 3 days).

Results:

We identified 76 eligible for analysis according to the above-mentioned criteria in our institution (male/female, 59/17). Forty-four were identified to the non-survivor group and 32 patients were recognized as the survivor group. The baseline parameters in the non-survivor and survivor groups were comparable with no significant differences in age (66.5 ± 18.1 vs. 66.0 ± 16.2, P=0.904), sex (32/12 vs. 27/5, P=0.355), hospital length of stay (31.1 ± 34.5 vs. 31.2 ± 26.1, P=0.991), SOFA (7.3 ± 2.5 vs. 6.6 ± 2.0, P=0.224), SAPS II (46.0 ± 8.8 vs.43.5 ± 9.2, P=0.234), cause for DIC (P=0.950), and underlying disease (P=0.383). The levels of anti-thrombin III (%) on the day just before the administration significantly lower in the non-survivor groups than in the survivor groups (50.1 ± 13.6 vs. 57.6 ± 12.5, P=0.016). The hemoglobin level in the 2nd day and 7th day after anti-thrombin III administration was significantly different between the non-survivor and survivor groups (9.9 ± 1.9 vs. 11.0 ± 2.0, P=0.017, and 9.4 ± 1.8 vs. 10.5 ± 1.6, P=0.006). The antithrombin III levels on the day of administration (AUC=0.672) demonstrated significantly better prediction of mortality than the antithrombin III levels on 1st day (AUC=0.552), 2nd day (AUC=0.624), and 7th day (AUC=0.593).

Conclusions:

Our study suggests that the antithrombin administration may be effective tools for DIC treatment, and may be more positively considered, especially in the cases of DIC, which is a frequent complication of septic shock, sepsis, and other critical disease entities and which is associated with a high level of mortality. Furthermore, our study also suggests that the total doses and periods of antithrombin administration, which recommended by national guidelines, may be insufficient, therefore prolongation of period and increase of total dose of antithrombin supplement might be necessary."

2. Consider organizing the Results section by key points of your results. For example, "patient characteristics", "ROC analysis", etc.

-Answer to comment:

We agree with the reviewer about that.

We would like to thank you for your kind consideration.

We have corrected the sentence in the revised manuscript as the reviewer pointed out as follows: (page 16, lines 376-379)

"These results demonstrate that the antithrombin III levels on the day of administration might be the best prediction tools for in-hospital mortality, and SAPS II, representing the state of patient clinical situation, could be a useful parameter for survival."

3. Table 1 contains too many different contents and is difficult to understand. I think data comparisons for On day, 1st day, 2nd day, and 7th day should be created in separate tables.

-Answer to comment:

We agree with the reviewer about that.

We would like to thank you for your kind consideration.

We have corrected the sentence in the revised manuscript as the reviewer pointed out as follows: (Table 1. supplementary)

		Non-Survivor (N=44)	Survivor (N=32)	Total (N=76)	P
	Age	66.5 ± 18.1	66.0 ± 16.2	66.2 ± 17.2	0.904
	Sex				0.355
	Male	32 (72.7%)	27 (84.4%)	59 (77.6%)	
	Female	12 (27.3%)	5 (15.6%)	17 (22.4%)	
	Hospital days	31.1 ± 34.5	31.2 ± 26.1	31.2 ± 31.1	0.991
	Cause for DIC				0.950
	Sepsis	10 (22.7%)	8 (25.0%)	18 (23.7%)	
	Trauma	10 (22.7%)	6 (18.8%)	16 (21.1%)	
	Respiratory failure	10 (22.7%)	8 (25.0%)	18 (23.7%)	
	Surgery/Rhabdomyolysis	9 (20.5%)	5 (15.6%)	14 (18.4%)	
	et cetera	5 (11.4%)	5 (15.6%)	10 (13.2%)	
	Underlying disease				0.383
	Arterial hypertension	13 (29.5%)	4 (12.5%)	17 (22.4%)	
	Diabetes	8 (18.2%)	9 (28.1%)	17 (22.4%)	
	COPD	9 (20.5%)	9 (28.1%)	18 (23.7%)	
	Cardiac comorbidities	4 (9.1%)	5 (15.6%)	9 (18.4%)	
	Dyslipidemia	5 (11.4%)	5 (15.6%)	10 (11.3%)	
	SOFA	7.3 ± 2.5	6.6 ± 2.0	7.0 ± 2.3	0.224
	SAPS II	46.0 ± 8.8	43.5 ± 9.2	44.9 ± 9.0	0.234
on day	D-dimer (ng/mL)	8346.0 ± 14478.4	6256.3 ± 7517.1	7466.1 ± 12025.8	0.416
	Thrombin time (sec)	34.9 ± 59.8	21.7 ± 9.2	29.4 ± 46.2	0.157
	Anti-thrombin III (%)	50.1 ± 13.6	57.6 ± 12.5	53.2 ± 13.6	0.016*
	FDP (microgram/mL)	109.2 ± 111.2	108.8 ± 103.6	109.0 ± 107.4	0.987
	PT (sec)	16.1 ± 4.1	15.1 ± 3.4	15.7 ± 3.8	0.273
	aPTT (sec)	47.3 ± 18.5	52.0 ± 68.2	49.3 ± 46.1	0.706
	INR	1.52 ± 0.4	1.44 ± 0.3	1.50 ± 0.3	0.340
	Fibrinogen (mg/dL)	374.7 ± 243.9	410.0 ± 176.7	389.6 ± 217.5	0.489
	Na (mmol/L)	139.0 ± 7.0	138.6 ± 6.0	138.9 ± 6.6	0.797
	K (mmol/L)	3.7 ± 0.5	3.9 ± 0.8	3.8 ± 0.7	0.379
	Cl (mmol/L)	103.9 ± 7.8	96.6 ± 25.4	100.9 ± 17.7	0.125
	pH (ABGA)	7.34 ± 0.2	7.45 ± 0.2	7.42 ± 0.2	0.262
	pO_2 (ABGA) (mmHg)	108.3 ± 61.4	108.9 ± 70.4	108.5 ± 64.9	0.966
	pCO_2 (ABGA) (mmHg)	47.0 ± 16.9	42.1 ± 13.4	44.9 ± 15.6	0.177
	$cHCO_3$ (ABGA) (mmol/L)	23.9 ± 6.5	24.8 ± 6.9	24.3 ± 6.6	0.565
	Base excess (ABGA) (mmol/L)	-0.7 ± 7.0	0.4 ± 7.5	-0.2 ± 7.2	0.509
	SpO_2(ABGA) (%)	93.1 ± 9.8	93.9 ± 8.7	93.4 ± 9.3	0.709
	Glucose	132.5 ± 46.1	145.4 ± 43.7	137.9 ± 45.3	0.221
	iCa (mg/dl)	1.9 ± 1.5	1.6 ± 1.3	1.8 ± 1.4	0.326
	Lactate (mmol/L)	2.4 ± 3.1	2.4 ± 3.0	2.4 ± 3.1	0.973
	WBC ($x10^3$/uL)	13.9 ± 7.8	17.4 ± 32.2	15.4 ± 21.6	0.556
	RBC ($x10^6$/uL)	3.2 ± 0.8	3.3 ± 0.6	3.3 ± 0.7	0.480
	Hemoglobin (g/dL)	9.9 ± 2.4	10.6 ± 1.9	10.2 ± 2.2	0.140
	Hematocrit (%)	29.3 ± 6.9	31.1 ± 5.6	30.1 ± 6.4	0.239
	Platelet ($x10^3$/uL)	125.2 ± 87.4	123.8 ± 80.5	124.6 ± 84.0	0.946
	Neutrophil (%)	84.9 ± 14.6	85.7 ± 11.1	85.2 ± 13.2	0.794
	Lymphocyte (%)	8.9 ± 13.3	7.5 ± 8.2	8.4 ± 11.4	0.573
	Monocyte (%)	5.6 ± 3.5	5.8 ± 3.9	5.7 ± 3.6	0.765
	Eosinophil (%)	0.4 ± 1.0	0.6 ± 1.6	0.5 ± 1.3	0.565
	Basophil (%)	0.2 ± 0.2	0.3 ± 0.5	0.2 ± 0.4	0.135
	AST(GOT) (IU/L)	162.4 ± 471.4	543.9 ± 1401.5	323.0 ± 987.5	0.147
	ALT(GPT) (IU/L)	96.4 ± 257.9	239.6 ± 591.8	156.7 ± 433.5	0.207
	Total bilirubin (mg/dL)	2.3 ± 2.9	1.8 ± 1.0	2.1 ± 2.3	0.313
	Direct bilirubin (mg/dL)	0.8 ± 1.5	0.6 ± 0.3	0.7 ± 1.2	0.279

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	Total protein (g/dL)	5.4 ± 1.0	5.4 ± 1.0	5.4 ± 1.0	0.955
	Albumin (g/dL)	3.0 ± 0.7	3.2 ± 0.7	3.1 ± 0.7	0.194
	BUN (mg/dL)	30.1 ± 17.0	28.0 ± 16.1	29.2 ± 16.6	0.603
	Creatinine (mg/dL)	1.1 ± 0.6	1.1 ± 0.6	1.1 ± 0.6	0.698
	Phosphate (mg/dL)	3.7 ± 1.9	3.3 ± 2.0	3.6 ± 1.9	0.347
	Amylase (U/L)	140.6 ± 124.7	139.9 ± 151.8	140.3 ± 135.8	0.982
	CRP (mg/dL)	10.9 ± 7.9	10.7 ± 6.8	10.8 ± 7.4	0.906
	Procalcitonin (ng/mL)	14.7 ± 36.6	11.1 ± 26.8	13.1 ± 32.6	0.639
	Presepsin (pg/mL)	927.3 ± 604.8	802.2 ± 158.2	874.6 ± 473.2	0.196
	Troponin-I (ng/mL)	0.6 ± 1.2	0.6 ± 1.2	0.6 ± 1.2	0.811
	Myoglobin (ng/mL)	856.9 ± 1472.9	1770.4 ± 2934.7	1241.6 ± 2238.2	0.113
	CK-MB (ng/mL)	9.0 ± 16.2	8.8 ± 12.9	8.9 ± 14.8	0.952
1st day	D-dimer (ng/mL)	8814.5 ± 12669.4	8528.4 ± 7775.7	8694.0 ± 10818.4	0.904
	Thrombin time (sec)	22.4 ± 13.9	20.8 ± 6.8	21.8 ± 11.4	0.506
	Anti-thrombin III (%)	87.2 ± 27.3	93.0 ± 31.5	89.7 ± 29.1	0.401
	FDP (microgram/mL)	82.7 ± 88.3	88.1 ± 54.7	85.0 ± 75.6	0.748
	PT (sec)	15.9 ± 6.0	15.6 ± 5.6	15.8 ± 5.8	0.803
	aPTT (sec)	48.1 ± 32.9	36.0 ± 13.5	43.0 ± 27.1	0.032*
	INR	1.58 ± 0.5	1.05 ± 0.5	1.54 ± 0.5	0.953
	Fibrinogen (mg/dL)	415.4 ± 275.4	477.9 ± 250.3	441.7 ± 265.2	0.314
	Na (mmol/L)	3.6 ± 0.6	3.9 ± 1.0	3.7 ± 0.8	0.123
	K (mmol/L)	3.6 ± 0.6	3.9 ± 1.0	3.7 ± 0.8	0.123
	Cl (mmol/L)	103.9 ± 8.0	103.7 ± 5.5	103.8 ± 7.0	0.870
	pH (ABGA)	7.31 ± 0.2	7.42 ± 0.1	7.40 ± 0.2	0.541
	pO_2 (ABGA) (mmHg)	94.5 ± 49.6	102.2 ± 51.2	97.8 ± 50.1	0.514
	pCO_2 (ABGA) (mmHg)	48.1 ± 18.1	45.7 ± 16.1	47.1 ± 17.2	0.555
	$cHCO_3$ (ABGA) (mmol/L)	23.9 ± 6.5	24.8 ± 6.9	24.3 ± 6.6	0.565
	Base excess (ABGA) (mmol/L)	-0.7 ± 8.7	0.6 ± 7.3	-0.2 ± 8.1	0.493
	SpO_2(ABGA) (%)	92.9 ± 7.5	93.5 ± 10.7	93.1 ± 8.9	0.792
	Glucose	158.1 ± 63.9	156.8 ± 63.9	157.5 ± 63.5	0.930
	iCa (mg/dl)	2.1 ± 1.4	2.2 ± 1.6	2.1 ± 1.5	0.681
	Lactate (mmol/L)	3.0 ± .9	2.4 ± 2.7	2.7 ± 3.4	0.370
	WBC ($x10^3$/uL)	12.2 ± 7.0	12.8 ± 6.1	12.5 ±6.6	0.704
	RBC ($x10^6$/uL)	3.3 ± 0.6	3.4 ± 0.7	3.3 ± 0.6	0.399
	Hemoglobin (g/dL)	10.2 ± 1.8	0.8 ± 2.2	10.4 ± 2.0	0.202
	Hematocrit (%)	29.8 ± 4.7	31.5 ± 6.6	30.5 ± 5.6	0.232
	Platelet ($x10^3$/uL)	125.1 ± 104.3	121.0 ± 98.0	123.4 ± 101.1	0.864
	Neutrophil (%)	85.1 ± 14.8	87.8 ± 7.8	86.3 ± 12.4	0.309
	Lymphocyte (%)	9.5 ± 15.2	6.8 ± 6.8	8.4 ± 12.4	0.290
	Monocyte (%)	4.9 ± 3.1	4.7 ± 2.9	4.8 ± 3.0	0.752
	Eosinophil (%)	0.5 ± 1.1	0.4 ± 0.8	0.4 ± .0	0.786
	Basophil (%)	0.3 ± 0.6	0.3 ± 0.4	0.3 ± 0.5	0.664
	AST(GOT) (IU/L)	333.5 ± 944.4	686.0 ± 1873.2	481.9 ± 1411.5	0.334
	ALT(GPT) (IU/L)	195.9 ± 652.8	299.4 ± 772.4	239.5 ± 702.6	0.530
	Total bilirubin (mg/dL)	2.4 ± 2.7	2.0 ± 1.2	2.2 ± 2.2	0.415
	Direct bilirubin (mg/dL)	1.3 ± 2.1	1.0 ± 0.3	1.2 ± 1.6	0.259
	Total protein (g/dL)	5.7 ± 0.9	5.8 ± 0.9	5.7 ± 0.9	0.518
	Albumin (g/dL)	3.2 ± 0.6	3.5 ± 0.6	3.3 ± 0.6	0.053
	BUN (mg/dL)	32.5 ± 20.7	30.1 ± 16.8	31.5 ± 19.1	0.600
	Creatinine (mg/dL)	1.1 ± 0.5	1.0 ± 0.6	1.1 ± 0.6	0.558
	Phosphate (mg/dL)	3.4 ± 2.0	3.1 ± 2.8	3.3 ± 2.3	0.597
	Amylase (U/L)	242.2 ± 488.7	183.1 ± 380.8	217.3 ± 444.7	0.570
	CRP (mg/dL)	10.9 ± 6.8	11.5 ± 6.1	11.1 ± 6.5	0.692
	Procalcitonin (ng/mL)	12.7 ± 27.3	6.1 ± 10.6	9.9 ± 21.9	0.153
	Presepsin (pg/mL)	1697.9 ± 804.3	1493.4 ± 554.1	1611.8 ± 712.8	0.194

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	Troponin-I (ng/mL)	1.4 ± 4.2	0.7 ± 0.9	1.1 ± 3.2	0.313
	Myoglobin (ng/mL)	1452.9 ± 4309.6	1340.7 ± 2866.2	1405.7 ± 3747.9	0.892
	CK-MB (ng/mL)	14.9 ± 43.3	7.1 ± 8.0	11.6 ± 33.4	0.245
2nd day	D-dimer (ng/mL)	11909.0 ± 15900.1	13621.6 ± 14762.2	12639.7 ± 15346.2	0.636
	Thrombin time (sec)	26.7 ± 42.9	30.5 ± 51.0	28.3 ± 46.2	0.728
	Anti-thrombin III (%)	105.5 ± 24.5	114.2 ± 19.3	109.2 ± 22.7	0.100
	FDP (microgram/mL)	35.5 ± 50.3	44.8 ± 26.5	39.4 ± 42.0	0.305
	PT (sec)	16.3 ± 8.4	14.2 ± 2.7	15.4 ± 6.7	0.116
	aPTT (sec)	40.9 ± 13.3	37.3 ± 14.6	39.4 ± 13.9	0.271
	INR	1.88 ± 2.2	1.32 ± 0.2	1.61 ± 1.7	0.163
	Fibrinogen (mg/dL)	429.7 ± 225.5	409.3 ± 231.1	421.1 ± 226.6	0.701
	Na (mmol/L)	140.6 ± 8.1	141.5 ± 7.3	141.0 ± 7.7	0.620
	K (mmol/L)	3.7 ± 0.6	3.9 ± 0.9	3.8 ± 0.8	0.347
	Cl (mmol/L)	102.8 ± 8.8	105.0 ± 7.5	103.7 ± 8.3	0.249
	pH (ABGA)	7.31 ± 0.2	7.44 ± 0.2	7.38 ± 0.2	0.162
	pO_2 (ABGA) (mmHg)	110.8 ± 42.5	102.5 ± 38.3	107.3 ± 40.8	0.384
	pCO_2 (ABGA) (mmHg)	40.7 ± 11.7	43.1 ± 13.2	41.7 ± 12.3	0.418
	$cHCO_3$ (ABGA) (mmol/L)	25.7 ± 8.1	26.1 ± 7.5	25.9 ± 7.8	0.836
	Base excess (ABGA) (mmol/L)	1.4 ± 8.2	1.9 ± 7.3	1.6 ± 7.8	0.747
	SpO_2(ABGA) (%)	93.7 ± 9.6	95.2 ± 6.7	94.3 ± 8.5	0.397
	Glucose	149.9 ± 44.8	158.6 ± 56.2	153.6 ± 49.7	0.454
	iCa (mg/dl)	2.2 ± 1.3	2.1 ± 1.5	2.2 ± 1.4	0.831
	Lactate (mmol/L)	2.0 ± 2.2	2.0 ± 1.4	2.0 ± 1.9	0.951
	WBC ($x10^3$/uL)	13.1 ± 7.8	18.2 ± 28.5	15.3 ± 19.4	0.329
	RBC ($x10^6$/uL)	3.1 ± 0.5	3.3 ± 0.7	3.2 ± 0.6	0.205
	Hemoglobin (g/dL)	9.9 ± 1.9	11.0 ± 2.0	10.3 ± 2.0	0.017*
	Hematocrit (%)	29.5 ± 5.4	32.2 ± 6.2	30.6 ± 5.9	0.046
	Platelet ($x10^3$/uL)	120.2 ± 85.5	122.7 ± 78.6	121.2 ± 82.1	0.899
	Neutrophil (%)	84.3 ± 16.4	87.8 ± 5.9	85.8 ± 13.1	0.193
	Lymphocyte (%)	9.3 ± 13.9	5.4 ± 3.1	7.7 ± 10.9	0.080
	Monocyte (%)	5.0 ± 3.8	5.4 ± 4.0	5.2 ± 3.9	0.700
	Eosinophil (%)	1.1 ± 2.3	0.7 ±1.1	0.9 ± 1.9	0.352
	Basophil (%)	0.2 ± 0.2	0.3 ± 0.4	0.3 ± 0.3	0.328
	AST(GOT) (IU/L)	214.8 ± 757.7	202.0 ± 502.3	209.4 ± 658.4	0.930
	ALT(GPT) (IU/L)	76.9 ± 123.3	154.8 ± 373.8	109.7 ± 260.7	0.264
	Total bilirubin (mg/dL)	2.6 ± 2.8	2.5 ± 1.6	2.6 ± 2.4	0.844
	Direct bilirubin (mg/dL)	0.9 ± 1.6	0.6 ± 0.4	0.8 ± 1.3	0.334
	Total protein (g/dL)	5.6 ± 0.9	5.9 ± 1.0	5.7 ± 1.0	0.099
	Albumin (g/dL)	3.3 ± 0.7	3.6 ± 0.7	3.4 ± 0.7	0.119
	BUN (mg/dL)	38.1 ± 22.0	32.3 ± 16.4	35.6 ± 19.9	0.211
	Creatinine (mg/dL)	1.2 ± 0.6	1.0 ± 0.5	1.1 ± 0.6	0.093
	Phosphate (mg/dL)	2.4 ± 1.2	1.8 ± 1.2	2.1 ± 1.2	0.057
	Amylase (U/L)	139.2 ± 217.1	131.1 ± 198.0	135.8 ± 207.9	0.869
	CRP (mg/dL)	11.7 ± 6.6	11.3 ± 6.9	11.5 ± 6.7	0.776
	Procalcitonin (ng/mL)	10.8 ± 20.2	12.5 ± 36.1	11.5 ± 27.7	0.813
	Presepsin (pg/mL)	1196.6 ± 571.2	1039.3 ± 270.6	1130.4 ± 472.7	0.115
	Troponin-I (ng/mL)	0.7 ± 1.9	0.4 ± 0.4	0.6 ± 1.4	0.345
	Myoglobin (ng/mL)	796.0 ± 1522.8	688.5 ± 703.0	750.7 ± 1239.6	0.682
	CK-MB (ng/mL)	5.6 ± 10.6	4.0 ± 2.3	4.9 ± 8.2	0.342
7th day	D-dimer (ng/mL)	5196.3 ± 4128.1	4987.6 ± 4271.3	5108.4 ± 4162.0	0.831
	Thrombin time (sec)	84.5 ± 24.2	83.5 ± 18.8	84.1 ± 21.9	0.834
	Anti-thrombin III (%)	63.6 ± 21.7	70.1 ± 16.2	66.3 ± 19.7	0.153
	FDP (microgram/mL)	21.5 ± 18.4	26.0 ± 26.9	23.4 ± 22.3	0.426
	PT (sec)	14.2 ± 1.9	14.1 ± 1.9	14.1 ± 1.9	0.817

aPTT (sec)	39.8 ± 12.1	36.5 ± 12.8	38.4 ± 12.4	0.254
INR	1.26 ± 0.2	1.27 ± 0.2	1.26 ± 0.2	0.609
Fibrinogen (mg/dL)	393.9 ± 201.2	375.2 ± 204.9	386.1 ± 201.6	0.692
Na (mmol/L)	139.5 ± 8.8	138.8 ± 8.5	139.2 ± 8.6	0.750
K (mmol/L)	4.1 ± 1.0	3.9 ± 0.6	4.0 ± 0.8	0.416
Cl (mmol/L)	104.3 ± 8.5	101.5 ± 19.8	103.2 ± 14.3	0.457
pH (ABGA)	7.30 ± 0.2	7.40 ± 0.1	7.40 ± 0.2	0.291
pO_2 (ABGA) (mmHg)	100.1 ± 41.4	97.2 ± 31.4	98.9 ± 37.3	0.737
pCO_2 (ABGA) (mmHg)	42.9 ± 10.5	39.5 ± 9.6	41.5 ± 10.2	0.152
$cHCO_3$ (ABGA) (mmol/L)	25.1 ± 5.8	25.9 ± 5.7	25.5 ± 5.7	0.557
Base excess (ABGA) (mmol/L)	0.0 ± 6.2	1.5 ± 5.3	0.6 ± 5.8	0.272
SpO_2(ABGA) (%)	92.6 ± .1	94.2 ± 5.0	93.3 ± 7.0	0.318
Glucose	153.9 ± 65.7	172.3 ± 81.7	161.7 ± 72.9	0.282
iCa (mg/dl)	2.8 ± 1.6	2.5 ± 1.6	2.7 ± 1.6	0.455
Lactate (mmol/L)	1.6 ± 1.1	1.8 ± 1.4	1.7 ± 1.3	0.450
WBC ($x10^3$/uL)	15.8 ± 8.8	16.0 ± 8.4	15.9 ± 8.5	0.923
RBC ($x10^6$/uL)	3.1 ± 0.7	3.4 ± 0.6	3.3 ± 0.6	0.071
Hemoglobin (g/dL)	9.4 ± 1.8	10.5 ± 1.6	9.9 ± 1.8	0.006*
Hematocrit (%)	29.6 ± 5.7	32.0 ± 5.3	30.6 ± 5.6	0.065
Platelet ($x10^3$/uL)	149.1 ± 105.6	184.1 ± 130.9	163.8 ± 117.4	0.201
Neutrophil (%)	81.9 ± 17.5	83.4 ± .9	82.5 ± 14.7	0.640
Lymphocyte (%)	10.4 ± 14.5	9.0 ± 5.6	9.8 ± 11.6	0.538
Monocyte (%)	5.1 ±4.1	5.3 ± 3.1	5.2 ± 3.7	0.863
Eosinophil (%)	1.4 ± 2.4	2.2 ± 4.1	1.7 ± 3.2	0.322
Basophil (%)	0.5 ± 1.0	0.4 ± 0.3	0.4 ± 0.8	0.415
AST(GOT) (IU/L)	77.4 ± 76.8	68.6 ± 71.3	73.7 ± 74.1	0.612
ALT(GPT) (IU/L)	71.5 ± 77.5	57.1 ± 61.0	65.4 ± 71.0	0.387
Total bilirubin (mg/dL)	4.8 ± 5.8	3.8 ± 3.4	4.4 ± 4.9	0.335

:

Direct bilirubin (mg/dL)	2.3 ± 2.7	2.1 ± 1.4	2.2 ± 2.3	0.658
Total protein (g/dL)	5.7 ± 0.8	5.7 ± 0.9	5.7 ± 0.9	0.852
Albumin (g/dL)	3.3 ± 0.7	3.4 ± 0.8	3.4 ± 0.7	0.763
BUN (mg/dL)	41.9 ± 25.5	28.1 ± 14.3	36.1 ± 22.5	0.004*
Creatinine (mg/dL)	1.3 ± 0.8	0.9 ± 0.7	1.2 ± 0.8	0.016
Phosphate (mg/dL)	3.5 ± 1.3	3.2 ± 0.8	3.3 ± 1.1	0.303
Amylase (U/L)	181.5 ± 142.4	161.6 ± 115.2	173.1 ± 131.2	0.517
CRP (mg/dL)	10.7 ± 7.3	7.8 ± 5.9	9.5 ± 6.9	0.065
Procalcitonin (ng/mL)	6.4 ± 19.8	2.6 ± 4.1	4.8 ± 15.4	0.224
Presepsin (pg/mL)	1694.9 ± 1021.7	1386.1 ± 396.2	1564.9 ± 828.8	0.073
Troponin-I (ng/mL)	0.5 ± 0.5	0.9 ± 2.3	0.7 ± 1.5	0.328
Myoglobin (ng/mL)	914.1 ± 726.0	1183.7 ± 2098.1	1027.6 ± 1462.7	0.490
CK-MB (ng/mL)	2.8 ± 3.1	7.7 ± 30.1	4.8 ± 19.7	0.365

:

4. The authors stated that multiple logistic regression analysis showed a significant difference in hemoglobin level in the 2nd day (p=0.0525), but the methods section states that p<0.05 is considered significant. Please explain this point.

-Answer to comment:

We agree with the reviewer about that.

We would like to thank you for your kind consideration.

We carefully tried to perform a variety of statistical verifications, and found significant results only in antithrombin III on the day just before the administration (p=0.016), aPTT (sec) on 1st day (p=0.032), Hemoglobin (g/dL) on 2nd day (p=0.017), Hemoglobin (g/dL) on 7th day (p=0.006), and BUN (mg/dL) on 7th day (p=0.004). (Table 1, 2 & Figure 1, 2). We carried out multiple logistic regression analysis by stepwise backward regressions, these efforts demonstrated significant odds ratio (OR) only on anti-thrombin III (%) on the day just before the administration day and SAPS II for the difference between the non-survivor and survivor groups (P=0.0483; OR, 1.0447; SE, 0.022; 95% CI of difference, 1.0003 to 1.0911 vs. P=0.0361; OR, 0.9370; SE, 0.031; 95% CI of difference, 0.8817 to 0.9958) (Table 3 & Figure 3). In these statistical verifications, hemoglobin level in the 2nd day showed insignificant difference between the non-survivor and survivor groups (P=0.0525; OR, 1.3165; SE, 0.141; 95% CI of difference, 0.9971 to 1.7382) (Table 3 & Figure 3).

We have corrected the sentence in the revised manuscript as the reviewer pointed out as follows:

(page 16, lines 365-369

"Multiple logistic regression analysis by stepwise backward regression demonstrated significant odds ratio (OR) on anti-thrombin III (%) on the day just before the administration, hemoglobin level in the 2nd day and SAPS II for the difference between the non-survivor and survivor groups (P=0.0483; OR, 1.0447; SE, 0.022; 95% CI of difference, 1.0003 to 1.0911 vs. P=0.0361; OR, 0.9370; SE, 0.031; 95% CI of difference, 0.8817 to 0.9958) (Table 3 & Figure 3)."

Reviewer B

This study researches the effect of antithrombin III supplementation in adults with Disseminated Intravascular Coagulation. While validations of antithrombin III have been conducted mainly in Japan and a few other countries, a consensus has not been reached. This

study is considered to provide useful information regarding the use of antithrombin III. On the other hand, the following information was unclear and should be corrected.

Major Revision Suggestions:

1. Abstract (Background and Objective) & Introduction:

Both sections raise concerns about the lack of age-specific guidelines, particularly noting the absence of information on children, pediatric and neonatal patients. However, this study focuses on adults. This could lead to considerable confusion for the reader. It would be easier to understand if the background and abstract were written in the vein of focusing on severe cases

-Answer to comment:

We agree with the reviewer about that.

We would like to thank you for your kind consideration.

This study focused on adults, and it was consistently complied with in whole manuscript.

We have corrected the sentence in the revised manuscript as the reviewer pointed out as follows: (page 10, lines 236, to page 11, lines 244)

"In an observational study 2019, Kim et al. reported high-dose antithrombin (AT) supplementation significantly improved 28-day mortality in septic shock patients with DIC [4], and Akahoshi et al. addressed targeted AT activity should be at least 70%, and ideally 80%, and sufficient AT doses to maintain this activity should be required to achieve better outcomes for DIC patients in Japan [5]. In most recent systematic review, meta-analysis and trial sequential analysis, the improvement of AT level in perioperative cardiopulmonary bypass surgery showed no significant effect on blood conservation, contrary to expectations this might increase in hospital mortality and the incidence of acute kidney injury [6]."

2. Abstract (Conclusion) & Conclusion:

The study examines the prognosis of patients treated with antithrombin III. While the authors suggest in their conclusion that antithrombin III are effective, the results show a higher percentage of non-survivors compared to survivors. Does this truly indicate the effectiveness of antithrombin III agents? The conclusion should probably limit its mention

to a review of the prognosis of patients treated with this drug, identifying several factors that determine prognosis (level of antithrombin III at the start of treatment, hemoglobin levels on day 2 and day 7).

-Answer to comment:

We agree with the reviewer about that.

We would like to thank you for your kind consideration.

Actually, the AT III level on day of administration showed significant statistical difference between the survivor groups and the non-survivor groups (P=0.016), but the AT III level in the 1st day, 2nd day and 7th day after AT III administration showed higher level in the survivor groups, unfortunately they did not show significant statistical difference (P=0.401, P=0.100, and P=0.153, respectively) (Table 1 & Figure 2).

We have corrected the sentence in the revised manuscript as the reviewer pointed out as follows: (page 15, lines 353-355)

"The clinical laboratory levels of anti-thrombin III (%) on the day just before the administration significantly lower in the non-survivor groups than in the survivor groups (50.1 ± 13.6 vs. 57.6 ± 12.5, P=0.016)."

Furthermore, we carefully tried to perform a variety of statistical verifications, and found significant results only in antithrombin III on the day just before the administration (p=0.016), aPTT (sec) on 1st day (p=0.032), Hemoglobin (g/dL) on 2nd day (p=0.017), Hemoglobin (g/dL) on 7th day (p=0.006), and BUN (mg/dL) on 7th day (p=0.004). (Table 1, 2 & Figure 1, 2). We carried out multiple logistic regression analysis by stepwise backward regressions, these efforts demonstrated significant odds ratio (OR) only on anti-thrombin III (%) on the day just before the administration day and SAPS II for the difference between the non-survivor and survivor groups (P=0.0483; OR, 1.0447; SE, 0.022; 95% CI of difference, 1.0003 to 1.0911 vs. P=0.0361; OR, 0.9370; SE, 0.031; 95% CI of difference, 0.8817 to 0.9958) (Table 3 & Figure 3). In these statistical verifications, hemoglobin level in the 2nd day showed insignificant difference between the non-survivor and survivor groups (P=0.0525; OR, 1.3165; SE, 0.141; 95% CI of difference, 0.9971 to 1.7382) (Table 3 & Figure 3).

We have corrected the sentence in the revised manuscript as the reviewer pointed out as follows:

(page 16, lines 365-369)

“Multiple logistic regression analysis by stepwise backward regression demonstrated significant odds ratio (OR) on anti-thrombin III (%) on the day just before the administration, hemoglobin level in the 2nd day and SAPS II for the difference between the non-survivor and survivor groups (P=0.0483; OR, 1.0447; SE, 0.022; 95% CI of difference, 1.0003 to 1.0911 vs. P=0.0361; OR, 0.9370; SE, 0.031; 95% CI of difference, 0.8817 to 0.9958) (Table 3 & Figure 3).”

(page 16, lines 375-378)

These results demonstrate that the antithrombin III levels on the day of administration might be the best prediction tools for in-hospital mortality, and SAPS II, representing the state of patient clinical situation, could be a useful parameter for survival.

3. Material and Methods:

Please clarify why the 1st, 2nd, and 7th days were chosen as evaluation points in this study.

-Answer to comment:

We agree with the reviewer about that.

We would like to thank you for your kind consideration.

As we mentioned in discussion paragraph, the antithrombin only has a biological half-life from 2 to 3 days (55-70 hours), therefore we would like to verify the level of AT III on the 1st day and 2nd day in the period of half-life, and to check out the level of AT III on the 7th day after the period of half-life.

We think that further larger studies are essential and needed to conclusively confirm these findings.

4. Results:

Reasons for the decrease in hemoglobin levels on the 2nd and 7th day in non-survivors could be varied. Please provide information on the following:

·The proportion of non-survivors and survivors who received transfusion therapy.

·The proportion of side effects post-administration of antithrombin III, particularly those involving bleeding.

-Answer to comment:

We agree with the reviewer about that.

We would like to thank you for your kind consideration.

We have corrected the sentence in the revised manuscript as the reviewer pointed out as follows:

(page 46, table 1)

		Non-Survivor (N=44)	Survivor (N=32)	Total (N=76)	P
Age		66.5 ± 18.1	66.0 ± 16.2	66.2 ± 17.2	0.904
Sex					0.355
Male		32 (72.7%)	27 (84.4%)	59 (77.6%)	
Female		12 (27.3%)	5 (15.6%)	17 (22.4%)	
Hospital days		31.1 ± 34.5	31.2 ± 26.1	31.2 ± 31.1	0.991
Cause for DIC					0.950
Sepsis		10 (22.7%)	8 (25.0%)	18 (23.7%)	
Trauma		10 (22.7%)	6 (18.8%)	16 (21.1%)	
Respiratory failure		10 (22.7%)	8 (25.0%)	18 (23.7%)	
Surgery/Rhabdomyolysis		9 (20.5%)	5 (15.6%)	14 (18.4%)	
et cetera		5 (11.4%)	5 (15.6%)	10 (13.2%)	
Underlying disease					0.383
Arterial hypertension		13 (29.5%)	4 (12.5%)	17 (22.4%)	
Diabetes		8 (18.2%)	9 (28.1%)	17 (22.4%)	
COPD		9 (20.5%)	9 (28.1%)	18 (23.7%)	
Cardiac comorbidities		4 (9.1%)	5 (15.6%)	9 (18.4%)	
Dyslipidemia		5 (11.4%)	5 (15.6%)	10 (11.3%)	
SOFA		7.3 ± 2.5	6.6 ± 2.0	7.0 ± 2.3	0.224
SAPS II		46.0 ± 8.8	43.5 ± 9.2	44.9 ± 9.0	0.234
Transfusion		11 (14.5%)	5 (6.6%)	16 (21.1%)	0.399
Major bleeding		1 (1.3%)	2 (3.6%)	3 (3.9%)	0.569
D-dimer (ng/mL)	on day	8346.0 ± 14478.4	6256.3 ± 7517.1	7466.1 ± 12025.8	0.416
	1st day	8814.5 ± 12669.4	8528.4 ± 7775.7	8694.0 ± 10818.4	0.904
	2nd day	11909.0 ± 15900.1	13621.6 ± 14762.2	12639.7 ± 15346.2	0.636
	7th day	5196.3 ± 4128.1	4987.6 ± 4271.3	5108.4 ± 4162.0	0.831
Thrombin time (sec)	on day	34.9 ± 59.8	21.7 ± 9.2	29.4 ± 46.2	0.157

5. Discussion (4th Paragraph):

The reasons why the proportion of non-survivors was higher than survivors despite the use of antithrombin III should be discussed. Was the sample size inadequate, or was there a bias in the patient population compared to previous reports, etc.

-Answer to comment:

We agree with the reviewer about that.

We would like to thank you for your kind consideration.

It is with great regret that our study showed a little poor survival rate (non-Survivor, N=44, 57.9% vs Survivor, N=32, 42.1%) in spite of active DIC mx, especially compared to previous good results. Please understand that this study is just containing a longitudinal single-institutional experience under retrospective analysis, and it is estimated that these drawbacks brought about poor outcome.

6. Discussion (5th Paragraph):

There is mention of the economic situation in Korea, what drugs are available in Korea for the treatment of DIC? For example, recombinant human soluble thrombomodulin is available in some countries. How do the different drugs available in Korea affect DIC treatment strategies? Please provide any information on DIC drugs available in Korea.

-Answer to comment:

We agree with the reviewer about that.

We would like to thank you for your kind consideration.

We have corrected the sentence in the revised manuscript as the reviewer pointed out as follows: (page 22, lines 516-522)

"For the treatment of DIC, most of medications are available in my country, South Korea, including antithrombin III concentrate, activated protein C and synthesized protease inhibitors, such as gabexate mesilate and nafamostat mesilate, etc. However, recombinant human soluble thrombomodulin, that binds thrombin which serves to augment the conversion of protein C to activated protein C and inhibits inflammation and organ injury caused by damage-associated molecular patterns, is not yet available in South Korea [20]."

7. Discussion (6th Paragraph - Limitation):

Specify what potential residual confounding factors are anticipated.

This overlaps with the content of the 5th paragraph, but if there are differences in the medications available for DIC treatment in South Korea and other countries, this should be noted as a limitation of the study.

-Answer to comment:

We agree with the reviewer about that.

We would like to thank you for your kind consideration.

We have corrected the sentence in the revised manuscript as the reviewer pointed out as follows: (page 22, lines 516-522)

"For the treatment of DIC, most of medications are available in my country, South Korea, including antithrombin III concentrate, activated protein C and synthesized protease inhibitors, such as gabexate mesilate and nafamostat mesilate, etc. However, recombinant human soluble thrombomodulin, that binds thrombin which serves to augment the conversion of protein C to activated protein C and inhibits inflammation and organ injury caused by damage-associated molecular patterns, is not yet available in South Korea [20]."

Minor Revision Suggestions:

1. Materials and Methods:

·Were patients in the intensive care unit? It is inferred from the calculation of SOFA and SAPS2 scores, but please specify the ward concerned.

·Does this study include patients who were concurrently using heparin? Please clarify.

-Answer to comment:

We agree with the reviewer about that.

We would like to thank you for your kind consideration.

We have corrected the sentence in the revised manuscript as the reviewer pointed out as follows: (page 12, lines 266-270)

"All the patients in this study were managed in the intensive care unit (ICU), and both the SOFA and SAPS II were calculated at the time of ICU admission. In the non-hemorrhaging patient with DIC, prophylactic anticoagulation with low doses of unfractionated heparin (UFH) or low molecular weight heparins (LMWH) was strongly the initiated."

2. Discussion (1st Paragraph):

The text is verbose. Information regarding the history of antithrombin is likely unnecessary.

-Answer to comment:

We agree with the reviewer about that.

We would like to thank you for your kind consideration.

The discussion was shortened and was made more concise.