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Clinical Article

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Efficacy of Serum Antithrombin III Test in Patients With Severe Traumatic Brain Injury

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ABSTRACT

Objective: Immune reactions following traumatic brain injury (TBI) cause many complications, including intravascular dissemination. Antithrombin III (AT-III) plays an important role in suppressing abnormal clot formation and ensuring hemostasis. Therefore, we investigated the efficacy of serum AT-III in patients with severe TBI.
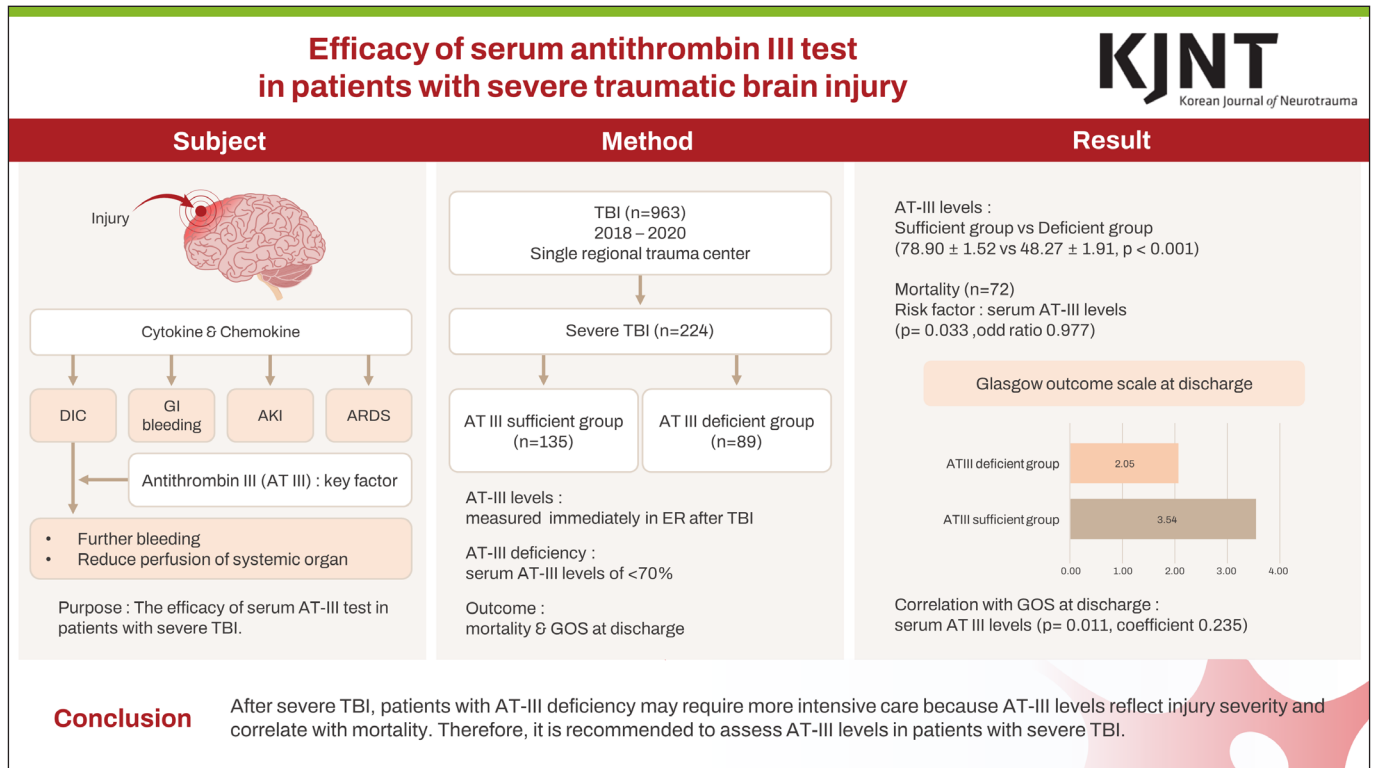
Methods: This retrospective study included 224 patients with severe TBI who visited a single regional trauma center between 2018 and 2020. AT-III levels were measured immediately after the TBI diagnosis. AT-III deficiency was defined as an AT-III serum level <70%. Patient characteristics, injury severity, and procedures were also investigated. Patient outcomes included Glasgow Outcome Scale scores at discharge and mortality.

Results: AT-III levels were significantly lower in the AT-III deficient group (n=89; 48.27% ± 1.91%) than in the AT-III sufficient group (n = 135, 78.90% ± 1.52%) (p < 0.001). Mortality occurred in 72 of the 224 patients (33.04%), indicating that there were significantly more patients in the AT-III-deficient group (45/89, 50.6%) than in the AT-III-sufficient group (27/135, 20%). Significant risk factors for mortality included the Glasgow Coma Scale score (P = 0.003), pupil dilatation (P = 0.031), disseminated intravascular coagulopathy (P = 0.012), serum AT-III level (P = 0.033), and procedures including barbiturate coma therapy (P = 0.010). Serum AT-III levels were significantly correlated with Glasgow Outcome Scale scores at discharge (correlation coefficient = 0.455, p < 0.001).

Conclusion: Patients with AT-III deficiency after severe TBI may require more intensive care during treatment, because AT-III levels reflect injury severity and correlate with mortality.

Keywords: Brain injury, traumatic; Antithrombin III; Blood coagulation disorder; Glasgow Outcome Scale; Mortality

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GRAPHICAL ABSTRACT

Efficacy of serum antithrombin III test in patients with severe traumatic brain injury

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Subject	Method	Result

Subject

Injury

Cytokine & Chemokine

DIC | GI bleeding | AKI | ARDS

Antithrombin III (AT III) : key factor

- Further bleeding
- Reduce perfusion of systemic organ

Purpose : The efficacy of serum AT-III test in patients with severe TBI.

Method

TBI (n=963)
2018 – 2020
Single regional trauma center

Severe TBI (n=224)

AT III sufficient group (n=135) | AT III deficient group (n=89)

AT-III levels :
measured immediately in ER after TBI

AT-III deficiency :
serum AT-III levels of <70%

Outcome :
mortality & GOS at discharge

Result

AT-III levels :
Sufficient group vs Deficient group
(78.90 ± 1.52 vs 48.27 ± 1.91, p < 0.001)

Mortality (n=72)
Risk factor : serum AT-III levels
(p= 0.033 ,odd ratio 0.977)

Glasgow outcome scale at discharge

ATIII deficient group   2.05
ATIII sufficient group   3.54

0.00   1.00   2.00   3.00   4.00

Correlation with GOS at discharge :
serum AT III levels (p= 0.011, coefficient 0.235)

Conclusion After severe TBI, patients with AT-III deficiency may require more intensive care because AT-III levels reflect injury severity and correlate with mortality. Therefore, it is recommended to assess AT-III levels in patients with severe TBI.

INTRODUCTION

Traumatic brain injury (TBI) induces an innate immune reaction, which causes problems in the brain and multiple organ dysfunction, including acute kidney injury, coagulopathy, acute respiratory distress syndrome (ARDS), and gastrointestinal bleeding.[8] The complications are caused by rapid cytokine release after TBI, and the resulting brain and systemic complications substantially impact patient mortality.[2]

Coagulopathy is a representative complication that affects mortality after severe TBI.[18] TBI-induced cytokine release induces hepatic inflammation, which impairs liver function. As a result, the production of coagulation factor is inhibited, and enzyme activation related to the coagulation cascade is inhibited. Subsequently, the release of brain-derived procoagulants and fibrinolytic molecules (tissue fibrinogen and tissue plasminogen activators) induces coagulopathy and excessive secretion of mediators and activators of leukocytes. This cascade of events increases the risk of further bleeding and reduces perfusion of systemic organs.[8,10]

Antithrombin III (AT-III), which plays an important role in the coagulation cascade, is a non-vitamin K-dependent protease that neutralizes the enzymatic activity of thrombin and regulates the actions of fibrinogen and thrombin during coagulation.[15] Therefore, AT-III plays an important role in preventing abnormal coagulation. After TBI, AT-III overactivation and abnormal function due to chemokine or cytokine expression cause excessive coagulation, and tissue plasminogen activator overactivation to eliminate excessive coagulation creates a disseminated intravascular coagulopathy (DIC) environment.[7] In addition, some studies

have reported that AT-III improves neurocognitive function via blood brain barrier stability by reducing neuromicrovascular permeability caused by its anti-inflammatory effect during TBI secondary injury.[5,6]

Therefore, we investigated the efficacy of serum AT-III test in patients with severe TBI.

MATERIALS AND METHODS

This study was approved by Institutional Review Board of Ulsan University Hospital (approval No. 2021-05-030-001), and the requirement for informed consent was waived.

Study design
The medical records of 963 patients who visited a single regional trauma center with TBI from 2018 to 2020 were retrospectively reviewed. Inclusion criteria were an initial Glasgow Coma Scale (GCS) score of <9, age of >18 years, and AT-III and coagulation factors measured in the emergency room. Exclusion criteria included severe bleeding due to poly-trauma, death in the emergency room, and serum AT-III level not measured in the emergency room. Of the 963 patients with TBI, 224 were eligible and included in this study.

Serum level of AT-III
AT-III levels were measured immediately after the patient arrived in the emergency room with severe TBI. The AT-III function test included heparin cofactor activity and chromogenic assays. The normal AT-III level was defined as 70%–130%. AT-III deficiency was defined as serum AT-III levels of <70%.[13] Patients with AT-III deficiency were infused with a loading dose of 2,000 IU of AT-III for 5 hours, followed by replacement at a dose of 3,000 IU/day for 2 days, according to the standards of the Korea Health Insurance Review and Assessment Service.

Clinical data collection
Patient clinical information was retrospectively obtained from medical charts, including sex, age, history of diabetes, hypertension, end-stage renal disease, previous stroke, previous cardiovascular disease, smoking, alcoholism, antiplatelet usage, and anticoagulant usage. Alcoholism was defined as the consumption of more than 14 standard drinks per week or 4 drinks per day.[3] Injury degree parameters included initial GCS score, shock, pupil dilatation, and trauma mechanism. The trauma mechanism was classified, depending on the cause of the traumatic incident, into car traffic accident (TA, driver or assistant), motorcycle TA, bicycle TA, pedestrian TA, cultivator accident, fall, slip, head collision, or assault. Initial GCS score was defined as the score obtained at the time of patient arrival to the emergency room after their accident. Shock was defined as requiring transfusion or inotropic agents with systolic blood pressure <90 mmHg at the time of admission to the emergency room. In laboratory tests, prothrombin time (PT); activated partial thromboplastin time (aPTT); platelet count; and levels of fibrinogen degradation product (FDP), D-dimer, fibrinogen, and AT-III were assessed immediately after visiting the emergency room, and these results were used for DIC classification according to the International Society for Thrombosis and Hemostasis scoring system.[1] For procedure data, craniectomy, therapeutic hypothermia, and barbiturate coma therapy were included. Patient outcome measures included mortality and Glasgow Outcome Scale (GOS) score at discharge.

Statistical analysis

Statistical analyses were performed using SPSS Version 21.0 (IBM Corp., Armonk, NY, USA). χ^2 tests, Fisher's exact tests, linear by linear tests, Student's *t*-tests, or Mann–Whitney tests were used to determine risk factors of mortality. Logistic regression analysis was performed using significant factors in the univariate analyses. The relationship between AT-III level and GOS score was analyzed using Pearson correlation analysis. In addition, multiple linear regression analysis was performed for factors that were significantly related to GOS scores in the simple correlation analysis. A *p*-value of <0.05 was considered to indicate statistical significance.

RESULTS

The AT-III levels were significantly lower in the AT-III deficient group (n=89; 48.27%±1.91%) compared with the AT-III sufficient group (n=135; 78.90%±1.52%) (*p*<0.001). At the time of arrival to the emergency room, GCS score (*p*<0.001), shock (*p*=0.005), pupil dilatation (*p*=0.010), and DIC (*p*<0.001) were significantly worse in the AT-III deficient group than in the AT-III sufficient group. Further, in blood tests, platelet count (*p*<0.001), PT (*p*<0.001), aPTT (*p*<0.001), FDP level (*p*<0.001), D-dimer level (*p*<0.001), and fibrinogen level (*p*<0.001) related to DIC diagnosis differed significantly between the two groups. As a result, more procedures were performed in the AT-III deficient group, including craniectomies (*p*<0.001), therapeutic hypothermia (*p*=0.018), and barbiturate coma therapy (*p*=0.001) (**TABLE 1**).

Mortality occurred in 72 of 224 patients (33.04%), indicating significantly more patients in the AT-III deficient group (45/89, 50.6%) than in the AT-III sufficient group (27/135, 20%). According to univariate analysis, injury degree parameters, including GCS score (*p*<0.001), shock (*p*<0.001), pupil dilatation (*p*<0.001), DIC (*p*<0.001), and serum AT-III levels (*p*<0.001), as well as craniectomy (*p*=0.027), therapeutic hypothermia (*p*<0.001), and barbiturate coma therapy (*p*<0.001) were significantly associated with mortality. However, based on multivariate analysis, injury degree parameters, including GCS score (*p*=0.003; odds ratio [OR], 0.801; 95% confidence interval [CI], 0.690–0.929), pupil dilatation (*p*=0.031; OR, 2.545; 95% CI, 1.089–5.946), DIC (*p*=0.012; OR, 3.341; 95% CI, 1.306–8.546), and serum AT-III level (*p*=0.033; OR, 0.977; 95% CI, 0.956–0.998), as well as barbiturate coma therapy (*p*=0.010; OR, 3.816; 95% CI, 1.378–10.563) were significantly associated with mortality (**TABLE 2**).

The average GOS score at discharge was 2.78±2.44 for all patients, which was significantly lower in the AT-III deficient group (2.05±0.25) than in the AT-III sufficient group (3.54±0.31) (*p*<0.001). The serum AT-III level significantly correlated with the GOS score at discharge (correlation coefficient=0.455, *p*<0.001) (**FIGURE 1**). In addition, GCS score (coefficient value=0.367, *p*<0.001), pupil dilatation (coefficient value=−0.313, *p*<0.001), DIC (coefficient value=−0.248, *p*<0.001), AT-III level (coefficient value=0.235, *p*=0.011), therapeutic hypothermia (coefficient value=−0.293, *p*<0.001), and barbiturate coma therapy (coefficient value=−0.315, *p*<0.001) were significantly correlated with GOS score at discharge (**TABLE 3**).

DISCUSSION

The association of AT-III with mortality after TBI has been reported in several studies, but debate about the replacement of AT-III is still ongoing.[7,17] In our study, patients with

TABLE 1. Baseline characteristics of the AT-III sufficient and deficient groups

Characteristics	AT-III sufficient group (n=135)	AT-III deficient group (n=89)	*p*-value
Patient characteristics			
Sex (male)	103 (76.3)	69 (77.5)	0.831
Age (years)	52.98±1.74	55.84±1.87	0.277
Hypertension	37 (27.4)	28 (31.5)	0.513
Diabetes	21 (15.7)	21 (23.6)	0.138
ESRD	3 (2.2)	2 (2.2)	1.000
Stroke	11 (8.1)	3 (3.4)	0.148
Cardiovascular disease	14 (10.4)	4 (4.5)	0.113
Smoking	60 (44.4)	49 (55.1)	0.120
Alcoholics	22 (16.3)	14 (15.7)	0.910
Antiplatelet	11 (8.1)	3 (3.4)	0.148
Anticoagulant	6 (4.4)	1 (1.1)	0.248
Injury degree			
GCS	8.68±0.33	6.72±0.38	**<0.001**
Shock	11 (8.1)	19 (21.3)	**0.005**
Pupil dilatation	38 (28.1)	40 (44.9)	**0.010**
Trauma mechanism			0.774
Car TA	9 (6.7)	3 (3.4)	
Pedestrian TA	25 (18.5)	19 (21.3)	
Motorcycle TA	14 (10.4)	15 (16.9)	
Bicycle accident	9 (6.7)	6 (6.7)	
Fall	26 (19.3)	17 (19.1)	
Slip	21 (15.6)	10 (11.2)	
Head collision	8 (5.9)	1 (1.1)	
Assault	1 (0.7)	1 (1.1)	
Others	22 (16.3)	17 (19.1)	
Laboratory findings			
DIC	20 (14.9)	63 (70.8)	**<0.001**
Platelet count (/μL)	19,115±7,861	11,325±6,264	**<0.001**
PT (sec)	12.59±2.15	20.45±19.98	**<0.001**
aPTT (sec)	31.45±19.28	45.69±27.16	**<0.001**
D-dimer level (μg/μL)	19.00±26.53	51.16±86.88	**<0.001**
FDP level (μg/μL)	79.06±90.50	154.71±132.57	**<0.001**
Fibrinogen (mg/dL)	231.93±113.83	119.58±72.87	**<0.001**
AT-III level (%)	78.90±1.52	48.27±1.91	**<0.001**
Procedure			
Craniectomy	86 (63.7)	80 (89.39)	**<0.001**
Therapeutic hypothermia	18 (13.3)	23 (25.8)	**0.018**
Barbiturate coma therapy	40 (29.6)	46 (51.7)	**0.001**

Values are presented as mean±standard deviation or number (%). Bold-styled values are considered statistically significant.
AT-III: antithrombin III, ESRD: end-stage renal disease, GCS: Glasgow Coma Scale, TA: traffic accident, DIC: disseminated intravascular coagulopathy, PT: prothrombin time, aPTT: activated partial thromboplastin time, FDP: fibrinogen degradation production.

AT-III deficiency had higher injury severity, and a higher proportion of patients required procedures, such as barbiturate coma therapy. Serum AT-III levels significantly correlate with injury severity in patients who experienced poly-trauma, and the AT-III levels play an important role in the systemic condition.[9,11] Therefore, serum AT-II levels may be considered a measure of the patient's initial injury severity in poly-trauma patients. Based on our results, serum AT-II levels may also be considered a measure of initial severity in solitary TBI patients without poly-trauma.

Mortality in patients with TBI significantly correlated with serum AT-III levels as well as GCS score, pupil dilatation, DIC, and barbiturate coma therapy, which were previously shown to be associated with mortality in TBI. As mentioned above, serum AT-III levels may be a predictor of injury severity and patient outcomes. Sufficient blood supply is required

TABLE 2. Risk factors of mortality in patients with severe traumatic brain injury

Risk factors	Mortality (n=77)	Univariate analysis	Multivariate analysis	
			p-value	Odds ratio (95% CI)
Patient characteristics				
Sex (male)	61 (79.2)	0.539		
Age (years)	52.45±21.54	0.735		
Hypertension	18 (23.7)	0.269		
Diabetes	16 (21.1)	0.608		
ESRD	3 (3.9)	0.332		
Stroke	6 (7.9)	0.571		
Cardiovascular disease	7 (9.2)	0.780		
Smoking	37 (48.7)	0.795		
Alcoholics	7 (9.2)	0.094		
Antiplatelet	6 (7.9)	0.777		
Anticoagulant	2 (2.6)	1.000		
Injury degree				
GCS	5.21±2.47	**<0.001**	**0.003**	**0.801 (0.690–0.929)**
Shock	23 (29.9)	**<0.001**	0.246	1.978 (0.624–6.268)
Pupil dilatation	51 (66.2)	**<0.001**	0.031	2.545 (1.089–5.946)
DIC	52 (69.3)	**<0.001**	0.012	3.341 (1.306–8.546)
Antithrombin III level	52.22±21.31	**<0.001**	0.033	0.977 (0.956–0.998)
Trauma mechanism		**0.496**		
Car TA	6 (7.8)			
Pedestrian TA	16 (20.8)			
Motorcycle TA	10 (13.0)			
Bicycle accident	3 (3.9)			
Fall	19 (24.7)			
Slip	7 (9.1)			
Head collision	1 (1.3)			
Assault	1 (1.3)			
Others	14 (18.2)			
Procedure				
Craniectomy	63 (81.8)	**0.027**	0.861	1.109 (0.349–3.526)
Therapeutic hypothermia	27 (35.1)	**<0.001**	0.348	1.714 (0556–5.278)
Barbiturate coma therapy	48 (62.3)	**<0.001**	0.010	3.816 (1.378–10.563)

Values are presented as mean±standard deviation or number (%). Bold-styled values are considered statistically significant.
CI: confidence interval, ESRD: end-stage renal disease, GCS: Glasgow coma scale, DIC: disseminated intravascular coagulopathy, TA: traffic accident.
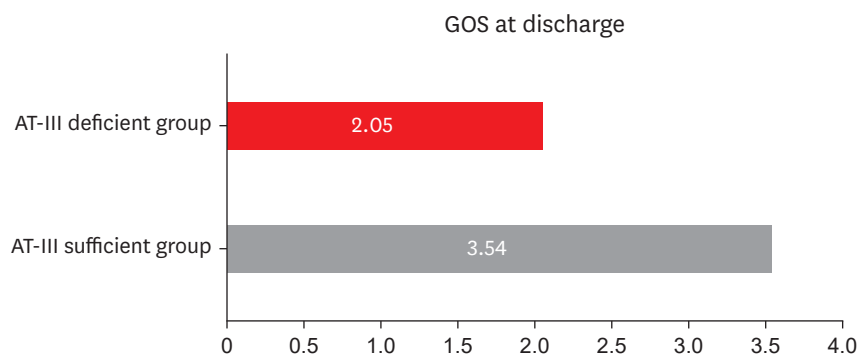

FIGURE 1. Comparison of the GOS scores between the AT-III sufficient and AT-III deficient groups (correlation coefficient=0.455, *p*<0.001).
GOS: Glasgow Outcome Scale, AT-III: antithrombin III.

for injured neuronal cells and the penumbra zone of the brain after TBI. The prevention of abnormal blood clot formation is necessary for sufficient microcirculation. However, AT-III deficiency causes additional brain edema, consequently leading to elevated intracranial

TABLE 3. Multiple linear regression analysis of factors affecting GOS at discharge

Variables	Regression coefficient	p-value
GCS	0.367	**<0.001**
Shock	−0.073	0.374
Pupil dilatation	−0.313	**<0.001**
DIC	−2.480	**<0.001**
AT-III	0.235	**0.011**
Craniectomy	−0.125	0.099
Therapeutic hypothermia	−0.293	**<0.001**
Barbiturate coma therapy	−0.315	**<0.001**

Bold-styled p-values are considered statistically significant.
GOS: Glasgow Outcome Scale, GCS: Glasgow Coma Scale, DIC: disseminated intravascular coagulopathy, AT-III: antithrombin III.

pressure (ICP) levels due to microinfarctions, resulting in abnormal coagulation.[5,14] In addition, the increased ICP develops into a negative cycle that causes additional decreases in brain perfusion, thereby deteriorating the neurologic outcome.

In addition to causing problems in the brain, lack of systemic AT-III increases the risk of acute renal injury caused by glomerular dysfunction due to abnormal coagulation; ARDS, which causes arterial-alveolar perfusion mismatch; and hepatic failure due to decreased hepatic perfusion.[4,8] Therefore, AT-III deficiency causes general deterioration through systemic organ failure. Deterioration of the general outcome due to AT-III deficiency was confirmed by the GOS score at discharge in the AT-III deficient group, which was significantly lower than that in the AT-III sufficient group. In addition, analysis of factors affecting GOS score at discharge revealed that GOS score at discharge was significantly positively correlated with AT-III level.

A previous study revealed that the serum AT-III test can reduce mortality and promote recovery in patients with severe illness, but its efficacy remains controversial.[16] Some recent studies on the efficacy of serum AT-III test in patients with TBI have been published, but these are preclinical studies, and no clinical trials have been reported to date.[5,6] In our study, AT-III replacement was administered to attenuate the increased mortality due to abnormal coagulation caused by AT-III deficiency. However, the effects of AT-III replacement could not be confirmed.[11] Many patients with AT-III deficiency have more severe TBIs. Thus, mortality may be higher in AT-III deficient patients despite AT-III replacement. Therefore, additional randomized control trials are needed to accurately determine the effects of AT-III replacement.

Limitation

One limitation of this study is the possible selection bias due to the retrospective nature of the study. In addition, patients with reduced liver function, such as chronic liver disease (CLD), may have AT-III deficiency regardless of injury severity. In patients with severe TBI, it is difficult to determine an accurate history of liver cirrhosis (LC), and imaging tests are needed to diagnose CLD, which cannot be performed in all patients. However, as the incidence of CLD was only 12.7 per 100,000, the effects of LC on AT-III were excluded.[12]

CONCLUSION

After severe TBI, patients with AT-III deficiency may require more intensive care because AT-III levels reflect injury severity and correlate with mortality. Therefore, it is recommended to assess AT-III levels in patients with severe TBI.

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