Research Paper: Risk Factors of Hospital-acquired Thrombocytopenia in Toxicological Intensive Care Unit

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ABSTRACT

Background: Platelet count is a readily available biomarker predicting disease severity and risk of mortality in the intensive care units (ICU). This study aims to describe the frequency, to assess the risk factors, and to evaluate the impact of thrombocytopenia on patient outcomes in a Toxicological ICU (TICU).

Methods: In this prospective observational Cohort study, we enrolled 184 patients admitted to our TICU from October 1st, 2019, to August 23rd, 2020. Mild/moderate and severe thrombocytopenia were defined as at least one platelet counts less than $150 \times 10^3/\mu\text{L}$ and $50 \times 10^3/\mu\text{L}$ during the ICU stay, respectively.

Results: Of 184 enrolled patients, 45.7% had mild to moderate thrombocytopenia and 5.4% had severe thrombocytopenia. Old age (OR: 1.042, 95%CI: 1.01-1.075, $P=0.01$), male gender (OR: 4.348, 95%CI: 1.33-14.22, $P=0.015$), increased international normalized ratio (INR) levels (OR: 3.72, 95%CI: 1.15-11.2, $P=0.028$), and administration of some medications including heparin (OR: 3.553, 95%CI: 1.11-11.36, $P=0.033$), antihypertensive drugs (OR: 2.841, 95%CI: 1.081-7.471, $P=0.034$), linezolid (OR: 13.46, 95%CI: 4.75-38.13, $P<0.001$), erythromycin (OR: 19.58, 95%CI: 3.23-118.86, $P=0.001$), and colistin (OR: 10.29, 95%CI 1.44-73.69, $P=0.02$) were the risk factors of hospital-acquired thrombocytopenia. The outcomes of patients with normal platelet count were significantly better than those who developed thrombocytopenia ($P<0.001$).

Conclusion: We found that thrombocytopenia could develop in almost 50% of patients admitted to TICU, which is associated with poor prognosis. Additionally, the platelet counts should be closely monitored to administer some medications (heparin, antihypertensive drug, and linezolid), especially in old patients.

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1. Introduction

Thrombocytopenia, defined as a reduction of platelet counts lower than $150000/\mu\text{L}$, is a concerning issue in the intensive care unit (ICU) [1-5]. Platelet count is a readily available biomarker predicting disease severity and risk of mortality in the ICU [1, 6, 7]. Based on some studies, the frequency of low platelet counts is between 15% and 58%, which can vary according to thrombocytopenia definition and clinical setting [3, 8, 9]. During ICU stay, developing thrombocytopenia is more associated with prognostic significance than low platelet counts on admission [10].

There have been some mechanisms generally attributed to thrombocytopenia, including decreased bone marrow production, sequestration usually in an enlarged spleen, and increased platelet distraction/consumption [11]. Additionally, this disorder can be precipitated due to some reasons, such as [12] nutritional insufficiency (folate deficiency), human immunodeficiency virus, chemotherapy or cytotoxic medications, infections, endocarditis, chronic liver diseases (cirrhosis), inflammatory diseases, metabolic disorders (hypercalcemia, hyperuricemia), tumor necrosis syndrome, and renal failure. Furthermore, based on Goldfrank's Toxicologic Emergencies and Harrison's Principles of Internal Medicine, some chemicals and medications can decrease the platelet count. These chemicals and medications include alcohol, diazepam, lorazepam, digoxin, valproate, carbamazepine, vancomycin, linezolid, penicillin, ranitidine, acetaminophen, and imipramine [11, 13]. Some of these medicines are routinely administered in ICUs [14], especially in toxicological ICUs (TICUs), which is a place that many patients are admitted with overdoses of mentioned medicines.

Spontaneous bleeding into vital organs, including the gastrointestinal tract, brain, heart, and adrenal glands, is the primary manifestation of thrombocytopenia, which may necessitate platelet transfusions [15]. Some studies assessed the risk factors of developing thrombocytopenia retrospectively [16-18]. The administration of heparin, vancomycin, nonsteroidal anti-inflammatory drugs before ICU admission, dialysis during the ICU stay, sepsis syndrome/septic shock, liver function abnormalities, and hemodynamic instability are the main risk factors attributed to this homeostatic disorder.

This study aimed to describe the frequency, to assess the risk factors, and to evaluate the impact of thrombocytopenia on patient outcomes in TICU.

2. Materials and Methods

2.1. Study design and participants

This prospective observational cohort study was conducted in the TICU of Lohman-Hakim Hospital in Tehran, Iran. The studied hospital is a unique tertiary care teaching and referral poison treatment center with an average of 25000 inpatients and outpatients annually. Consecutive patients admitted to the TICU from October 1st, 2019, to August 23rd, 2020, were eligible for the study if they were aged 12 years or older and expected to be in the TICU for more than 72 hours. The exclusion criteria included thrombocytopenia (platelet counts $<150 \times 10^3/\mu\text{L}$) [17] on admission, and also the history of platelet disorders (e.g., idiopathic thrombocytopenic purpura, congenital thrombocytopenia, hypersplenism), hematologic malignancies, use of chemotherapy (in the last 30 days before admission), and mechanical heart valves.

For data analysis, thrombocytopenia was defined as at least one platelet counts less than $150 \times 10^3/\mu\text{L}$ and severe thrombocytopenia as at least one platelet counts less than $50 \times 10^3/\mu\text{L}$ during the ICU stay [17]. Therefore, 84 thrombocytopenic patients were designated as the case group, and 100 patients with no record of platelet count less than $150 \times 10^3/\mu\text{L}$ on admission and during ICU stay were designated as the control group. The informed consent was obtained from the patients or their next of kin. The study was approved by the Ethics Review Committee in Research Deputy Department of Shahid Beheshti University of Medical Sciences, Tehran, Iran (REC Code: IR.SBMU.RETECH.REC.1398.368).

Demographic data (age, sex, underlying disease), type of poisoning, vital signs, glomerular filtration rate (GFR), paraclinical factors, ICU and poison ward length of stay, medications in a period of ICU stay, all complications during ICU stay, and outcomes were recorded for all patients. Lab tests were assessed at baseline, including complete blood count (white blood cells [WBCs], red blood cells [RBCs], hemoglobin [Hb], hematocrit [Hct], platelets [PLTs]), liver enzymes (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]), sodium, potassium, albumin, bilirubin-total, urea, creatinine (Cr), creatine phosphokinase (CPK), prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR). PLTs were also re-

corded daily throughout the treatment course. GFR was calculated using the Cockcroft-Gault formula [19].

2.2. Statistical analysis

The statistical analysis was performed in SPSS v. 18, Chicago, Ill, USA). The categorical variables were expressed as frequency (percentage) and numerical variables as Mean $\pm$ SD. The categorical variables were univariately compared using the χ^2 test and other quantitative variables using the student's t test. A P value of less than 0.05 was considered statistically significant. Multivariable logistic regression using backward likelihood ratio (LR) selection procedure was used to determine the independent predictors of thrombocytopenia incidence. The dependent variable was thrombocytopenia occurrence (condition of platelet counts less than $150 \times 103/\mu\text{L}$ during the ICU stay). The independent variables were selected for submission to the model if the univariate P value was <0.05 and had less than 10% missing data. The following variables were submitted to the model: age, gender, dialysis demand, the incidence of rhabdomyolysis or anuria or oliguria, prescription of heparin, antihypertensive medications, or antibiotic medications (ciprofloxacin, linezolid, meropenem, erythromycin, colistin, levofloxacin), body temperature of patients on admission, level of AST, ALT, potassium, urea, creatinine, CPK, PT, INR, GFR, and duration of ventilation. For the determination of severe thrombocytopenia predictors, we conducted a binary logistic regression. The platelet counts less than $50 \times 103/\mu\text{L}$ during the ICU stay was the dependent variable, and age, gender, level of INR, and prescription of heparin or linezolid were independent variables. The goodness of fit of the models was assessed using the area under the receiver Operator Characteristic Curve (ROC) calculation and the Hosmer-Lemeshow chi-square statistic.

3. Results

3.1. Baseline characteristic

One hundred and eighty-four patients (124 men and 60 women with a Mean $\pm$ SD age of 39.43 ± 16.27 years) were included in this study. A total of 84 (45.7%) and 10 (5.4%) patients precipitated mild/moderate and severe thrombocytopenia during ICU stay, respectively. Univariate analysis revealed a significant difference in some baseline characteristics between patients who developed thrombocytopenia (case group) and those who did not (control group) (Table 1). Patients in the case group were significantly older than patients in the control group (42.012 ± 16.1 vs 37.26 ± 16.21 years, $P=0.048$). Among

different patients admitted to the Loghman-Hakim Hospital Poison Center, those who were poisoned by methadone, were more likely to be thrombocytopenic ($P=0.001$). Besides, methadone poisoning was significantly higher in male patients (57 [46.0%] in male vs 7 [11.7%] in female, $\chi^2=21$, $P<0.001$). Complications such as rhabdomyolysis ($P=0.017$), acute tubular necrosis ($P=0.03$), pulmonary thromboembolism ($P=0.007$), cardiac arrest ($P=0.29$), anuria or oliguria ($P=0.015$) and dialysis demand ($P=0.002$) seemed to be associated with thrombocytopenia. Some of the medications increased the risk of thrombocytopenia. These medications include fentanyl ($P=0.019$), norepinephrine ($P=0.039$), antihypertensive drugs ($P=0.049$), heparin ($P=0.006$), erythromycin ($P=0.012$), amphotericin B ($P=0.002$), ciprofloxacin ($P=0.036$), colistin ($P=0.002$), linezolid ($P<0.001$), meropenem ($P=0.031$), and levofloxacin ($P=0.007$). The analysis revealed that concomitant administration of erythromycin and methadone was significantly higher in patients who develop thrombocytopenia than those who did not (8 [88.9%] vs 1 [11.1%] respectively, $\chi^2=7.1$, $P=0.008$). Furthermore, data revealed that body temperature at the time of administration ($P=0.01$) and the serum levels of AST ($P=0.013$), potassium ($P=0.008$), creatinine ($P=0.002$), urea ($P=0.01$), CPK ($P=0.039$), and the level of PT ($P=0.002$), and INR ($P=0.002$) in patients who developed thrombocytopenia were significantly higher than those who did not. The ICU length of stay ($P=0.021$), the number of cases needed mechanical ventilation ($P=0.029$), and also duration of ventilation ($P<0.001$) were higher in patients who developed thrombocytopenia compared to patients with normal platelet count.

3.2. Outcome

The patients in the control group had more favorable outcomes than those who suffered from thrombocytopenia (Table 1). The rate of death was significantly higher in patients who developed severe or mild to moderate thrombocytopenia compared to those who did not ($P<0.001$), whereas the number of cured patients in the control group was significantly higher than thrombocytopenic patients ($P<0.001$).

3.3. Multivariable analysis

The multivariable logistic regression model for mild to moderate and severe thrombocytopenia occurrence is depicted in Table 2. The independent predictors of mild to moderate thrombocytopenia were age (OR: 1.042, 95%CI: 1.01-1.075, $P=0.01$), gender (OR: 4.348, 95%CI: 1.33-14.22, $P=0.015$), level of INR at the time

Table 1. Univariate analysis of baseline characteristics of 184 patients

Demographics		No. (%) / Mean±SD			P
		Control (n=100)	Case (n=84)	Statistic/ χ^2 /t	
	Age (y)	37.26±16.21	42.012±16.1	t=1.99	0.048
Gender,	Male	58 (46.8)	66 (53.2)	$\chi^2=8.8$	0.003
	Female	42 (70)	18 (30)		
Poisoning	Benzodiazepine	52 (61.9)	32 (38.1)	3.5	0.059
	Methadone	24 (37.5)	40 (62.5)	11.23	0.001
	Tramadol	10 (55.6)	8 (44.4)	0.012	0.914
	Amphetamine	10 (52.6)	9 (47.4)	0.025	0.874
	Aluminum phosphide	7 (46.7)	8 (53.3)	0.388	0.533
	Opiate	18 (54.5)	15 (45.5)	0.001	0.98
	Tricyclic antidepressant	5 (71.4)	2 (28.6)	0.856	0.355
Medication history	Heart medications	4 (30.8)	9 (69.2)	6.3	0.043
	Pulmonary medications	0 (0)	2 (100)	11.06	0.004
	Neurological medications	8 (34.8)	15 (65.2)	7.07	0.029
	Gastrointestinal medications	0 (0)	1 (100)	3.076	0.215
	Sedative medications	4 (36.4)	7 (63.6)	9.99	0.007
Complications during ICU stay	Sepsis	5 (38.5)	8 (61.5)	1.4	0.233
	Rhabdomyolysis	18 (39.1)	28 (60.9)	5.72	0.017
	Acute tubular necrosis (ATN)	1 (14.3)	6 (85.7)	4.71	0.03
	Deep vein thrombosis (DVT)	3 (30)	7 (70)	2.53	0.112
	Pulmonary thromboembolism	0 (0)	6 (100)	7.38	0.007
	Disseminated intravascular coagulation (DIC)	2 (66.7)	1 (33.3)	0.187	0.67
	Multiple organ failure (MOF)	1 (33.3)	2 (66.7)	0.543	0.461
	Cardiac arrest	9 (34.6)	17 (65.4)	4.75	0.029
	Acute respiratory distress syndrome	9 (52.9)	8 (47.1)	0.015	0.903
	Anuria or oliguria	14 (36.8)	24 (63.2)	5.915	0.015
	Dialysis	9 (29)	22 (71)	9.63	0.002
Medications during ICU stay	Midazolam	80 (51.6)	75 (48.4)	2.5	0.112
	Acetaminophen	21 (53.8)	18 (46.2)	0.005	0.944
	Gabapentin	0 (0)	3 (100)	3.63	0.057
	Vitamin B6	7 (23.3)	23 (76.7)	13.9	<0.001
	Vitamin K	4 (66.7)	2 (33.3)	0.38	0.54

Demographics	No. (%) / Mean±SD			P
	Control (n=100)	Case (n=84)	Statistic/ χ^2 /t	
Folic acid	4 (66.7)	2 (33.3)	0.38	0.54
Pulmonary medications	22 (66.7)	11 (33.3)	2.46	0.117
Diabetic medications	12 (66.7)	6 (33.3)	1.22	0.27
Ranitidine	70 (50.7)	68 (49.3)	2.92	0.087
Pantoprazole	41 (51.2)	39 (48.8)	0.547	0.459
Anti-vomiting	31 (50)	31 (50)	0.712	0.399
Fentanyl	76 (50.3)	75 (49.7)	5.47	0.019
Methadone	35 (47.3)	39 (52.7)	2.48	0.115
Norepinephrine (NEP)	16 (40)	24 (60)	4.24	0.039
Furosemide	14 (41.2)	20 (58.8)	2.92	0.088
Antihypertensive medications, No. (%)	30 (44.8)	37 (55.2)	3.9	0.049
Clopidogrel	1 (25)	3 (75)	1.42	0.233
Heparin	67 (48.6)	71 (51.4)	7.48	0.006
Aspirin	8 (66.7)	4 (33.3)	0.758	0.376
Amikacin	14 (45.2)	17 (54.8)	1.27	0.26
Erythromycin	6 (28.6)	15 (71.4)	6.35	0.012
Acyclovir	1 (20)	4 (80)	2.44	0.118
Ampicillin-Sulbactam	9 (52.9)	8 (47.1)	0.015	0.903
Piperacillin-Tazobactam	7 (36.8)	12 (63.2)	2.62	0.106
Amphotericin B	1 (9.1)	10 (90.9)	9.5	0.002
Cefazolin	2 (66.7)	1 (33.3)	0.187	0.66
Ceftazidime	5 (35.7)	9 (64.3)	2.12	0.145
Ciprofloxacin	27 (43.5)	35 (56.5)	4.4	0.036
Ceftriaxone	45 (50)	45 (50)	1.34	0.247
Clindamycin	49 (51)	47 (49)	0.884	0.347
Colistin	8 (33.3)	16 (66.7)	4.91	0.027
Linezolid	15 (22.1)	53 (77.9)	45.32	<0.001
Meropenem	46 (46.9)	52 (53.1)	4.64	0.031
Imipenem	18 (72)	7 (28)	3.63	0.057
Teicoplanin	4 (36.4)	7 (63.6)	1.52	0.217
Levofloxacin	4 (23.5)	13 (76.5)	7.17	0.007
Vancomycin	45 (60)	30 (40)	1.63	0.202

Demographics		No. (%) / Mean±SD			P
		Control (n=100)	Case (n=84)	Statistic/ χ^2 /t	
Medications during ICU stay	Gentamycin	4 (80)	1 (20)	1.36	0.243
	Valproate	7 (87.5)	1 (12.5)	3.7	0.054
	Dexamethazone	31 (45.6)	37 (54.4)	3.34	0.068
	Haloperidol	13 (72.2)	5 (27.8)	2.57	0.109
	Tranexamic acid	0 (0)	2 (100)	2.407	0.121
	Amiodaron	1 (33.3)	2 (66.7)	0.543	0.461
Vital sign (range)	Temperature (°C)	37.06±0.388	37.24±0.532	t=2.6	0.01
	Heart rate (/min)	93.14±18.1	93.96±20.2	t=0.292	0.771
	Respiratory rate (/min)	16.45±4.2	15.71±5.3	t=1.05	0.294
	Systolic pressure (mm Hg)	114.01±21.36	114.47±25.3	t=0.134	0.89
	Diastolic pressure (mm Hg)	70.49±14.04	69.36±16.94	t=0.496	0.62
Paraclinical factor (range)	Oxygen saturation (%)	93.94±5.9	93.4±7.2	t=0.561	0.575
	WBC($\times 10^3/\mu\text{L}$)	11.65±4.9	12.13±6.1	t=0.36	0.71
	RBC($\times 10^6/\mu\text{L}$)	4.78±0.73	4.77±0.76	t=0.037	0.971
	Hb (g/dL)	14.01±2.57	14.48±2.53	t=1.23	0.22
	Hct (%)	42.093±6	42.77±6.9	t=0.711	0.48
	PLT($\times 10^3/\mu\text{L}$)	83.66±230.36	295.05±732.47	t=2.54	0.013
	AST (U/L)	70.25±197.66	612.42±2542.7	t=1.95	0.055
	ALT (U/L)	137.83±3.7	138.2±3.5	t=0.695	0.488
	Sodium (mEq/L)	4.05±0.56	4.35±0.87	t=2.7	0.008
	Albumin b (g/dL)	3.82±0.55	3.63±0.65	t=1.36	0.177
	Bilirubin-Total (mg/dL)	1.06±0.8	1.23±1.31	t=0.94	0.35
	Creatinine (mg/dL)	1.25±0.54	1.65±1.03	t=3.2	0.002
	Urea (mg/dL)	39.32±25.57	52.44±39.37	t=2.62	0.01
	Creatine phosphokinase (U/L)	1681.97±5099.02	3817.4±7823.1	t=2.09	0.039
	Alkaline phosphatase (U/L)	206.16±109.93	193.27±55.17	t=1.004	0.317
	Prothrombin time (s)	13.45±3.01	14.83±2.7	t=3.135	0.002
	Partial thromboplastin time (s)	32.28±9.74	34.41±11.83	t=1.3	0.198
	International normalized ratio	1.19±0.37	1.44±0.63	t=3.17	0.002
	ICU length of stay, Mean±SD, d	14.83±12.39	19.44±14.12	t=2.33	0.021

Demographics		No. (%) / Mean±SD			P
		Control (n=100)	Case (n=84)	Statistic/ χ^2 /t	
	Poison Ward length of stay, Mean±SD, d	2.68±3.54	2.89±7.62	t=0.249	0.803
	Duration to admit, Mean±SD, d	7±5.6	11.29±16.1	t=1.3	0.2
Paraclinical factor (range)	Mechanical ventilation, No. (%)	68 (44.7)	84 (55.3)	$\chi^2=4.8$	0.029
	Duration of ventilation, Mean±SD, d	10.86±12.87	18.38±14.5	t=3.65	<0.001
	GFR, Mean±SD, mL/min	74.64±23.75	65.13±29.53	t=2.37	0.019
Mild to moderate thrombocytopenic patients' outcome	Cure	83 (83)	42 (50)	22.82	<0.001
	Cure with sequel	2 (2)	5 (6)	1.95	0.163
	Death	15 (15)	37 (44)	18.99	<0.001
Severe thrombocytopenic patients' outcome	Cure	124 (71.3)	1 (10)	16.29	<0.001
	Cure with sequel	7 (4)	0 (0)	0.42	0.52
	Death	43 (24.7)	9 (90)	19.88	<0.001

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of admission (OR: 3.72, 95%CI: 1.15-11.2, P=0.028), and prescription of some medicines, including linezolid (OR: 13.46, 95%CI: 4.75-38.13, P<0.001), heparin (OR: 3.553, 95%CI: 1.11-11.36, P=0.033), erythromycin (OR: 19.58, 95%CI: 3.23-118.86, P=0.001), colistin (OR: 10.29, 95%CI: 1.44-73.69, P=0.02), and antihypertensive medications (OR: 2.841, 95%CI: 1.081-7.471, P=0.034). The independent predictors of severe thrombocytopenia were age (OR: 1.04, 95%CI: 1.002-1.078,

P=0.036) and prescription of linezolid (OR: 4.19, 95%CI: 1.022-17.15, P=0.047).

The goodness of fit of the models was assessed using the area under the receiver ROC calculation and the Hosmer-Lemeshow chi-square statistic. Both regression models for mild/moderate and severe thrombocytopenia fitted well. The area under the ROC for mild/moderate thrombocytopenia model was 0.89 (95%CI: 0.844-0.936, P<0.001), and for severe thrombocytopenia mod-

Table 2. Multivariable logistic regression model for hospital-acquired mild/moderate and severe thrombocytopenia

Independent Variables	<150000/mm ³ (mild to moderate)			Independent Variables	<50000/mm ³ (Severe)		
	OR	95% CI	P		OR	95% CI	P
Age	1.042	1.01-1.075	0.01	Age	1.04	1.002-1.078	0.036
Gender	4.348	1.33-14.22	0.015	Linezolid	4.19	1.022-17.15	0.047
International normalized ratio. admit	3.72	1.15-12	0.028	-	-	-	-
Antihypertensive medication	2.841	1.081-7.471	0.034	-	-	-	-
Heparin	3.553	1.11-11.36	0.033	-	-	-	-
Erythromycin	19.58	3.23-118.86	0.001	-	-	-	-
Colistin	10.29	1.44-73.69	0.02	-	-	-	-
Linezolid	13.46	4.75-38.13	<0.001	-	-	-	-

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Figure 1. Receiver-operator characteristic (ROC)

Curve for the multivariable logistic regression model for the prediction of (A) hospital-acquired mild/moderate thrombocytopenia and (B) hospital-acquired severe thrombocytopenia.

el was 0.753 (95%CI: 0.598-0.908, $P=0.007$) (Figure 1). The Hosmer-Lemeshow chi-square statistic for the mild/moderate thrombocytopenia model was 5.11 ($P=0.745$), and for the severe thrombocytopenia model was 9.31 ($P=0.317$).

4. Discussion

Thrombocytopenia, as the most prevalent hematological disorder in ICU, is a well-known life-threatening complication that has a substantial prognostic significance related to the patient's outcome [3, 8, 9, 14]. Based on some studies, the prevalence of thrombocytopenia was reported to be 15%-85% during the ICU stay depending on the study population, which was consistent with our findings. Different poisons, including alcohol, opioid, sedative-hypnotic drugs, heavy metals, aluminum phosphide, and also the prescription of some medications like antibiotics (including linezolid, vancomycin, β -Lactams, rifampin, fluoroquinolones) during TICU stay might result in thrombocytopenia [20-26]. According to our multivariate model, age, gender, INR levels, administration of heparin, antihypertensive medications, and some antibiotics, including linezolid, erythromycin, and colistin, were the main predictors of mild to moderate thrombocytopenia. Furthermore, age and linezolid prescription were the only factors that increased the risk of severe thrombocytopenia.

The platelet count was relatively stable in middle-aged people, whereas it might drop in older people [27]. It is well documented that aging affects platelet count and function, which originate from the change in the hema-

topoietic tissue, vascular health, and blood composition. Thrombocytopenia was more prevalent in male patients. The heterogeneity in the cause of poisoning between men and women might explain this finding. For instance, methadone poisoning was significantly higher in male patients, and thrombocytopenia was more prevalent in patients with methadone poisoning. It was similar to previous studies, which indicated that methadone might result in thrombocytopenia, especially in old age men [28].

Antihypertensive drugs like thiazide diuretics and angiotensin receptor blockers might induce thrombocytopenia through the reduction of the Renin-angiotensin System (RAS) activation, myelosuppression, and the acceleration of immune-mediated platelet destruction [29, 30].

Heparin-induced Thrombocytopenia (HIT) is an immune system response in which the platelet factor 4 (PF4) forms an immune complex with heparin and immunoglobulin G (IgG). The formed immune complex binds to the platelet surface receptors which results in platelet destructions and thrombocytopenia [31, 32]. Besides, heparin could result in elevated INR levels [33] as it was observed in thrombocytopenic patients (case group).

It was suggested that antibiotics lead to Drug-induced Thrombocytopenia (DIT) through the direct myelosuppression and immune-mediated platelet destruction [26]. As we observed in this study, linezolid and colistin have the potential to induce thrombocytopenia [26, 34]. It was frequently reported that the oxazolidinones, e.g., linezolid, may result in peripheral destruction of thrombocytes. Baseline platelet count, creatinine clearance, and end-

stage renal disease are the main risk factors of linezolid-induced thrombocytopenia [35-37]. In a case report, the thrombocytopenia was manifested in a 5-year-old female following a colistin prescription. After exclusion of all other probable causes, it was revealed that the colistin was the causative factor for thrombocytopenia development. Furthermore, the levels of thrombocytes returned to normal following the discontinuation of colistin [34].

Thrombocytopenia is not determined as an adverse effect of erythromycin; however, this drug is a cytochrome P450 3A4 inhibitor which could interact with some medications that are cytochrome substrates [38] and thrombocytopenia is their adverse effects like methadone [39, 40]. Similar to previous studies, we showed that the concomitant administration of erythromycin and methadone (a medication with thrombocytopenia induction potential) [28] was significantly higher in patients who develop thrombocytopenia than those who did not.

Previous studies showed that thrombocytopenia occurrence during ICU stay was accompanied by poor prognosis [4, 41]. Strauss R. et al. (2002) reported that the risk of bleeding in mild to moderate thrombocytopenia was three times and in severe thrombocytopenia was six times higher than those with normal counts of platelets [4]. In this study, the data revealed that the outcomes of patients with hospital-acquired thrombocytopenia were poor. Both mild/moderate and severe thrombocytopenia were significantly associated with increased mortality rates.

5. Conclusion

In conclusion, the frequency of mild/moderate and severe thrombocytopenia was 45.7% and 5.4%, respectively. The main risk factors of thrombocytopenia in TICU were old age, male gender, increased INR levels at the time of admission, administration of heparin, antihypertensive medications, and antibiotics, including linezolid, erythromycin, and colistin. Moreover, the main factors which may predict severe thrombocytopenia are old age and linezolid administration. Therefore, the platelet counts should be monitored closely to administer the mentioned medications, especially in old patients. Further prospective studies with large sample sizes are needed to conduct more detailed investigations about the factors that predict the development of thrombocytopenia in TICU.

Ethical Considerations

Compliance with ethical guidelines

The study protocol was approved by the Ethics Review Committee in Research Deputy Department of Shahid Beheshti University of Medical Sciences, Tehran, Iran (REC Code: IR.SBMU.RETECH.REC.1398.368).

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Author's contributions

All authors were equally contributed in preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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