

## Original Research Article

# A prospective study to assess serum level of soluble thrombomodulin as early marker of acute traumatic coagulopathy in polytrauma patients

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**Received:** 29 August 2021

**Revised:** 30 September 2021

**Accepted:** 02 October 2021

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### ABSTRACT

**Background:** Coagulopathy following major trauma is conventionally attributed to activation of coagulation factors. We hypothesized that early coagulopathy is due to tissue hypoperfusion and investigated thrombomodulin (TM) as early marker of endothelial injury in poly trauma patient.

**Methods:** This was a prospective cohort study of major trauma patients admitted to a single trauma center. Blood was drawn within 10 minutes of arrival for analysis of TM. We assess its association with blood transfusion, length of hospital stays and mortality.

**Results:** A total of 90 patients were enrolled. An increasing lactate was associated with high soluble TM. High TM was significantly associated with increased mortality, blood transfusion requirements, hospital stay.

**Conclusions:** Acute traumatic coagulopathy (ATC) occurs only in the presence of tissue hypoperfusion which we have measured in form of lactate and coagulopathy measured using international normalized ratio (INR) as standard. Admission serum TM can be predictive of clinical outcomes following major trauma.

**Keywords:** ATC, Serum TM, Polytrauma, Blood transfusion, Lactate

### INTRODUCTION

Coagulation abnormalities are common following major trauma, and are associated with poor outcomes.<sup>1</sup> Classically, traumatic coagulopathy is thought to be due to the consumption of coagulation factors and dilution from intravenous blood and fluid therapy.<sup>2</sup> Coagulopathy is therefore currently managed by coagulation factor replacement such as with fresh frozen plasma and cryoprecipitate. Two recent studies have identified an acute coagulopathy that is present on arrival in the emergency department in approximately one quarter of major trauma patients.<sup>3,4</sup> Patients arriving with a coagulopathy were 4 times more likely to die than those with normal coagulation.

### Diagnosis of ATC

The presence of ATC should be considered in all trauma patients, especially when high-energy trauma is involved. A high degree of suspicion must be maintained when there is evidence of significant bleeding (tachycardia, weak pulses, hypotension, impaired consciousness, oliguria, signs of poor clinical perfusion), hypoperfusion (base deficit greater than 6 mmol/L and an increase in lactate >4), and particularly in patients with severe injuries.<sup>5</sup> Unfortunately, the lack of well-defined diagnostic criteria for ATC impedes early identification and treatment. Prolongation of PT, INR and activated thromboplastin time (APTT) have been used by most authors to diagnose ATC.<sup>6</sup>

In this study we hypothesize can TM be used as marker of ATC in polytrauma patient. Secondly, we tried to assess its association with number of blood transfusion, mortality and length of hospital ICU stay. We have also compared TM levels with PT and INR, can we replace it with conventional coagulopathy test and TM association with lactate and base deficit.

## METHODS

### Study design

This was a single centre, prospective study of major trauma patients presenting directly to a level 1 trauma centre between May 2019 and June 2020.

### Patient selection

Poly trauma patients were enrolled from emergency room of trauma surgery department after taking their written consents. Polytrauma was defined as one having injury in two (2) or more than two (2) regions. Patient having Injury severity score >16 was recruited in the study.

Specific emergency departmental protocols were followed for treatment of trauma patient, based on ATLS protocols. A detailed Performa regarding clinical and epidemiological information were filled. Clinical profile of each case was recorded. All adult trauma patients who met criteria for full trauma team activation and presented to us within 24 hours of injury were eligible for enrollment into the study.

Patients younger than 18 years and referred or transferred from other hospitals, pregnant females were immediately excluded. Patients were excluded if they were on anticoagulant medications or a known bleeding diathesis. We have received the clearance from institutional ethical committee, the study has been conducted in department of trauma surgery at all India institute of medical sciences, Rishikesh.

### Sampling technique

As part of standard trauma management, one member of the trauma team is designated to gain intravenous access via a 14- or 16-gauge cannula in the forearm. A 10 mL research sample of blood was drawn from this line, along with the standard trauma laboratory tests within 10 minutes of arrival in the emergency department. The sample was placed in a citrated tube and sent immediately to the hospital's trauma laboratory where it was spun down, plasma extracted, and stored in a -80°C freezer.

### Sample analysis

Total 90 samples were analyzed at the conclusion of the study by researchers who were blinded to all patient data. Normal ranges of 2 standard deviations from the mean

were determined by testing 20 normal samples. Serum TM levels were determined using ELISA kit by @Diacclone. Normal value taken for TM is 0.3 to 3 ng/ml (Diclone ELISA kit).

### Data collection

Data were collected prospectively on patient demographics, the injury time, mechanism (blunt or penetrating) and severity, prehospital fluid administration, the time of arrival in the trauma room, and admission vital signs. The injury severity score (ISS) was used as a measure of the degree of tissue injury. PT, INR and an arterial blood gas to obtain lactate level and base deficit (BD) were drawn at the same time as the research sample as part of the standard management of major trauma patients. The lactate and base deficit were used as a measure of the degree of tissue hypoperfusion. BD greater than 6 mEq/L and lactate greater than 4mmol/L worse outcome in trauma patients.<sup>7-10</sup>

### Outcome measures

Primary outcome was to study level of serum TM as early marker of ATC in polytrauma patient, along with that to investigate it's with length of stay (ICU-LOS), blood transfusion (BT) and outcome (mortality), lactate and base deficit. Lastly to compare between conventional coagulation profile (PT, INR) with TM.

### Statistical analysis

Data was analysed by statistical software R-studio. Categorical data was expressed as frequency and percentage. Quantitative data was expressed in terms of mean SD, median, min and max. Mann Whitney U test was used to compare TM values between ATC and NO ATC patient. Since TM did not follow the assumption of normality so that Spearman correlation coefficient was used to show the correlation between the quantitative variable. Sensitivity specificity, PPV, NPV Were calculated for TM, considering PT and INR as classification variable as used conventionally. P<0.05 was considered as statistically significant.

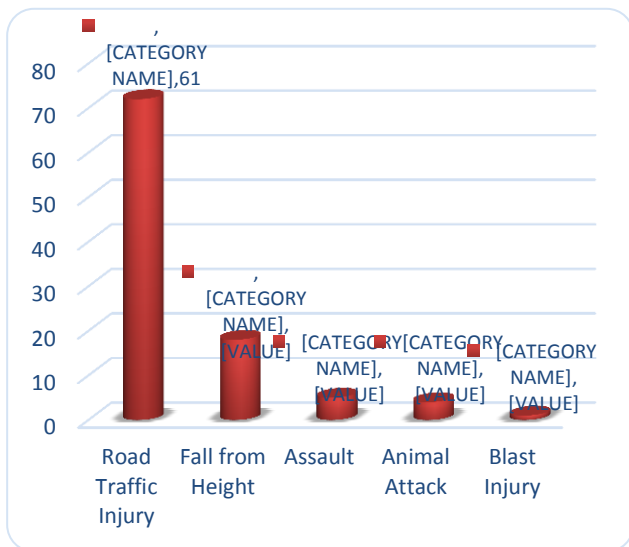
## RESULTS

The study includes 89 polytrauma patients (n=90, one sample excluded). Demographic and clinical profile described in (Table 1). Out of which 75 (84%) were males and 14 (16%) were females. The mean age of the patients was 35.9±17.3 years. The minimum age of the patient was 17 years while the maximum age was 80 years. The ISS score was ranged from 16 to 75 with average of 24.7±8.8. The range of GCS score was between 3 to 15 with mean±SD of 11.6±4.1. The average span of trauma patients stay in ICU was calculated to be 5.1±13.6 with range 0 to 104 days. The score for total unit of blood transfusion (BT) was ranged between 0-46 with mean of 9.4±8.5.

Our data of poly trauma patient shows road traffic injury remain leading cause of causality followed by fall from height and assault, animal attack and blast injury in decreasing order Distribution of mechanism of injury described in (Figure 1).

**Table 1: Demographic and clinical profile of patients.**

Variables, (n=89)	Mean ± SD	Median (min-max)
Age (Years)	35.9±17.3	30 (17-80)
SBP (<100)	102.3±16.9	103 (60-168)
DBP (<60)	69.7±15.5	70 (30-110)
ISS (>16)	24.7±8.8	25 (16-75)
GCS	11.6±4.1	15 (3-15)
HR (>100)	126.8±21.4	125 (78-172)
BD (>6)	-10.2±5.9	-9.1 (-25-8.8)
HB	8.8±2.1	8.5 (4.5-17)
INR	1.7±2.1	1.5 (0.5-20)
PT	18.5±6.1	18 (9-39)
TM	4.2± 2.1	4.2 (0.4-10)
ICU stay	5.1±13.6	0 (0-104)
Length of stays in hospital	7.9±7.6	6.5 (0-35)
Total BT	9.4±8.5	8 (0-46)



**Figure 1: Distribution of mechanism of injury.**

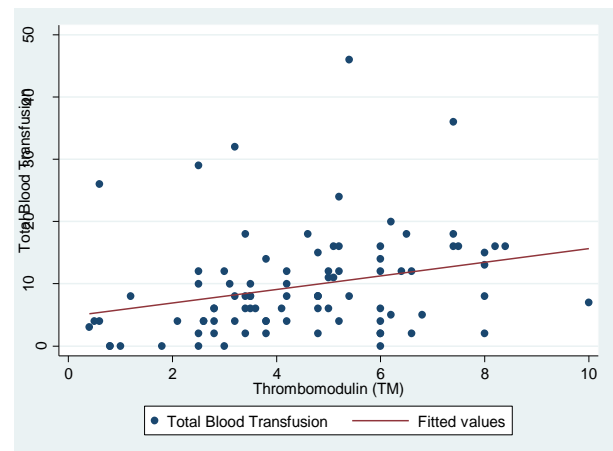
The primary objective of our study was to assess the level of soluble TM in polytrauma patient and its association with ATC, and here we defined ATC as prothrombin level as more than 18. Normal value taken for TM is 0.3 to 3 ng/ml (Diclone ELISA kit). In our study level of TM in polytrauma patient was 4.2±2.1 and ranged from 0.4 to 10. Further, the 89 patients were divided into ATC and no ATC patients using clinical cut-off of ≤18 of PT variable. Thus, 89 patients were classified as ATC (n=33) and No ATC (n=56) patient. Among no ATC patients the TM range was 0.5 to 10 with average of 4.03±2.1, while in ATC patients the range was 0.4 to 8.4 with average of 5.16±1.84. The difference in means of TM values

between ATC patient and no ATC patient was found statistically significant at 5% level of significance (p=0.0122) (Table 2).

**Table 2: The level of soluble TM in polytrauma patient and its association with ATC.**

Variables	TM (Mean ± SD)	TM median (min-max)
No ATC, PT ≤18, (n=56)	4.03±2.11	3.8 (0.5-10)
ATC, PT>18, (n=33)	5.16±1.84	5.1 (0.4-8.4)
Total, (n=89)	4.2±2.1	4.2 (0.4-10)
P value	0.0122	

We tried correlate TM level with blood transfusion, ICU and hospital stay and mortality. The data in (Table 3) depicts that TM was positively correlated with blood transfusion (r=0.27, p=0.009). It reveals that patients with higher TM value will require more blood transfusion (Figure 2). However, it did not show any correlation with length of stay in hospital and ICU stay. Those people who died had higher value of TM (5.3±2.1) as compared to mean level of TM in survived (4.1±2.1) difference in means of TM value between Survive and expired was found statistically significant (p=0.0116).



**Figure 2: Association of blood transfusion with TM.**

To detect the diagnostic ability of TM in comparison to PT and INR sensitivity and specificity along with PPV AND NPV was calculated (Table 3). Clinical cut-off of PT (≤18) and INR (≤1.50) was used to test the diagnostic ability of TM (≤3.0) with conventional markers. The diagnostic accuracy of TM in respect of PT was 54% with 21 true negative and 27 true positive case the sensitivity of TM was 43% while specificity was 77%. Area under the curve shows poor classification ability to detect the disease to non-disease.

In case of INR, the sensitivity and specificity of TM was poor (40% and 63%). The area under the curve below 50, indicate that TM is not an appropriate marker to detect

disease. Thus, it can be concluded that TM cannot be replaced as a marker to detect ATC patient. However, it was observed that TM (0.67) and INR (0.77) has almost similar area under the curve and the difference was not statistically significant (p=0.186) for classification for ATC and No-ATC patient (Figure 3).

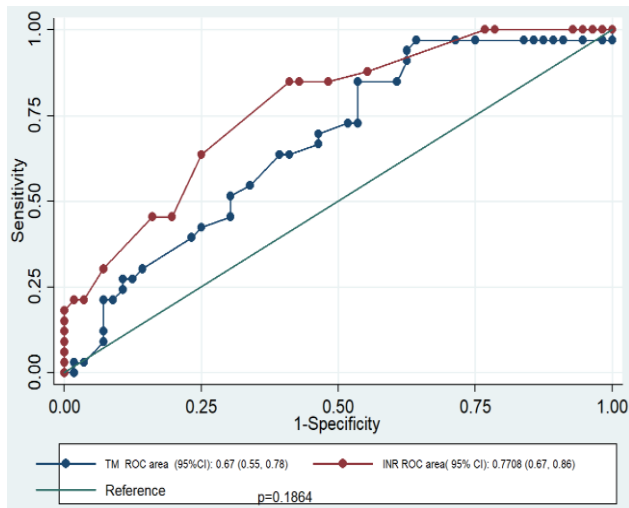
Finally, we have studied the relation between TM and base deficit and lactate. TM shows positive relationship with base deficit i.e. As value of TM increases, value of base deficit increases. Similar correlation is seen with positive correlation with lactate (Table 5).

**Table 3: Correlation between length of stay, blood transfusion and mortality with TM.**

Variables	R (correlation coefficient), Mean±SD	P value
<b>Length of stays</b>	0.1587	0.1739
<b>Blood transfusion</b>	0.275	0.0091
<b>Mortality</b>		
Survived, (n=66)	4.1±2.1	0.0116
Dead, (n=23)	5.39±2.10	

**Table 4: Comparisons of conventional coagulation profile (PT and INR) with TM.**

Variables	PT ≤18	PT>18	Diagnostic accuracy	ROC area	Sensitivity	Specificity	PPV (%)	NPV (%)
<b>TM vs PT</b>								
TM								
≤3	21	6	48/89=54%	0.60	43 (31-56)	77 (58 -91)	35	77
>3	35	27						
<b>TM vs INR</b>								
TM								
≤3	17	10	42/89=48%	0.48	40 (28 - 53)	63 (42-80)	34	63
>3	37	25						



**Figure 3: Similar area under the curve and the difference was not statistically significant (p=0.186) for classification for ATC and no-ATC patient.**

**Table 5: Association between lactate and base deficit with TM.**

Variables	R, (p)
<b>Lactate</b>	0.07 (0.025)
<b>Base deficit</b>	0.22 (0.037)

**DISCUSSION**

Coagulopathy is a common phenomenon in traumatized patients as well as a marker of injury severity. Abnormal coagulation favors continuous loss of blood, increasing the risk of morbidity and death from uncontrolled

bleeding. Coagulopathy in trauma has long been considered to develop after the initial injury due to acidosis, hypothermia, loss and hemodilution of coagulation factors as a consequence of shock, and aggressive intravenous fluid resuscitation.<sup>11</sup> This condition has been termed ATC and is an indicator of poor prognosis independent of injury severity. ATC is associated with increased mortality (up to 8 times and 4 times increase at 24 hours and 30 days resp.), more blood transfusions, longer ICU and hospital stay, and higher incidence of multiple organ failure.<sup>11</sup>

Incidence of ATC at ED admission is 37% of all patients. Males were more affected than females (70.5% vs. 29.5%) and in 86% the mechanism of injury is blunt forces. The incidence of ATC is also associated with ISS. The 26 out of 33 (78%) patients with coagulopathy had an ISS more than or equal to 16 at hospital admission and the frequency of coagulopathy increased with higher ISS scores. This data is almost consistent with study conducted by Magele et al.<sup>12</sup> It was a retrospective study using the trauma registry database where n=29353 and out of this 42% were in ATC at the time of admission

This study represents a very clear investigation of coagulation system following major trauma there is no significant fluid resuscitation or any confounding medical therapy before blood sampling therefore alteration of coagulation system represents the effect of injury itself. TM remains one of the biomarkers of endothelial dysfunction is not recommended for routine laboratory investigation in polytrauma patient. Very few studies have examined the role of serum TM as a biomarker to predict the clinical course of ATC.

The aim of this study is to investigate the association of serum TM with ATC. Unfortunately, the lack of well-defined diagnostic criteria for ATC impedes early identification and treatment. Prolongation of PT and activated thromboplastin time (APTT), INR have been used by most authors to diagnose ATC.<sup>13-15</sup> Cohen et al established the presence of ATC if PT and APTT were 1.5 times over the normal values.<sup>14</sup> We have taken patient under ATC group where PT >18 sec and TM level >3 ng/ml. The difference in means of TM values between ATC patient and no ATC patient was found statistically significant at 5% level of significance ( $p=0.0122$ ) (Table 2). This result made us to reach at the conclusion that TM is biomarker for endothelial injury and patient with ATC have significant raise level of TM.

In general, trauma patients with ATC are at high risk to develop organ dysfunction and failure with prolonged ICU and overall hospital stay as well as increased mortality. Some studies reported an up to 4-fold increase in mortality if coagulopathy is present upon ER arrival after severe multiple injuries.<sup>16,17</sup> MacLeod et al reported coagulation abnormalities early after trauma to represent independent predictors of mortality even in the presence of other risk factors.<sup>17</sup> Our data presented here confirm these finding. We found positive correlation of TM with blood transfusion and mortality; however, no relation was found with hospital stay.

Unfortunately, an established definition of ATC is not available, which delays the diagnosis and hamper the treatment. Prolongation of PT and activated thromboplastin time (APTT) have been used by most authors to diagnose ATC.<sup>17</sup> Brohi et al in 2012 established the presence of ATC if PT and APTT were 1.5 times over the normal values.<sup>14</sup> While these tests are simple and widely available, they have several limitations. PT and APTT reflect hemostasis in plasma (as opposed to whole blood), during the first 60 seconds of clotting (whereas the complete coagulation process lasts between 15 to 30 minutes), and exclude the fibrinolysis stage from the analysis. Additionally, these tests have a turnaround time of 30-45 minutes, are carried out at 37°C and pH 7.5, and do not consider the presence of hypothermia, acidosis, hypocalcemia, or anemia.<sup>12</sup> The use of devices that allow for rapid determination of PT and APTT (point of care) has been proposed. Although the use of these devices allows rapid availability of results, they still have to be validated. In view of this limitation of conventional coagulopathy test, we tried to rectify this measuring TM level in ATC patient and compare both, we found TM cannot be use as an alternative to PT and INR if we define ATC with these parameters. It is a multifactorial entity, factor like hypothermia, acidosis, hypo and hyper coagulopathy, this could be the possible reason for discordance between PT, INR and TM.

Next, we have studied Association between Lactate and Base deficit with TM and we found TM shows positive

relationship with Base deficit and Lactate. Cohen and Brohi et al identify variations with the BD in other coagulation proteins. Increasing BD was associated with a rise in the levels of soluble TM and a fall in protein C levels. There was a close inverse relationship between soluble TM and protein C levels (TM <28: 85%, TM >43: 68%;  $p=0.02$ , upper-lower quartile comparison).<sup>18</sup>

### Limitation

This project has certain restrains, majority of the work has been done during covid pandemic with lot of constrains, firstly we have small sample size. ATC is multifactorial, association of TM with other factor like hypothermia, acidosis, other coagulopathy parameter like fibrinogen, platelet count, other endothelial injury maker should be taken into consideration to mark TM as diagnostic test

### CONCLUSION

Incidence of ATC is 37% and consistent with literature finding. This study demonstrates that serum TM level, a biomarker of endothelial injury shows significant increase in ATC. The presence of ATC was associated with the severity of injury.

Serum TM level may be a useful tool in diagnosing disease severity and mortality. In this study we try to correlate blood transfusion, mortality and hospital stay with TM and we found positive correlation with blood transfusion and mortality, in contrast to ICU stay, no statistical difference was there. This probably due to severity of injury leads to early demise with high mortality rate and small duration of stay.

The aggravation of the established coagulopathy is further triggered by hypothermia and we measure degree of shock with level of lactate and base deficit and it is positive association with TM and lactate.

Measurements of serum TM may help to early recognize the development of ATC, activate to prevent early mortality and limited use of blood product to allow for more appropriate therapeutic strategies.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: The study was approved by the Institutional Ethics Committee of All India Institute of Medical Sciences, Rishikesh vide letter No. AIIMS/IEC/19/597 dated 8/02/2020*

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**Cite this article as:** Kataria R, Azam MQ, Negi G, Kumar A, Sarkar B, Uniyal M. A prospective study to assess serum level of soluble thrombomodulin as early marker of acute traumatic coagulopathy in polytrauma patients. *Int Surg J* 2021;8:3381-6.