

Incidence and risk factors for thrombocytopenia in the intensive care units of a tertiary hospital in northern India

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Background. In Western countries, incidence of thrombocytopenia in intensive care units (ICUs) has been found to be 13 - 44%. We chose to study the incidence, risk factors and transfusion requirements of thrombocytopenia in tertiary care ICUs in northern India.

Objective. To study the incidence and risk factors of thrombocytopenia in a mixed ICU.

Methods. This prospective observational 6-month cohort study was conducted in two 22-bedded medical-surgical ICUs. Patients aged 18 years or older with an ICU stay of at least 2 days were included.

Results. Thrombocytopenia ($<150\,000/\text{dL}$) occurred in 190 (38%) of the 500 patients studied. Thrombocytopenia was present on admission in 41 (8%) patients. Of the remaining patients, 149 (32%) developed new-onset thrombocytopenia (NOT) – thrombocytopenia developing in patients with platelet count more than $150\,000/\text{U}$ on admission – during ICU stay. Incidence and prevalence were 30% and 38%, respectively. ICU mortality was 13%. Thrombocytopenia was commonly associated with sepsis, disseminated intravascular coagulation, heparin and certain antibiotics. Cause could not be established in 10 patients. Underlying coronary artery disease and sepsis correlated with thrombocytopenia. Mortality was higher in patients with NOT (15.4 v. 8.7%, $p=0.003$). Compared with non-thrombocytopenic patients, patients with NOT required more blood product transfusions (57.7 v. 38.4%, $p=0.000$) and mechanical ventilation (23.5 v. 13.5%, $p=0.008$). No difference was observed in length of hospital stay and bleeding risk between the two groups.

Conclusion. We found incidence and prevalence of thrombocytopenia in the ICU comparable with internationally reported figures. NOT was associated with higher mortality and morbidity and may be considered as a marker of disease severity.

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Thrombocytopenia is one of the most commonly observed laboratory abnormalities in the intensive care unit (ICU),^[1] with incidence ranging from 13% to 44%.^[1] Thrombocytopenia has been found to predispose patients to increased bleeding risk, increasing morbidity and mortality.^[2] It is also considered a marker of disease severity.^[3]

The aetiology of thrombocytopenia in the ICU is multifactorial. Sepsis, malignancy, presence of invasive catheters and various medications such as heparin and antibiotics have been found associated with thrombocytopenia. Because of the many confounding factors, establishing the cause of thrombocytopenia in critically ill patients is challenging.^[4,5]

Different aspects of thrombocytopenia have been examined in various studies. The majority of these studies are Western, retrospective or have a small sample size. Until now, Indian literature has been silent on the prevalence of thrombocytopenia in the ICU. A Korean group recently evaluated thrombocytopenia in the ICU,^[6] the sole study from Asian countries so far. This prompted us to study the incidence, risk factors and impact on outcome of thrombocytopenia in the mixed ICU of our tertiary, multispecialty hospital in northern India.

Methods

This was a prospective, observational cohort study. Consecutive patients aged 18 years or older admitted to our medical-surgical ICU for at least 2 days were included. The study was conducted over a period of 6 months (October 2012 - March 2013). Patients were excluded if they had history of cardiac surgery, pregnancy, platelet disorders, haematological malignancy, recent chemotherapy, splenectomy, ICU stay of <48 hours, were <18 years of age or had a history of readmission to the ICU during the same

hospital stay. Platelet counts were measured daily from ICU admission to ICU discharge.

The necessary approvals were obtained from the Medanta Institutional Review Board (Ref. no.: 198/2012). Informed consent was obtained from the patients or their relatives prior to data collection. The study was registered at the Clinical Trial Registry of India (CTRI) (Ref. no.: CTRI/2012/05/002620).

The primary study objective was to assess thrombocytopenia incidence and associated risk factors. Secondary objectives were to study the effect of thrombocytopenia on bleeding risk and transfusion requirements in the ICU. The outcomes of length of hospital stay, ICU discharge and mortality were also studied.

Definitions

Thrombocytopenia was defined as two or more consecutive platelet counts $<150\,000/\mu\text{L}$, obtained at least 12 hours apart. Lowest platelet count during the ICU stay was considered the nadir platelet count. Disseminated intravascular coagulation (DIC) was defined by presence of elevated D-dimer along with two of the following criteria: prolonged prothrombin time, increased fibrinogen degradation products, and decreased fibrinogen or platelet counts. Drug-induced thrombocytopenia was considered present if there was resolution of thrombocytopenia after discontinuation of the suspected drug.

Heparin-induced thrombocytopenia (HIT) was diagnosed using 4T scoring (Table 1) and if there was recovery in platelet count after discontinuation of unfractionated heparin or low-molecular-weight heparin. Major bleeding was defined as any intracranial bleed or any bleed associated with a fall in haemoglobin by at least 2 g/dL.

Data collection

The following variables were recorded: general demographic characteristics including age, gender, comorbidities, reason for ICU admission; severity of illness by APACHE (Acute Physiology and Chronic Health Evaluation) II score calculation; biochemical parameters of complete blood count, liver function tests, kidney function tests, coagulation assays and any other special blood investigations if conducted; a comprehensive list of drugs patients were receiving in ICU; various interventions performed in ICU such as mechanical ventilation and haemodialysis; frequency and products of blood transfusions, if any; complications such as bleeding episodes or thromboembolic events; and any use of vasopressors.

Statistical analysis

Analysis included profiling of patients for different demographic and clinical parameters, comorbidity and risk factors. Descriptive analysis of quantitative data was expressed as means and standard deviations (SDs). Ordinal data were expressed as percentages, medians and ranges. Data normality was tested using the Kolmogorov-Smirnov test. For quantitative

parameters satisfying normality assumptions, the independent Student's *t*-test was used to draw inferences between groups. Cross-tables were generated to illustrate the relationships between parameters and comparisons were made using the χ^2 test. Stepwise multiple logistic regressions were performed for parameters. A *p*-value of <0.05 was considered statistically significant. The entire statistical analysis was performed using SPSS software version 19.0 (IBM Corp., USA).

Results

A total of 500 patients were enrolled in the study. Of these, 41 (8.2%) had thrombocytopenia on admission. Of the remaining 459 patients, 149 (32.5%) had new-onset thrombocytopenia (NOT) during their ICU stay. The median APACHE II score at the time of ICU admission was 11.0 (interquartile range (IQR) 1 - 32), and the predicted death rate was 5 - 10%. Median length of ICU stay was 4 days (IQR 1 - 35). Median length of hospital stay was 11 days (IQR 1 - 149). Thrombocytopenia incidence was 30% and prevalence during the study period was 38%. ICU mortality was 13%. The baseline patient demographic profile is shown in Table 2.

Table 1. The 4T scoring system of HIT^[7]

	2	1	0
Thrombocytopenia	>50% platelet fall to nadir ≥ 20	30 - 50% platelet fall or nadir 10 - 19	<30% platelet fall or nadir <10
Timing* of onset of platelet fall (or other sequelae of HIT)	Days 5 - 10, or \leq day 1 with recent heparin (past 30 days)	>day 10 or timing unclear; or <day 1 with recent heparin (past 31 - 100 days)	<day 4 (no recent heparin)
Thrombosis or other sequelae	Proven new thrombosis, skin necrosis, or acute systemic reaction after intravenous unfractionated heparin bolus	Progressive or recurrent thrombosis, erythematous skin lesions or suspected thrombosis (not proven)	None
Other cause(s) of platelet fall	None evident	Possible	Definite

HIT: The 'Four Ts' (2, 1 or 0 for each of four categories: maximum possible score = 8). Pretest probability score: 6 - 8 indicates high; 4 - 5 intermediate; and 0 - 3 low.

*First day of immunising heparin exposure considered day 0.

Table 2. Baseline characteristics of patients (N=500)

Parameters	n (%)
Age (years), mean (SD)	56.8 (16.6)
Male	330 (66.0)
APACHE II score, mean (SD)	12.0 (7.1)
Medical history	
Hypertension	222 (44.4)
Diabetes mellitus	91 (18.2)
Cardiovascular disease	70 (14.0)
Chronic renal failure	33 (6.6)
Chronic liver disease	15 (3.0)
Chronic obstructive pulmonary disease	31 (6.2)
Neurological disorders	20 (4.0)
Reason for ICU admission	
Respiratory	90 (18.0)
Sepsis	301 (60.2)
Fluid overload	28 (5.6)
Cardiovascular problem	41 (8.2)
Postoperative	19 (3.8)
Others	21 (4.2)
ICU length of stay (days), mean (SD)	5.8 (5.5)
ICU mortality	65 (13.0)

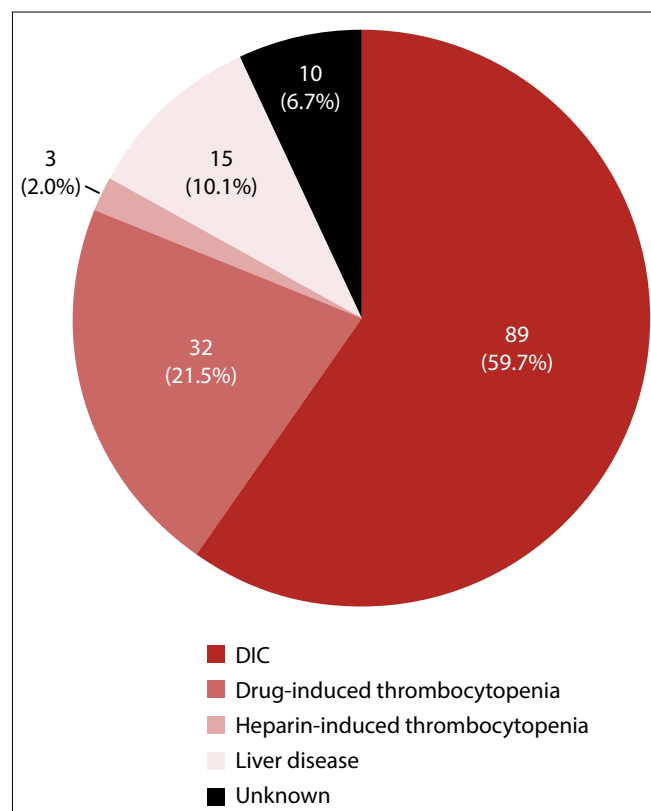


Fig. 1. Causes of new-onset thrombocytopenia.

Causes of NOT

A total of 149 patients developed thrombocytopenia during their ICU stay. Thrombocytopenia was diagnosed secondary to sepsis with disseminated intravascular coagulation in 89 patients (59.7%) and drug-induced thrombocytopenia was thought to be present in 31 (21.5%) patients. Thrombocytopenia was due to underlying liver disease in 15 (10.1%) patients. HIT was diagnosed, based on 4T scoring, in 3 (2.0%) patients. Cause of thrombocytopenia could not be ascertained in 10 (6.7%) patients. During the work-up for NOT, 41 patients refused to give consent for bone marrow examination. Causes of NOT and drug-induced thrombocytopenia are shown in Fig. 1 and Table 3, respectively.

Use of antibiotics, including meropenem, cefuroxime, cefepime, tazobactam, vancomycin, levofloxacin, linezolid, and low-molecular-weight heparin, correlated with thrombocytopenia, as did underlying coronary artery disease and sepsis ($p < 0.05$).

APACHE II score was significantly higher in patients with NOT compared with those without thrombocytopenia (13 v. 11, $p = 0.003$). Patients with NOT required significantly more packed red-cell and platelet transfusions (5.4 v. 2.3%, $p = 0.000$) and had significantly higher ICU mortality (15.4 v. 8.7%, $p = 0.003$). The majority of transfusions were given prophylactically before procedures in the thrombocytopenia group. Blood products transfused were mainly fresh-frozen plasma and platelets. Patients with NOT required mechanical ventilation and inotropes more frequently (57.7 v. 38.4%, $p = 0.000$; 23.5 v. 13.5%, $p = 0.008$, respectively).

There was no difference in duration of ICU and hospital stay or bleeding risks between the two groups. Use of invasive devices such as central-line and arterial-line catheters was not different between the groups and haemodialysis requirements also did not vary. Comparison between patients with or without NOT is depicted in Table 4.

Table 3. Causes of drug-induced thrombocytopenia (N=32)

Cause	n (%)	p-value
Carbapenem	12 (8.05)	0.002*
Cephalosporin	5 (3.35)	0.000*
Fluoroquinolones	3 (2.01)	0.000*
Glycopeptides	6 (3.35)	0.002*
Oxazolidinone	5 (3.35)	0.040*
β -lactamase/ β -lactamase inhibitors	1 (0.67)	0.277

*p-value < 0.05, statistically significant.

Discussion

Thrombocytopenia is one of the most common haematological disorders seen in critically ill patients. Prevalence has been found to be around 50% and incidence varies between 13% and 44%.^[8,9] In our cohort, 41 patients (8.2%) had pre-existing thrombocytopenia at the time of ICU admission and 149 patients (32.4%) developed thrombocytopenia during their ICU stay. Our incidence of 30% and prevalence of 38% were consistent with observations made internationally.^[6,10,11] This is despite our study definition for thrombocytopenia of two platelet count readings <150 000/ μ L at least 12 hours apart. This is unlike previous investigations with thrombocytopenia defined as platelet count <150 000/ μ L, or fall in platelet count by at least 50% from the time of ICU admission.

The majority of studies of thrombocytopenia in ICU are from North America or Europe. Among studies from Asian countries, a prospective study was conducted in Singapore, examining thrombocytopenia incidence in septic critically sick patients only.^[12] A study from Korea reported an incidence of 37.1%. Therefore, this is the first prospective study of thrombocytopenia incidence in a general ICU on the Asian subcontinent. As discussed earlier, our figures were comparable with those found internationally.

We discovered underlying coronary artery disease and sepsis on admission as major risk factors for developing thrombocytopenia in

critically ill patients. Unlike previous studies, blood transfusions, postoperative status, pulmonary artery catheterisation and respiratory failure were not identified as risk factors.^[11,13] The association of thrombocytopenia with sepsis can be explained on the basis of an underlying DIC process. Other mechanisms implicated in sepsis-induced thrombocytopenia are immune-mediated platelet destruction and haemophagocytic syndrome.^[14,15] An association between coronary artery disease and thrombocytopenia has not been reported before and the underlying pathophysiological mechanism for this observation needs further consideration. It may be related to the use of antiplatelet medication in these patients; however, this needs further investigation.

Systematic and extensive investigations are required to establish the cause of thrombocytopenia in ICU, the aetiology of which is multifactorial and complicatedly linked. The work-up of thrombocytopenia in our study left scope for improvement, as 41 (27.5%) patients refused bone marrow examination. Within these constraints, sepsis with DIC was the most common cause, occurring in 59.7% of patients. The second-most common cause was drug-induced thrombocytopenia, occurring in 21.4% of patients. Implicated drugs were mainly antibiotics such as teicoplanin, levofloxacin, cefuroxime, meropenem, vancomycin, linezolid, and cefepime and tazobactam combinations.

Table 4. Comparison between patients with or without NOT

Variable	Patients with NOT (N=149), n (%)	Patients without NOT (N=310), n (%)	p-value
Age (years), mean (SD), median	57.3 (16.9), 59	56 (16.4), 58	0.454
Male	99 (66.4)	201 (64.8)	0.673
ICU stay (days), mean (SD), median	6.1 (5.6), 4	5.3 (5.2), 3	0.151
Hospital stay (days), mean (SD), median	15.0 (10.9), 12	17.9 (19.4), 11	0.086
APACHE II score, mean (SD), median	13.0 (7.3), 13	10.9 (6.8), 11	0.003*
Haemodialysis	6 (4.0)	20 (6.5)	0.530
ICU mortality	37 (15.4)	23 (8.7)	0.003*
Mechanical ventilation	86 (57.7)	119 (38.4)	0.000*
Bleeding risk	8 (5.4)	7 (2.3)	0.079
Transfusion requirement	33 (22.1)	29 (9.4)	0.000*
Inotropes	35 (23.5)	42 (13.5)	0.008*
Invasive catheters	103 (69.1)	218 (70.3)	0.539
Dialysis	6 (4.0)	20 (6.5)	0.239
Coronary artery disease	15 (10.1)	46 (14.8)	0.043*
Sepsis	101 (67.7)	154 (49.6)	0.004*
Respiratory failure	39 (26.2)	36 (11.6)	0.617
Postoperative status	2 (1.3)	14 (4.5)	0.132

*p-value < 0.05, statistically significant.

However, we did not find any associations between thrombocytopenia and anticonvulsants, diuretics or H2 blockers, as reported in previous studies.^[6,11] Establishing drug-induced thrombocytopenia remains difficult, as the diagnostic criteria are based on the recovery of platelet count after the drug is discontinued and there is no gold standard for its diagnosis.

HIT was considered separately from drug-induced thrombocytopenia in our study. Its incidence was found to be 2%, which is in tandem with an internationally reported incidence of 1% - 5%.^[16] We employed 4T scoring for diagnosing HIT because of non-availability of the functional and antigen assays used for detecting HIT antibodies.^[17,18] All these tests have moderate to high negative predictive value and a low positive predictive value similar to the 4T scoring system. A 4T score of 5 - 8 on a scale of 0 - 8 reflects intermediate to high probability of HIT. The magnitude of HIT in Asian countries has not been systematically studied so far although there have been occasional case reports of HIT from the area.

In our study, thrombocytopenia patients did not have any bleeding episodes. They required more platelet and fresh-frozen plasma transfusions compared with the non-thrombocytopenia group, and these were mostly prophylactic transfusions carried out if any surgical procedures or interventions were planned. Previous studies have reported increased bleeding episodes and more transfusion requirements in critically sick patients with thrombocytopenia.^[9,11,19-21] As observed in previous studies,^[22] our thrombocytopenia patients had more frequent need for mechanical ventilation and inotropes. We observed a higher ICU mortality among thrombocytopenia patients compared with the non-thrombocytopenia group (15.4 v. 8.7%, $p=0.03$); this may be because thrombocytopenia patients were much more sick than those who did not develop thrombocytopenia. This correlates with the observation that the APACHE II score at the time of ICU admission was higher in those who eventually developed thrombocytopenia during their ICU stay (13 v. 11, $p=0.003$). Thus, thrombocytopenia may reflect severity of critical illness.

Many previous studies have observed poor outcomes with thrombocytopenia.^[20,23-27] There have been reports indicating that the rate of platelet decline or recovery from thrombocytopenia may have important prognostic value in diseases such as sepsis and acute respiratory distress syndrome (ARDS).^[21,22,24,26]

Our study had several limitations. Firstly, this study was conducted at a single tertiary care centre in a northern part of India. Figures may not be truly representative of the entire country. The need for a robust work-up for thrombocytopenia cannot be over-emphasised. This was the second drawback of the study, as evaluation of cause of thrombocytopenia could have been more extensive and systematic. A third limitation was the non-availability of HIT antibody detection tests, which could have influenced the diagnosis.

Major strengths of this study were its prospective nature and adequate sample size.

Conclusions

Thrombocytopenia occurs frequently in critically ill patients. It should be viewed generally as an indicator of illness severity, and also has prognostic significance because of its association with increased morbidity, hospital resource utilisation and increased mortality. Its

potential as a predictor of complications of ARDS and hospital-acquired pneumonia needs to be explored further. However, it remains necessary to evaluate this disorder at the earliest opportunity, as about 25% of cases are drug-associated and can be rapidly reversed with withdrawal of the offending drug, especially heparin. Rate of decline and delayed count recovery need further evaluation but may prove useful as urgently needed prognostic indicators.

Declaration. The authors declare that an abstract of this study was published in the *Indian Journal of Critical Care Medicine* as part of a poster presentation at CRITICARE-2015, Bengaluru, India.

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