Prevalence, Risk Factors and Outcomes of Platelet Transfusion Refractoriness in Critically Ill Patients: A Retrospective Cohort Study

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Abstract

Background: Refractoriness to platelet transfusion is an understudied phenomenon in critically ill patients. Our objective was to evaluate the prevalence, risk factors and clinical outcomes of platelet refractoriness among patients in a tertiary-care intensive care unit (ICU).

Methods: A retrospective cohort study included all patients (age >14 years) who were admitted to a tertiary-care medical-surgical ICU between 2011 and 2016 and received ≥2 platelet transfusions during their ICU stay. We calculated platelet increment (PI) and corrected count increment (CCI).

Results: A total of 267 patients were enrolled in the study, collectively receiving 1357 transfusions with a median of 3 (interquartile range: 2-6) transfusions per patient. The median pretransfusion platelet count was 31.0 x10^9/L (interquartile range: 16.0, 50.0) with a median PI of 6 x10^9/L (interquartile range: -5, 24). The prevalence of platelet transfusion refractoriness was 54.8% based on PI and 57.0% based on CCI. The two methods had excellent concordance in diagnosing refractoriness (kappa coefficient: 0.939). Refractoriness was more common in patients admitted by Hepatology, Liver Transplant, and Hematology services (69.7%, 69.2%, and 55.6%, respectively). On multivariable logistic regression, younger age was the only significant predictor of refractoriness (odds ratio per year increment: 0.975, 95% CI: 0.951-0.999). Finally, refractoriness was associated with increased length of stay in the ICU (p=0.02), but not with mortality.

Conclusions: We demonstrated excellent concordance between PI and CCI for the diagnosis of platelet transfusion refractoriness. Platelet transfusion refractoriness was highly (>50%) prevalent in critically ill patients. However, it was not associated with increased mortality.

Background

Thrombocytopenia is commonly seen in critically ill patients. Its incidence and prevalence during intensive care unit (ICU) admission have been reported to be 13-44.1% and 8.3-67.6%, respectively.[1] The variability in epidemiology reflects heterogeneity in patient characteristics and differing thrombocytopenia thresholds.[1] Thrombocytopenia is associated with increased mortality, prolonged ICU and hospital stay, bleeding as well as blood product consumption.[1, 2] Prophylactic and therapeutic platelet transfusion is a common practice in the ICU; however, patients may experience platelet transfusion refractoriness, a phenomenon in which the expected post-transfusion platelet count increment is not achieved.

Platelet transfusion refractoriness is predominantly reported in patients with hematologic disorders,[3] and its prevalence varies among studies from 10 to 34%.[4-6] The prevalence was 34% in severe aplastic anemia patients,[4] 27.6% in patients receiving multiple platelet transfusions,[5] and 10% in patients with acute myeloid leukemia receiving induction chemotherapy.[6] Causes can be immune and non-immune. Immune-mediated refractoriness is mainly due to allo-immunization to human platelet antigens and human leukocyte antigens (anti-HLA antibodies), which is more common.[7, 8] When associated with HLA
alloimmunization, refractoriness causes increased platelet requirements and delayed bleeding.[9] However, anti-HLA antibodies account for less than 30% of total causes of refractoriness,[5] and not all patients who get allo-immunized to HLA antigens develop refractoriness.[7] Strategies, such as leukocyte reduction, UV-B irradiation, and use of apheresis platelets, have reduced the incidence of immune-mediated platelet refractoriness,[6] making non-immune etiologies, such as ABO-incompatibility, transfusion of old platelets, sepsis, disseminated intravascular coagulation (DIC), splenomegaly, bleeding, and medications, underlie most cases of platelet refractoriness.[7, 10-12] Most of these factors are commonly seen in the ICU.

Irrespective of the underlying etiology, platelet transfusion refractoriness is a clinically important problem in the ICU. It has been associated with increased complications and mortality.[7, 10] However, there is paucity of studies on the prevalence and clinical significance of platelet refractoriness in the ICU setting. Thus, the objectives of this study were to explore the prevalence, risk factors, and clinical outcomes of platelet transfusion refractoriness among patients admitted to the general ICU of a tertiary-care hospital.

Methods

Patients and setting

This was a retrospective cohort study that was conducted in the adult noncardiac ICUs of King Abdul-Aziz Medical City, Riyadh, Saudi Arabia. The Institutional Review Board of the Ministry of National Guard Health Affairs approved this study. The hospital was a tertiary-care center in Riyadh, with a capacity of >1000 beds treating a variety of medical conditions including hematology, oncology and hematopoietic stem cell transplantation. The ICUs collectively had 60 beds servicing medical, surgical and trauma patients. Multi-disciplinary consultant-based teams provided care with in-house on-call physicians 24 hours per day, 7 days per week.[13] Platelets were transfused at the discretion of the treating ICU team as no related protocol existed during the study period. Typically, the prophylactic transfusion threshold was platelets count < 10-20 x10^9/L and therapeutic threshold < 50 x10^9/L in the presence of active bleeding or when an invasive procedure was required. In our institution, all units of platelets were leukocyte reduced; irradiated platelets were dispatched preferentially to hematology/ hematopoietic stem cell transplantation patients where available; apheresis platelets were given upon the request of the treating team; otherwise pooled platelets were given.

The study patients included all adults (≥14 years old) admitted to the ICU between 2011 and 2016, and received at least two platelet transfusions during the ICU admission. For patients with more than one ICU admission within the same hospitalization, only the first admission was considered.

Data collection and definitions

Data were collected from different sources, primarily the electronic medical records, ICU administrative database and hospital blood bank database. Collected variables included patient demographics, clinical characteristics on admission (diagnosis, admission category, Glasgow Coma Scale (GCS) and Acute
Physiologic Assessment and Chronic Health Evaluation (APACHE) II score. The date, time, type (pooled or apheresis), irradiation status, and dose of each transfusion were noted. Platelet count on admission, nadir platelet count during ICU admission, and the platelet counts before and after each transfusion were recorded. When no platelet count could be found in between two or more platelet transfusions, those transfusions were added up and considered as one. When available, we measured the spleen size of each patient within 30 days of admission based on imaging studies in the hospital Picture Archiving and Communication System. Assessed outcomes were platelet transfusion refractoriness, the interval to next platelet transfusion, ICU and hospital length of stay, ICU and hospital mortality, duration of mechanical ventilation, and new tracheostomy insertion.

In this study, we defined refractoriness to platelet transfusions as a platelet increment (PI) of $< 10 \times 10^9$/L on at least two consecutive occasions within the same ICU admission. PI was calculated by subtracting the pre-transfusion from the post-transfusion platelet count. We also used a definition based on the corrected count increment (CCI) for comparison.

CCI adjusts the PI for the amount of platelets transfused and for body surface area, and is calculated using the following formula:

$$\text{CCI} = \frac{\text{Post-Transfusion Platelet Count} - \text{Pre-Transfusion Platelet Count}}{\text{Body Surface Area}}$$

The absolute number of platelets per platelet unit was estimated at as $30 \times 10^{10}$ for each unit of apheresis platelets, and $5.5 \times 10^{10}$ for each unit of pooled platelets. Body surface area was calculated using the Mosteller formula as:

$$\text{Body Surface Area} = \sqrt{\frac{\text{Weight} \times \text{Height}}{10}}$$

Patients with CCI $< 5 \times 10^9$/L on at least two consecutive occasions were considered platelet transfusion refractory. Splenomegaly was defined as a splenic craniocaudal diameter of $>13$ cm on an abdominal CT scan or an abdominal ultrasound. Thrombocytopenia was defined as platelet count $<150 \times 10^9$/L. DIC was recorded as a likelihood score adapted from the sepsis-induced coagulopathy score, where a higher score indicated a higher likelihood of DIC.

**Statistical Analysis**

Platelet transfusion refractoriness was analyzed using a “wide” data format, where each row represented a different patient. The interval to next transfusion, representing transfusion frequency, was analyzed using a “long” data format, where each row represented a single transfusion. The patient cohort was stratified according to platelet transfusion refractoriness. The interval to next transfusion was categorized into two groups depending on the time from the previous transfusion (group 1, $< 48$ hours; group 2, 48 hours; or more). Continuous variables were presented as medians with the first and third quartiles (Q1, Q3). Categorical variables were presented as frequencies with percentages. The characteristics and outcomes of the different groups were compared using the Kruskal-Wallis or the chi-square tests, as appropriate. The diagnosis of platelet transfusion refractoriness by PI was compared against that by CCI using kappa statistics, sensitivity and specificity.
A binary logistic regression model was used to identify predictors of platelet transfusion refractoriness. Unique variables with p-values < 0.2 on univariate analysis were included, in addition to variables with higher p-values that were deemed clinically relevant. The independent variables entered in the model were age, APACHE II score, admission as trauma versus medical and surgical admission, hematologic malignancy, chronic liver disease, presence of splenomegaly, sepsis, shock, baseline platelet count, DIC likelihood score and type and irradiation status of first platelet product received. The results were reported as odds ratio (OR) and 95% confidence interval (CI). Data was analyzed using SPSS v 25 and R Statistical Package v 3.4.3. P-values < 0.05 were considered statistically significant.

Results

**Characteristics of patients**

Between 2011 and 2016, 259 patients required platelet transfusion on ≥ 2 occasions and were included in the study, collectively receiving 1357 platelet transfusions. The characteristics of the study patients are summarized in Table 1. The median age was 58 years (Q1, Q3: 43.5, 70), most (57.5%) patients were males and 84.9% were admitted for a medical reason. About a third (35.5%) had cancer, almost two thirds (63.3%) were in shock on ICU admission, 59.8% were septic and 20.1% had a form of bleeding.

**Table 1:** General characteristics of patients by platelet transfusion refractoriness status
| Patient Characteristics                  | Total (N=259) | Yes (N=142) | No (N=117) | P value |
|------------------------------------------|---------------|-------------|-------------|---------|
| **Age (years)**                          | Median (Q1, Q3) | 58.0 (43.5, 70.0) | 57.0 (42.2, 68.0) | 60.0 (46.0, 72.0) | 0.11 |
| Male Sex ✘                                | N (%)         | 149 (57.5%) | 81 (57.0%) | 68 (58.1%) | 0.86 |
| Body Mass Index (kg/m²)                  | Median (Q1, Q3) | 27.3 (22.4, 32.3) | 27.9 (22.3, 32.9) | 26.6 (22.6, 31.4) | 0.40 |
| Obese > 30 kg/m²                         | N (%)         | 94 (37.5%) | 54 (39.4%) | 40 (35.1%) | 0.60 |
| Body Surface Area (m²)                   | Median (Q1, Q3) | 1.8 (1.6, 1.9) | 1.8 (1.7, 1.9) | 1.8 (1.6, 1.9) | 0.42 |
| **Admission Category**                   | N (%)         |            |             |         | 0.03 |
| Medical                                  | 220 (84.9%) | 125 (88.0%) | 95 (81.2%) |         |       |
| Surgical                                 | 30 (11.6%) | 16 (11.3%) | 14 (12.0%) |         |       |
| Trauma                                   | 9 (3.5%) | 1 (0.7%) | 8 (6.8%) |         |       |
| Chronic Cardiac Disease /238 patients² | N (%)         | 35 (15.2%) | 18 (13.6%) | 17 (17.3%) | 0.44 |
| Chronic Immune Disease /238 patients²   | N (%)         | 89 (38.7%) | 47 (35.6%) | 42 (42.9%) | 0.26 |
| Chronic Liver Disease /238 patients²    | N (%)         | 48 (20.9%) | 35 (26.5%) | 13 (13.3%) | 0.01 |
| Chronic Respiratory Disease /238 patients² | N (%)     | 17 (7.4%) | 12 (9.1%) | 5 (5.1%) | 0.25 |
| Chronic Renal Disease /238 patients*     | N (%)         | 29 (12.6%) | 14 (10.6%) | 15 (15.3%) | 0.29 |
| APACHE II Score                          | Median (Q1, Q3) | 25.0 (20.0, 30.0) | 25.0 (21.0, 30.0) | 24.0 (20.0, 28.5) | 0.40 |
| Glasgow Coma Scale on ICU admission      | Median (Q1, Q3) | 14.0 (9.5, 15.0) | 14.0 (9.0, 15.0) | 14.0 (10.0, 15.0) | 0.97 |
| Mechanical Ventilation /238 patients*    | N (%)         | 191 (83.0%) | 110 (83.3%) | 81 (82.7%) | 0.89 |
| PaO2/FiO2 Ratio                          | Median (Q1, Q3) | 178.5 (113.2, 270.5) | 176.0 (112.2, 258.0) | 182.0 (114.0, 282.5) | 0.38 |
| Shock                                    | N (%)         | 164 (63.3%) | 91 (64.1%) | 73 (62.4%) | 0.78 |
| Sepsis                                   | N (%)         | 155 (59.8%) | 88 (62.0%) | 67 (57.3%) | 0.44 |
| Septic shock                             | N (%)         | 149 (57.5%) | 84 (59.2%) | 65 (55.6%) | 0.56 |
| DIC likelihood score                     | Median (Q1, Q3) | 5.0 (4.0, 6.0) | 5.0 (4.0, 6.0) | 5.0 (4.0, 5.0) | 0.04 |
| Active bleeding                          | N (%)         | 52 (20.1%) | 27 (19.0%) | 25 (21.4%) | 0.64 |
| Active cancer                            | N (%)         | 92 (35.5%) | 47 (33.1%) | 45 (38.5%) | 0.37 |
| Hematological Cancer                     | N (%)         | 75 (29.0%) | 38 (26.8%) | 37 (31.6%) | 0.39 |
| Organ transplant                         | N (%)         | 13 (5.0%) | 9 (6.3%) | 4 (3.4%) | 0.28 |
| Splenomegaly /182 patients*              | N (%)         | 65 (36.5%) | 40 (43.5%) | 25 (29.1%) | 0.046 |
| Platelet count on ICU admission (x10⁹/L)| Median (Q1, Q3) | 53.5 (28.0, 98.8) | 49.0 (26.0, 93.0) | 59.0 (35.0, 108.0) | 0.11 |
| Thrombocytopenia on admission (< 150)    | N (%)         | 226 (87.6%) | 123 | 103 | 0.85 |
| x10^9/L | N (%) | (87.2%) | (88.0%) | P value |
|---------|-------|---------|---------|---------|
| Severe thrombocytopenia on admission (< 50 x10^9/L) | N (%) | 118 (45.7%) | 72 (51.1%) | 46 (39.3%) | 0.06 |
| Lowest platelet count during ICU Stay (x10^9/L) | Median (Q1, Q3) | 18.0 (10.0, 29.0) | 14.0 (7.0, 28.0) | 19.0 (11.0, 34.0) | 0.001 |
| INR | Median (Q1, Q3) | 1.6 (1.3, 2.0) | 1.6 (1.3, 2.2) | 1.6 (1.2, 2.0) | 0.38 |
| Lactic acid (mmol/L) | Median (Q1, Q3) | 2.9 (1.7, 6.0) | 2.9 (1.5, 5.9) | 3.0 (1.8, 6.1) | 0.47 |
| Creatinine (μmol/L) | Median (Q1, Q3) | 142.5 (73.8, 256.2) | 145.0 (82.2, 260.2) | 134.5 (65.8, 232.0) | 0.33 |
| Bilirubin (μmol/L) | Median (Q1, Q3) | 40.0 (19.0, 107.2) | 40.0 (19.0, 106.0) | 40.0 (19.5, 107.5) | 0.99 |
| Transfusion count | Median (Q1, Q3) | 4.0 (2.0, 6.0) | 5.0 (3.0, 8.0) | 3.0 (2.0, 4.0) | < 0.001 |
| Platelet transfusion refractory (CCI definition) | N (%) | 146 (57.0%) | 139 (98.6%) | 7 (6.1%) | < 0.001 |

### Transfusion Characteristics

| Total (N=1357) | No (N=431) | Yes (N=926) | P value |
|----------------|------------|-------------|---------|
| Platelet Count Prior to Transfusion (x10^9/L) | Median (Q1, Q3) | 31.0 (17.0, 52.0) | 33.0 (18.0, 54.0) | 31.0 (16.0, 52.0) | 0.17 |
| Transfusion Dose (Units) | Median (Q1, Q3) | 6.0 (6.0, 12.0) | 6.0 (6.0, 6.0) | 6.0 (6.0, 12.0) | < 0.001 |
| Platelet Increment (x10^9/L) | Median (Q1, Q3) | 6.0 (-5.0, 24.0) | 21.0 (9.0, 42.0) | 2.0 (-8.0, 14.0) | < 0.001 |
| Corrected Count Increment (x10^9/L) | Median (Q1, Q3) | 2.8 (-2.0, 10.8) | 10.3 (3.8, 18.8) | 0.6 (-3.7, 5.8) | < 0.001 |
| Platelet product | N (%) | 138 (10.2%) | 196 (14.4%) | 750 (55.3%) | 182 (13.4%) | 19 (6.7%) |
| Apheresis | 138 (10.2%) | 196 (14.4%) | 750 (55.3%) | 182 (13.4%) | 19 (6.7%) |
| Apheresis-Irradiated | 196 (14.4%) | 72 (16.7%) | 242 (56.1%) | 59 (13.7%) | 18 (4.2%) |
| Pooled | 750 (55.3%) | 40 (9.3%) | 242 (56.1%) | 59 (13.7%) | 18 (4.2%) |
| Pooled-Irradiated | 182 (13.4%) | 72 (16.7%) | 242 (56.1%) | 59 (13.7%) | 18 (4.2%) |
| Mixed** | 91 (6.7%) | 124 (13.4%) | 508 (54.9%) | 123 (13.3%) | 73 (7.9%) |

* For variables with missing data, the number of valid observations is reported.
** "Mixed" indicates aggregate transfusions that were derived from transfusions with 2 or more different platelet products.

APACHE: Acute Physiologic Assessment and Chronic Health Evaluation; DIC: disseminated intravascular coagulation; ICU: intensive care unit; INR: international normalized ratio, Q1: first quartile, Q3: third quartile
The majority (87.6%) of the patients had thrombocytopenia (platelet count < $150 \times 10^9/L$) on admission with count < $50 \times 10^9/L$ present in 45.7%. The rest (12.4%) developed thrombocytopenia during their ICU stay. The median platelet count on admission was $53.5 \times 10^9/L$ (Q1, Q3: 28, 98.8). The median platelet nadir was $18 \times 10^9/L$ (Q1, Q3: 10, 29). Each patient received platelet transfusion on a median of 4 (Q1, Q3: 2, 6) occasions. The median dose of the platelet transfusions was 6 pooled units (Q1, Q3: 6, 12) or their equivalent. The majority of the platelets transfused were pooled un-irradiated (55.3%), while pooled-irradiated platelets accounted for 13.4%, apheresis platelets accounted for 10.2%, and apheresis-irradiated platelets accounted for 14.4%.

The median time interval to next transfusion was 1 day (1, 2). The post-transfusion platelet count was taken a median of 5.0 hours (Q1, Q3: 2.94, 7.58; range: 0, 40 hours) after transfusion. There was no significant difference in PI across the different intervals to next transfusion as described in Figure 1.

**Prevalence of platelet transfusion refractoriness**

More than half of the patients (54.8%) had platelet transfusion refractoriness by PI and 57.0% by CCI increment. The median PI was $6 \times 10^9/L$ (Q1, Q3: -5, 24), and the median CCI was 2.8 (Q1, Q3: -2.0, 10.8). There was strong agreement between refractoriness diagnosis by PI and CCI (kappa coefficient: 0.929, 95% CI: 0.884-0.968; p<0.001). Assuming CCI increment is more accurate for diagnosing platelet transfusion refractoriness, diagnosis by PI had 95.2% sensitivity (95% CI: 90.4-98.1%) and 98.2% specificity (95% CI: 93.6-99.8%). Figure 2A describes the relationship between PI and CCI according to the platelet type.

**Predictors of platelet transfusion refractoriness**

As shown in Table 1, the admission category, splenomegaly, chronic liver disease, and higher number of transfusions were associated with platelet transfusion refractoriness on univariate analysis. Trauma patients were the least likely to develop refractoriness (11.1%) compared with medical (56.8%) and non-trauma surgical patients (53.3%). Particularly of note, the admitting services of Hepatology, Liver Transplant, and Hematology had the highest rates of refractoriness (69.7%, 69.2%, and 55.6%, respectively) (Figure 2B). Of patients with splenomegaly, 61.5% developed refractoriness compared to 46.0% of those with non-enlarged spleens (p=0.046). There was a modest, but statistically significant increase in DIC likelihood among refractory (median: 5, Q1, Q3: 4, 6) compared to non-refractory patients (median: 5, Q1, Q3: 4, 5) (p=0.04). On the other hand, no association of statistical significance could be discerned between refractoriness and presence of sepsis on admission, bleeding, hematological cancer, or shock.

The multivariable logistic regression model showed younger age to be the only statistically significant predictor of refractory status (OR: 0.975, 95% CI: 0.951-0.999). APACHE II score tended to be significant (OR: 1.064, 95% CI: 0.996-1.136; p=0.065).

**Factors associate with the time to next platelet transfusion**
Several factors predisposed to an earlier next transfusion (Table 2). These include the pre-transfusion platelet count (p<0.001), platelet dose (p=0.04), PI following transfusion (p<0.001), and the particular platelet product used (p< 0.001). Re-transfusion within 2 days was less frequent with non-irradiated pooled platelets (50.7%, compared to 63.6% for apheresis non-irradiated, 62.0% for apheresis irradiated, and 69.4% for pooled irradiated).

| Table 2: Characteristics of platelet transfusions by the time to next transfusion |
|-------------------------------|------------------|------------------|------------------|--------------------------|
|                               | Total (N=1118)   | Less than 2 days (N=643) | 2 days or more (N=475) | P value |
| Transfusion Dose (Units) Median (Q1, Q3)  | 6.0 (6.0, 12.0) | 6.0 (6.0, 12.0) | 6.0 (6.0, 6.0) | 0.04 |
| Platelet Increment (x10⁹/L) Median (Q1, Q3)  | 6.0 (-5.0, 24.0) | 5.0 (-6.0, 19.0) | 9.0 (-4.0, 29.0) | < 0.001 |
| Platelet Count Prior to Transfusion (x10⁹/L) Median (Q1, Q3)  | 31.0 (16.0, 50.0) | 28.0 (14.0, 45.0) | 37.0 (19.0, 58.0) | < 0.001 |
| Platelet product | N (%)   | Transfusion Dose (Units) Median (Q1, Q3)  | 6.0 (6.0, 12.0) | 6.0 (6.0, 12.0) | 6.0 (6.0, 6.0) | 0.04 |
| Apheresis | 111 (9.9%) | 71 (11.0%) | 40 (8.4%) | < 0.001 |
| Apheresis-Irradiated | 163 (14.6%) | 101 (15.7%) | 62 (13.1%) |
| Pooled | 608 (54.4%) | 310 (48.2%) | 298 (62.7%) |
| Pooled-Irradiated | 157 (14.0%) | 109 (17.0%) | 48 (10.1%) |
| Mixed | 79 (7.1%) | 52 (8.1%) | 27 (5.7%) |

* Mixed indicates aggregate transfusions that were derived from transfusions with 2 or more different platelet products.

Q1: first quartile, Q3: third quartile

Outcomes

Table 3 describes the outcomes of patients. The median ICU length of stay for all patients was 13 days (Q1, Q3: 7, 23), and the median hospital length of stay was 28 days (Q1, Q3: 16, 58). ICU and hospital mortality were both high, at 59.1% and 73%, respectively.

Table 3: Outcomes of patient by platelet refractory tatus
|                          | Total (N=259) | Yes (N=142) | No (N=117) | P value |
|--------------------------|---------------|-------------|------------|---------|
| **ICU mortality**        |               |             |            |         |
| N (%)                    | 153 (59.1%)   | 86 (60.6%)  | 67 (57.3%) | 0.55    |
| **Hospital mortality**   |               |             |            |         |
| N (%)                    | 189 (73.0%)   | 105 (73.9%) | 84 (71.8%) | 0.70    |
| **New tracheostomy**     |               |             |            |         |
| /238 patients*           | N (%)         | 25 (10.9%)  | 19 (14.4%) | 6 (6.1%) | 0.046   |
| **Duration of mechanical ventilation (days)** | Median (Q1, Q3) | 10.0 (6.0, 17.0) | 10.0 (5.0, 15.8) | 12.0 (6.0, 19.5) | 0.15 |
| /238 patients*           |               |             |            |         |
| **ICU length of stay (days)** | Median (Q1, Q3) | 13.0 (7.0, 23.0) | 16.0 (8.0, 26.0) | 12.0 (6.0, 21.0) | 0.02 |
| **Hospital length of stay (days)** | Median (Q1, Q3) | 28.0 (16.0, 58.0) | 33.0 (16.0, 62.5) | 27.0 (14.0, 47.0) | 0.11 |

* For variables with missing data, the number of valid observations is reported.
ICU: intensive care unit, Q1: first quartile, Q3: third quartile

Compared to non-refractory patients, those with platelet transfusion refractoriness had a longer stay in the ICU (median of 16 days compared to 12 days, p=0.015). However, there was no difference in either hospital or ICU mortality. Refractory patients were more likely to have a new tracheostomy tube insertion (p=0.046), but with similar duration of mechanical ventilation (p=0.15).

**Discussion**

Refractoriness to platelet transfusions has been associated with adverse clinical outcomes including prolonged hospital stay, increased risk of bleeding as well and mortality.[9, 10, 19] Much of the published literature on this challenging clinical problem has been described in patients with hematologic malignancies or stem cell transplantation with reported prevalence in the range of 28-44%.[20, 21] To our knowledge, this phenomenon has not been previously examined in patients admitted to the ICU. In this analysis, we report on the prevalence and clinical outcome of patients with platelet transfusion refractoriness from a large cohort of critically ill patients in a large tertiary-care center.

We observed that > 50% of critically ill patients had evidence of platelet transfusion refractoriness. Such value exceeded prior reports on prevalence in patients with other disorders. This was in spite of the fact that all the platelet products given at our institution were leucocyte reduced, which is well known to reduce the incidence of alloimmunization and thus ultimately enhance PI post transfusion.[6] Refractoriness was more prevalent in patients admitted under Hematology or Hepatology services, in spite of the fact they preferentially receive apheresis platelets, where available, which typically contain higher platelet content.

A number of factors may impact post transfusion increment and deserve further elaboration, including platelet source and manipulation, ABO matching and duration of storage in blood bank.[22] Being a large tertiary-care and trauma center, the platelet storage time is expected to be short. Furthermore, the majority of platelet products given in this analysis were from pooled platelets rendering the platelet source and
content to be more homogenous. It is possible that the noted prevalence herein is overestimated as the measured post transfusion count was done after a median of five hours. However, we did not observe a clear relation between the calculated post-transfusion PI and the time post transfusion. It is also important to highlight that previous reports showed that 67-72% of transfused platelets survive the 24-hour mark.[6, 23]

The use of the CCI formula is the standard method to measure platelet recovery and survival post transfusion.[24, 25] However, it is cumbersome to use in routine clinical practice; thus more pragmatic tools such as the PI is routinely utilized. In light of this, we compared these two tools and observed a high concordance. Such information is significant for two reasons; first, calculation of the CCI is frequently based on estimates, not actual counts, of platelet content which is subject to variation. Second, with emergence of such data showing equivalence among the two methods, clinicians would likely opt to use the more practical PI calculation.[23]

Lastly, we aimed to examine the clinical endpoints of platelet refractoriness specifically in regards to time to next transfusion, length of stay in hospital and overall mortality. As expected, patients with shorter time to next transfusion were more likely to have a lower baseline count as well as lower PI. We also found that patients with platelet transfusion refractoriness had high mortality, but it was similar to that of patients who did not have refractoriness. Prior data in patients with hematologic malignancies reported that early and late deaths were more common in the refractory group, predominantly due to fatal hemorrhage.[26] We speculate the differing conclusions seen could be due to increased incidence of immune causes of refractoriness in patients with hematologic malignancies. Such alloimmunization renders the patient more refractory and ultimately at increased risk for severe bleeding episodes.

This analysis carries limitations particularly with regards to its retrospective design and single center analysis. Furthermore, measurements of platelet count ideally should be carried out within an hour post transfusion to offset any pooling of platelets that subsequently occurs in the spleen. However, as eluted to previously, we do not feel this has had a major impact in this analysis given the lack of correlation between the post count measure and elapsed time. A number of important points should be highlighted. First, to our knowledge, this is the first analysis of platelet refractoriness in the critical care setting and sheds some insight on the prevalence and outcome in such patients. Second, we used two methods to estimate platelet refractoriness and demonstrate they were concordant. Finally, unlike patients with hematologic malignancies, survival in critically ill patients was not impacted by platelet refractoriness possibly as the underlying mechanisms of refractoriness are different among these patients. Such observations require further validation.

In conclusion, critically ill patients receiving at least two transfusions of platelets had high (>50%) prevalence of platelet transfusion refractoriness, defined by PI and CCI. There was excellent concordance between PI and CCI for refractoriness diagnosis, suggesting that the more practical method (PI) is acceptable in this patient population. The mortality rate of our patients was high, but platelet transfusion refractoriness was not associated with increased mortality.
List Of Abbreviations

APACHE: Acute Physiologic Assessment and Chronic Health Evaluation

CCI: corrected count increment

CI: confidence interval

DIC: disseminated intravascular coagulation

ICU: intensive care unit

OR: odds ratio

PI: platelet increment

Q: quartile

Declarations

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Contributions

Conception and design of the work: SA, AOA. AA, HMD; Acquisition of data: SA, AOA. AA. Analysis of data: SA, EM, HMD. Interpretation of data: SA, AOA. AA, EM, MD, HMD. Manuscript Draft: SA, AOA. AA, MD, HMD. Manuscript revision: SA, AOA. AA, EM, MD, HMD. All authors read and approved the final manuscript.

Ethics declarations

Ethics approval and consent to participate

This study was approved by the Institution Review Board of the Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia. Informed consent was waived.
Consent for publication

Not applicable.

Competing interests

All authors declare no competing interest.

References

1. Hui P, Cook DJ, Lim W, Fraser GA, Arnold DM: The frequency and clinical significance of thrombocytopenia complicating critical illness: a systematic review. *Chest* 2011, 139(2):271-278.

2. Williamson DR, Albert M, Heels-Ansdell D, Arnold DM, Lauzier F, Zarychanski R, Crowther M, Warkentin TE, Dodek P, Cade J et al: Thrombocytopenia in critically ill patients receiving thromboprophylaxis: frequency, risk factors, and outcomes. *Chest* 2013, 144(4):1207-1215.

3. Rebulla P: Refractoriness to platelet transfusion. *Curr Opin Hematol* 2002, 9(6):516-520.

4. Klingemann HG, Self S, Banaji M, Deeg HJ, Doney K, Slichter SJ, Thomas ED, Storb R: Refractoriness to random donor platelet transfusions in patients with aplastic anaemia: a multivariate analysis of data from 264 cases. *Br J Haematol* 1987, 66(1):115-121.

5. Legler TJ, Fischer I, Dittmann J, Simson G, Lynen R, Humpe A, Riggert J, Schleyer E, Kern W, Hiddemann W et al: Frequency and causes of refractoriness in multiply transfused patients. *Ann Hematol* 1997, 74(4):185-189.

6. Trial to Reduce Alloimmunization to Platelets Study G: Leukocyte reduction and ultraviolet B irradiation of platelets to prevent alloimmunization and refractoriness to platelet transfusions. *N Engl J Med* 1997, 337(26):1861-1869.

7. Hod E, Schwartz J: Platelet transfusion refractoriness. *Br J Haematol* 2008, 142(3):348-360.

8. Laundy GJ, Bradley BA, Rees BM, Younie M, Hows JM: Incidence and specificity of HLA antibodies in multitransfused patients with acquired aplastic anemia. *Transfusion* 2004, 44(6):814-825.

9. Toor AA, Choo SY, Little JA: Bleeding risk and platelet transfusion refractoriness in patients with acute myelogenous leukemia who undergo autologous stem cell transplantation. *Bone Marrow Transplant* 2000, 26(3):315-320.

10. Kerkhoffs JL, Eikenboom JC, van de Watering LM, van Wordragen-Vlaswinkel RJ, Wijermans PW, Brand A: The clinical impact of platelet refractoriness: correlation with bleeding and survival. *Transfusion* 2008, 48(9):1959-1965.

11. Nijsten MW, ten Duis HJ, Zijlstra JG, Porte RJ, Zwaveling JH, Paling JC, The TH: Blunted rise in platelet count in critically ill patients is associated with worse outcome. *Crit Care Med* 2000, 28(12):3843-3846.

12. Slichter SJ, Davis K, Enright H, Braine H, Gernsheimer T, Kao KJ, Kickler T, Lee E, McFarland J, McCullough J et al: Factors affecting posttransfusion platelet increments, platelet refractoriness, and
platelet transfusion intervals in thrombocytopenic patients. Blood 2005, 105(10):4106-4114.

13. Arabi Y, Alshimemeri A, Taher S: Weekend and weeknight admissions have the same outcome of weekday admissions to an intensive care unit with onsite intensivist coverage. Crit Care Med 2006, 34(3):605-611.

14. Kaufman RM, Djulbegovic B, Gernsheimer T, Kleinman S, Tinmouth AT, Capocelli KE, Cipolle MD, Cohn CS, Fung MK, Grossman BJ et al: Platelet transfusion: a clinical practice guideline from the AABB. Ann Intern Med 2015, 162(3):205-213.

15. Kouno T, Katsumata N, Mukai H, Ando M, Watanabe T: Standardization of the body surface area (BSA) formula to calculate the dose of anticancer agents in Japan. Jpn J Clin Oncol 2003, 33(6):309-313.

16. Pozo AL, Godfrey EM, Bowles KM: Splenomegaly: investigation, diagnosis and management. Blood Rev 2009, 23(3):105-111.

17. Crowther MA, Cook DJ, Meade MO, Griffith LE, Guyatt GH, Arnold DM, Rabbat CG, Geerts WH, Warkentin TE: Thrombocytopenia in medical-surgical critically ill patients: prevalence, incidence, and risk factors. J Crit Care 2005, 20(4):348-353.

18. Iba T, Levy JH, Raj A, Warkentin TE: Advance in the Management of Sepsis-Induced Coagulopathy and Disseminated Intravascular Coagulation. J Clin Med 2019, 8(5).

19. Meehan KR, Matias CO, Rathore SS, Sandler SG, Kallich J, LaBrecque J, Erder H, Schulman KA: Platelet transfusions: utilization and associated costs in a tertiary care hospital. Am J Hematol 2000, 64(4):251-256.

20. Sarkodee-Adoo C, Schiffer CA: Platelet transfusion support for patients with cancer and hematologic malignancies. Curr Opin Hematol 1996, 3(5):347-354.

21. Stanworth SJ, Navarrete C, Estcourt L, Marsh J: Platelet refractoriness—practical approaches and ongoing dilemmas in patient management. Br J Haematol 2015, 171(3):297-305.

22. Trulzzi DJ, Assmann SF, Strauss RG, Ness PM, Hess JR, Kaufman RM, Granger S, Slichter SJ: The impact of platelet transfusion characteristics on posttransfusion platelet increments and clinical bleeding in patients with hypoproliferative thrombocytopenia. Blood 2012, 119(23):5553-5562.

23. Jaime-Perez JC, Vazquez-Hernandez KE, Jimenez-Castillo RA, Fernandez LT, Salazar-Riojas R, Gomez-Almaguer D: Platelet Survival in Hematology Patients Assessed by the Corrected Count Increment and Other Formulas. Am J Clin Pathol 2018, 150(3):267-272.

24. Apelseth TO, Bruserud O, Wentzel-Larsen T, Hervig T: Therapeutic efficacy of platelet transfusion in patients with acute leukemia: an evaluation of methods. Transfusion 2010, 50(4):766-775.

25. Karafin M, Fuller AK, Savage WJ, King KE, Ness PM, Tobian AA: The impact of apheresis platelet manipulation on corrected count increment. Transfusion 2012, 52(6):1221-1227.

26. Comont T, Tavitian S, Bardiaux L, Fort M, Debiol B, Morere D, Berard E, Delabesse E, Luquet I, Martinez S et al: Platelet transfusion refractoriness in patients with acute myeloid leukemia treated by intensive chemotherapy. Leuk Res 2017, 61:62-67.
**Figures**

![Graph](image)

**Figure 1**

The Relationship between Platelet Increment and the Time Interval to the First Post-transfusion Platelet Count. There was no relationship between the calculated post-transfusion platelet increment and the number of hours until the post-transfusion platelet count was drawn.
Figure 2

Platelet Counts Pre- and Post-transfusion by the type of platelet transfused (Panel A) and Admitting Service (Panel B). Pearson Correlation $r$ was 0.904 for apheresed, 0.901 for apheresed irradiated, 0.962 for mixed, 0.936 for pooled and 0.937 for pooled irradiated. Mixed indicates aggregate transfusions that were derived from transfusions with 2 or more different platelet products.
Supplementary Files

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