# Assessment of thrombocytopenia in critically ill patients

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***Background*** Thrombocytopenia is commonly observed among critically ill patients.

***Aim*** The aim of this study was to evaluate the incidence, risk factors, and the outcome of thrombocytopenia in patients admitted to the respiratory intensive care unit (RICU).

***Materials and methods*** Data were collected from 50 adult patients admitted to the RICU in a 6-month period. The baseline platelet count was measured and was repeated every other day during the RICU stay period. Thrombocytopenia was defined as platelet count of less than 150´10$^9$/l.

***Results*** The incidence of thrombocytopenia was 20% (10 patients). The overall mortality was 16%, of which 50% of the patients were having thrombocytopenia. The thrombocytopenic group had a higher mortality (40 vs. 10%, $P < 0.05$), a lower admission platelet count (215.3 ± 85.6 vs. 252.8 ± 73.2, $P < 0.05$), a lower nadir platelet count (111.1 ± 22.6 vs. 213.9 ± 53.2, $P < 0.001$), an increased transfusion requirement (30 vs. 2.5%, $P < 0.05$), and increased septic shock (40 vs. 2.5%, $P < 0.05$) compared with the nonthrombocytopenic group. Comorbidities, indications for RICU admission, the length of RICU stay, mechanical ventilation, days on mechanical ventilation, admission severity scores, bleeding, ICU-related complications, and medications administrated during the RICU stay did not differ significantly. A prolonged RICU stay of more than 15 days carried a 4.7 times higher incidence of development of thrombocytopenia. Thrombocytopenia differed significantly between survivors and nonsurvivors ($P < 0.05$), with a significant effect on mortality ($P = 0.034$).

***Conclusion*** Thrombocytopenia is common among critically ill patients and affects the mortality significantly. Prolonged ICU stay and septic shock are among the risk factors for thrombocytopenia. *Egypt J Broncho* 8:143–148


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**Keywords:** critically ill, ICU, platelets, respiratory intensive care unit, thrombocytopenia

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## Introduction

Thrombocytopenia is defined as a platelet count of less than 150 × 10$^9$/l [1–5]. The various comorbidities in the severely ill patient affect platelet homeostasis, and consequently, thrombocytopenia is very common in critically ill patients treated in the ICU. Furthermore, thrombocytopenia in critically ill patients is associated with an increased duration of hospital stay and increased mortality [3,4,6–9].

This study aimed at evaluating the incidence, risk factors, and the outcome of thrombocytopenia in patients admitted to the respiratory intensive care unit (RICU).

## Materials and methods

This prospective observational study was conducted on all adult patients admitted to the RICU of both Ain Shams University Hospital and Abbassia Chest Hospital more than 72 h in the period between January 2012 and July 2012. For all patients, demographic data, comorbidities, detailed medical history taking (from the patients or relatives), thorough clinical examination, routine laboratory investigation, plain chest radiography, baseline arterial blood gases analysis, primary diagnosis, and the cause of admission to the RICU were documented. Recording of complications and interventions during the RICU stay were performed for all patients including the duration of RICU stay, mechanical ventilation (MV), days of MV, bleeding, and the need for blood transfusion. The severity of illness was evaluated with first-day scores including the Acute Physiology and Chronic Health Evaluation II (APACHE II) score [10], the Sequential Organ Failure Assessment (SOFA) score [11], Simplified Acute Physiology Scores II (SAPS II) [12], and the Multiple Organ Dysfunction Score (MODS) [13]. For all patients, estimation of the first-day baseline platelet count was performed and was repeated every other day during the whole period of RICU stay using Horiba ABX micros 60, Sysmex, and Medonic (San Diego, USA), with identification of the day of occurrence of thrombocytopenia±the day of occurrence of bleeding, and the day of blood or platelet transfusion. A normal platelet count was regarded as platelet count of at least 150 × 10$^9$/l. Thrombocytopenia was defined as platelet count of less than 150 × 10$^9$/l [1–5]. The nadir platelet count refers to the lowest platelet count recorded during the RICU stay. Patients were divided into two groups: the thrombocytopenia group with a platelet count of less than 150 × 10$^9$/l at any time during

their RICU stay and the nonthrombocytopenia group with a platelet count of at least 150 × $10^9$/l. Exclusion criteria included patients with thrombocytopenia on admission, a history of platelet disorders, hematological malignancies, splenectomy, recent radiotherapy and/or chemotherapy, or patients on bone marrow-platelet suppressive agents. The study was approved by the institutional ethics committee.

### Statistical analysis

Parametric numerical data were expressed as mean ± SD, whereas nonparametric numerical data were expressed as median, interquartile range, frequency, and percentage. The Student *t*-test was used to assess the statistical significance of the difference between two study group means. The Mann–Whitney *U*-test was used to assess the statistical difference of nonparametric variables between two study groups. The $\chi^2$-test was applied to examine the relationship between two qualitative variables. The Fisher exact test was used to examine the relationship between two qualitative variables when the expected count was less than 5 in more than 20% of cells. Logistic regression was applied to predict the presence or the absence of an outcome on the basis of a set of independent variables. Statistical significance was set at *P* value less than 0.05. Statistical analyses were performed utilizing the Statistical Package for Social Sciences software (SPSS for Windows, version 15.0; SPSS Inc., Chicago, Illinois, USA).

## Results

During the 6-month study period, 50 patients were admitted to the RICU. Table 1 shows the baseline characteristics and the outcome of all included patients. The mean ± SD age was 54.3 ± 14.7 years, with a range of 25–86 years: 29 (58%) patients were male and 21 (42%) were female. The major indication for RICU admission was respiratory failure (32 cases). Patients had a median first-day APACHE II score of 20, a median first-day SOFA score of 4, a median first-day SAPS II of 40, and a median first-day MODS of 5. The median duration of RICU stay was 7 days; 31 cases were mechanically ventilated with 5 days' median duration of MV. RICU mortality was 16%, of which 50% of the cases were thrombocytopenic. Thrombocytopenia developed in 10 (20%) patients. A total of six patients (12% of the study population) experienced a bleeding event, four of which were among patients with thrombocytopenia. Other ICU-related complications included septic shock in five patients, acute respiratory distress syndrome in three patients, and ventilator-associated pneumonia in one patient. Blood transfusion was required in four patients, and three of them were patients with thrombocytopenia. All patients under study were receiving drugs that cause thrombocytopenia: 14 patients received unfractionated heparin (UFH) and 11 patients received low-molecular-weight heparin (LMWH); drugs inducing thrombocytopenia other than UFH and LMWH included antimicrobials (penicillin, cephalosporins, rifampicin, vancomycin), NSAIDs, and antacids (ranitidine).

**Table 1 Baseline characteristics and outcomes of all patients**

| Variables | Values |
|---|---|
| Age[a] (years) | 54.3 ± 14.7 (53.5) |
| Sex (M/F) [*n* (%)] | 29/21 (58/42) |
| Admission APACHE II[a] | 20.2 ± 9.6 (20) |
| Admission SOFA[a] | 5.2 ± 4.3 (4) |
| Admission SAPS II[a] | 40.1 ± 13 (40) |
| Admission MODS II[a] | 5.9 ± 3.1 (5) |
| Days in RICU[a] | 11.7 ± 12.8 (7) |
| Days in RICU [*n* (%)] (days) | |
| ≤15 | 38 (76) |
| >15 | 12 (24) |
| MV [*n* (%)] | 31 (62) |
| Days on MV[a] | 11.3 ± 15.1 (5) |
| Hemoglobin[a] | 12.7 ± 2.6 (13) |
| Total leukocytic count[a] | 12.3 ± 6 (12) |
| Co-morbidity [*n* (%)] | |
| No | 9 (18) |
| Cardiac | 33 (66) |
| Diabetes | 19 (38) |
| Hepatic | 5 (10) |
| Indication for RICU admission [*n* (%)] | |
| Respiratory failure | 32 (64) |
| Sepsis | 7 (14) |
| Lung mass | 1 (2) |
| Pleural disease | 4 (8) |
| Pulmonary embolism | 2 (4) |
| Cardiac disease | 4 (8) |
| Use of drug-induced thrombocytopenia [*n* (%)] | |
| UFH + others | 14 (28) |
| LMWH + others | 11 (22) |
| Others | 25 (50) |
| Thrombocytopenia [*n* (%)] | 10 (20) |
| Platelet count on admission | 245 ± 76.4 |
| Nadir platelet count | 193 ± 63.8 |
| Blood transfusion [*n* (%)] | 4 (8) |
| Complications [*n* (%)] | |
| Bleeding | 6 (12) |
| VAP | 1 (2) |
| ARDS | 3 (6) |
| Septic shock | 5 (10) |
| Outcome [*n* (%)] | |
| Survival | 42 (84) |
| Death | 8 (16) |

APACHE, acute physiology and chronic health evaluation; ARDS, acute respiratory distress syndrome; LMWH, low-molecular-weight heparin; MODS, multiple organ dysfunction score; MV, mechanical ventilation; RICU, respiratory intensive care unit; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment; UFH, unfractionated heparin; VAP, ventilator-associated pneumonia, [a]Data in parentheses represent median.

### Risk factors associated with the development of thrombocytopenia

The thrombocytopenic group had a higher mortality (40 vs. 10%, $P < 0.05$), a lower admission platelet count (215.3 ± 85.6 vs. 252.8 ± 73.2, $P < 0.05$), a lower nadir platelet count (111.1 ± 22.6 vs. 213.9 ± 53.2, $P < 0.001$), increased transfusion requirement (30 vs. 2.5%, $P < 0.05$), and increased septic shock (40 vs. 2.5%, $P < 0.05$) compared with the nonthrombocytopenic group. No significant difference was observed between the two groups ($P > 0.05$) in terms of age, sex, comorbidities, indication for RICU admission, the length of RICU stay, MV, days on MV, admission severity scores, baseline hemoglobin, the baseline total leukocytic count, bleeding, ventilator-associated pneumonia, acute respiratory distress syndrome, and medications administrated during the RICU stay (Table 2, Figs 1 and 2). When a cutoff of 15 days was used for the length of RICU stay, the difference was statistically significant between thrombocytopenic and nonthrombocytopenic patients ($P = 0.046$), and the risk of having thrombocytopenia among cases staying more than 15 days in RICU was 4.7 times higher.

### Factors affecting the outcome

Only thrombocytopenia affected the outcome of patients: thrombocytopenia increases significantly among nonsurvivors ($P = 0.041$). Other variables including MV and admission severity scores did not differ significantly (Table 3).

### Risk factors for ICU-acquired mortality

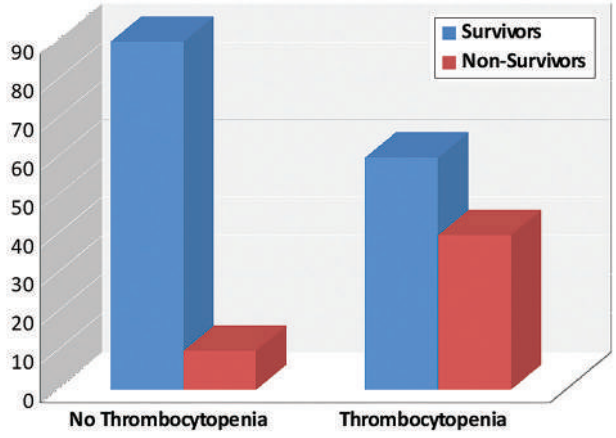
The effect of various independent factors on the primary outcome mortality was investigated using a multivariate analysis: thrombocytopenia was the only independent factor affecting mortality. Other independent factors including APACHE II, SOFA, SAPS II, and MODS did not significantly affect mortality ($P > 0.05$, Table 4).

## Discussion

Although thrombocytopenia appears as a common finding in the ICU, yet it is still unclear whether thrombocytopenia is the cause or just a risk factor for ICU-related mortality. The present study demonstrated that the incidence of thrombocytopenia of at least one platelet count of less than 150 × $10^9$/l was 20% among medical patients in RICU. A wide range for the incidence of thrombocytopenia has been presented in previous studies (13–44.1%) [4,6,9]; some results were comparable among the medical-surgical adult ICU (22.6%) [9] and the pediatric ICU (19.6%) [14]. Relatively higher results were obtained in medical adult ICUs (37.1%) [15], medical-surgical adult ICUs (40%) [16], a predominantly medical adult ICU (41%) [3], and medical adult ICUs (44%) [4]. Different types of patients under study as well as differences in the cutoff for defining thrombocytopenia likely explain this wide variation.

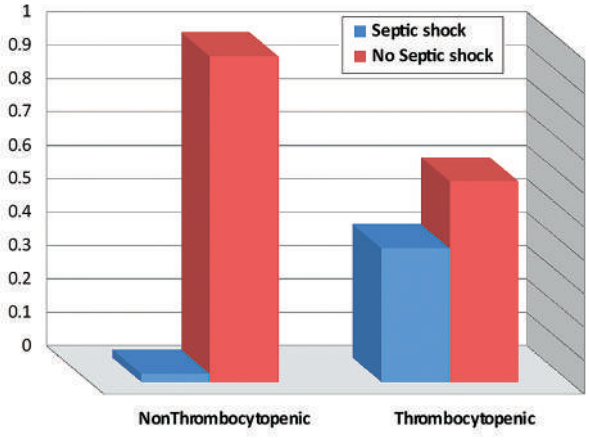
The primary outcome in this study was ICU mortality, which occurred in 16% of the cases, including 40% of thrombocytopenic patients compared with 10% of nonthrombocytopenic patients. Thus, mortality was significantly higher in the thrombocytopenic group. Similar results were obtained in other studies [3,4,8,9,14–16]. Possible explanations for the increased mortality in patients with thrombocytopenia include the following: first, thrombocytopenia is a marker of severe organ dysfunction, which is frequently seen in patients with a greater disease severity. Second, many instances of thrombocytopenia are associated with the underlying disease processes that necessitated intensive care. Third, thrombocytopenia is associated with hemostatic derangement and the complications associated with this condition such as bleeding, transfusion, and thrombosis, which may adversely affect the patient's prognosis [15].

**Fig. 1**




Comparison between the outcome in thrombocytopenic and nonthrombocytopenic patients.

**Fig. 2**




Distribution of septic shock in the study population.

Thrombocytopenia commonly results in bleeding. Accordingly, the incidence of bleeding in this study was 5% of the nonthrombocytopenic patients, but this incidence increased to 40% in patients with thrombocytopenia. All patients with thrombocytopenia who developed bleeding had a platelet count greater than $100 \times 10^9$/l on the days of occurrence of bleeding, except for one patient whose platelet count was less than $100 \times 10^9$/l on the days of bleeding. This observation was documented in another study, and a reasonable explanation was presented this study [3] through the assumption that factors other than the absolute platelet count, including associated disorders of coagulation or of platelet function and the rate and direction of change in platelet count [17,18], must be considered in assessing bleeding risk in thrombocytopenia patients. Another study in patients with hematological disorders and severe thrombocytopenia found that the mean platelet volume predicted bleeding more reliably than the platelet count [19].

Sepsis was found to be the most common risk factor for the development of thrombocytopenia in the ICU in several studies [2,5,8,20]. In our study, sepsis as an indication for RICU admission did not differ significantly between patients with or without RICU-acquired thrombocytopenia

**Table 2 A comparison between thrombocytopenic and nonthrombocytopenic patients**

| Variables | No thrombocytopenia (*n* = 40) | Thrombocytopenia (*n* = 10) | *P* |
|---|---|---|---|
| Age[a] (years) | 55.0 ± 15.2 | 51.6 ± 12.6 | 0.521 |
| Sex [*n* (%)] | | | |
| Male | 23 (57.5) | 6 (60) | 1 |
| Female | 17 (42.5) | 4 (40) | |
| Admission APACHE II[a] | 19.9 ± 9.8 | 21.6 ± 9.4 | 0.613 |
| Admission SOFA[a] | 5.3 ± 4.7 | 4.9 ± 2 | 0.782 |
| Admission SAPS II[a] | 40.1 ± 13.8 | 40 ± 9.7 | 0.983 |
| Admission MODS II[a] | 5.8 ± 3.2 | 6.5 ± 2.5 | 0.529 |
| Days in RICU[a] | 8.9 ± 5.6 | 23 ± 24 | 0.096 |
| Days in RICU [*n* (%)] (days) | | | |
| ≤15 | 33 (82.5) | 5 (50) | 0.046 |
| >15 | 7 (17.5) | 5 (50) | |
| MV [*n* (%)] | 22 (55) | 9 (90) | 0.067 |
| Days on MV[a] | 7.09 ± 6.34 | 21.56 ± 24.04 | 0.06 |
| Hemoglobin[a] | 12.5 ± 2.6 | 13.3 ± 3 | 0.457 |
| Total leukocytic count[a] | 12.5 ± 6.3 | 11.7 ± 4.5 | 0.688 |
| Indication for RICU admission [*n* (%)] | | | |
| Respiratory failure | 26 (65) | 6 (60) | 0.941 |
| Sepsis | 4 (10) | 3 (30) | 0.133 |
| Lung mass | 1 (2.5) | 0 (0) | 1 |
| Pleural disease | 4 (10) | 0 (0) | 0.571 |
| Pulmonary embolism | 1 (2.5) | 1 (10) | 0.363 |
| Cardiac disease | 4 (10) | 0 (0) | 0.571 |
| Use of drug-induced thrombocytopenia [*n* (%)] | | | |
| UFH + others | 10 (25) | 4 (40) | 0.436 |
| LMWH + others | 9 (22.5) | 2 (20) | 1 |
| Others | 21 (52.5) | 4 (40) | 0.725 |
| Thrombocytopenia [*n* (%)] | | | |
| Platelet count on admission[a] | 252.8 ± 73.2 | 215.3 ± 85.6 | 0.032 |
| Nadir platelet count[a] | 213.9 ± 53.2 | 111.1 ± 22.6 | 0.0001 |
| Blood transfusion [*n* (%)] | 1 (2.5) | 3 (30) | 0.022 |
| Complications [*n* (%)] | | | |
| Bleeding | 2 (5) | 4 (40) | 0.6 |
| VAP | 1 (2.5) | 0 (0) | 1 |
| ARDS | 1 (2.5) | 2 (20) | 0.098 |
| Septic shock | 1 (2.5) | 4 (40) | 0.004 |
| Outcome [*n* (%)] | | | |
| Survival | 36 (90) | 6 (60) | 0.041 |
| Death | 4 (10) | 4 (40) | |

APACHE, acute physiology and chronic health evaluation; ARDS, acute respiratory distress syndrome; LMWH, low-molecular-weight heparin; MODS, multiple organ dysfunction Score; MV, mechanical ventilation; RICU, respiratory intensive care unit; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment; UFH, unfractionated heparin; VAP, ventilator-associated pneumonia; [a]Data in parentheses represent median; [a]Data represent mean ± SD.

**Table 3 A comparison between patients' outcomes regarding selected variables**

| Variables | Outcomes | | *P* |
|---|---|---|---|
| | Survivors (*n* = 42) | Nonsurvivors (*n* = 8) | |
| Thrombocytopenia [*n* (%)] | 6 (14.3) | 4 (50) | 0.041 |
| MV [*n* (%)] | 24 (57.1) | 7 (87.5) | 0.134 |
| APACHE II (mean ± SD) | 24.54 ± 7.36 | 24.43 ± 11.73 | 0.975 |
| SOFA (mean ± SD) | 6.67 ± 5.29 | 6.86 ± 2.85 | 0.190 |
| SAPS (mean ± SD) | 43.92 ± 10.27 | 50.43 ± 18.70 | 0.235 |
| MODS (mean ± SD) | 6.92 ± 2.34 | 8.71 ± 3.99 | 0.141 |

APACHE, acute physiology and chronic health evaluation; MODS, multiple organ dysfunction score; MV, mechanical ventilation; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment.

**Table 4 Multivariate analysis for the effect of independent variables on mortality**

| Variables | 95% CI | OR | *P* |
|---|---|---|---|
| Thrombocytopenia | 1.213–13.081 | 141.068 | 0.034 |
| APACHE II | 0.635–0.806 | 1.024 | 0.078 |
| SOFA | 0.62–1.022 | 1.685 | 0.932 |
| SAPS | 0.899–1.057 | 1.242 | 0.503 |
| MODS | 0.931–2.014 | 4.357 | 0.075 |

APACHE, acute physiology and chronic health evaluation; CI, confidence interval; MODS, multiple organ dysfunction Score; OR, odds ratio; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment.

possibly because only seven patients were admitted to the RICU because of sepsis; these findings have not been consistent among different studies [4,14], possibly because these studies might have included more patients with sepsis. Septic shock, a RICU-acquired complication, was more common among patients with thrombocytopenia, suggesting a possible important risk factor for the development of thrombocytopenia. Our study has revealed that severity scores did not differ significantly between nonthrombocytopenic and patients with thrombocytopenia. This observation is in accordance with the insight that such scores are static, their mortality predictions based on the worst values of selected variables recorded during the initial 24 h of admission to the ICU. Consequently, these severity scoring systems do not take into consideration subsequent changes caused by the natural course of the disease or by therapy [3]. Although the authors developing MODS found that the increase in MODS over the course of ICU stay correlated better with the ICU mortality rate than the admission severity indices [13], yet only admission MODS was available in our study without daily MODS over the entire ICU period. Thus, the outcome was not only a function of the severity of the admission illness, but also of the degree of functional deterioration developed by the patient during the ICU stay period.

Although the mean length of RICU stay was not among the risk factors for the development of thrombocytopenia, yet when considering a cutoff of more than 15 days, patients were 4.7 times more at risk for the development of thrombocytopenia than patients staying in the RICU for less than 15 days.

Many drugs commonly used in the ICU can cause thrombocytopenia, and most ICU patients receive a large number of different drugs [21]. Heparin-induced thrombocytopenia is a well-described complication of heparin therapy with an incidence of 1–5% when UFH is used, but less than 1% with LMWH [22]. Surprisingly, the intake of drugs causing thrombocytopenia in our study carried no significant difference between thrombocytopenic and nonthrombocytopenic patients. These results were similar to other study [4] where the administration of drugs including heparin, penicillin, cephalosporins, and proton pump inhibitors was not.

Many previous studies have reported an association between thrombocytopenia and poor outcomes [3,9,15,23]. Our study revealed that only thrombocytopenia differed significantly between survivors and nonsurvivors. Other studies [4,14] showed a similar significant association between mortality and platelet counts, and yet in one of these studies [4], the APACHE II score differed significantly between survivors and nonsurvivors. This discrepancy could be attributed to the daily recording of APACHE II scores in this study rather than the admission APACHE II score recorded in our study. The impact of thrombocytopenia significantly affected the outcome of patients in our study. Similarly, other studies on thrombocytopenia reported that thrombocytopenia is recognized as an independent risk factor for mortality in ICU patients [3,5,7,9].

This study has the advantage of excluding patients with thrombocytopenia on admission to the RICU to evaluate the effect of the RICU on the development of thrombocytopenia. Moreover, the patients under study were medical RICU patients excluding the highest risk for the development of thrombocytopenia seen in other patients, especially in trauma cases.

In conclusion, thrombocytopenia is common in critically ill patients admitted to the RICU and was associated with increased mortality. Moreover, thrombocytopenia represents an independent predictor for mortality. Prolonged ICU stay and septic shock are among the risk factors for developing thrombocytopenia.

Finally, the recording of the baseline platelet count for critically ill patients admitted to the ICU is recommended with further continuous monitoring of the platelet count during the whole ICU stay, especially for patients with septic shock and for those with a prolonged ICU stay.

## Acknowledgements

### Conflicts of interest

There are no conflicts of interest.

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