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WORD COUNT 3715
TIME SUBMITTED 16-DEC-2024 12:31AM
PAPER ID 113540497

AMPH
AMALTEA MEDICAL PUBLISHING HOUSE
https://medscience.center/journals/
Words count – 3,712

**TYPE OF ARTICLE:** Original Article

# Post-transfusion platelet increments in hematology patients: A prospective observational study

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## ABSTRACT

**Background and objectives.** Post-transfusion platelet (PLT) increment may vary widely and greatly impact clinical and transfusion practice. This prospective study aimed to assess post-transfusion PLT increment in all hematology patients as well as to assess post-transfusion PLT increment and the ratio of ineffective PLT transfusion in different groups of hematology patients.

**Material and methods.** Blood samples for PLT counts were drawn in the morning before transfusion, and then 1 and 16-24 hours after transfusion. Post-transfusion PLT increment was assessed using formulas for Count Increment (CI) and Corrected Count Increment (CCI) to correct CI for the patient's body weight and number of transfused platelets. Hematology patients were divided into four groups: CHEMO group, patients receiving chemotherapy; AUTO group, patients receiving autologous hematopoietic stem cell transplantation (HSCT); ALLO group, patients receiving allogeneic HSCT.

**Results.** Over a two-month period 197 PLT transfusion were transfused to 51 patients. Median 1-hour and 24-hour CI after transfusion of one pooled PC was 23 and 14 x $10^9$/L, respectively.

Median CCI and ratios of ineffective PLT transfusion 1 hour after transfusion were not statistically different between various groups. Median 24-hour CCI between various groups were statistically different: AUTO (10.0 x $10^9$/L), CHEMO (8.8 x $10^9$/L), and ALLO (4.8 x $10^9$/L) ($p < 0.01$), as well as ratios of ineffective PLT transfusion using 24-hour CCI: AUTO (15.6%), CHEMO (32.0%), and ALLO (46.6%) (p=0.003).

**Conclusion.** Allogeneic HSCT patients had the lowest post-transfusion PLT increment 24 hours after transfusion and the highest ratio of inefficient transfusion, thus representing patient population with challenging PLT transfusion needs.

**Keywords:** platelet increment, platelet transfusion, platelet concentrate, hematology patients

**Abbreviations (in alphabetical order):**

ALLO group - patients receiving allogeneic hematopoietic stem cell transplantation
AUTO group - patients receiving autologous hematopoietic stem cell transplantation
CCI - Corrected Count Increment
CHEMO group - patients receiving chemotherapy
CI - Count Increment (CI)
GVHD - Graft versus host disease
HSCT - hematopoietic stem cell transplantation
PLT - Platelet

## INTRODUCTION

Platelet (PLT) transfusions have effectively reduced the incidence of severe hemorrhagic complications associated with chemotherapy-induced thrombocytopenia [1]. Almost all hematology patients regardless of treatment type: autologous hematopoietic stem cell transplantation (HSCT), allogeneic HSCT, or intensive chemotherapy will receive one or more PLT transfusions, mainly prophylactically [2,3]. This makes hematology patients the most intensive platelet users [4].

However, post-transfusion PLT increment may vary widely and greatly impact transfusion and clinical practice. Lower PLT increment may increase the risk of bleeding. Furthermore, low post-transfusion PLT increment may lead to sooner meeting transfusions trigger and consequently higher PLT utilization. Repeated low post-transfusion PLT increment is also associated with adverse patient outcomes [5]. A 1-hour PLT count increment (CI) represents PLT recovery, while a 24-hour PLT CI represents PLT survival [6]. PLT CI is influenced by the number of transfused platelets and the patient's blood volume [7]. Therefore, to increase accuracy

corrected count increment (CCI) is used to correct CI for the patient's body weight and the dose of PLTs. PLT concentrates (PCs) quality varies greatly and depends on many factors: donors, doses, machines, filters, devices, additive solutions, shelf life, etc [8]. Therefore, hospital transfusion services should evaluate post-transfusion PLT increment of the PCs they use. Significantly different risks of grade ≥ 2 WHO bleeding and the effectiveness of prophylactic PLT transfusion to prevent bleeding between different groups of hematology patients have been already reported [2,9–11].

Only a few studies analyzed PLT recovery and survival among different groups of hematology patients so far [1,12–14]. Those studies are older and do not reflect changes in transplant practices such as changes in conditioning and Graft versus host disease (GVHD) prophylaxis regimens utilizing more anti-thymocyte globulin and post-transplantation cyclophosphamide [15], donor-type for allogeneic HSCT that shifted in recent years toward unrelated and haploidentical related donors, as well as older recipients' age. Therefore, the objectives of this prospective study were to assess post-transfusion PLT increment in all hematology patients as well as to assess post-transfusion PLT increment and the ratio of ineffective PLT transfusion in different groups of hematology patients.

## MATERIALS AND METHODS

### Ethical approval

The study was approved by the Ethics Committee of the University Hospital Centre Zagreb (Approval number: 8.1-20/41-2, February 24th, 2020.) and all patients gave written informed consent prior to inclusion.

### Inclusion criteria

All adult patients receiving pool PCs transfusions who were admitted to the Division of Hematology to receive chemotherapy or autologous or allogeneic hematopoietic stem cell transplantation (HSCT) from 14 February 2020 to 14 April 2020.

### Exclusion criteria

Patients confirmed refractory to PLT transfusions, defined as a 24-hour CCI <4.5 on two or more consecutive occasions were not included in the study. PLT transfusions during bleeding episodes were excluded from the assessment.

**Data collection**

PLT transfusion data (date and time of transfusion, PLT dose, PC type, PC ABO and RhD type) were collected from a database of the hospital transfusion service. Demographic (date of birth, gender, height, and weight) and clinical data (primary diagnosis, type of treatment, presence of bleeding, pre- and post-transfusion PLT count) were collected from patient electronic medical records.

**Platelet concentrates production**

PCs were supplied by the Croatian Institute of Transfusion Medicine (CITM). Pooled PCs were obtained by manually pooling four buffy coats (Teruflex BP-KIT, Terumo) from whole blood donors. All PCs were leukoreduced and resuspended in PLT additive solution (SSP+, MacoPharma). Based on CITM quality control data, on average pooled PCs contain $2.9 \pm 0.42 \times 10^{11}$ PLT. Since the PLT count of each pooled PC was not routinely measured those data were used for calculations.

**Platelet transfusion**

Prophylactic PLT transfusions were indicated if the PLT counts were the following: $<10 \times 10^9$/L in stable patients, $<20 \times 10^9$/L in patients with additional risk factors for bleeding (sepsis, fever ≥38°C, coagulopathy, mucositis, acute promyelocytic leukemia, GvHD) and at higher PLT counts prior to invasive procedures according to international guidelines as previously extensively described [3]. All transfused PCs were x-ray irradiated before issuing and ABO identical or compatible in case of ABO nonidentical HSCT transplantation. For minor ABO-incompatible transplantations, the recipient's ABO-type; for major ABO-incompatible recipients, the donor's ABO-type; and for bidirectional ABO-incompatible patients, AB group PCs were transfused.

**Post-transfusion platelet increment assessment**

PLT count was measured at the hospital laboratory using an automated counter the Sysmex XN-10 (Sysmex, Kobe, Japan). The pretransfusion PLT count was obtained in the morning and this count was used for ordering PLT transfusion. Blood samples for posttransfusion PLT counts were drawn 1 h after each transfusion, and repeat blood samples were drawn the next morning, 16-24 hours after transfusion. Out of 197 PLT transfusion, for nine is missing 1-hours and for seven 24-hour posttransfusion PLT count measurements are missing because the patients

were undergoing diagnostic procedures or interventions, or had been discharged from the hospital at the time of the planned sample collection.

For some PLT transfusions, 1 and 24-hour posttransfusion counts were missing if the patients had some diagnostics procedures or interventions immediately after transfusion or were discharged from the hospital.

Post-transfusion PLT increment was assessed using the following formulas [16]:

Count Increment (CI) = C2 – C1, where C1 is the pre-transfusion PLT count and C2 is the post-transfusion PLT count.

$$\text{Corrected Count Increment (CCI)} = \frac{[\text{Post-transfusion count } (\mu L)] - [\text{Pre-transfusion count} (\mu L) \times \text{BSA } (m^2)]}{\text{Number of platelets transfused } (\times 10^{11}/\mu L)}$$

$$\text{Body surface area (BSA)} = \frac{\sqrt{\text{Height (cm)} \times \text{Weight (kg)}}}{3600}$$ Mosteller formula [17]

According to the international recommendation, a PLT transfusion was considered ineffective if 1 hour - CCI <7.5 and/or 24-hour CCI <4.5 [6].

In order to compare post-transfusion platelet increment patients were divided based on treatment stratification into three groups: CHEMO group, patients receiving induction or consolidation chemotherapy; AUTO group, patients receiving autologous hematopoietic stem cell transplantation (HSCT); ALLO group, patients receiving allogeneic HSCT during current admission.

**Statistical analysis**

Categorical variables were presented as frequencies and percentages. Continuous variables were tested for normality of data distribution using Kolmogorov-Smirnov tests. Not normally distributed continuous data were presented as medians with interquartile ranges (IQRs). Kruskal-Wallis test was used to compare differences between platelet doses and patient groups and Dunn test for post-hoc analysis. All statistical analyses were performed using SPSS version 28.0.0.1. (SPSS, Inc., Chicago, IL) and a p-value of less than 0.05 was considered significant.

## RESULTS

### Patients

A total of 51 patients received at least one PC during the study period. Patient characteristics are summarized in Table 1. In our study, 17 (33.3%) patients were in the AUTO group, 13 (25.5%) in the ALLO group, 21 (41.2%) in the CHEMO group.

**Table 1.** Patient characteristics [*place for table 1*]

### Platelet increment comparing different dose

Overall, based on 197 PLT transfusion 293 PCs were transfused: 59 (29.9%) as double and 138 (70.1%) as single-unit transfusions. As shown in Table 2 median 1-hour CCI after transfusion of one pooled and two PC was 15.3 and 14.8 x $10^9$/L (p = 0.808), while 24-hour CCI after transfusion after transfusion was 8.7 and 8.3 x $10^9$/L, respectively (p = 0,610).

**Table 2.** Platelet increment (CI and CCI) after transfusion of one and two units of pooled PCs [*place for table 2*]

### Platelet increment in different groups of hematology patients

The median 1-hour CCI (interquartile range [IQR]) for AUTO, CHEMO and ALLO groups were respectively 10.0, 14.3 and 13.3 x $10^9$/L (Fig. 1A). No significant difference between various groups of hematology patients was identified (p = 0.679). Post-hoc analysis did not show statistically significant difference between the different groups.

The median 24-hour CCI for each group in AUTO, CHEMO and ALLO groups were respectively 10.3, 8.0 and 4.8 x $10^9$/L (Fig. 1B). The Kruskal-Wallis test showed a statistically significant difference between the three groups (p < 0.01). Post-hoc analysis showed a significant difference between the ALLO and AUTO groups (p < 0.01), as well as between ALLO and CHEMO groups (p = 0.015). There was no significant difference between the AUTO and CHEMO groups (p = 0.102).

**Figure 1**. **A**. 1-hour CCI in different groups of hematology patients; **B**. 24-hour CCI in different groups of hematology patients. [*place for figure 1A and B*]

### The ratio of ineffective platelet transfusions in different groups of hematology patients

As shown in Table 3 ratios of ineffective PLT transfusions measuring 1-hour CCI were not statistically different: 8.8% in the AUTO group, 20.0% in the CHEMO, and 21.7% in the ALLO groups (p=0.266). On the other hand, ratios of ineffective PLT transfusion using 24-hour

CCI were statistically different: in the AUTO group was 15.6%, while in the CHEMO was 32.0% and even 46.6% in the ALLO group (p=0.003).

**Table 2**. Ratio of ineffective platelet transfusions in different groups of hematology patients [*place for table 1*]

## DISCUSSION

Our study assessed post-transfusion PLT increment in hematology patients. As expected, the study found no significant differences in the 1-hour and 24-hour CCI after the transfusion of one and two pooled PC units. In our study, one pooled PC on average contained 3.0 x $10^{11}$/L and raised the median 1-hour and 24-hour PLT count by 23 x $10^9$/L and 14 x $10^9$/ L, respectively. This is comparable to the PLT increment of PCs with similar PLT counts. One adult PLT dose (one PC) in the UK contains around 2.9 x $10^{11}$ PLTs and typically raises the PLT count by 20 – 40 × $10^9$/L [18]. In Canada mean PLT count in pooled PLT is 2.98 ± 68 x $10^{11}$ and the expected increase in the PLT count is 15 – 25 x $10^9$/L [19].

The difference between groups of hematology patients in 1-hour CCI was not significant. However, there was a significant difference in 24-hour CCI in the ALLO group compared to AUTO ($p < 0.01$) and CHEMO groups ($p= 0.015$). The mechanisms responsible for poor PLT increment are still unclear and controversial [20]. Poor 1-hour PLT increase is considered to be immune-related, as a result of incompatibilities of PLT non-specific antigens, such as ABO, human leukocyte antigen class I (HLA-I) [21–23], and PLT-specific antigens named human PLT antigen (HPA) [5,24]. Whereas, poor 24-hour PLT increase is not immune-related and is considered to be a result of various clinical factors such as infection, fever (≥38◦C), disseminated intravascular coagulation, splenomegaly, heparin administration, bleeding, graft-versus-host disease. and intravenous antimycotic use (e.g. amphotericin B, penicillin and sulfonamides, vancomycin, ganciclovir). According to the explanation above, poor 24-hour CCI in our allogeneic HSCT patients was a consequence of non-immune-related factors, leading to increased PLTs consumption. The fact that autologous HSCT patients are usually stable and in remission and have a short period of thrombocytopenia after transplantation could explain why they had satisfied PLT increments. Several articles analyzed factors influencing low PLT increment in patients undergoing HSCT and the results were not corresponding [12–14,25], meaning that with the exception of already known there may be also some unidentified factors that may play important roles in insufficient PLT increment.

Contrary to our findings, Benediktsson et al. studied in detail the longitudinal development of PLT increment and found no difference in the mean CCI between different hematology groups in the first 24 hours post-transfusion [1]. This discrepancy could be the result of the exclusion

conditions and treatments with a very high demand for PLT transfusions in Benediktsson's study, such as acute promyelocytic leukemia, anti-thymocyte globulin or amphotericin B therapy < 3 days prior to the PLT transfusion. The results of our study give a more realistic insight into the real-life clinical setting of HSCT transplantation because we didn't have so strict exclusion criteria.

The median 24-hour CCI of 4.8 x $10^9$/L and 46.6% of ineffective PLT transfusions in allotransplanted patients are in line with the results reported by Balduini and colleagues. They found a mean 16-hour CCI of 5.7 x $10^9$/L and even 54.4% of ineffective PLT transfusions in children undergoing allotransplantation [14]. Two studies also reported a poor response to PLT transfusion and a high ratio of inefficient transfusions in allogeneic transplanted patients [12,13].

There are several limitations of our study. In the estimation of CCI in our study mean number of PLT in PC was used instead of the PLT count of each PC, which could influence our results. We did not collect detailed patients' clinical data during the study. Therefore, we were unable to further analyze the impact of different clinical factors on PLT increments.

## CONCLUSION

In conclusion, allogeneic HSCT patients had the lowest post-transfusion PLT increment 24 hours after transfusion and the highest ratio of inefficient transfusion, thus representing patient population with challenging PLT transfusion needs.

## ACKNOWLEDGEMENTS

We wish to thank the staff of the Division of Hematology at University Hospital Centre Zagreb for their assistance in the study.

**Conflict of interest: none declared**

**Financial support: none declared**

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## TABLES

**Table 1. Patient characteristics**

| Characteristics | n | Value |
|---|---|---|
| Gender | | |
| Male | n (%) | 29 (57) |
| Female | n (%) | 22 (43) |
| Age | years, median (range) | 59 (20-78) |
| Diagnosis | | |
| Acute myeloid leukemia | n (%) | 18 (34) |
| Acute lymphoblastic leukemia | n (%) | 4 (8) |
| Chronic myeloid leukemia | n (%) | 2 (4) |
| Myelodysplastic syndromes | n (%) | 3 (9) |
| Lymphoma | n (%) | 12 (24) |
| Multiple myeloma | n (%) | 12 (24) |
| Treatment stratification | | |
| Allogeneic HSCT | n (%) | 13 (26) |
| Autologous HSCT | n (%) | 17 (33) |
| Chemotherapy | n (%) | 21 (41) |

**Table 2. Platelet increment (CI and CCI) after transfusion of one and two units of pooled PCs**

| Variables | 1 unit of pooled PC | | 2 units of pooled PCs | |
|---|---|---|---|---|
| | Transfusion (N) | Median (range) (x $10^9$/L) | Transfusion (N) | Median (range) (x $10^9$/L) |
| 1-hour CI | 126 | 23.0 (2.0 - 90.0) | 47 | 44.0 (-1 - 98.0) |
| 24-hour CI | 133 | 14.0 (-6 - 96) | 57 | 28.0 (-9.0 - 94) |
| 1-hour CCI | 126 | 15.3 (1.2 - 53.9) | 47 | 14.8 (-0.3 - 52.9) |
| p = 0.808 | | | | |
| 24-hour CCI | 133 | 8.7 (-3.7 - 62.1) | 57 | 8.3 (-3.1 - 28.7) |
| p = 0.679 | | | | |

Legend: CI-Count Increment, CCI- Corrected Count Increment, PC-Platelet Concentrate

**Table 3. Ratio of ineffective platelet transfusions in different groups of hematology patients**

Legend: AUTO group, patients receiving autologous hematopoietic stem cell transplantation;

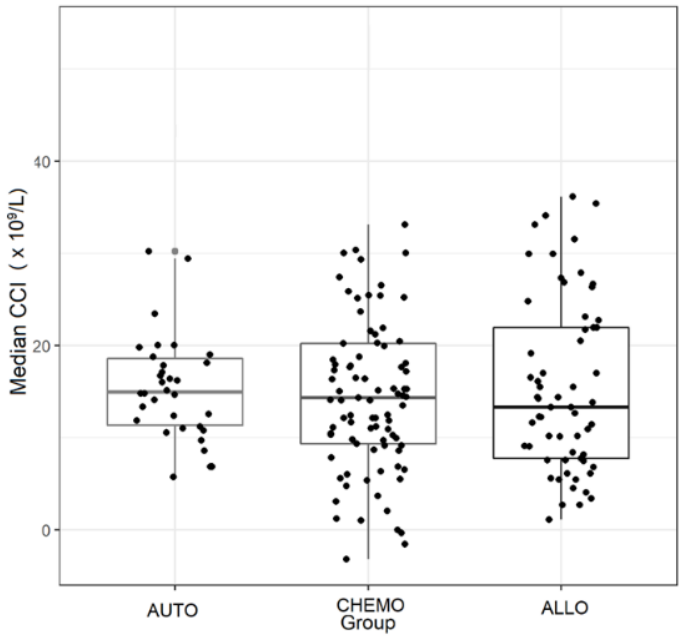
| Patient groups | Patient (N) | 1-hour CCI | | | | | 24-hour CCI | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | <7.5 x $10^9$/L | | ≥7.5 x $10^9$/L | | Total PLT transfusion (N) | <4.5 x $10^9$/L | | ≥4.5 x $10^9$/L | | Total PLT transfusion (N) |
| | | N | % | N | % | | N | % | N | % | |
| AUTO | 17 | 3 | 8.8 | 31 | 91.2 | 34 | 5 | 15.6 | 27 | 84.4 | 32 |
| CHEMO | 21 | 18 | 20.0 | 72 | 80.0 | 90 | 31 | 32.0 | 66 | 68.0 | 97 |
| ALLO | 13 | 13 | 21.7 | 47 | 78.3 | 60 | 34 | 46.6 | 39 | 53.4 | 73 |
| Total | 51 | 34 | 18.5 | 150 | 81.5 | 184 | 70 | 34.7 | 132 | 65.3 | 202 |

CHEMO group, patients receiving chemotherapy; ALLO group, patients receiving allogeneic HSCT; OTHER, patients undergoing invasive procedures

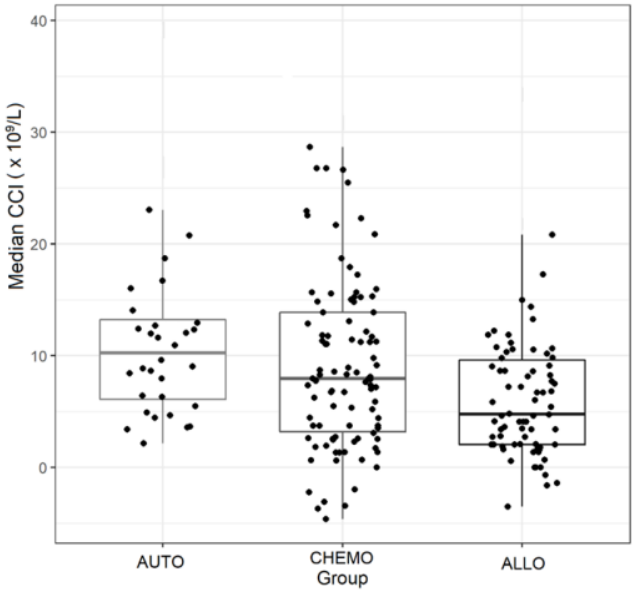
## FIGURES

**Figure 1.**

**A) 1-hour CCI in different groups of hematology patients**



**B) 24-hour CCI in different groups of hematology patients**




Legend CCI. Boxplot with black line, box, whiskers (median, interquartile range [IQR], "minimum"/"maximum", and outliers). AUTO group, patients receiving autologous hematopoietic stem cell transplantation; CHEMO group, patients receiving chemotherapy; ALLO group, patients receiving allogeneic HSCT.