Original article

Prevalence, causes and outcomes of thrombocytopenia among patients in medical intensive care units

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Abstract:

Objective: *The study aimed to identify the prevalence, causes, outcomes and prognostic factors for survival of patients with thrombocytopenia in a medical ICU.* ***Material and Methods:*** *This comprised a retrospective study conducted at Maharaj Nakorn Chiang Mai Hospital. Data were collated from adult patients admitted to a medical ICU with a platelet count ≤ 100 x10^9/L from January 2016 to December 2019. Clinical characteristics, outcomes and data were analyzed to investigate the prognostic factors for survival.* ***Results:*** *Of 2,039 patients admitted to a medical ICU, thrombocytopenia was prevalent in 182 cases (8.9%). The most common cause of thrombocytopenia was infections (85%). Mean platelet count during the thrombocytopenic period and platelet nadir were 55.8±27.9 x10^9/L and 34.6±26.5 x10^9/L, respectively. Mean duration of thrombocytopenia was 11.9+4.1 days, and rate of bleeding complications and mortality were 30.7% and 67.0%, respectively. Survival analysis revealed that age ≥ 80 years (HR 1.99; 95%CI: 1.16-3.39, p = 0.012) and low nadir hemoglobin (Hb) (HR 0.88; 95%CI: 0.81-0.97, p = 0.01) were the variables significantly associated with increased mortality.* ***Conclusion:*** *The prevalence of thrombocytopenia in a medical ICU was 8.9% with a mortality of 67.0%. Infection was the most common cause. Age ≥ 80 years and low nadir Hb were associated with higher mortality rate.*

Keywords : ● *Thrombocytopenia* ● *Intensive care unit* ● *Platelet* ● *Medical intensive care unit*

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นิพนธ์ต้นฉบับ

ความชุก สาเหตุ และผลของภาวะเกล็ดเลือดต่ำในหอผู้ป่วยวิกฤติทางอายุรกรรม

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บทคัดย่อ

วัตถุประสงค์ *เพื่อหาความชุก สาเหตุ ผลลัพธ์ และปัจจัยที่มีผลต่อการเสียชีวิตของภาวะเกล็ดเลือดต่ำในหอผู้ป่วยวิกฤติอายุรกรรม* ***วิธีการวิจัย*** *การศึกษาแบบย้อนหลังในโรงพยาบาลมหาราชนครเชียงใหม่ รวบรวมผู้ป่วยซึ่งเข้ารับการรักษาในหอผู้ป่วยวิกฤติอายุรกรรมที่มีภาวะเกล็อดเลือดต่ำ ≤ 100 x10^9/ลิตร ตั้งแต่มกราคม 2016 ถึงธันวาคม 2019 โดยเก็บข้อมูลลักษณะทางคลินิก ผลลัพธ์ และทำการวิเคราะห์ปัจจัยที่มีผลต่อการเสียชีวิต* ***ผลการศึกษา*** *จากผู้ป่วยซึ่งเข้ารับการรักษาในหอผู้ป่วยวิกฤติอายุรกรรม 2,039 ราย พบว่า 182 ราย (ร้อยละ 8.9) มีภาวะเกล็ดเลือดต่ำ สาเหตุที่พบบ่อยที่สุดคือการติดเชื้อ (ร้อยละ 85) ระดับเกล็ดเลือดเฉลี่ยในช่วงที่มีภาวะเกล็ดเลือดต่ำ และเกล็ดเลือดต่ำสุดเท่ากับ 55.8±27.9 x10^9/ลิตร และ 34.6±26.5 x10^9/ลิตร ตามลำดับ ระยะเวลาเฉลี่ยของภาวะเกล็ดเลือดต่ำเท่ากับ 11.9+4.1 วัน อัตราการเกิดภาวะแทรกซ้อนเลือดออกและอัตราการเสียชีวิตเท่ากับร้อยละ 30.7 และ 67 ตามลำดับ การวิเคราะห์ปัจจัยที่มีผลต่อการเสียชีวิตพบว่าอายุ ≥ 80 ปี (HR 1.99; 95%CI: 1.16-3.39, p = 0.012) และระดับฮีโมโกลบินต่ำสุด (HR 0.88; 95%CI: 0.81-0.97, p = 0.01) เป็นปัจจัยที่มีผลอย่างมีนัยสำคัญ* ***สรุป*** *ความชุกของภาวะเกล็ดเลือดต่ำในหอผู้ป่วยวิกฤติอายุรกรรมเท่ากับร้อยละ 8.9 และมีอัตราการเสียชีวิตร้อยละ 67 การติเชื้อเป็นสาเหตุที่พบบ่อยที่สุด อายุ ≥ 80 ปี และระดับฮีโมโกลบินที่ต่ำสัมพันธ์กับอัตราการเสียชีวิตที่สูงขึ้น*

คำสำคัญ : ● *ภาวะเกล็ดเลือดต่ำ* ● *หอผู้ป่วยวิกฤติ* ● *เกล็ดเลือด* ● *หอผู้ป่วยวิกฤติอายุรกรรม*

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Introduction

Thrombocytopenia has been found in about 40% of critically ill patients.[1] Multiple mechanisms contribute to thrombocytopenia including increased platelet destruction or consumption, decreased platelet production, abnormal platelet sequestration and hemodilution.[1] The most common mechanism involved is increased platelet consumption as a result of infections, drugs or bleeding.[2] For any given individual patient in the intensive care unit (ICU), more than one mechanism is frequently responsible for thrombocytopenia. For example, thrombocytopenia among patient with sepsis results from decreased production as well as increased destruction of platelets.

A prospective study in Canada reported that the incidence of developing thrombocytopenia during ICU admission was 46% and respiratory tract infection was the major cause.[3] In that study developing thrombocytopenia in the ICU was associated with prolonged length of stay as well as an increase in adverse clinical outcomes including mortality.[3] Another study revealed a decreased platelet count of 30% was associated with a doubling in mortality rate.[4] A further study found that combined thrombocytopenia and adult respiratory distress syndrome had a high predictive value for mortality.[5] Others reported that hematologic abnormalities associated with increased morbidity and mortality were disseminated intravascular coagulation (DIC)[6] and the presence of nucleated red blood cells (NRC) in peripheral blood.[7,8] On the other hand, one study showed that thrombocytopenia was not associated with adverse clinical outcomes.[9]

Changes in platelet count among critically ill patients exhibited different patterns among survivors and nonsurvivors. Among survivors, the platelet count returned to the pre-admission level by the end of the first week and continued to rise above the admission level. In contrast, no subsequent increase was noted in platelet count in the nonsurvivor group.[10]

In Thailand, the Southeast Asia Acute Kidney Injury (SEA-AKI) study group developed and proposed the THAI-ICU score as a simplified severity score for critically ill patients in a limited resource setting. Thrombocytopenia was one of the six factors that predicted adverse clinical outcomes, including mortality.[11]

Most related studies aimed to explore prognostic factors contributing to adverse outcomes among critically ill patients. However, scarce data is available about clinical features and prognostic factors of mortality among patients with thrombocytopenia in a medical ICU.

Material and Methods

This retrospective cohort study was conducted among patients receiving a diagnosis of thrombocytopenia in the medical ICU at Maharaj Nakorn Chiang Mai Hospital from January 1, 2016 to December 31, 2019 and was approved by the institutional review board (IRB) of the Faculty of Medicine, Chiang Mai University. The patients were discovered by searching for the ICD-10 code D696 (thrombocytopenia). The primary objective was to determine the prevalence and causes of thrombocytopenia among patients in a medical ICU. Secondary objectives were to determine the outcomes including mortality rate, bleeding complications and risk factors of mortality of patients with thrombocytopenia in a medical ICU.

Inclusion criteria comprised adults aged at least 18 years old admitted to the medical ICU from January 1, 2016 to December 31, 2019. The admission criteria to the medical ICU were acute respiratory failure requiring mechanical ventilation, unstable hemodynamic status, the need for hemodynamic monitoring, multiple comorbidities and acute illness requiring close monitoring. Data from patients presenting chronic thrombocytopenia before admission were excluded. Information about demographic data, clinical manifestations, diagnosis, laboratory findings, causes of thrombocytopenia, clinical course including date of thrombocytopenia, date of recovery, presence of DIC, presence of NRC in peripheral blood, bleeding complications and mortality were collected. The prevalence of thrombocytopenia was calculated

and prognostic factors including DIC and NRC were analyzed. Thrombocytopenia was defined as a platelet count < 100 x10^9/L, and definition of sepsis was based on international guidelines.[12] Overt DIC was defined as a score at least 5 according to the International Society of Thrombosis and Hemostasis (ISTH) scoring system of DIC.[13]

Statistical analyses

Demographic data including prevalence, degree of thrombocytopenia, duration of thrombocytopenia and recovery time of study participants were described using mean with standard deviation (SD) or median with inter-quartile range as appropriate. Comparison between the groups was analyzed using a t-test and the Chi-square test. Any exploratory factor associated with mortality was assessed using the Cox proportional hazard model (univariable and multivariable analysis). A *p*-value of < 0.05 in a two-sided test was considered statistically significant. All statistical analyses were performed using Stata, Version 16.0. Because the prevalence of thrombocytopenia according to the THAI-ICU score study was 20%, the hypothesis was for an 80% power [1-β] and a significance level of 95%, so the calculated sample size was 246 patients for this study.

Results

One hundred and eighty-two of 2,039 patients in the medical ICU had thrombocytopenia resulting in a prevalence of 8.9%. Clinical characteristics of patients with thrombocytopenia are shown in Table 1. One hundred and one patients (55.4%) were male, and the mean age was 62.1+18.1 years. Thirty patients (16.8%) had documented thrombocytopenia but platelet count returned to normal before ICU admission. Hypertension (28.5%) and diabetes (17.5%) were the most common comorbidities. Clinical and laboratory findings at the onset of thrombocytopenia are shown in Table 2. Sepsis and DIC were documented in 85.6% and 18.7% of patients, respectively.

Clinical course, laboratory findings, ad outcomes of patients with thrombocytopenia are shown in Tables 3 and 4. Mean initial platelet count was 118.9±9.26 x10^9/L. Patients developed thrombocytopenia 5.1±4.6 days after the date of admission. Mean platelet count during the thrombocytopenic period was 55.8±27.9 x10^9/L with a nadir platelet of 34.6±26.5 x10^9/L. Mean duration of thrombocytopenia was 11.9±4.1 days. The most com-

Table 1 Clinical characteristics of the patients

Clinical parameter	Total (n = 182)
Age (years), mean±SD	62.13±18.12
Sex, n (%)	
Female	81 (44.51)
Male	101 (55.49)
History of thrombocytopenia, n (%)	30/178* (16.85)
Underlying disease, n (%)	
Diabetes mellitus	32 (17.58)
Hypertension	52 (28.57)
COPD	11 (6.04)
Stroke	10 (5.49)
MI	2 (1.10)
Dyslipidemia	21 (11.54)
CKD	22 (12.09)
Cirrhosis or liver disease	17 (9.34)
Malignancy	36 (19.78)
HIV	4 (2.20)
Rheumatoid arthritis	2 (1.10)
SLE	7 (3.85)
Neurological diseases	7 (3.85)
AF	6 (3.30)
Bed-ridden status	2 (1.10)
Thyroid diseases	2 (1.10)
Asthma	3 (1.65)
Bone marrow failure	4 (2.20)
Osteoporosis	2 (1.10)
Others	101 (55.49)
History of alcohol drinking, n (%)	34/179* (18.99)
Smoking history, n (%)	24 (13.19)
Pack-year, mean±SD	16.17±7.95

COPD: Chronic obstructive pulmonary disease; MI: Myocardial infarction; CKD: Chronic kidney disease; HIV: Human immunodeficiency virus; SLE: Systemic lupus erythematous; AF: Atrial fibrillation. *only patients with available data

Table 2 Clinical and laboratory findings at the onset of thrombocytopenia

Clinical and Laboratory Finding	Total (n = 182)
Sepsis, n (%)	155/181* (85.64)
BUN (mg/dL), mean±SD	42.31±24.03
Creatinine (mg/dL), mean±SD	2.57±2.40
DIC (overt and non-overt), n (%)	34/181* (18.78)
Fibrinogen (mg/dL), mean±SD	296.25±159.84
PTT (seconds), mean±SD	40.54±27.40
PT (seconds) mean±SD	17.03±8.47
NRC (cells/100 WBC), mean±SD	3.90±9.21

BUN: Blood urea nitrogen; DIC: Disseminated intravascular coagulation; PTT: Partial thromboplastin time (normal range 28.6-39.4 seconds); PT: Prothrombin time (normal range 10.3-12.7 seconds); NRC: Nucleated red cells; WBC: White blood cells. *only patients with available data

Table 3 Clinical course and blood cell count.

Clinical Course (n = 182)	Platelet Count ($x10^9$/L) Mean±SD	White Blood Cells ($x10^9$/L) Mean±SD	Hemoglobin (g/dL) Mean±SD
On intensive care unit admission	118.9±9.26	12.25±1.35	9.93±2.92
At onset of thrombocytopenia	60.42±28.03	12.13±1.69	9.31±2.86
Nadir	34.65±26.54	10.95±1.16	8.61±2.54
During thrombocytopenic period	55.80±27.88	-	-

Table 4 Other clinical courses and outcomes

Clinical Course and Outcomes	Total (n = 182)
Duration of nonthrombocytopenic period (days), mean±SD	5.13±4.58
Duration of thrombocytopenic period (days), mean±SD	11.97±4.13
Death within 28 days, n (%)	125 (68.68)
Death in admission, n (%)	122 (67.03)
Recovery and transfer to ward or discharge	60 (32.97)
Cause of thrombocytopenia, n (%)	
Infection	155 (85.16)
Drug*	10 (5.49)
Immune**	2 (1.10)
Others***	15 (8.25)
Bleeding complications, n (%)	56 (30.7)
UGIH	41 (73.2)
Hemoptysis	4 (7.2)
LGIH	2 (3.5)
Others#	9 (16.1)

WBC: White blood cells; Hb: Hemoglobin; UGIH: Upper gastrointestinal hemorrhage; LGIH: Lower gastrointestinal hemorrhage

*Drug-induced thrombocytopenia; meropenem (1), ceftriaxone (1), linezolid (1), methotrexate (1), topiramate (1), missing data (10)

**Immune induced thrombocytopenia; systemic lupus erythematosus (2)

***Other: consumption from upper gastrointestinal hemorrhage (1), hemoptysis (1), missing data (13)

Other: hematoma (3), ecchymosis (1), intramuscular bleeding (1), hemothorax (2), bleeding hemorrhoid (1), Subdural hematoma (1)

mon cause of thrombocytopenia was infection (85.2%), followed by platelet consumption from bleeding (8.3%) and drug-induced thrombocytopenia (5.5%). None of our patients experienced heparin-induced thrombocytopenia (HIT).

One hundred and twenty-two patients with thrombocytopenia died in admission leading to a mortality rate of 67.0%. The main cause of mortality was infection (86.8%) with approximately one third (33.5%) being from pneumonia, followed by septicemia (9.9%) and urinary tract infection (9.3%). In the noninfectious group, causes of mortality included congestive heart failure (3.3%) and upper gastrointestinal hemorrhage (GIH) (2.7%). Fifty-six (30.7%) patients had bleeding complications including upper GIH (73.2%), hemoptysis (7.2%), lower GIH (3.5%), hematoma (3.5%), hemothorax (3.5%), ecchymosis (3.5%), intramuscular bleeding (1.7%), bleeding hemorrhoid (1.7%) and subdural hematoma (1.7%).

From the univariable analysis, risk factors significantly associated with higher mortality rate were categorized in two groups consisting of risk factors at baseline and during the clinical course. Firstly, risks at baseline included age ≥ 80 years (HR 1.93, 95%CI: 1.16-3.20, $p = 0.01$), atrial fibrillation (HR 3.26, 95%CI: 1.31-8.09, $p = 0.01$), and bed-ridden status (HR 8.64, 95%CI: 2.05-36.4, $p < 0.01$). Secondly, risks during the clinical course which were prolonged prothrombin time (PT) (HR 1.01, 95%CI: 1.04-1.08, $p < 0.01$), low hemoglobin (Hb) level at onset of thrombocytopenia (HR 0.93, 95%CI: 0.86-0.99, $p = 0.03$), low nadir Hb (HR 0.88, 95%CI: 0.80-0.96, $p < 0.01$) and presence of NRC in a blood smear (HR 1.02, 95%CI: 1.01-1.04, $p = 0.01$) (Table 5). Presence of DIC (HR 1.51, 95%CI: 0.9-2.3, $p = 0.07$) was not significantly associated with higher mortality rate.

From the multivariable analysis using backward elimination regression, patients' age ≥ 80 years (HR 1.99, 95%CI: 1.16-3.39, $p = 0.01$) and low nadir Hb (HR 0.88, 95%CI: 0.81-0.97, $p = 0.01$) were significantly associated with mortality.

Discussion

The prevalence of thrombocytopenia among patients in the medical ICU in this study was 8.9%, while related studies reported a prevalence of 20 to 50%.[1] A large

Table 5 Univariable and multivariable analysis of risk factors associated with all-cause mortality

Characteristic	Univariable Analysis		Multivariable Analysis	
	HR (95%CI)	*p*-value	HR (95%CI)	*p*-value
Age (years)				
< 60	Ref.			
60-79	1.16 (0.73-1.84)	0.53	1.09 (0.675-1.763)	0.72
≥ 80	1.93 (1.16-3.20)	0.01	1.99 (1.16-3.39)	0.01
AF	3.26 (1.31-8.09)	0.01	2.31 (0.91-5.88)	0.08
Bed-ridden status	8.64 (2.05-36.4)	< 0.01	-	-
BUN	1.01 (1.00-1.02)	0.04	1.01 (1.00-1.02)	0.04
Presence of NRC in blood smear	1.02 (1.01-1.04)	0.01	-	-
Presence of DIC	1.51 (0.90-2.30)	0.07	-	-
Hb at onset of thrombocytopenia	0.93 (0.86-0.99)	0.04	-	-
Nadir Hb	0.88 (0.80-0.96)	< 0.01	0.88 (0.81-0.97)	0.01
Median PT	1.01 (1.04-1.08)	< 0.01	1.06 (1.04-1.08)	< 0.01
Platelet level on admission	0.98 (0.95-1.00)	0.04	0.96 (0.94-0.99)	0.005

AF: Atrial fibrillation; BUN: Blood urea nitrogen; NRC: Nucleated red cells; DIC: Disseminated intravascular coagulation; Hb: Hemoglobin; PT: Prothrombin time

prospective cohort study in Canada found that almost 50% of critically ill patients presented thrombocytopenia.[3] The lower prevalence of thrombocytopenia in our study as compared with related studies might have been due to different inclusion and admission criteria. The study carried out in Canada[3] defined thrombocytopenia as a platelet count ≤ 150 $x10^9$/L instead of 100 $x10^9$/L and enrolled patients in both medical and surgical ICUs[11] compared with only patients in the medical ICU in this study. In addition, the retrospective nature of our study might have resulted in incomplete data about thrombocytopenia among some patients. However, the prevalence was comparable with the THAI-ICU score study carried out in Thailand showing a prevalence of 8.3% using the same definition of thrombocytopenia.[11]

Similar to related studies, the most common cause of thrombocytopenia was infection (85.1%)[3,14] although we cannot exclude the possibility of combined causes of thrombocytopenia among some patients. A retrospective cohort study in two tertiary hospitals in Canada found a high prevalence (16.8%) and incidence (27.7%) of thrombocytopenia among 980 patients with septic shock at and during ICU admission, respectively.[15] A prospective cohort study carried out in Korean medical ICUs also found that 66.7% of patients with thrombocytopenia resulted from sepsis with DIC and subsequently from drug-induced thrombocytopenia (18%).[14] Drug-induced thrombocytopenia was found in only 5.5% of patients in this study and no patients presented HIT. These findings support the lower prevalence of HIT among medical than in surgical patients.[16] However this condition should be carefully evaluated among patients developing thrombocytopenia after heparin therapy.[17]

According to this study, risk factors associated with mortality with the univariable analysis were age ≥ 80 years, atrial fibrillation, bed-ridden status, low nadir Hb, PT prolongation and presence of NRC in peripheral blood. These findings were consistent with related studies.[4] A French cohort study of patients in an ICU without thrombocytopenia at the time of admission reported that older age and comorbidities were adverse predictors of hospital mortality in addition to a 30% decline in platelet count.[4] Similar to other studies, the presence of peripheral blood NRC was a strong predictor of critically ill patients' mortality.[7,8] The presence of NRC might be associated with hemolysis in DIC. Prior studies showed mortality among patients with DIC progressively increased across the ISTH score and the overall mortality in these studies was around 20-60%.[6,13,18] However, our study did not show that DIC was independently associated with mortality. We hypothesize that it might be due to the high mortality rate in the present study, differing populations between studies as well as a variation in the criteria of ICU admission. The medical ICU in this study provided care to patients with malignancy and extreme age leading to higher mortality rates. Similar to a related study, a lower nadir Hb level or anemia was associated with increased mortality.[19] In contrast to a recent meta-analysis study, this study showed a significant association between anemia and all-cause mortality among patients in the ICU.[20]

This study also demonstrated that about one third of patients with thrombocytopenia experienced nonmortality bleeding complications especially GIH. A retrospective study from the US revealed a borderline association between thrombocytopenia among hospitalized medical patients and GIH.[21] In addition, thrombocytopenia was found to be associated with platelets, red blood cells and fresh frozen plasma transfusion in related studies.[3,21] The benefits of platelet transfusion among nonbleeding patients with thrombocytopenia remain unclear.[22,23] As this study obtained limited data regarding the transfusion requirement, future prospective studies are warranted.

This study reveals the prevalence, clinical course and outcomes of patients with thrombocytopenia in Thai medical ICUs. The limitations of this study included an inadequate number of enrolled patients and the possibility of incomplete data due to its retrospective nature. As the mortality rate and complications between patients with and without thrombocytopenia were not analyzed in our study, a future study is warranted to investigate this aspect.

In conclusion, the prevalence of thrombocytopenia in the medical ICU was 8.9% and was associated with a mortality rate of 67.0%. Infection was the most common cause of thrombocytopenia. Patient's age ≥ 80 years old and a low nadir Hb were associated with a higher mortality rate.

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