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Citation	Shock, 30(6), 649-652 https://doi.org/10.1097/SHK.0b013e318173e396
Issue Date	2008-12
Doc URL	http://hdl.handle.net/2115/40198
Rights	This is a non-final version of an article published in final form in Shock. 30(6):649-652, December 2008
Type	article (author version)
File Information	30-6_p649-652.pdf

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Title page

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The response of antithrombin III activity after supplementation decreases in proportion to the severity of sepsis and liver dysfunction

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Running head

Response of antithrombin supplementation in sepsis

Abstract

The decrease in the antithrombin III activity is thought to result from consumption by ongoing coagulation, degradation by neutrophil elastase, capillary leak syndrome, and impaired synthesis. A retrospective data analysis of patients with sepsis was conducted to investigate the response of antithrombin III activity after supplementation in patients with sepsis, and to determine what factors affect the response of antithrombin III activity.

The study included 42 sepsis, 75 severe sepsis and 65 septic shock patients, who were administrated antithrombin III. Antithrombin III activity, platelet counts, coagulation and fibrinolytic markers were collected before administration and 24 hr after the supplementation.

In the patients with septic shock, the response of antithrombin III activity after supplementation was 0.37 ± 1.21%/IU/kg body weight, which was significantly lower in comparison to those in the patients with sepsis (1.81 ± 1.75; $P < 0.001$) or severe sepsis (1.36 ± 1.65; $P < 0.001$). The patients with liver dysfunction had significantly lower

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response to antithrombin III activity than that of the patients without liver dysfunction ($P < 0.0001$). A stepwise multiple-linear regression analysis revealed that the severity of sepsis and liver function were independent predictors for the response to antithrombin III activity. These results suggest that the response to antithrombin III supplementation may be affected by both a systemic inflammation and impaired synthesis in patients with sepsis.

KEY WORDS — anticoagulation, capillary leak syndrome, disseminated intravascular coagulation, multiple organ dysfunction syndrome, pharmacokinetics, septic shock, systemic inflammatory response syndrome

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INTRODUCTION

Sepsis is defined as a systemic inflammatory response syndrome (SIRS) induced by infection, which is frequently associated with disseminated intravascular coagulation (DIC). DIC induces impairments in microcirculation and contributes to later multiple organ dysfunction syndrome (1,2). This sequential pathophysiology is frequently complicated with the depletion of antithrombin III activity (1,2). The decrease in antithrombin III level has been thought to result from consumption by ongoing coagulation, degradation by neutrophil elastase, capillary leak syndrome, and impaired synthesis (2-7). The level of antithrombin III has been reported to be a good prognostic factor for the prediction of subsequent death (1).

Recently, several studies showed evidence suggesting the benefit of antithrombin III supplementation therapy for septic patients with low antithrombin III activity (8-12). In the KyberSept trial, patients with severe sepsis received 30,000 IU antithrombin III with a loading dose of 6,000 IU followed by a continuous IV infusion of

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6,000 IU per day for 4 days (8). In the treated patients, the antithrombin III levels were elevated by 115%, and the supplementation therapy improved the 90-day prognosis of the patients treated without heparin (8). Wiedermann *et al* (9) showed that treatment with high-dose antithrombin III increased the survival rate in the patients with severe sepsis and a high risk of death in the KyberSept trial. Baudo *et al*. (10) reported that antithrombin III replacement therapy reduced mortality in patients with septic shock. Eisele *et al*. (11) and Hoffmann *et al*. (12) also reported that antithrombin III supplementation therapy is beneficial in the treatment of patients with sepsis. However, no study has previously shown that the response of antithrombin III activity after supplementation in patients with sepsis, and what factors affect the response of antithrombin III activity. To elucidate these questions, the response of antithrombin III activity was investigated after supplementation of the patients with sepsis.

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MATERIALS AND METHODS

Patient Selection and Data Collection

From January 2003 to December 2006, all patients with sepsis admitted to the intensive care unit (ICU) and treated with antithrombin III were enrolled in the study. Patients with severe liver cirrhosis or previous liver transplantation were excluded. Patients who received fresh frozen plasma were also excluded. The clinical backgrounds of the patients and the measured variables were retrospectively collected from computer-based patient records. The antithrombin III activity, platelet counts, coagulation and fibrinolytic markers were collected in the morning on the day of antithrombin III supplementation (before administration), and the levels of antithrombin III activity were all measured in the next morning (24 hour interval). The platelet count, coagulation, fibrinolytic markers, and other usual laboratory data were prospectively examined based on our daily routine ICU protocols. Antithrombin III activity in this laboratory was measured using the Chromogenic substrate method (TESTZYM S ATIII Daiichi Pure Chemicals CO., LTD., Tokyo, Japan).

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Definitions

Sepsis, severe sepsis and septic shock were defined according to the definition of the American College of Chest Physicians/Society of Critical Care Medicine consensus conference (13). Organ failure was assessed by the sequential organ failure assessment (SOFA) score (14). Liver dysfunction was defined as SOFA score for liver ≥ 3. Scoring system for Japanese Association for Acute Medicine (JAAM) DIC was used for diagnosis of DIC. The JAAM DIC diagnostic algorithm for scoring DIC includes following variables as platelet counts, prothrombin time, fibrin/fibrinogen degradation products level, and systemic inflammatory response score. The details of the algorithm have been presented elsewhere (15).

Intervention and Treatment

The clinical indications for using antithrombin III in the ICU were based on the guidelines set by the Japanese Ministry of Health,

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Labor and Welfare. According to the established guidelines, 30 IU/kg antithrombin III concentration (Mitsubishi Pharma Corporation, Osaka, Japan; ZLB Behring K.K., Tokyo, Japan; Nihon Seiyaku, Tokyo, Japan) are administered for over an hour when the patient is diagnosed to have a severe deficiency of antithrombin III associated with low platelet counts, coagulation and fibrinolytic abnormality. DIC treatment requires anticoagulant therapy with gabexate mesilate (ONO PHARMACEUTICAL CO., LTD, Osaka, Japan). All patients were automatically administered ~700-2,000 IU heparin/day for anticoagulation of the arterial, central venous, or pulmonary arterial catheters. For the prevention of deep venous thrombosis, an intermittent pneumatic compression was used and no patients received prophylactic heparin administration. Heparin was not administered for DIC. A platelet concentrate was administered when the platelet counts were less than 30 x 10^9/L.

Statistical Analysis

Unless otherwise indicated, all measurements are expressed

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as the mean ± SD. The SPSS 15.0J statistical software package (SPSS Inc., Chicago, Illinois) was used for all statistical calculation analysis. Comparisons between the groups were made using the Kruskal-Wallis test, the Mann-Whitney U test, and the chi square test. *Post hoc* multiple comparisons were made by the Mann-Whitney U test with Bonferroni correction and the chi square test with Bonferroni correction. The Spearman rank correlation was calculated to assess the correlation between severity of sepsis and other variables. A stepwise multiple-linear regression analysis was used to assess the relationship between the response of antithrombin III after supplementation and variables as follows; gender, age, SIRS score, total SOFA score, SOFA scores for each organs, total input/output balance, complication of JAAM DIC, JAAM DIC score, platelet counts, prothrombin time, fibrinogen level, D-dimer level, fibrin/fibrinogen degradation products level, 28-day outcome, length of ICU stay, and severity of sepsis. A value of $P < 0.05$ was considered to be statistically significant.

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RESULTS

Patient characteristics

The overall number of patients who were admitted to the ICU during the study period was 2,649. In the present study, antithrombin III was administered a total of 182 times to 42 patients with sepsis, 75 patients with severe sepsis and 65 patients with septic shock. The infection sites of these patients are presented in Table 1. Table 2 shows the patients characteristics. The initial antithrombin III activity levels and dose of antithrombin III administered to the patients were identical among the three groups. The total input/output balance was not different among the three groups on the day of antithrombin III administration. There were significant differences in the SOFA score, the frequency of DIC, DIC score, and 28-day outcome among the three groups ($P < 0.01$). The SOFA score was different in each of the severity groups of sepsis ($P < 0.05$). The frequency of DIC and DIC score in the patients with sepsis were lower than that in the patients with either severe sepsis or septic shock ($P < 0.05$). The 28-day

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survival rate in the patients with sepsis was higher than that in the patients with severe sepsis or septic shock ($P < 0.01$).

The evaluation of the correlation between the severity of sepsis and other variables were as follows: The SOFA score increased in proportion to the severity of sepsis ($\rho = 0.696$, $P < 0.0001$). The JAAM DIC score of the patients significantly increased in proportion to the severity of sepsis ($\rho = 0.232$, $P = 0.002$).

Response to antithrombin III supplementation

The responses of antithrombin III activity after supplementation in the three groups are presented in Fig. 1. In the patients with septic shock, the response of antithrombin III activity was 0.37 ± 1.21%/IU/kg body weight, which was significantly lower than that of the patients with sepsis or severe sepsis ($P < 0.001$). In the sepsis and severe sepsis groups, one unit antithrombin III per kg body weight increased antithrombin III activity by 1.81 ± 1.75% and 1.36 ± 1.65%, respectively. The response of antithrombin III activity decreased in proportion to the severity of sepsis ($\rho = -0.370$, $P <$

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0.0001).

Fig. 2 demonstrates the response to antithrombin III activity after supplementation in patients with and without liver dysfunction. The patients with liver dysfunction had a significantly lower response of antithrombin III activity after supplementation than that of the patients without liver dysfunction (0.82 ± 1.55 vs. 1.86 ± 1.61, P < 0.0001). The patients without DIC had a significantly higher response to antithrombin III activity after supplementation than that of the patients with DIC (1.26 ± 1.68 vs. 0.97 ± 1.57, P =0.041).

A stepwise multiple-liner regression analysis revealed that severity of sepsis (regression coefficient, -0.581; SE, 0.156; standardized coefficient, –0.272; t, -3.730; P<0.0001) and SOFA score for liver (regression coefficient, -0.285; SE, 0.090; standardized coefficient, –0.232; t, -3.181; P=0.002) were independent predictors for the response of antithrombin III activity after supplementation (R^2 for the entire model, 0.168).

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DISCUSSION

This study demonstrated that the response to antithrombin III activity after supplementation decreased in proportion to the severity of sepsis and liver dysfunction. The DIC score and the SOFA score also significantly increased in proportion to the severity of sepsis. The 28-day survival rate in the patients with sepsis was higher than that in the patients with severe sepsis or septic shock.

In patients with sepsis, the decrease in the antithrombin III level is thought to result from: 1) consumption by ongoing coagulation; 2) degradation by neutrophil elastase; 3) capillary leak syndrome; and 4) impaired synthesis (2-7,16).

Sepsis is defined as a SIRS due to infection (13). The three major events of systemic inflammation are activation of neutrophil and endothelium, vasodilatation, increased permeability of the vessel and exudation of plasma (17,18). The systemic inflammation leads to activation of coagulation with thrombin generation in the circulating blood, and ultimately accelerates a consumption of antithrombin III (3,4,17,18). In addition to the accelerated consumption of

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antithrombin III due to systemic activation of coagulation, a degradation by the neutrophil elastase results in lower response of antithrombin III activity in patients with septic shock (2,6,17). Disseminated intravascular coagulation is considered to occur under these conditions (6,18). Disseminated intravascular coagulation, a frequent complication of systemic inflammation and sepsis, is also associated with neutrophil and endothelial activation, leading to neutrophil elastase release (6,18). In the present study, the frequency of DIC increased in proportion to the severity of sepsis. Furthermore, the patients with DIC had significantly lower response to antithrombin III activity after supplementation than those patients without DIC

The activation of neutrophils and endothelium associated with systemic inflammation results in the increased permeability of the vessels and exudation of plasma (capillary leak syndrome) (17,18). Capillary leak syndrome is one of the reasons for the reduction of response of antithrombin III supplementation in patients with septic shock (2,16,19,20). Patients with septic shock need frequent

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intravenous drip infusion because of the increased permeability of the vessels. In the present study, however, the total input/output balance after supplementation with antithrombin III were identical among the three groups, which suggests that capillary leak syndrome but not hemodilution were responsible for the lower response to antithrombin III activity in the patients with septic shock.

In previous review articles (2,6), a dysfunction of liver synthesis was described as one of the reasons for the reduction of antithrombin III in patients with sepsis. However, no previous reports showed a relation between liver dysfunction and antithrombin III activity in the patients with sepsis. The present study was the first report showing that the severity of liver dysfunction was a negative predictor for the response of antithrombin III activity after supplementation in patients with sepsis. Dhainaut *et al*. (21) reviewed the hepatic response to sepsis and reported that many proinflammatory mediators inhibit antithrombin III synthesis in hepatocytes. However, the detailed mechanisms of the inhibition antithrombin III synthesis were not explained in the present study.

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The present study demonstrated that the two main factors affecting antithrombin III activity are the severity of sepsis and liver dysfunction as statistical results by the multiple-linear regression analysis. The results also clearly indicated that inflammation and synthesis, and not the SOFA and DIC scores, play important roles in the antithrombin III activity after supplementation.

Previous studies (5,22) described the pharmacokinetic characteristics of antithrombin III. Blauhut *et al* (22) showed that one unit of antithrombin III per kg body weight increased antithrombin III activity by 1.0 ± 0.1% in acute DIC patients but 1.80 ± 0.22%/IU/kg body weight in a steady state. Ilias *et al* (5) reported the pharmacokinetics of antithrombin III in patients with severe sepsis. They indicated that the elimination half-life and response rate of antithrombin III in patients with severe sepsis are markedly reduced (1.75 ± 0.42%/IU/kg body weight) in comparison to healthy controls (5). In the present study, 86% of the patients with septic shock had simultaneous complications of liver dysfunction. In these patients, the mean response to antithrombin III supplementation was 0.28 ±

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1.19%/IU/kg body weight. The response was clearly lower than the results from Blauhut (22) and Ilias *et al* (5). Collectively, these data suggest that the severity of sepsis as well as the severity of liver dysfunction synergistically reduce the response to antithrombin III activity after supplementation.

In conclusion, this study demonstrated that the response to antithrombin III supplementation was affected by both systemic inflammation due to sepsis and by impaired synthesis associated with liver dysfunction. Furthermore, consumption of antithrombin III by DIC might also play some role in the low response of the antithrombin III activity after supplementation.

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TABLE 1. **Infection site of the patients**

	Sepsis (n=42)	Severe sepsis (n=75)	Septic shock (n=65)	Total
Lung	25	42	20	87
Thoracic cavity	4	8	5	17
Abdominal cavity	5	13	36	54
Urinary tract	3	6	1	10
Blood stream	5	4	3	12
Soft tissue	0	2	0	2

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TABLE II. **Characteristics of the patients and outcome**

	Sepsis (n=42)	Severe sepsis (n=75)	Septic shock (n=65)	*P* value
Gender (male/female)	15 / 27	57 / 18 *	50 / 15 *	<0.0001
Age (year)	65 ± 11	68 ± 14	62 ± 20	0.063
Initial antithrombin III activity (%)	59.7 ± 19.4	58.3 ± 12.7	55.5 ± 14.7	0.275
Antithrombin III dose (IU/kg)	32.5 ± 12.9	31.7 ± 9.7	29.4 ± 11.3	0.085
SOFA score	6.7 ± 2.4	11.5 ± 3.4 *	15.2 ± 3.6 *$^{+}$	<0.0001
Total input/output balance (ml/kg/day)	-1.6 ± 3.4	-4.6 ± 3.5	10.3 ± 3.7	0.064
JAAM DIC (yes/no)	11 / 31	43 / 32 *	40 / 15 *	0.0007
JAAM DIC score	3.0 ± 1.9	3.7 ± 1.8 *	3.9 ± 1.5 *	0.0051
ICU stay (days)	10.7 ± 1.2	18.0 ± 2.3	13.2 ± 1.4	0.259
28-day outcome (survived/died)	41 / 1	39 / 36 *	46 / 19 *	<0.0001

Comparisons among the three groups were made using the Kruskal-Wallis test or the chi square test: *, $P < 0.05$ vs. sepsis; $^{+}$, $P < 0.05$ vs. severe sepsis; n, number; SOFA, sequential organ failure assessment; JAAM DIC, disseminated intravascular coagulation by Japanese Association for Acute Medicine scoring system; ICU intensive care unit.

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FIGURE LEGENDS

Figure 1.

The response of antithrombin III activity after supplementation in the patients with sepsis, severe sepsis, and septic shock. In the patients with septic shock, the response of antithrombin III activity was significantly lower than those of the patients with sepsis and severe sepsis ($P < 0.001$). Data are presented by box and whisker plots. The central horizontal bars, boxes, and error bars indicated the median, the 25th to 75th percentiles, and the 10th to 90th percentiles, respectively.

Figure 2.

The response of antithrombin III activity after supplementation in the patients with and without liver dysfunction. The patients with liver dysfunction had significantly lower response of antithrombin III activity after supplementation than that of the patients without liver

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dysfunction ($P < 0.0001$). Data are presented by box and whisker plots. The central horizontal bars, boxes, and error bars indicated the median, the 25th to 75th percentiles, and the 10th to 90th percentiles, respectively.

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Figure 1.

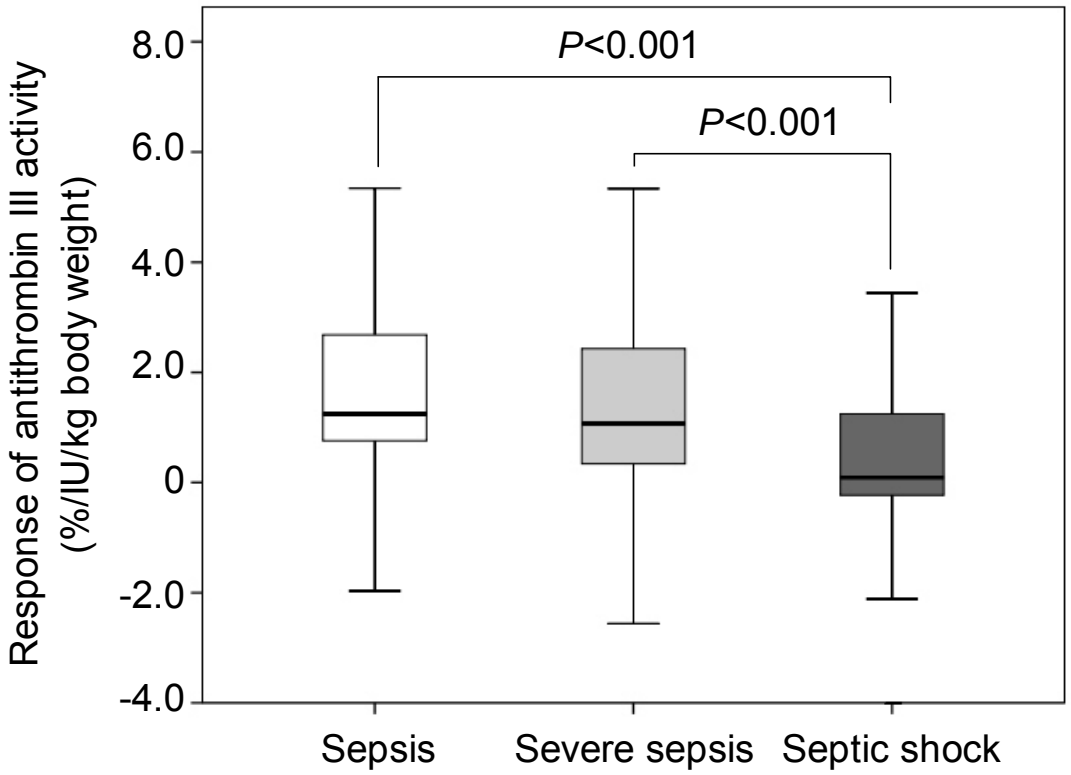

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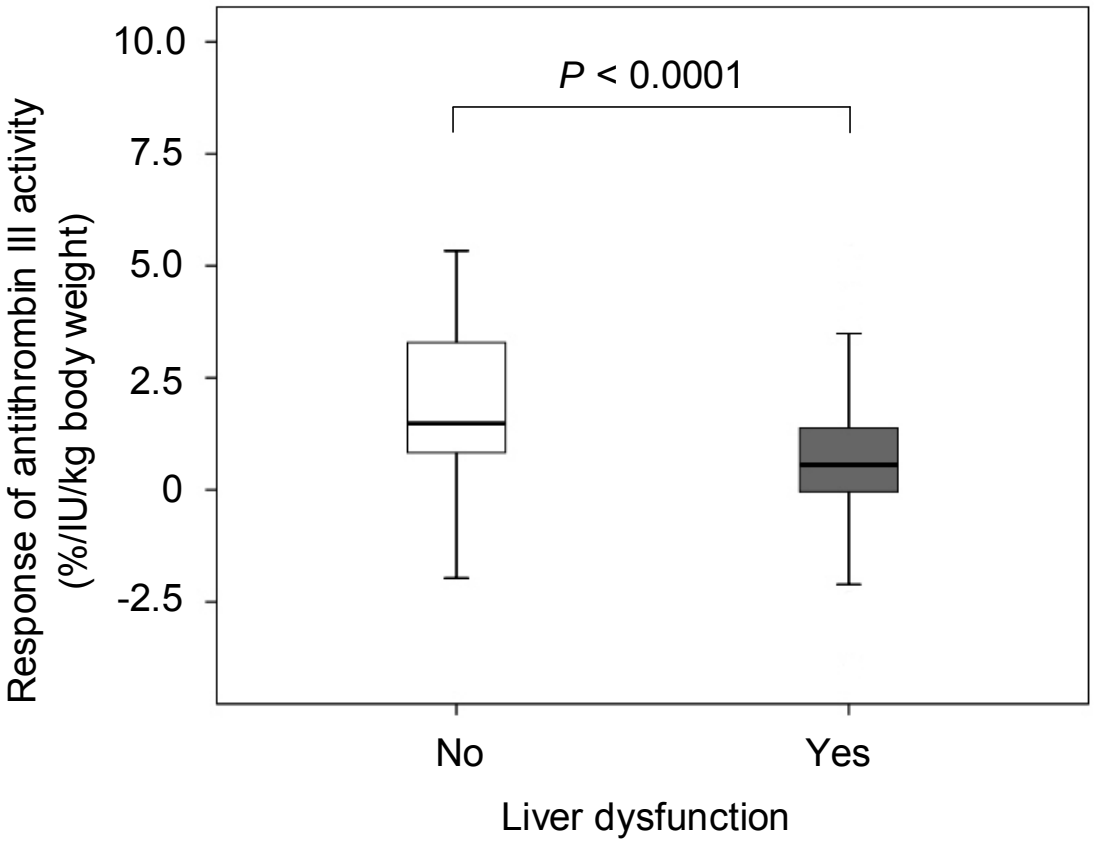
Figure 2.



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