

Antithrombin III levels in critically ill surgical patients: do they correlate with VTE?

Umar F Bhatti,¹ Navpreet K Dhillon,² Russell Mason,¹ Andrew Wang,¹ Yassar M Hashim,¹ Galinos Barmparas ,¹ Eric J Ley ¹

¹Department of Surgery, Cedars-Sinai Medical Center, Los Angeles, California, USA
²Department of Surgery, R Adams Cowley Shock Trauma Center, Baltimore, Maryland, USA

Correspondence to

Dr Eric J Ley; Eric.Ley@cshs.org

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ABSTRACT

Objective Antithrombin III (ATIII) deficiency may result from hereditary or acquired reduction in ATIII levels and is associated with an increase in venous thromboembolism (VTE) in the general population. VTE is a potentially preventable complication in the critically ill surgical patients. The objective of this study was to evaluate the relation between ATIII levels and VTE in surgical intensive care unit (SICU) patients.

Methods All patients admitted to the SICU from January 2017 to April 2018 who had ATIII levels drawn were included in the study. An ATIII level below 80% of normal was considered low. The rate of VTE during the same admission was compared among patients with normal and low levels of ATIII. Prolonged length of stay (LOS >10 days) and mortality were also measured.

Results Of the 227 patients included, 59.9% were male. The median age was 60 years. Overall, 66.9% of patients had low ATIII levels. Trauma patients had a higher rate of normal ATIII levels, whereas those weighing more than 100 kg had a higher rate of low ATIII levels. Patients with low ATIII levels had higher VTE rates compared with those with normal ATIII levels (28.9% vs. 16%, $p=0.04$). Patients with low ATIII levels also had prolonged LOS (76.3% vs. 60%, $p=0.01$) and increased mortality (21.7% vs. 6.7%, $p<0.01$). Trauma patients with VTE were more likely to have normal ATIII levels (38.5% in low ATIII cohort vs. 61.5% VTE in normal ATIII cohort, $p<0.01$).

Conclusion Critically ill surgical patients with low ATIII levels have higher incidence of VTE, longer LOS, and higher mortality. In contrast, critically ill trauma patients may have high incidence of VTE even with normal ATIII levels.

Level of evidence III.

BACKGROUND

The incidence of deep vein thrombosis (DVT) ranges from 1 out of 100 000 in childhood to as high as 1% to 2% among elderly patients.¹ Venous thrombosis is a consequence of complicated interactions between inherited and acquired coagulation abnormalities.² Mortality rates from venous thromboembolism (VTE) may be as high as 12% for inpatients and up to 30% for outpatients on a 3-year follow-up.³ VTE is common in critically ill patients, with a reported rate of 3.6%.⁴ Despite its impact, there is a gap in the understanding of the pathophysiology of VTE in critically ill patients. A better understanding of the cellular pathways implicated in pathogenesis of VTE, including the antithrombin

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Antithrombin III (ATIII) deficiency is associated with increased venous thromboembolism (VTE) in surgical patients. ATIII deficiency and its relation to VTE in critically ill surgical patients have not been studied previously.

WHAT THIS STUDY ADDS

⇒ Low ATIII levels are related to increased VTE in critically ill surgical patients, longer length of stay, and higher mortality. However, this relationship does not stand true for critically ill trauma patients.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings of this study support identifying patients with low ATIII levels and considering timely VTE prophylaxis in these patients. This study also provides framework for our future studies looking at larger samples of different subsets of surgical patients and the relation of ATIII deficiency and VTE incidence in these patients.

III (ATIII) pathway, may provide avenues to develop treatment strategies for VTE.

ATIII is a glycoprotein synthesized in the liver that plays a critical role in the regulation of coagulation cascade. As an inhibitor of factor IIa (thrombin), factor IXa, factor Xa, factor XIa, and factor XIIa, ATIII regulates the intrinsic arm of the coagulation cascade.⁵ A deficiency in ATIII is associated with an increase in the incidence of VTE.⁶ Although ATIII deficiency has a low prevalence in the general population (0.02%), it is more prevalent among patients with a history of VTE.^{2,7} Likewise, patients with overt and mild ATIII deficiency have a significantly increased VTE risk.⁸ Patients in the surgical intensive care unit (SICU) are at an increased risk of developing VTE; however, the relationship between ATIII levels and VTE rates in this group of patients remains unknown. The aim of this study was to evaluate the the relationship between ATIII levels and the incidence of VTE in patients in the SICU. Our hypothesis was that low levels of ATIII would be associated with a higher VTE rate.

METHODS

The patients admitted to the SICU at a level I trauma center were prospectively screened over a 16-month period, from January 2017 to April

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2018. Patients who had ATIII levels drawn on admission to the SICU were included in the study. ATIII activity levels greater or equal to 80% were considered normal.⁸ Patients were subsequently divided into two cohorts: those with normal and those with low ATIII levels. This stratification was based on the first ATIII value that was available. Demographics and relevant clinical data, including age, sex, weight, and length of stay (LOS) were collected. We defined prolonged ICU LOS as stay longer than 10 days after admission to the ICU. A screening protocol was used to detect VTE based on clinical suspicion. VTE diagnosis was made using venous duplex and/or CT pulmonary angiography; the images were interpreted by a board-certified vascular surgeon and a radiologist, respectively.

The primary outcome was the rate of clinically significant VTE, including DVT and pulmonary embolism. An additional analysis was performed to compare low and normal ATIII cohorts in the subgroups of patients who were diagnosed with VTE.

Data were analyzed using Microsoft Excel V.2016 and summarized as percentages for categorical variables and as means or medians with IQRs for continuous variables. Comparisons of central tendencies were conducted with two-tailed t-test and Mann-Whitney U test where appropriate. A p value of <0.05 was considered statistically significant.

RESULTS

A total of 227 patients were included in the analysis. Of these, 59.9% were male; the median age was 60 years; and the median weight was 74.1 kg. Patients from different surgical services were included in this study, including trauma surgery (27.3%), hepatobiliary (HPB) surgery/liver transplant surgery (34.8%), general surgery (17.6%) and thoracic/vascular surgery (20.3%). In total, 152 patients (67.0%) had low ATIII levels, and 57 (25.1%) had a documented VTE (table 1).

The low and normal ATIII level cohorts were similar with respect to age (age ≥ 65 years; 41.4% vs. 34.7%, $p=0.33$) and sex (male; 57.9% vs. 61.3%, $p=0.62$). However, there were more patients weighing above 100 kg in the low ATIII cohort (12.5% vs. 1.3%, $p<0.01$) (table 2).

On subgroup analysis, trauma patients were significantly more likely to have normal ATIII levels (32.2% in low ATIII cohort vs. 67.7% in normal ATIII cohort, $p<0.01$). HPB surgery/liver transplant and general surgery patients were more likely to have low ATIII levels (HPB surgery/transplant: 91.1% in low ATIII cohort vs. 8.8% in normal ATIII cohort, $p<0.001$; general

Table 2 Comparison of patient characteristics with low and normal ATIII levels

Characteristics	Low ATIII, n=152	Normal ATIII, n=75	P value
Age >65 years, n (%)	63 (41.4)	26 (34.7)	0.33
Male, n (%)	88 (57.9)	46 (61.3)	0.62
Weight, >100 kg, n (%)	19 (12.5)	1 (1.3)	<0.01
Low ATIII is <80% activity; normal ATIII is >80% activity. ATIII, antithrombin III.			

surgery: 80% in low ATIII cohort vs. 20% in normal ATIII cohort, $p<0.001$). No difference was observed in the ATIII levels in the thoracic/vascular surgery patients (table 3).

The VTE rate was significantly higher in the low ATIII cohort compared with the normal ATIII cohort (29.6% vs. 16%, $p=0.03$). A longer LOS (>10 days) was more likely in the low ATIII cohort (76.3% vs. 60.0%, $p=0.01$). Similarly, we noted that mortality during the same admission was significantly higher in the low ATIII cohort compared with the normal ATIII cohort (21.7% vs. 6.7%, $p<0.01$) (table 4).

Trauma patients were more likely to have VTE with normal ATIII levels (38.5% in low ATIII cohort vs. 61.5% VTE in normal ATIII cohort, $p<0.01$). ATIII levels were not associated with VTE in HPB surgery/liver transplant and general surgery patients. In contrast, low ATIII levels were associated with VTE in thoracic/vascular patients (100% in low ATIII cohort vs. 0% in normal ATIII cohort) (table 5).

We also performed a multivariate analysis on patients with VTE and those without VTE, adjusting for age >65 years, weight >100 kg, LOS >10days, ATIII as continuous variable and low ATIII (ATIII <80). We found that LOS was longer in VTE group compared with no VTE group (80.7% in VTE cohort vs. 63.5% in no VTE cohort, $p=0.016$). When taken as a continuous variable, we did not find a significant difference in ATIII levels between the two cohorts, as shown in table 6. We did find a trend toward low ATIII in the VTE group when compared with no VTE group (77.2% in VTE cohort vs. 64.7% in no VTE cohort, $p=0.081$).

DISCUSSION

Our data on patients in the SICU support what was previously observed in the general population, that is, low levels of ATIII are associated with higher incidence of VTE.^{2,3} Patients with less than 80% serum levels of ATIII are known to have higher rates of VTE.^{8,9} Prior studies to delineate the role of ATIII in VTE pathogenesis were performed in a variety of patient populations; however, there are limited data on the association of ATIII levels with VTE in patients in the SICU. Besides establishing the association between low ATIII levels and VTE in patients in the SICU,

Table 1 Demographic data

Characteristics	n=227
Age, years (IQR)	60 (47–71.5)
Male, n (%)	136 (59.9)
Weight (kg)	
Median (IQR)	74.1 (60.4–86.8)
Patient type, n (%)	
Trauma	62 (27.3)
HPB surgery/transplant	79 (34.8)
ACS/general surgery	40 (17.6)
Thoracic/vascular	46 (20.3)
ICU LOS (days)	
Median (IQR)	18 (8.5–31.5)
Mortality, n (%)	38 (16.7)
VTE, n (%)	57 (25.1)
ACS, acute care surgery; HPB, hepatobiliary; ICU LOS, intensive care unit length of stay; VTE, venous thromboembolism.	

Table 3 Subgroup analysis of patient types with low and normal ATIII levels

Characteristics	Low ATIII, n=152	Normal ATIII, n=75	P value
Trauma, n (%)	20 (32.2)	42 (67.7)	<0.01
HPB surgery/transplant, n (%)	72 (91.1)	7 (8.8)	<0.001
General surgery, n (%)	32 (80)	8 (20)	<0.001
Thoracic/vascular, n (%)	28 (60.1)	18 (39.1)	0.08
Low ATIII is <80% activity; normal ATIII is >80% activity. % reported as in group percentage. ATIII, antithrombin III; HPB, hepatobiliary.			

Table 4 Comparison of outcomes between low ATIII group and normal ATIII group

Outcome	Low ATIII, n=152	Normal ATIII, n=75	OR (95% CI)	P value
VTE, n (%)	45 (29.6)	12 (16.0)	2.2 (1.1 to 4.4)	0.03
ICU LOS >10 days, n (%)	116 (76.3)	45 (60)	2.1 (1.2 to 3.9)	0.01
Mortality, n (%)	33 (21.7)	5 (6.7)	3.9 (1.4 to 10.4)	<0.01

Low is <80% activity; normal is >80% activity.
ATIII, antithrombin III; ICU, intensive care unit; LOS, length of stay; VTE, venous thromboembolism.

we note that low ATIII levels were associated with a prolonged LOS and a significantly increased mortality.

Our study also suggests that different subgroups of patients in the SICU have variable ATIII levels. Trauma patients were more likely to have normal ATIII levels compared with other patients, which may indicate that the acute nature of trauma provides little time for ATIII levels to decrease. In their prospective cohort study, Vincent *et al* showed that only 17.5% (22 of a cohort of 126 trauma patients) presented with ATIII levels below 80%. This is consistent with our study.¹⁰ Previously, Miller *et al* demonstrated that the ATIII levels in trauma patients were variable and that there were certain factors that contributed to low ATIII levels in this population, including base deficit of <4, Injury Severity Score of >15 and blood transfusion.¹¹ As the half life of ATIII is about 3 days,¹² the day at which the ATIII level is drawn after the traumatic event may affect the level. A series of thrombogenic events occur after trauma¹³; therefore, the ATIII levels and VTE rates in trauma patients may not follow a definitive pattern. This variability may explain why in our study the VTE rate in trauma patients was in fact higher in patients with normal ATIII levels. In contrast, there is some evidence that suggests that supratherapeutic ATIII levels are protective against VTE in trauma.^{14, 15} The correlation between ATIII levels and VTE rates in trauma patients is complex and warrants further investigation.

In support of the previous finding that chronic disease processes can result in ATIII deficiency,¹⁶ we observed that HPB, liver transplant, and general surgery patients admitted to the SICU were more likely to have lower levels of ATIII. The chronic nature of these disease processes can explain this finding.

Obesity is associated with a 6.2-fold increase in the risk of VTE.¹⁷ This is mediated by the metabolic derangements associated with obesity leading to a multitude of disturbances in blood coagulation pathways, including enhanced platelet activation, elevated concentrations of coagulation factors and impaired fibrinolysis.¹⁸ We found that ATIII levels were low in patients weighing over 100 kg. Decreased ATIII activity and a resultant increase in activation of coagulation factors may be implicated in increased VTE rates in obese patients.

Table 5 Comparison of ATIII levels among patients with a VTE

	+VTE, n=57	Low ATIII with +VTE, n=44	Normal ATIII with +VTE, n=13	P value
VTE rate among trauma patients, n (%)	13 (21)	5 (38.5)	8 (61.5)	<0.01
VTE rate among HPB surgery/transplant patients, n (%)	21 (26.5)	18 (85.7)	3 (14.2)	0.29
VTE rate among general surgery patients, n (%)	11 (27.5)	9 (81.8)	2 (18.2)	0.67
VTE rate among thoracic/vascular patients, n (%)	12(26)	12 (100)	0 (0.0)	<0.001

Low ATIII is <80% activity; normal ATIII is >80% activity.
ATIII, antithrombin III; HPB, hepatobiliary; VTE, venous thromboembolism.

Table 6 Comparison of outcomes between VTE and no VTE groups

	VTE (n=57)	No VTE (n=170)	P value
Age >65, n (%)	20 (35.1)	67 (39.4)	0.56
Weight >100 kg, n (%)	7 (12.2)	16 (9.4)	0.53
LOS >10 days, n (%)	46 (80.7)	108 (63.5)	0.016
ATIII level, median (IQR)	64 (25–103)	65 [17.25–112.75]	0.66
Low ATIII, n (%)	44 (77.2)	110 (64.7)	0.081

Low is <80% activity; normal is >80% activity.
ATIII, antithrombin III; LOS, length of stay; VTE, venous thromboembolism.

The incidence of VTE in elderly patients is high; in the general population, the risk increases by 0.6% each year after the age of 80 years.¹⁹ In our study, 22.4% of patients above 65 years had VTE. We did not find a statistically significant difference in ATIII levels between patients above 65 years and their younger counterparts, though we observed that the proportion of patients in the low ATIII group was significantly higher in this age group.

We also compared the patients with VTE to those without VTE and found that patients with VTE had a longer LOS and a trend toward low ATIII levels when compared with patients without VTE. We think that with a larger sample size, a statistically significant difference in ATIII levels may be shown in patients with VTE, though this warrants future studies to further delineate this association.

We acknowledge that our study has several limitations. First, the small sample size of 227 patients limits the ability to perform a detailed subgroup analysis. In this proof-of-concept study, we intended to delineate the correlation between ATIII levels and VTE in patients in the SICU to help analyze if ATIII activity can be a component of guidelines for VTE prophylaxis.²⁰ Further studies with a larger sample size are currently being undertaken for a more comprehensive analysis. Second, our study did not include data on VTE prophylaxis and fresh frozen plasma transfusion to correct any coagulopathy. These interventions can modify the study findings. Third, our analysis did not account for any underlying coagulopathic conditions, such as malignancy, which may contribute to increased VTE rates. Fourth, the decision to draw ATIII levels was based on clinical suspicion and not a standardized framework. Using clinical suspicion only may be the reason the rate of VTE in the study sample was high. Fifth, the patients studied had ATIII levels drawn at different times after admission to the SICU, which was at the discretion of the team taking care of the patient. We used the first drawn ATIII levels to standardize the data collection process as best as possible. Sixth, in this study, we noted that the HPB surgery/liver transplant patients with lower ATIII levels had a higher incidence of VTE, longer LOS, and higher mortality. Liver transplant patients may be in the SICU prior to transplant, and therefore, their ICU days may be skewed longer. Also, their ATIII

levels preoperatively can be vastly different from their postoperative ATIII levels.

CONCLUSION

Patients presenting to the SICU with low ATIII levels are likely to have higher rates of VTE. Our study also indicates that low ATIII levels in patients in the SICU are associated with a higher mortality rate and a longer LOS. Trauma patients are more likely to have normal ATIII levels, whereas obese patients and those with chronic diseases may have lower ATIII levels. Patients in the SICU with VTE have a longer LOS and a trend toward low ATIII levels. The findings of this study support identifying patients with low ATIII levels, considering timely VTE prophylaxis in these patients, and warrant further investigation to delineate the association of low ATIII with VTE.

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ORCID iDs

Galinos Barmparas <http://orcid.org/0000-0001-8309-6797>
Eric J Ley <http://orcid.org/0000-0002-6036-3837>

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