What is the Significance of Thrombocytosis in Patients With Trauma?

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Background: **The incidence and risk factors for the development of thrombocytosis after trauma have not been well established. Although it has been suggested that the occurrence of this sequela may be associated with adverse events, there are also limited data regarding outcomes of patients developing posttraumatic thrombocytosis. The objective of this study was to determine the incidence of, risk factors for, and sequela of posttraumatic thrombocytosis.**

Methods: **A retrospective review of all trauma intensive care unit (ICU) admissions between July 1998 and December 2005 identified patients with early (≤7 days), late, and no thrombocytosis. Bivariate analysis was used to compare the clinical and demographic characteristics with outcomes between the three patient groups.**

Results: **A total of 3,484 patients were admitted to the ICU during the 7-year study period. After exclusions, the study population consisted of 3,286 patients. The overall incidence of thrombocytosis was 18.7%; early thrombocytosis was found in 72 patients, and late thrombocytosis was identified in 542 patients. All complications examined were significantly higher in patients with thrombocytosis. Overall, the venous thromboembolic rate was 2.4%; for patients with thrombocytosis it was 4.6% compared with 1.9% in patients without thrombocytosis. Overall mortality was 15.4%, but was significantly lower in patients with thrombocytosis (3.8% vs. 18.1%, $p < 0.0001$). Independent risk factors for the development of thrombocytosis included obesity, laparotomy, blunt injury, Injury Severity Score >16, mechanical ventilation, Chest Abbreviated Injury Score >3, and tachycardia.**

Conclusion: **Thrombocytosis is a common finding among patients with trauma admitted to the ICU. The occurrence of both early and late thrombocytosis is associated with significantly higher rates of complications, particularly venous thromboembolism. However, patients developing posttraumatic thrombocytosis may have a significantly lower mortality compared with those without this sequela of injury.**

Key Words: **Thrombocytosis, Trauma, Outcome.**

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Reactive or secondary thrombocytosis, defined as an increase in platelet count above $450 \times 10^3/mm^3$, may occur in response to various stimuli. These include systemic infections, inflammatory conditions, bleeding, tumors, and trauma. The incidence of posttraumatic thrombocytosis has not been well defined, although previous investigators have suggested that this finding may be present in up to 25% of patients with trauma.[1–4] The most common causes of reactive thrombocytosis among patients with trauma are likely infectious processes, although this finding has also been associated with acute lung injury and acute respiratory distress syndrome.[5]

The significance of elevated platelet counts in critically ill patients has not been clearly elucidated, although this sequela has generally been considered a benign finding. Some authors have suggested, however, that thrombocytosis in this setting may actually be associated with improved outcomes.[1] Traditional concerns regarding the association between thrombocytosis and thromboembolic complications have also proven controversial, with different investigators reporting evidence for[6] and against[2,5] this association.

The purpose of our study was to (1) establish the incidence of reactive thrombocytosis among patients with trauma hospitalized in the intensive care unit (ICU), (2) determine the sequela of this finding, particularly regarding thromboembolic complications, and (3) define the risk factors for development of thrombocytosis in this population.

PATIENTS AND METHODS

This is a retrospective study of all patients with trauma admitted to the surgical intensive care unit (SICU) at the Los Angeles County and University of Southern California Medical Center, between July 1998 and December 2005. Patients were identified through a prospectively maintained Trauma Registry and the SICU database. This study was approved by the Institutional Review Board and adhered to established guidelines on the treatment of human subjects.

Patient-specific data were abstracted from the two database onto an Excel work sheet (Microsoft Excel 2003, Microsoft Corporation, Redmond, WA). Data elements included age, gender, mechanism of injury (blunt vs. penetrating), injury sustained

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and operative procedures identified by ICD-9 code, admission vitals (heart rate, systolic blood pressure, Glasgow Coma Scale score), body mass index, laboratory values (serial platelet counts), Abbreviated Injury Score, Injury Severity Score (ISS), and outcomes such as hospital and intensive care unit length of stay, deep venous thrombosis, pulmonary embolism, and hospital mortality.

Thrombocytosis was defined as a peak platelet count of greater than or equal to $450 \times 10^3/mm^3$. We further divided patients with thrombocytosis into those with early thrombocytosis, occurring within 7 days, and delayed thrombocytosis, developing after 7 days. Extreme thrombocytosis was defined as peak platelet counts greater than $1{,}000 \times 10^3/mm^3$. In our analysis, we compared demographics and outcomes for (1) patients with and without thrombocytosis ($\geq 450 \times 10^3/mm^3$), (2) early ($\leq$7 days) versus late (>7 days thrombocytosis) and (3) no thrombocytosis to both thrombocytosis and extreme thrombocytosis.

Bivariate analysis was performed to compare the patients with no thrombocytosis, early thrombocytosis, and late thrombocytosis with each of the demographic or clinical characteristics and outcomes. The Kruskal-Wallis nonparametric test was used for testing the difference of means for continuous variables, and the χ^2 test was used for testing the difference of proportions for categorical variables. The step-down Bonferroni p values were used for the adjustment of multiple paired comparisons. Variables with a p value of ≤ 0.2 from the bivariate analysis were entered into a stepwise logistic regression model to identify the independent risk factors for presence or absence of thrombocytosis and for early or late thrombocytosis. From the analysis, adjusted odds ratio and 95% confidence interval were derived for each risk factor in the model. An adjusted $p < 0.05$ was considered statistically significant. All statistical analysis was performed using the SAS System, version 8.2 (SAS Institute, Cary, NC).

RESULTS

During the 7.5-year study period, a total of 3,483 patients with trauma were admitted to the SICU. Of those, 197 patients (5.7%) were excluded for some evidence of splenic injury: 164 patients (4.7%) underwent splenectomy, 6 patients (0.2%) underwent partial splenectomy, and 27 patients (0.8%) underwent splenorrhaphy. The remaining 3,286 patients composed our study population. The study population was primarily men (79.4%), mostly injured by blunt mechanism (64.7%), had an average age of 36.7 ± 19.0, and were severely injured (ISS of 19.3 ± 13.8).

Overall, thrombocytosis developed in 614 patients (18.7%). The mean onset occurred at 15.4 ± 86.9 days (median 9.9 days); reaching their highest platelet count value at a mean of 23.7 ± 134.6 days (median 13.7 days). Normalization of platelet values occurred at a mean of 59.2 ± 276.4 days (median 16.7 days) in 294 (47.9%) of the patients. Patients who developed thrombocytosis had a significantly higher number of surgical interventions: craniotomy or craniectomies ($p = 0.0003$), laparotomies ($p < 0.0001$), and orthopedic procedures ($p < 0.0001$).

The patients were divided into three groups: those without thrombocytosis (2,672 [81.3%] patients), early thrombocytosis (72 [2.2%] patients), and delayed thrombocytosis (542 [16.5%] patients). The admission characteristics of these three groups are shown in Table 1. Of note, patients with thrombocytosis were significantly more injured ($p < 0.0001$) than were patients without thrombocytosis. Patients with early thrombocytosis were noted to have the highest platelet count of 550.8 ± 129.4 occurring at a mean of 2.0 ± 2.7

Table 1 Comparison of Patient Characteristics on Admission by Thrombocytosis Group

Variables	No Thrombocytosis (N = 2,672)	Early Thrombocytosis (N = 72)	Delayed Thrombocytosis (N = 542)	No Thrombocytosis vs. Thrombocytosis (*p*)	Early vs. Delayed Thrombocytosis (*p*)
Age (yrs)					
Mean ± SD	36.7 ± 19.4	34.5 ± 19.1	36.6 ± 16.9	1.00	1.00
≥55, % (n)	17.7 (473/2,672)	11.1 (8/72)	14.4 (78/542)	0.06	0.47
Gender					
Male, % (n)	79.0 (2,109/2,671)	75.0 (53/71)	82.5 (447/542)	0.29	0.29
ISS					
Mean ± SD	18.8 ± 12.7	16.8 ± 9.1	23.6 ± 12.1	<0.0001	<0.0001
≥16, % (n)	56.5 (1,506/2,668)	54.2 (39/72)	74.2 (400/539)	<0.0001	0.0005
BMI					
Mean ± SD	26.6 ± 5.9	27.2 ± 12.9	28.2 ± 6.3	<0.0001	0.01
≥30, % (n)	24.6 (638/2,593)	26.1 (18/69)	32.9 (178/541)	<0.0001	0.28
Mode of injury					
Blunt, % (n)	63.7 (1,703/2,672)	65.3 (47/72)	69.6 (377/542)	0.03	0.50
AIS, % (n)					
Head >3	22.9 (613/2,672)	25.0 (18/72)	26.0 (141/542)	0.25	0.89
Chest >3	10.6 (282/2,672)	6.9 (5/72)	17.0 (92/542)	<0.0001	0.04
Abdomen >3	10.3 (276/2,672)	6.9 (5/72)	18.3 (99/542)	<0.0001	0.02
Extremity >3	2.1 (57/2,672)	1.4 (1/72)	3.5 (19/542)	0.21	0.48

ISS, Injury Severity Score; BMI, body mass index; AIS, Abbreviated Injury Score.

Table 2 Comparison of Complications by Thrombocytosis Group

Complications	No Thrombocytosis (N = 2672), % (n)	Early Thrombocytosis (N = 72), % (n)	Delayed Thrombocytosis (N = 542), % (n)	No Thrombocytosis vs. Thrombocytosis (*p*)	Early vs. Delayed Thrombocytosis (*p*)
Had a complication	17.1 (458/2,672)	29.2 (21/72)	55.5 (301/542)	<0.0001	<0.0001
MODS	5.4 (144/2,672)	4.2 (3/72)	10.5 (57/542)	<0.0001	0.10
Sepsis*	3.0 (80/2,672)	1.4 (1/72)	15.5 (84/542)	<0.0001	0.002
Pneumonia†	5.3 (142/2,672)	9.7 (7/72)	27.3 (148/542)	<0.0001	0.002
ARDS	2.9 (77/2,672)	4.2 (3/72)	7.8 (42/542)	<0.0001	0.34
DVT	0.9 (24/2,672)	0.0 (0)	2.2 (12/542)	0.06	0.37
PE	1.0 (26/2,672)	1.4 (1/72)	2.8 (15/542)	0.003	0.69
ARF	2.3 (60/2,672)	1.4 (1/72)	4.8 (26/542)	0.007	0.23

* Sepsis: diagnosed using the criteria outlined in the Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: http://www.survivingsepsis.org.

† Pneumonia: diagnosed on the basis of the CDC surveillance definition of nosocomial pneumonia.

MODS, multiorgan dysfunction syndrome; ARDS, acute respiratory distress syndrome; DVT, deep venous thrombosis; PE, pulmonary embolism; ARF, acute renal failure.

Table 3 Comparison of Outcomes by Thrombocytosis Peak Level

Outcome	No Thrombocytosis (N = 2,672)	Thrombocytosis 450–1,000 (N = 573)	Thrombocytosis >1,000 (N = 41)	*p**
Had a complication, % (n)	17.1 (458/2,672)	51.3 (294/573)	68.3 (28/41)	<0.0001
MODS, % (n)	5.4 (144/2,672)	9.6 (55/573)	12.2 (5/41)	<0.0001
Sepsis, % (n)	3.0 (80/2,672)	13.8 (79/573)	14.6 (6/41)	<0.0001
Pneumonia, % (n)	5.3 (142/2,672)	24.6 (141/573)	34.2 (14/41)	<0.0001
ARDS, % (n)	2.9 (77/2,672)	7.0 (40/573)	12.2 (5/41)	<0.0001
DVT, % (n)	0.9 (24/2,672)	1.9 (11/573)	2.4 (1/41)	0.0231
PE, % (n)	1.0 (26/2,672)	2.8 (16/573)	0.0 (0/41)	0.0058
ARF, % (n)	2.3 (60/2,672)	4.7 (27/573)	0.0 (0/41)	0.0146
Length of stay				
ICU				
Mean ± SD	5.9 ± 7.7	18.8 ± 13.7	20.8 ± 21.0	<0.0001
Median	4.0	16.0	21.0	
Hospital				
Mean ± SD	12.4 ± 13.3	32.0 ± 25.1	34.7 ± 20.1	<0.0001
Median	8.0	27.0	30.0	
Mortality, % (n)	18.1 (483/2,664)	3.9 (22/567)	2.6 (1/39)	<0.0001

* Mantel-Haenszel χ^2 for trend.

MODS, multiorgan dysfunction syndrome; ARDS, acute respiratory distress syndrome; DVT, deep venous thrombosis; PE, pulmonary embolism; ARF, acute renal failure; ICU, intensive care unit.

days, whereas delayed thrombocytosis developed at a mean of 17.2 ± 92.3 days and reached the highest platelet count of 690.4 ± 199.2 at a mean of 26.6 ± 143.0 days.

Table 2 compares the complications between patients with and without thrombocytosis as well as early versus delayed thrombocytosis. Patients who developed thrombocytosis had a statistically significant higher incidence of all complications (52.4% vs. 17.1%, $p < 0.0001$) compared with patients who did not develop thrombocytosis. In addition, patients with thrombocytosis had a significantly higher rate of PE (2.6% vs. 1.0%, $p = 0.003$) and a higher rate of deep vein thrombosis that approached significance (2.0% vs. 0.9%, $p = 0.06$) compared with those without thrombocytosis.

Forty-one patients (1.2%) developed extreme thrombocytosis. A higher incidence of thromboembolic complications was not observed in these patients compared with patients with platelet counts between 450 and 1,000 × 10^3/mm^3 (Table 3).

The overall mortality rate of the study population was 15.4%. Patients who developed thrombocytosis had a significantly lower mortality (3.8% vs. 18.1%; $p < 0.0001$), longer ICU length of stay (14.7 ± 12.4 days vs. 5.9 ± 7.7 days; $p < 0.0001$), and longer hospital length of stay (27.0 ± 21.1 days vs. 12.4 ± 13.3 days; $p < 0.0001$) compared with those without thrombocytosis (Table 4). Independent risk factors for developing thrombocytosis are demonstrated in Table 5.

DISCUSSION

Reactive thrombocytosis is considered a normal response after inflammatory insults, such as infection, surgery, or trauma.[3] In fact, several studies have suggested that the failure to normalize, or even the failure to develop elevations in platelet count in the face of such insults is predictive of decreased survival.[3,4] Our present examination found that thrombocytosis occurs in almost one fifth of patients with trauma requiring ICU admission. The majority of these patients

Table 4 Comparison of Outcome by Thrombocytosis Group

Outcome	No Thrombocytosis (N = 2,672)	Early Thrombocytosis (N = 72)	Delayed Thrombocytosis (N = 542)	No Thrombocytosis vs. Thrombocytosis	Early vs. Delayed Thrombocytosis
Mortality					
Percent (n)	18.1% (483/2,664)	5.6% (4/72)	3.6% (19/534)	<0.0001	0.52
ICU LOS					
Mean ± SD	5.9 ± 7.7	9.4 ± 11.5	19.9 ± 13.2	<0.0001	<0.0001
Median	4.0	6.0	17.0		
Hospital LOS					
Mean ± SD	12.4 ± 13.3	20.1 ± 17.0	33.9 ± 25.2	<0.0001	<0.0001
Median	8.0	15.0	28.0		

LOS, length of stay; ICU, intensive care unit.

Table 5 Stepwise Logistic Regression to Identify Independent Risk Factors for Thrombocytosis

Step	Variable	R^2 Added	Cumulative R^2	Adjusted OR (95% CI)	Adjusted p
1	Ventilated	0.0613	0.0613	3.25 (2.43–4.43)	<0.0001
2	Laparotomy	0.0173	0.0786	2.31 (1.85–2.89)	<0.0001
3	Blunt injury	0.0183	0.0969	1.86 (1.49–2.35)	<0.0001
4	Heart rate >100	0.0087	0.1056	1.46 (1.21–1.77)	<0.0001
5	ISS ≥16	0.0059	0.1115	1.35 (1.09–1.67)	0.0067
6	BMI ≥30	0.003	0.1145	1.29 (1.05–1.58)	0.0167
7	Ethnicity	0.0058	0.1203		0.019
	• Black vs. Asian			1.11 (0.72–1.70)	0.64
	• Hispanic vs. Asian			1.02 (0.74–1.44)	0.90
	• Other vs. Asian			1.61 (0.93–2.74)	0.08
	• White vs. Asian			1.50 (1.03–1.19)	0.035
8	Chest AIS >3	0.0018	0.1221	1.33 (1.00–1.75)	0.0459

The analysis was based on 3,072 subjects. Variables in the model included age ≥55, BMI ≥30, blunt, heart rate >100, male, systolic blood pressure ≤90, ISS ≥16, Glasgow Coma Scale ≤8, head AIS >3, chest AIS >3, abdomen AIS >3, extremity AIS >3.

BMI, body mass index; AIS, Abbreviated Injury Score.

(88%) developed delayed thrombocytosis (>7 days). This delayed group was more severely injured and required a significantly greater number of surgical interventions. Overall, patients with posttraumatic thrombocytosis were significantly more likely to develop complications, including venous thromboembolism (VTE), than counterparts without elevated platelet counts. Thrombocytosis was also associated with longer ICU and hospital length of stay. All of these differences were most pronounced among the delayed group. Interestingly, however, elevated platelet levels were also associated with substantially lower mortality.

Previous examinations have demonstrated that postinjury and postsurgical thrombocytosis is a common finding; particularly among trauma, neurosurgical, and orthopedic patients.[1,2,7] These studies have also suggested that thrombocytosis may be associated with higher injury severity. In this examination we noted similar findings, documenting an overall incidence of posttraumatic thrombocytosis of 18.7%. We likewise found that patients developing thrombocytosis had a statistically significant elevation in mean ISS and a higher incidence of both severe (Abbreviated Injury Score >3) chest and abdominal injury compared with patients who did not develop thrombocytosis.

The risk of thromboembolic events remains the greatest concern regarding thrombocytosis. To date, however, a relationship between elevated platelet counts and these adverse events has not been well established. In a study of 36 patients with posttraumatic thrombocytosis, Valade et al.[2] found that these patients had no increased risk of VTE compared with counterparts who did not develop an elevation of platelets. In another examination conducted by Griesshammer et al.,[5] the investigators examined the outcomes of 732 patients with thrombocytosis. This group found that reactive or secondary thrombocytosis was only rarely associated with VTE, at a rate of only 1.6%. They concluded that unless additional risk factors are present, reactive thrombocytosis is not associated with significant risk for thromboembolic events. In our present examination, we found that there was a trend toward increased deep vein thrombosis, and a significantly higher rate of pulmonary embolism ($p < 0.0032$) recorded among patients developing thrombocytosis after trauma. The overall incidence of VTE in our population was 2.4%, a rate consistent with earlier studies of patients with trauma, suggesting comparable populations and thresholds for diagnostic interventions, such as ultrasound and computed tomography scan. The confines of our retrospective examination, however, prevented us from any meaningful attempt to determine whether the greater number of thromboembolic complications was attributable to thrombocytosis itself or the associated higher injury severity. In addition, the documentation of the rationale

for, and technique of antiplatelet therapy among these patients could not be clearly elucidated for analysis. Prospective study is warranted to address these critical issues.

The relationship between thrombocytosis and improved survival is an interesting association that has been suggested by the findings of several examinations.[1–4] In the aforementioned study by Valade et al.,[2] the investigators found that despite the fact that patients with trauma manifesting elevated platelet counts had a greater severity of illness, the ICU mortality was comparable between patients with and without thrombocytosis. Analysis of our population found that despite a significantly higher mean ISS among patients with thrombocytosis, there was a statistically significant decrease in overall mortality (3.8% vs. 18.1%). The reason for this finding remains unclear. Perhaps, the ability to mount a reactive thrombocytosis in the face of severe trauma serves as a marker for patient ability to successfully initiate adaptive mechanisms of response to injury burden. Further research in this arena is needed to establish the significance of this finding.

The risk factors for posttraumatic thrombocytosis have not been clearly defined. Numerous studies have shown that infections, particularly pneumonias, and adult respiratory distress syndrome or acute lung injury may cause reactive thrombocytosis.[2,5,6] After adjustment for confounders, we found that mechanical ventilation, laparotomy, blunt injury, and tachycardia were independent risk factors for the development of this sequela. We also noted that acute renal failure was a more common complication among patients developing posttraumatic thrombocytosis. The significance of this finding is unknown, because the temporal relationship between thrombocytosis and renal failure was not clear in all cases. This precluded the establishment of thrombocytosis as a cause, or a sequela of renal failure. Nevertheless, this was an interesting finding that warrants further investigation.

To identify the reasons behind these outcomes differences, there is a significant need to better understand the endocrine factors and cellular interactions that are taking place during posttraumatic thrombocytosis. Although it has been suggested that the clonal thrombocytosis associated with myeloproliferative disorders is more likely to result in thrombotic complications than that of nonclonal reactive causes,[8,9] abnormalities in platelet function in these populations are continuing to be better defined. Identified alterations of platelet function in the setting of these diseases have included increased local growth factor release, decreased alpha-adrenergic expression and unresponsiveness to epinephrine, abnormal expression of platelet glycoproteins, and alterations in thromboxane synthesis.[9,10,11] By comparison, significantly less is known about cytokine and platelet function during posttraumatic thrombocytosis. It has been suggested that platelet function after other causes of reactive thrombocytosis, such as infection or iron-deficiency anemia, may not be as significantly affected by cytokine alterations.[12,13] Until the role of cytokine and qualitative platelet function specifically during posttraumatic thrombocytosis is better examined, these potential associations, however, will not remain well defined.

There is a considerable need for additional study of posttraumatic thrombocytosis not only to better define the biochemical results of this finding, but also to identify its clinical significance. Is it possible that the occurrence of these platelet elevations represent an early manifestation of recovery in severely injured patients? If this is the case, is there a threshold beyond which this potential marker of recovery becomes a dysfunctional response, and why? What patient populations are prone to development of reactive thrombocytosis after injury, and who among these individuals is most likely to develop adverse sequelae? The answers to these questions warrant additional research, ideally in the context of a large, well-designed prospective examination.

Our study has important limitations. The retrospective design precluded the consistent establishment of the temporal relationship between thrombocytosis and outcomes. The ability to effectively determine this interaction, through a prospective study, might better provide the ability to distinguish complications as cause or effect of posttraumatic thrombocytosis. Additionally, consistent documentation of the implementation and goals of antiplatelet therapy was lacking. The role of these therapies remains undefined in this setting and need to be defined. Finally, the database used for our review did not include information regarding blood products. Had this information been available, it might have provided an interesting insight into the transfusion requirements and practices used in the care of the patients.

As has been demonstrated in previous examinations, our study confirms that reactive thrombocytosis is a common finding among patients with trauma requiring ICU care. We also noted that thrombocytosis was associated more commonly with severely injured patients and occurred more frequently among patients requiring operative procedures and developing complications. Despite these associations, reactive thrombocytosis was associated with significantly better survival. In contrast to earlier examinations, we noted that there does seem to be a higher incidence of thromboembolic complications in this study population.

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