Zagazig University Medical Journals
www.zumj.journals.ekb.eg

FREQUENCY, PATTERN AND PROGNOSTIC SIGNIFICANCE OF THROMBOCYTOPENIA IN MEDICAL INTENSIVE CARE UNITS

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ABSTRACT

Background: The 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.

Objective: The purpose of this study to determine the period prevalence of thrombocytopenia whether admission thrombocytopenia (AT) or new onset thrombocytopenia (NOT) among Egyptian patients in medical ICU of Zagazig university hospital. To identify pattern of thrombocytopenia in critically ill patients including etiology, severity and timing pattern. To identify the impact of thrombocytopenia on the patients' outcome in MICU.

Methods: This study was conducted in the Medical Intensive Care Unit (MICU) of the Internal Medicine Department Zagazig University Hospitals, Egypt, in the period extending from March 2017 to March 2018.

Results: The study included 400 patients admitted consecutively to MICU of internal medicine hospital in Zagazig university fulfilling the inclusion criteria, sixty-six patients were excluded from the study because of incomplete data (17 patients), loss of follow up within the ICU (24 patient). 359 patients were eligible for analysis, those patients were classified into two groups.

Conclusion: Thrombocytopenia is a frequent laboratory finding among critically in patients, which is generally correlated to the severity of illness. Most cases of thrombocytopenia are detected at time of admission and the rest of them develop during ICU stay. Among our Egyptian patients the most common cause of thrombocytopenia on admission is the chronic liver disease with liver cirrhosis, while the most common cause of thrombocytopenia which develop during ICU stay is sepsis. Thrombocytopenia is generally associated with higher APACHE II score when compared to normal platelet count indicating that it is associated with higher degree of morbidity and expected higher mortality rate.

Key words; Thrombocytopenia, Frequency, Pattern, Prognostic Significance, Heparin; Intensive care units; Mortality

INTRODUCTION

Thrombocytopenia is commonly defined as a platelet count of $<150\times10^9$/L[1]. Some authors apply a cut off of 100×10^9/L for ICU patients[2], and others further specify platelet counts of 50×10^9/L as severe thrombocytopenia[3]. Absolute platelet counts alone are not sufficient to characterize thrombocytopenia in critically ill patients; also, the time course of platelet counts provides important information. For example, a platelet count decline of > 50% compared to the baseline value can be normal after cardiac surgery, but if it occurs in the second week of ICU treatment, it may reflect pathologic platelet count courses[4]. This should prompt further diagnostic workup, even if the absolute platelet count is still within a range not associated with a substantial increase in the bleeding risk. The same applies if there is an absence of a platelet count rise within 5 days after ICU admission. Therefore, a

comprehensive definition of thrombocytopenia platelet counts, platelet nadir, and course of the platelet count during the ICU stay[5].

Thrombocytopenia is well recognized in critically ill patients and is a risk factor for mortality. A systematic review of thrombocytopenia in critically ill patients reported that its frequency varied widely, with some studies describing rates of more than 50%. Common limitations of the identified studies included variable definitions of thrombocytopenia, small sample sizes (many studies were single center) [3].

A low platelet count is a frequently encountered hematological abnormality in patients treated in intensive care units (ICUs). Although severe thrombocytopenia (platelet count <20 × 109/l) can be associated with bleeding, even moderate-degree thrombocytopenia is associated with organ failure and adverse prognosis. The etiology for thrombocytopenia in ICU is often multifactorial and correcting one etiology may not normalize the low platelet count[6].

Thrombocytopenia in ICU patients has been associated with adverse outcomes such as prolonged length of hospital stay and decreased survival. However, many of these studies were retrospective and performed in European or North American ICUs[7]. Because, the incidence and prognostic significance of new onset thrombocytopenia (NOT) in Asians is not known, Lim et al designed a study to investigate the incidence of NOT, including Heparin-Induced Thrombocytopenia (HIT), in a cohort of Korean medical ICU patients and to examine its impact on outcomes, they found that new onset thrombocytopenia was associated with longer ICU stay and increased mortality among Koreans.

One approach to identify potential causes of thrombocytopenia that require specific interventions is to consider the dynamics of platelet count changes. The relative decrease in platelet counts within the first 3 to 4 days after major surgery is informative about the magnitude of the trauma or blood loss, whereas the dynamic of the platelet count course thereafter shows whether or not the in ICU patients should include the absolute physiologic compensatory mechanisms are working. A slow and gradual fall in platelet counts developing over 5 to 7 days is more likely to be caused by consumptive coagulopathy or bone marrow failure, whereas any abrupt decrease (within 1–2 days) in platelet counts manifesting after an initial increase in platelet counts approximately 1 to 2 weeks after surgery strongly suggests immunologic causes, including heparin-induced thrombocytopenia, other drug induced immune thrombocytopenia, and post transfusion purpura[8].

Thrombocytopenia is common in ICU patients during the first 4 days and is correlated with the severity of the underlying illness or tissue damage. A poor prognosis is indicated by platelet counts that do not recover or show a progressive decrease 5 days after admission. The most common causes for a low platelet count in ICU patients are sepsis, massive tissue trauma, and DIC. Treatment should target the underlying disease. In most circumstances, the risk of bleeding associated with thrombocytopenia is lower than expected in critically ill patient sand platelet transfusions are only indicated in bleeding patients or before invasive interventions[5].

Thrombocytopenic patients have a higher prevalence of bleeding, greater transfusion requirements, a longer ICU stay, and higher mortality. Sequential measurements of platelet counts are readily available markers of disease progression. A drop in platelet count is an unfavorable prognostic sign and needs urgent clarification. In medical ICU patients, newly acquired thrombocytopenia is mostly associated with septic shock, bacteremia, or DIC[9].

PATIENTS AND METHODS

- This study was conducted in the Medical Intensive Care Unit (MICU) of the Internal Medicine Department Zagazig University Hospitals, Egypt, in the period extending from March 2017 to March 2018.
- **Type of study:** Prospective cohort study

Patients:

The study included 400 patients admitted consecutively to MICU of internal medicine hospital in Zagazig university fulfilling the inclusion criteria, sixty-six patients were excluded from the study because of incomplete data (17 patients), loss of follow up within the ICU (24 patient). 359 patients were eligible for analysis, those patients were classified into two groups according to platelet count on admission:

- **Group I: Patients with normal platelet count on admission (**≥150×10^9/L**)**

Included 227 patients (63.2%), 99 of them (43.6%) were males and the remaining 128 (56.4%) were females, their ages range from 18 to 92 years with mean age 59 ± 17.4 years. These patients were classified into two subgroups according to the occurrence of thrombocytopenia during ICU stay into**:**

- **Group Ia: Patients with persistently normal platelet count:** Included 170 patients (47.4%), 76 of them (44.7%) were males and the remaining 94 (55.3%) were females, their ages range from 18 to 90 years with mean age 58 ± 17.3 years.
- **Group Ib: Patients who developed thrombocytopenia during ICU stay (New onset thrombocytopenia, NOT) (< 150 × 10^9/L):** Included 57 patients (15%), 23 of them (40.3%) were males and the remaining 34 (59.7%) were females, their ages range from 18 to 92 years with mean age 63 ± 17 years.
- **Group II: Patients with thrombocytopenia on admission:** Included 132 (36.8%) patients, seventy-two (54%) of them were males and the remaining 60 (45.5%) were females, their ages range from 20 to 89 years with mean age 59 ± 14 years.

Inclusion criteria:

- Patient admitted to medical ICU because of any medical emergency.
- Age ≥ 18 year of both sex

Exclusion criteria:

- The patient previously admitted to the ICU during the period of study.
- Incomplete data or loss of follow up while in ICU.
- Refusal of patient or his relatives to participate in the study.

- **<u>Ethical clearance:</u>**

Written informed consent was taken from the patients or the first degree relative to participate in the study. Approval for performing the study was obtained from internal medicine and medical biochemistry department, Zagazig University Hospitals after taking Institutional Review Board (IRB) approval (IRB:1940/9-3-2015).

Methods

- All patients of this study were subjected to the following assessment.

(I) <u>Full history and thorough physical examination:</u>

This was taken from the patient or his first degree relative according to the included work sheet with emphasis on emergency problems of patients during admission to the ICU and their chronic medical problems, thorough medical examination was conducted with special attention to pulse, body temperature, heart rate, respiratory rate, mental status and blood pressure which was measured by mercury sphygmomanometer with the patient recumbent in bed with arm supported and positioned at the level of the heart.

(II) <u>Routine investigations:</u> including

A. Routine laboratory investigations:

All these investigations were done according to methods applied in the clinical pathology and laboratories of Zagazig University hospitals and included:

- blood smear
- Complete blood count (by automated blood counter).

Platelet count during routine CBC was assessed immediately after admission to MICU and then every other day during ICU stay.

Thrombocytopenia was defined as platelet count < 150 × 10^9/L, then we classified patients with thrombocytopenia into various grades of severity according to the degree of thrombocytopenia **(Sharma B, et al 2007)**:

- Mild thrombocytopenia (platelet count <150 - 100× 10^9/L)
- Moderate thrombocytopenia (platelet count <100 - 50× 10^9/L)
- Severe thrombocytopenia (platelet count < 50 - 20× 10^9/L)
- Very severe thrombocytopenia (platelet count <20 × 10^9/L)

- Liver function tests: serum bilirubin (total and direct), serum albumin, serum alanine transferase and aspartate transferase measured by kinetic method **(Thomas, 1998).**
- Renal function tests: serum creatinine (Henry, 1974), serum urea by colorimetric method **(Fawcett and Scott, 1960)**.
- Bleeding profile: INR, Prothrombin Time (PT) and Partial Thromboplastin Time (PTT).
- Random Blood Glucose.
- Arterial blood gases (ABG) and acid base balance.

Other routine investigations: include

- Pelvi-abdominal ultrasonography.
- Any other investigations needed during ICU stay.

(III) Severity assessment:

By using one of the most commonly used scoring systems in patients with critical illness in ICU which is **APACHE II score**. Acute Physiology And Chronic Health Evaluation II is a severity-of-disease classification system (Knaus et al., 1985), one of several ICU scoring systems. The APACHE II is measured during the first 24 h of ICU admission; the maximum score is 71. A score of 25 represents a predicted mortality of 50% and a score of over 35 represents a predicted mortality of 80%. The APACHE II severity score has shown a good calibration and discriminatory value across a range of disease processes and remains the most commonly used international severity scoring system worldwide.

(IV) Follow up: until discharge from ICU for: CBC every other day, ICU mortality, Duration of ICU stay

RESULTS

Table 1 Demographics and baseline clinical and laboratory characteristics and outcome of study patients:

		Mean	Std. Deviation
Age (year)		59	16.3
Pulse (beat/min.)		93	12
Temperature (^{o}C)		37.3	0.6
MAP (mmHg)		88	24
DBP (mmHg)		72	19
SBP (mmHg)		119	35
Platelets (× 10^{9}/L)		204	125
Hemoglobin (g/dl)		10.2	2.9
Hematocrit %		29.8	8.7
WBC (× 10^{9}/L)		13.9	11.5
Creatinine (mg/dl)		2.9	3.2
AST (U/L)		54	82
ALT (U/L)		36	62
Total protein (g/dl)		6.6	4
Albumin (g/dl)		2.9	0.8
Bilirubin (mg/dl)		1.6	3.1
ICU Days (day)		9.2	8
APACHE II SCORE		17.3	6.7
		No.	%
Gender	Male	171	47.6%
	Female	188	52.4%
Fate	Survived	220	61.3%
	Deceased	139	38.7%

Table 2 Causes of ICU admission among study population:

	Frequency	Percent
Uremia	59	15.50%
Hepatic Encephalopathy	51	14.20%
Variceal bleeding	45	12.50%
Cerebral Infarction	42	11.70%
Intracranial hemorrhage	19	5.30%
Heart Failure	17	4.70%
Respiratory Failure	17	4.70%
Septic Shock	12	3.30%
Acute LRTI	11	3.10%
Hyperglycemic coma	11	3.10%
PUD	10	2.80%
Hypovolemic shock	9	2.50%
Hematological Malignancy	6	1.70%
Acute Coronary Syndrome	4	1.20%
Rapid AF	4	1.10%
SLE	4	1.10%
Aplastic Anemia	3	0.80%
CNS infection	3	0.80%
HRS	3	0.80%
ITP	3	0.80%
Poisoning	3	0.80%
Status epilepticus	3	0.80%
DVT+PE	2	0.60%
GBS	2	0.60%
HELLP	2	0.60%
Lower GI Bleeding	2	0.60%
Ulcerative Colitis	2	0.60%
Acute Pancreatitis	1	0.30%
DIC	1	0.30%
Hemophilia	1	0.30%
Hypoglycemic coma	1	0.30%
Moexedema coma	1	0.30%
Myathenia Gravis	1	0.30%
Neuroleptic Malignant Synd.	1	0.30%
Hypercalcemia	1	0.30%
Pleural effusion	1	0.30%
Sickle Cell Anemia	1	0.30%

Table 3 Demographics and baseline clinical and laboratory characteristics of the two main groups of study:

	Normal Platelet count on admission (No.= 227)			Admission Thrombocytopenia (No. = 132)				
	Mean ± Stand. Deviation			Mean ± Stand. Deviation			t	P
Age (year)	59.2	±	17.4	58.7	±	14.4	0.25	0.801
Pulse (beat/min.)	94	±	12	92	±	13	0.94	0.348
Temperature (^{o}C)	37.4	±	0.5	37.1	±	0.7	1.28	0.201
MAP (mmHg)	91	±	26	82	±	17	3.63	**<0.001**
DBP (mmHg)	75	±	21	68	±	15	3.48	**<0.001**
SBP (mmHg)	124	±	39	110	±	24	3.69	**<0.001**
Platelets (× 10^9/L)	274	±	103	83	±	37	20.70	**<0.001**
Hemoglobin (g/dl)	10.6	±	3.0	9.3	±	2.6	4.13	**<0.001**
Hematocrit %	31.4	±	9.0	27.3	±	7.6	4.40	**<0.001**
WBC (× 10^9/L)	13.6	±	6.9	14.3	±	12.6	-0.23	0.819
Creatinine (mg/dl)	3.2	±	3.3	2.4	±	3.1	2.39	**0.017**
AST (U/L)	48	±	84	65	±	79	-1.84	0.067
ALT (U/L)	35	±	72	37	±	42	-0.27	0.790
Total protein (g/dl)	6.6	±	4.0	6.4	±	4.3	0.45	0.657
Albumin (g/dl)	3.1	±	0.8	2.6	±	0.6	6.39	**<0.001**
Bilirubin (mg/dl)	1.0	±	1.7	2.8	±	4.4	-5.38	**<0.001**

		No.	%	No.	%	X^2	P value
Gender	Male	99	43.6%	72	54.5%	4.00	**0.046**
	Female	128	56.4%	60	45.5%		

Table 4 Prevalence of admission and new onset thrombocytopenia in the study.

	Frequency	Percent
Admission thrombocytopenia (Group II)	132	36.8 %
New onset thrombocytopenia (Group Ib)	57	15.8 %
Total thrombocytopenia	189	52.6 %
Persistently Normal platelet count (Group Ia)	170	47.4 %
Total	359	100%

Table 5 Prevalence of early and late new onset thrombocytopenia

	No.	Percent
Early NOT	18	31.6%
Late NOT	39	68.4%
Total NOT	57	100%

Table 6 Frequency of total thrombocytopenia in the different age groups among study population

		Thrombocytopenia		Normal platelet count		X^2	P value
		No.	%	No.	%		
Age Groups (years)	<40	27	55.1%	22	44.9%	2.033	0.566
	40-59	47	48.5%	50	51.5%		
	60-79	84	45.9%	99	54.1%		
	≥80	12	40.0%	18	60.0%		
Total		170	47.4%	189	52.6%		

Table 7 Comparison of demographics and baseline clinical and laboratory characteristics between total thrombocytopenic patients and the patient with persistently normal platelet count:

	Persistently Normal Platelet count (No.= 170)			Total Thrombocytopenia (No. = 189)				
	Mean ± Stand. Deviation			Mean ± Stand. Deviation			**t**	**P**
Age (year)	58	±	17	60	±	15	-1.22	0.223
Pulse (beat/min.)	92	±	12	94	±	13	-1.32	0.187
Temperature (^oC)	37.4	±	0.4	37.3	±	2.8	0.46	0.645
SBP (mmHg)	128	±	38	111	±	29	4.78	**<0.001**
DBP (mmHg)	77	±	20	68	±	17	5.0	**<0.001**
MAP (mmHg)	94	±	25	82	±	21	5.05	**<0.001**
Platelets ($\times 10^9$/L)	292	±	105	125	±	81	16.95	**<0.001**
Hemoglobin (g/dl)	10.6	±	2.8	9.8	±	3	2.67	**0.008**
Hematocrit %	31	±	8.6	28.7	±	8.8	2.67	**0.008**
WBC ($\times 10^9$/L)	14.1	±	6.3	14.5	±	11.2	-0.16	0.873
Creatinine (mg/dl)	3.4	±	3.5	2.5	±	2.9	2.75	**0.006**
AST (U/L)	40	±	59	67	±	97	-3.05	**0.002**
ALT (U/L)	29	±	40	42	±	7	-1.92	0.056
Total protein (g/dl)	6.37	±	0.97	6.14	±	1.06	2.16	**0.032**
Albumin (g/dl)	3.1	±	0.8	2.7	±	0.7	4.98	**<0.001**
Bilirubin (mg/dl)	0.9	±	1.8	2.3	±	3.9	-4.10	**<0.001**
	No.		**%**	**No.**		**%**	***X*²**	**P value**
Gender Male	76		44.7%	95		50.3%	1.11	0.292
Female	94		55.3%	94		49.7%		

***Table* 8** Comparison between different groups and subgroups of the study regarding demographics and baseline clinical and laboratory characteristics and outcome:

		Persistently Normal platelet count (n=170)			**New onset thrombocytopenia (n=57)**			**Thrombocytopenic on admission (n=132)**			**F**	**P value**
		Mean ± Stand. Deviation			Mean ± Stand. Deviation			Mean ± Stand. Deviation				
Age (year)		58	±	17.3	63	±	17.1	58.7	±	14.4	2.10	0.123
Pulse (beat/min.)		92	±	12	98	±	12 **a**	92	±	13 **b**	4.73	**0.009**
Temperature (^{o}C)		37.6	±	0.4	37.6	±	0.6	37.1	±	3.3	1.05	0.353
SBP (mmHg)		128	±	38	112	±	39 **a**	110	±	24 **a**	11.47	**<0.001**
DBP (mmHg)		77	±	20	68	±	22 **a**	68	±	15 **a**	12.15	**<0.001**
MAP (mmHg)		94	±	25	82	±	28 **a**	82	±	17 **a**	12.75	**<0.001**
Platelets ($\times 10^{9}$/L)		292	±	105	222	±	72 **a**	82	±	37 **a,b**	248.8	**<0.001**
Hemoglobin (g/dl)		10.6	±	2.8	10.7	±	3.5	9.3	±	2.6 **a,b**	8.59	**<0.001**
Hematocrit %		31.1	±	8.6	32	±	10.3	27.3	±	7.6 **a,b**	9.91	**<0.001**
WBC ($\times 10^{9}$/L)		13.6	±	6.3	13.6	±	8.5	14.2	±	11	0.026	0.974
Creatinine (mg/dl)		3.42	±	3.51	2.7	±	2.47 **a**	2.4	±	3.04 **a**	3.94	**0.020**
AST (U/L)		41	±	59	72	±	131 **a**	65	±	79 **a,b**	4.79	**0.009**
ALT (U/L)		29	±	40	53	±	124 **a**	37	±	42 **a,b**	3.18	**0.043**
Total protein (g/dl)		6.4	±	0.97	6.3	±	1.1	6.1	±	1.04 **a**	3.92	**0.021**
Albumin (g/dl)		3.1	±	0.8	3.0	±	0.8	2.5	±	0.6 **a,b**	20.64	**<0.001**
Bilirubin (mg/dl)		0.9	±	1.8	1.1	±	1.6	2.7	±	4.4 **a,b**	14.49	**<0.001**
		No.		**%**	**No.**		**%**	**No.**		**%**	X^2	**P value**
Gender	**Male**	76		44.7 %	23		40.4%	72		54.5%	4.32	0.115
	Female	94		55.3 %	34		59.6%	60		45.5%		

* **a** = **Significant difference in comparison with group of normal platelet count**

* **b = Significant difference in comparison with group of new onset thrombocytopenia**

Table 9 Frequency of different causes of thrombocytopenia among patients with admission thrombocytopenia (n=132).

	Frequency	Percent (%)
Liver cirrhosis + Hypersplenism	86	65.2
Sepsis	24	18.2
Bone marrow disease	10	7.6
SLE	3	2.3
ITP	3	2.3
Dilutional	2	1.5
DIC	2	1.5
HELLP	1	0.8
Unknown	1	0.8
Total	132	100

***Table* 10** Frequency of admission thrombocytopenia according to severity.

	Frequency	**Percent**
Very Severe (platelet count <20 $\times 10^{9}$/L)	18	13.6%
Sever (platelet count <50 - 20 $\times 10^{9}$/L)	8	6.1%
Moderate (platelet count <100 - 50 $\times 10^{9}$/L)	57	43.2%
Mild (platelet count <150 - 100 $\times 10^{9}$/L)	49	37.1%
Total	**132**	**100.0%**

Table 11 Frequency of different causes of thrombocytopenia among patients with new onset thrombocytopenia (NOT) (n=57).

	Frequency	Percent (%)
Sepsis	22	38.6 %
Dilutional	18	31.6 %
Drug induced	10	17.5 %
DIC	3	5.3 %
Unknown	4	7 %
Total	57	100%

Table 12 Frequency of new onset thrombocytopenia according to severity (n=57):

	Frequency	Percent
Very Severe (platelet count <20 $\times 10^9$/L)	3	5.3%
Sever (platelet count <50 - 20 $\times 10^9$/L)	4	7%
Moderate (platelet count <100 - 50 $\times 10^9$/L)	20	35.1%
Mild (platelet count <150 - 100 $\times 10^9$/L)	30	52.6%
Total	**57**	**100.0%**

Table 13 Comparison of severity and outcome of the two main groups of study:

		Normal Platelet count on admission (No.= 227)			Admission Thrombocytopenia (No. = 132)				
		Mean ± Std. Deviation			Mean ± Std. Deviation			**t**	**P**
ICU Days (day)		10	±	8.8	7.5	±	6	3.07	**0.002**
APACHE II Score		17.2	±	6.8	17.3	±	6.6	-0.08	0.940
		No.		**%**	**No.**		**%**	**X^2**	**P**
Fate	**Survived**	135		59.5%	85		64.4%	0.85	0.356
	Deceased	92		40.5%	47		35.6%		

Table 14 Comparison of severity and outcome between different groups and subgroups of the study:

		Persistently Normal platelet count (n=170)			**New onset thrombocyte-openia (n=57)**			**Admission Thrombocytopenia (n=132)**			**F**	**P**
		Mean ± Standard Deviation			**Mean ± Standard Deviation**			**Mean ± Standard Deviation**				
ICU Days (day)		8.9	±	7.9	13.9	±	10	7.5	±	6	13.92	**<0.001**
APACHE II Score		16.5	±	6.5	19	±	7.3	17	±	6.6	4.13	**0.017**
		No.		**%**	**No.**		**%**	**No.**		**%**	**X^2**	**P**
Fate	**Survived**	112		65.9%	23		40.4%	85		64.4%	12.58	**0.002**
	Deceased	58		34.1%	34		59.6%	47		35.6%		

Table 15 Least significant difference between study groups regarding APACHE II score:

	Admission Thrombocytopenia (17±6.6)	**New onset Thrombocytopenia** (19±7.3**)**
Admission Thrombocytopenia (17±6.6)	-	**0.043 ***
Persistently Normal Platelet Count (16.5±6.5**)**	0.306 (NS)	**0.004 ****

(NS): Non significant - (*): Significant - (**): Highly significant

***Table* 16** Least significant difference between study groups regarding ICU days:

	Admission Thrombocytopenia (7.5±6 day)	**New onset thrombocytopenia (13.9±10 day)**
Admission Thrombocytopenia (7.5±6 day)	-	**<0.001 ****
Persistently Normal Platelet Count (8.9±7.9 day)	0.09 (NS)	**0.01 ***

(NS): Non significant - (*): Significant - (**): Highly significant

Table 17 Comparison of fate between study groups and subgroups**.**

	Admission Thrombocytopenia (mortality rate= 35.6%)	**New onset thrombocytopenia (mortality rate= 59.6%%)**
Admission Thrombocytopenia (mortality rate= 35.6%)	-	**0.002 ****
Persistently Normal Platelet Count (mortality rate= 34.1%)	0.788 (NS)	**<0.001 ****

(NS): Non significant - (*): Significant - (**): Highly significant

***Table* 18** Comparison of severity and outcome between total thrombocytopenic patients and the patient with persistently normal platelet count

		Persistently Normal Platelet count (No.= 170)			Total Thrombocytopenia (No. = 189)				
		Mean ± Stand. Deviation			Mean ± Stand. Deviation			**t**	**P**
ICU Days (day)		8.9	±	8	9.5	±	8	-0.64	0.526
APACHE II Score		16	±	6	18	±	7	-2.03	**0.043**
		No.		**%**	**No.**		**%**	X^2	**P**
Fate	**Survived**	112		65.9%	108		57.1%	2.88	0.090
	Deceased	58		34.1%	81		42.9%		

Table 19 Comparison of the patients' fate in relation to the cause of Thrombocytopenia among total thrombocytopenic patients (n=189).

	Patients Fate				X^2	P value
	Survived		Deceased			
	No.	%	No.	%		
Liver cirrhosis+ Hypersplenism	60	69.8%	26	30.2%	**42.96**	**<0.001**
Sepsis	10	21.7%	36	78.3%		
Dilutional	12	60.0%	8	40.0%		
Bone marrow disease	7	70.0%	3	30.0%		
Drug induced	9	90.0%	1	10.0%		
SLE	3	100.0%	0	0.0%		
DIC	2	40.0%	3	60.0%		
HELLP	1	100.0%	0	0.0%		
ITP	3	100.0%	0	0.0%		
Unknown	1	20.0%	4	80.0%		
Total	108	57.1%	81	42.9%		

Table 20 Comparison of the patients' fate in relation to the onset of thrombocytopenia during ICU stay (NOT).

		Patient Fate		X^2	P value
		Survived	Deceased		
NOT	Early	11 (61.1%)	7 (38.9%)	4.71	**0.03**
	Late	12 (30.8%)	27 (69.2%)		

Table 21 Comparison of patients' fate in relation to severity of new onset thrombocytopenia during ICU stay.

		Nadir Platelet count	t	P value
		Mean (± Standard deviation)		
NOT (n=57)	Survived (n=23)	93 (±39)	-0.561	0.577
	Deceased (n=34)	99 (±40)		

Table 22 Comparison between early and late NOT regarding duration of ICU stay

		ICU days		t	P value
		Mean	Standard deviation		
NOT	Early (n=18)	8.7	6.3	-2.744	**0.008**
	Late (n=39)	16.5	11.3		

Table (27): Relative risk of mortality between NOT and patient with persistently normal platelet count.

	Deceased	Survived	Total
NOT	34	23	57
Normal	58	112	170

***Table* 23** Relative risk of mortality between patient with admission thrombocytopenia and patient with persistently normal platelet count.

	Deceased	Survived	Total
AT	47	85	132
Normal	58	112	170

***Table* 24** Relative risk of mortality between patient with admission thrombocytopenia and patient with new onset thrombocytopenia.

	Deceased	Survived	Total
NOT	34	23	57
AT	47	85	132

***Table* 25** Relative risk of mortality between total patient with thrombocytopenia and patient with persistently normal platelet count.

	Deceased	Survived	Total
Thrombocytopenia	81	108	189
Normal Platelet Count	58	112	170

***Table* 26** Relative risk of mortality between Late and early new onset thrombocytopenia.

	Deceased	Survived	Total
Late NOT	27	12	39
Early NOT	7	11	18

DISCUSSION

A low platelet count is a common encountered hematological abnormality frequently encountered in critical patients in intensive care units (ICUs). Although very severe thrombocytopenia (platelet count <20 $\times 10^9$/L) can be associated with bleeding, even moderate-degree thrombocytopenia is associated with organ failure and adverse prognosis[6].

Thrombocytopenia is the most common coagulation disorder in the ICU with a prevalence of 15 to 60% depending on the cutoff used for defining thrombocytopenia (150 or 100 $\times 10^9$/L), studied population, duration and the course during ICU stay[10]. The incidence may also differ depending on the predominant clinical presentations dealt with in each ICU, that can vary in different centres (e.g. cardiac surgery centers versus liver transplantation units) and on the type of care provided (surgical, medical or mixed) [1].

Many investigators evaluated the problem of thrombocytopenia in the critically ill patients and its impact on their outcomes among western countries, for example[11,12,13,14]. Also some Asian studies were conducted for studying the same problem among Asian critical patients[7,15].

Among Egyptian patients, the thrombocytopenia was studied in 2011 among small number of patients (70) admitted to Cairo university hospital with multiorgan failure[10], also **Mohammad et al**[17] had evaluated thrombocytopenia and its impact on patients' outcomes among 50 patients admitted to respiratory intensive care unit (RICU) in Ain Shams university hospital, no other known studies had studied thrombocytopenia in Egyptian critical patients.

Because of the restricted locality (Cairo governorate) in Egypt and the restricted study sample (small number with specific illness) of the previous Egyptian studies, we have designed this study to determine the period prevalence of thrombocytopenia (both admission and newly occurring thrombocytopenia in ICU) among larger number of critically ill patients in Sharkia governorate admitted to our medical ICU in Zagazig university hospitals, those patients were admitted with different diagnoses, also we aimed to detect the pattern of this thrombocytopenia regarding the etiology, severity and timing of occurrence. Finally, we tried to determine the impact of thrombocytopenia on patients outcome and if it has a prognostic significance or not.

This prospective cohort study had been carried out in our medical ICU of internal medicine department in the period from March 2017 to March 2018. Out of **400** patients who were included in this study who were chosen consecutively during this period of time **41** patients were excluded due to incomplete data or loss of follow up and the

remaining **359** patients were included in the study.

Our study revealed that the prevalence of thrombocytopenia (platelet count **<150 ×109/L**) among critically ill patients at admission is **36.8%** and the new onset thrombocytopenia represents **15.8%** giving the total prevalence of thrombocytopenia about **52.6%**. Some previous studies had shown variable figures, **Khurana et al[1]. (2017)** revealed that thrombocytopenia in ICU (including both at time of admission and occurring in ICU stay) represents **37.6%** of cases, while **Lim et al[7]** has found that the incidence of new-onset thrombocytopenia in ICU was **37.1%** after exclusion of the patients with admission thrombocytopenia, while smaller incidence was determined in a large scale Canadian cohort study which was conducted in mixed coronary, medical, general and surgical ICUs, including 20,696 patients. This Canadian study showed prevalence of thrombocytopenia on admission in **13.3%** of patients and incident thrombocytopenia, occurred during ICU stay, in **7.8%** of patients[12]. This controversial result can be explained by studying thrombocytopenia at lower level (considering thrombocytopenia when platelet count <100 $\times10^9$/L), resulting in considering all patients with mild thrombocytopenia (platelet count between 150 $\times10^9$/L and 100 $\times10^9$/L) as nonthrombocytopenic in that study[12]. An Egyptian study, which was conducted in Ain Shams university in 2014 among patients admitted to a respiratory intensive care unit (RICU) (one category of ICU patients), showed an incidence of new onset thrombocytopenia of **20%** (10/50 cases) after exclusion of the patients with thrombocytopenia on admission[17].

Vanderschueren et al[18] detected that **41%** of the patients admitted to medical ICU reported thrombocytopenia (platelet count <150 $\times10^9$/L) during their ICU stay at least once. So, the prevalence of thrombocytopenia is different in different ICU according not only to patients' number but also due to the underlying disease of admission and different drugs that are used during ICU stay, so we have to look for the drug that may affect platelet count in ICU.

We found in our study that the majority **(80%)** of patients admitted with thrombocytopenia had mild or moderate thrombocytopenia (platelet count ≥50 $\times10^9$/L), while the remaining **(20%)** of patients had severe or very severe admission thrombocytopenia (platelet count <50×10^9/L or <20×10^9/L respectively) and in those developed new onset thrombocytopenia during their ICU stay, **87.7%** of them had mild or moderate thrombocytopenia, while **12.3%** of them had severe or very severe thrombocytopenia. Generally, platelet count <50 $\times10^9$/L (severe and very severe thrombocytopenia) was found in **9.2%** (33/359) of our study patients.

Comparable results were found in previous study by **Marco-Schulke et al[19]**, who found that the prevalence of severe thrombocytopenia (platelet count <50 $\times10^9$/L) among critically ill patients was **6.3%** (37 of 587 cases) and its incidence was associated with serum albumin level, serum bilirubin level and sepsis, also **Stanworth et al[3]** found in a multicenter observational study in UK that severe thrombocytopenia (platelet count <50×10^9/L) documented in about 4.1% (78/1881) of critically ill patients in the first 24 hour of ICU admission, and **Mark et al[20]** had detected severe thrombocytopenia in 3.5% of their critical patients. Different result was detected by **Vandijck et al[11]**, who found that **41.8%** of their patient with thrombocytopenia had platelet count <50×10^9/L (thrombocytopenia was severe in 28.4% and very severe in 13.4%), this different result most probably was due to different nature of admission disease, they selected patients with documented nosocomial bloodstream infection so the prevalence of sepsis among those patients was very high.

In our study we found that liver cirrhosis with hypersplenism, sepsis and bone marrow disease were the commonest causes of admission thrombocytopenia (65.2%, 18.2% and 7.6% respectively), the same causes (but in different order) were found by **Vanderschueren et al[18]**, who had found that sepsis, liver disease with hypersplenism, primary hematologic disorder and medication (other than cytotoxic drugs) were the

commonest causes of thrombocytopenia in their critically ill patients (47.8%, 18.4%, 8.8% and 8.8% respectively). This difference may be due to the higher prevalence of chronic liver disease in our critically ill patients compared to its prevalence in those critically ill Belgian patients explaining that liver disease and cirrhosis with hypersplenism was the commonest cause of thrombocytopenia among our patients.

Maan et al[16] stated that the prevalence of thrombocytopenia in chronic liver diseases ranges from 6 % among non-cirrhotic patients with chronic liver disease to 70 % among patients with liver cirrhosis, so the high percentage of liver cirrhosis **(65.2%)** as a cause of admission thrombocytopenia was due to the high prevalence of liver cirrhosis among our study egyptian patients including those admitted due to complications of liver cell failure **(27.6%)** or any other medical emergency, these complications included hepatic encephalopathy, variceal bleeding and hepatorenal syndrome (HRS) (14.2%, 12.5% and 0.8% respectively).

The frequency of thrombocytopenia among 100 Egyptian patients with chronic hepatitis C virus as studied by **Mohamed**[21] was 24/100 (24%), mild thrombocytopenia was the commonest grade (17%) then moderate one (6%) and lastly severe thrombocytopenia (1%). The percentages of different thrombocytopenia grades are higher among the decompensated cirrhotic patients of our study who were constituting high percentage of patients admitted either due to liver cirrhosis complication (variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis or hepatorenal syndrome) or any other medical emergency.

In this study we found that the mortality rate among all patients with thrombocytopenia was **42.9%** (**35.6%** in patients with admission thrombocytopenia and **59.6%** in patients who developed thrombocytopenia during ICU stay), similar to our results, the mortality rate in critically ill patients with thrombocytopenia was found to be **44%** (22/50) by **Khurana and Deoke**[15], also **Lim et al**[7] detected that mortality rate among those who developed new onset thrombocytopenia was **36.2%** compared to a rate of 10.3% among the non-thrombocytopenic patients in their Korean study. In most previous studies there was generally an association between thrombocytopenia and increased ICU mortality rate[4,12,17].

In our study there was no significant impact for thrombocytopenia in general on ICU stay and mortality compared to patients **with normal platelet** count, while we found that total thrombocytopenia (both admission thrombocytopenia and new onset thrombocytopenia) had slightly increased (RR) of mortality by 1.3 folds than those with persistently normal platelet count. Similar results were found by **Dunaiceva et al**[22]**.** They did not find statistically significant difference in ICU mortality between patients with thrombocytopenia and without thrombocytopenia (30 [52.6%] VS 14 [34.1%], P=0.099), also they did not find significant difference in ICU stay duration between the two group (7 [3-18] VS 7 [3-14], P=0.908).

We found that there is no impact of admission thrombocytopenia among our patients on ICU stay duration and ICU mortality compared to patients with normal platelet count (7.5±6 **VS** 8.9±7.9 and 35.6% **VS** 34.1%, P=0.09 & 0.788 respectively), also we did not find any increase in relative risk (RR) of mortality in admission thrombocytopenia (AT) patients compared to those with persistently normal platelet count. In contrast to our results, **Hariharan and Paddle**[23] found that there is a correlation between low admission platelet counts and adverse outcome, and they have demonstrated that the correlation between platelet count and predicted mortality exists across the spectrum of platelet values. This different result may be due to different patients' characteristics and main causes of admission. In our study the prevalence of chronic liver disease was high and it was responsible for most cases of admission thrombocytopenia, that was not found in **Hariharan and Paddle study**.

The current study identified that NOT was associated with longer ICU stay and higher ICU mortality rate compared to both admission thrombocytopenia (AT) and normal platelet count, also we found that

NOT had increased (RR) of mortality by 1.7 fold than AT, indicating that NOT has a prognostic significance associating with poorer outcomes. Similar results were obtained by **Mark et al[20], Elgohary et al[10] and Lim et al[7]** who identified that NOT was associated with longer ICU stay and higher ICU mortality when compared to patients without thrombocytopenia. In contrast to our results, **Khurana and Deoke[15]** found statistically insignificant higher mortality rate among patients who had thrombocytopenia on admission (AT) than those who developed it later during hospital stay (NOT), out of 39 patients who presented with thrombocytopenia on admission, 19 patients (48%) died during the hospitalization and those who developed thrombocytopenia later on during the hospitalization mortality rate was 27.3% among them (P = 0.20).

Also, **Vanderschueren et al[18]** found that 18 of 193 patients (9.3%) who never became thrombocytopenic died in the ICU vs. 31 of 89 patients (34.8%) who were thrombocytopenic at admission (p <0.001) and vs. 15 of 47 patients (31.9%) who developed thrombocytopenia during ICU stay (p = 0.002), but there was insignificant difference between thrombocytopenic at admission and those with NOT regarding mortality rate. The difference between our results and that obtained by others may be due to their small sample size of their study (50 patients) and also the difference in causes of admission as most of our patients had chronic liver disease.

Furthermore, our study revealed that the late occurrence of NOT (after 48 hours of admission) was associated with poorer outcome including longer ICU stay (8.7 VS 16.5 days, P=0.008) and higher rate of ICU mortality (69.2% VS 38.9%, P=0.03) when compared to early onset NOT (within 48 hours of admission), also we found that late NOT increased (RR) of mortality by 1.8 fold than early NOT. This comparison between early and late thrombocytopenia during ICU stay was done before by **Akca et al[24]** when they found that late thrombocytopenia is more predictive of death than early thrombocytopenia.

In our study we detected that among causes of newly developed thrombocytopenia (NOT) sepsis was the commonest cause and also the cause associated with the highest mortality rate **(78.3%)** which is consistent with **Lim et al[7]** who stated that sepsis with DIC was the most frequent cause of NOT with 46 patients (66.7 %), followed by drug-induced thrombocytopenia (18.8%), HIT (2.9%), and liver disease (1.4%). In seven patients, the cause of thrombocytopenia could not be determined, in this study sepsis related thrombocytopenia had adverse outcome. This study has several limitations including: Lack of long term outcome assessment, Inclusion of patients with different diagnoses, specially patients with stroke who require long ICU stay.

CONCLUSION

Thrombocytopenia is a frequent laboratory finding among critically in patients, which is generally correlated to the severity of illness. Most cases of thrombocytopenia are detected at time of admission and the rest of them develop during ICU stay.

Among our Egyptian patients the most common cause of thrombocytopenia on admission is the chronic liver disease with liver cirrhosis, while the most common cause of thrombocytopenia which develop during ICU stay is sepsis.

Thrombocytopenia is generally associated with higher APACHE II score when compared to normal platelet count indicating that it is associated with higher degree of morbidity and expected higher mortality rate.

The admission thrombocytopenia was associated with shorter ICU stay without increased mortality in comparison with persistently normal platelet count, but patients who developed thrombocytopenia during ICU stay had longer durations of admission and higher mortality rate than both patients with admission thrombocytopenia and those with persistently normal platelet count.

The late onset of thrombocytopenia during ICU stay (during first 48 hours of admission) was associated with poorer outcome than its early onset.

Immediate detection of thrombocytopenia among critically ill patients specially that develop during ICU stay and proper urgent

management of main morbidity causes to improve outcome.

Further studies in different centers (large scale) is necessary to assess impact of thrombocytopenia on long term outcome focusing on specific causes of admission among Egyptian patients.

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How to Cite This Article: Khalil OA, Yousif MM, Abdallah AA, Morad MH, Abdel-Rahman EA and Elgendy SA. Frequency, Pattern and Prognostic Significance of Thrombocytopenia in Medical Intensive Care Units. ZUMJ 2019; 25 (1); 132-148.