Original Research

The Donor – Recipient Weight Ratio is a Reliable Marker for Cell Yield in Hematopoietic Stem Cell Donations

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Abstract

Bone marrow transplants remain an import source of hematopoietic stem cells for patients suffering from specific diseases like aplastic anemia, for pediatric patients with malignant and non-malignant blood cell disorders, and for situations in which graft-versus-host disease (GvHD) is a concern. Identifying the optimal donor to achieve a 3-5 x 10^8/kg of recipient weight TNC yield may be challenging. In an analysis of 687 consecutive donors, donor and procedure characteristics were related to TNC/kg of recipient weight using Spearman correlation coefficients as well as linear and multiple regression analysis. We found correlations between donor WBC (r = 0.17), donor platelet counts (r = 0.15), donor BMI (r = 0.10), and the percentage of donor estimated blood volume accessed for harvesting (r = -0.57) with TNC/kg of recipient weight. The strongest correlation existed between the donor-recipient weight ratio and the TNC/kg (r = 84). In a multivariate regression analysis, the donor-recipient weight ratio influenced the TNC/kg of recipient weight more significantly (adjusted R^2 = 0.84) than all other related variables put together. The minimal donor-recipient weight ratio associated with a TNC/kg of at least 3x10^8/kg of recipient weight was 0.8 (mean 3.425; 95% CI 2.01, 5.8). Using this donor-recipient ratio provides national bone marrow donor registries with a
practical and simple measure to assure optimal cell yield outcomes in hematopoietic stem cell donations.

**Keywords**

Stem cell transplant; bone marrow donation; donor characteristics

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### 1. Introduction

Allogeneic hematopoietic cell transplants (HCT) are an important part of treatment for a variety of malignant and non-malignant blood cell disorders. Today, 80% of cell grafts are retrieved through peripheral blood stem cell (PBSC) collections from unrelated donors. Bone marrow transplants, however, remain an important source of hematopoietic stem cells (HSC) for patients suffering from specific diseases like aplastic anemia, for pediatric patients with malignant and non-malignant blood cell disorders, and for situations in which graft-versus-host disease (GvHD) is a concern [1-6]. They are the focus of this study. Total nucleated cell (TNC) doses of 3-5 x 10^8 per kilogram of recipient weight are targeted for optimal cell engraftment and recipient survival, while TNC doses below 2 x 10^7/kg are considered inadequate [7-9].

Identifying the optimal donor under these circumstances may be challenging. Studies in the past have tried to determine donor characteristics that align best with optimal total nucleated cell (TNC) yield. Donor weight, body mass index (BMI), white blood cell (WBC) count, hemoglobin (Hb) and platelet counts have correlated positively with cell yields while harvest volume, the percentage of donor’s estimated blood volume harvested, female sex, and recipient weight have correlated negatively [10-15]. With a multitude of factors potentially aligning positively or negatively with harvest cell yields, national bone marrow donor registries may find it difficult to assign the best suited donor to their respective recipient.

This study aims to stratify and simplify the process by investigating if a single, easily identifiable factor – such as the donor-recipient weight ratio – can be used to facilitate the selection of well-matched donor-recipient pairs.

### 2. Materials and Methods

#### 2.1 Donors

All sequential donors who underwent a bone marrow harvest between January 2018 and October 2021 at the Georgetown University Blood and Marrow Collection Program (BMCP) were analyzed by retrospective review of data extracted manually from electronic medical records. Four donations were excluded from the analysis because their marrow was targeted for cryopreservation at a bone marrow bank without a designated recipient.

#### 2.2 Collection

All donors underwent the same, highly standardized procedure using 11 gauge 6-hole chronOS™ needles by DePuy Synthes® through bilateral single access points along the posterior iliac crest.
under general anesthesia. Marrow was retrieved in 10-15 ml aliquots and 3 advancements through the same needle insertion site, before redirecting the harvest needle. Intra-operative TNC (ioTNC) counts were taken after 600ml of collection to estimate the total volume of marrow required. Donor total blood volumes (BV) were estimated mathematically prior to the procedure using the Nadler formula (BV = 0.3669 x height in meters³ + 0.03219 x weight in kg + 0.6041 for males; BV = 0.3561 x height³ + 0.03308 x weight + 0.1833 for females) [16], and harvest volumes were restricted to the lower number of 20ml/kg of donor weight or 1,500ml total for men, and 18ml/kg or 1,500ml for women respectively. The 1,500 ml threshold was exceeded in some cases of donors with high BMI to satisfy TNC requests, as long as harvest volumes stayed within the 20ml/kg limit for men and 18ml/kg for women.

2.3 Statistical Analysis

The primary outcome variable of interest was the TNC yield per kg of recipient weight. Secondary outcomes included a determination of the size of influence donor characteristics had on the variance of TNC/kg of recipient weight. Anthropometric and hematological donor characteristics were summarized using mean and range for continuous variables. The association between donor characteristics and TNC/kg of recipient weight was analyzed by simple and multivariate linear regression models. TNC counts and continuous variables were log-transformed to produce normally distributed residuals and facilitate interpretation and graphic representation. R² were computed for each variable. Backward logistic elimination was applied to incorporate all variables with a conceivable effect on the outcome (TNC/kg) using 95% confidence intervals after analysis of variance inflation factors to control for collinearity between variables. Two-sided p values of less than 0.05 were considered statistically significant. Data analyses were performed using Stata® 16th edition statistical software.

3. Results

During the study period, 691 bone marrow harvests were collected. 687 were included in the analysis. 228 recipients were children of up to 40 kg of weight, while 459 recipients weighed more than 40 kg. Overall recipient weights ranged from 3 kg to 145 kg (mean 56.6 kg). Donor and procedure characteristics are summarized in table 1.

No significant differences were noted between female and male donors in important variables such as BMI, donor-recipient weight ratio and bone marrow harvest cell yield/mL, while other variables such as WBC and platelet counts, marrow volume collected, donor estimated blood volume accessed for harvesting, TNC/kg collected, and donor age showed minor differences that reached statistical significance mostly because of the large sample size. It was therefore deemed appropriate to analyze data from male and female donors jointly.

Six female donors had a Hb < 11g/dL (1 donor had Hb < 10g/dL), while 2 male donors had Hb < 12g/dL on the day of the procedure. All had donated an auto-unit of blood to be re-infused after the procedure. Ten donors had platelet counts below 150 (10⁹/L) on the day of the procedure. All had shown levels above 150 (10⁹/L) during their clearance physical exam and were clinically healthy on the day of the procedure. The same applied to 25 donors with WBC <4 (10⁹/L). All had higher levels during their clearance physical, and all of them did clinically well during and after the procedure.
Transplant centers requested a mean TNC count of 4.9 x 10^8/kg of recipient weight. This threshold was met or passed in 71.9% of cases allowing for a 10% error margin. In 9 cases (1.3%) the engraftment threshold of 2 x 10^8/kg of recipient weight was not met. The mean TNC count per kg of recipient weight for these donors was 1.84 x 10^8 (95% CI 1.73, 1.94). All these cases showed a significant weight differential between a lighter donor and a heavier recipient with a weight gap averaging 47.5 kg (95% CI 28.9, 66.1).

The donor-recipient weight ratio was strongly related to the TNC/kg of recipient weight in a univariate Spearman correlation analysis (r=0.84; p<0.0001). Positive Spearman correlation coefficients with the TNC/kg of recipient weight could also be established for donor WBC (r=0.17; p<0.0001), donor platelet count (r=0.15; p=0.0001), and donor BMI (r=0.10; p=0.0074). Of note, the comparatively low R-values for these correlations indicate a much weaker correlation with TNC/kg of recipient weight than that for the donor-recipient weight ratio. The percentage of donor’s blood volume accessed for harvesting was negatively correlated with the TNC/kg (r=-0.57; p<0.0001), while donor age, weight, hemoglobin and the size of the bone marrow collection did not correlate with the TNC/kg of recipient weight (Figure 1).
Figure 1 Logarithmically adjusted association between TNC/kg or recipient weight and donor BMI, donor-recipient weight ratio, procedure TNC yield per ml, donor platelet count, donor WBC, and percentage of estimated blood volume harvested. Indicated are also line of best fit and 95% confidence intervals.

Next, the variables that were significantly related to TNC/kg of recipient weight were subjected to a stepwise multivariate regression analysis with backward elimination after excluding collinearity between variables in an analysis of variance inflation factors (VIF). All variables had VIF < 2.3 (mean VIF 1.55) indicating a low level of potential collinearity. The donor-recipient weight ratio on its own provided 81% of the TNC/kg variance. Within the complete model, donor platelet count effects on TNC/kg of recipient weight were no longer significant. The remaining variables explained 89% of TNC/kg variance. The donor-recipient weight ratio contributed the greatest part of the TNC/kg variance.
variance (84%), more than the effects of the other variables combined. It appears that the donor-weight ratio can function reliably as a predictor for TNC/kg of recipient weight levels (Table 2).

**Table 2** linear (left) and multivariate (right) regression analysis with backward elimination of donor variable effects on TNC/kg of recipient weight.

| Coefficient (95% CI; p) | R² | Coefficient (95% CI; p) | Adj. R² |
|-------------------------|----|-------------------------|--------|
| Donor-recipient weight ratio | 1.71 (1.64, 1.77; 0.000)* | 0.81 | 1.86 (1.80, 1.92; 0.000)* | 0.84 |
| % donor blood volume harvested | -0.38 (-0.43, -0.34; 0.000)* | 0.29 | 0.18 (0.16, 0.21; 0.000)* | 0.21 |
| TNC/ml x 10⁶ | 0.46 (0.39, 0.52; 0.000)* | 0.23 | 0.34 (0.31, 0.37; 0.000)* | 0.45 |
| Donor WBC | 0.36 (0.12, 0.60; 0.003)* | 0.02 | -0.11 (-0.19, -0.02; 0.014)* | 0.01 |
| Donor BMI | 0.10 (0.02, 0.19; 0.013)* | 0.01 | -0.11 (-0.13, -0.07; 0.000)* | 0.08 |
| Donor platelets | 0.01 (0.00, 0.02; 0.002)* | 0.01 | 0.0 | 0.0 |
| Full model | | | | 0.89 |

* Indicates statistically significant correlation

To establish a minimum donor-recipient weight ratio for a reliable prediction of adequate TNC/kg of recipient weight, four donor-recipient weight ratio categories were analyzed that can be easily applied by national bone marrow donor registries (Table 3). A median TNC/kg of recipient weight of at least 3 x 10⁸ could only be achieved with a donor-recipient weight ratio above 0.8. At this level only 2.5% of cases did not achieve the minimum of 2 x 10⁸/kg required for engraftment.

**Table 3** TNC/kg of recipient weight for different donor-recipient weight ratios.

| Donor-recipient weight ratio | 95% CI | 90% CI | Median |
|-----------------------------|--------|--------|--------|
|                             | NCx10⁵/kg | NCx10⁵/kg | NCx10⁸/kg |
| ≤ 0.6 (n = 6) | 1.74 – 1.98 | 1.9 – 1.93 | 1.915 |
| > 0.6 - ≤ 0.8 (n = 51) | 1.88 – 5.1 | 1.99 – 4.6 | 2.84 |
| > 0.8 - ≤ 1 (n = 104) | 2.01 – 5.8 | 2.21 – 5.39 | 3.425 |
| > 1 (n = 525) | 2.02 – 39.4 | 2.04 – 39.21 | 5.58 |
| Total (n = 686) | 1.74 – 39.4 | 1.75 – 39.21 | 4.7 |

4. Discussion

The successful engraftment and survival of HLA-matched recipients depend to some extent on the number of hematopoietic stem cells transplanted. TNC counts of 3-5 x 10⁸ per kg of recipient weight have been established as optimal [7-9, 17]. Overall, cell yields achieved through bone marrow harvesting has declined over the recent years. Prokopishyn et al. [18] reported fewer centers performing sufficient procedure numbers to maintain previously achieved TNC yield standards. Donor characteristics associated with higher cell yields include donor weight [10, 14] and BMI [19, 20], donor WBC [19-21] and platelet counts [11, 22], while female sex [15, 19], increasing
age [21], higher harvest volumes [10, 13-15] and higher percentages of blood volume harvested [14] were associated with lower cell yields.

While many studies focus on the TNC yield achieved in bone marrow harvests, few studies relate these to recipient requirements. Anthias et al. [13] reported that donors weighing less than their recipients are less likely to meet a goal of $4 \times 10^8$ cells/kg or recipient weight. What is missing to date is a practical and easily applicable guideline for national bone marrow donor registries to select the optimal donor for a respective HLA-matched recipient. We believe to have established a standard of reasonable certainty for the prediction of a $3 \times 10^8$ TNC per kg of recipient weight applying a minimum donor-recipient weight ratio of 0.8. In our analysis the donor-recipient weight ratio influenced TNC per kg counts far more than all the other potentially related factors taken together.

The influence of some factors may be transient. For example, the role of WBC and platelet counts on hematopoiesis appear to depend on cytokine interactions between granulopoiesis, thrombopoiesis and hematopoietic progenitor cells in closely related respective stem cell niches within the bone marrow [23-29]. These interactions vary with the individual’s exposure to environmental stimuli [30, 31]. Other factors like the donor’s BMI appeared to have a positive influence on achieved cell counts when looked at individually. The effect reversed to a negative influence when analyzed together with other factors in a multivariate analysis.

This study is a single center study from the largest bone marrow harvest center associated with the National Marrow Donor Program in the United States. All procedures were performed by a small cadre of dedicated trained physicians and nurse practitioners following the same technical procedural standards and protocols. As a result, inter-center variations could be eliminated, and inter-individual variations kept to a minimum.

5. Conclusion

Assigning the best possible donor to an HLA-matched stem cell recipient is a difficult task for matching programs and donor centers. Multiple donor characteristics have been suggested to facilitate the selection, but simple and practical guidelines are missing for donor selection. We suggest using a donor-recipient weight ratio of 0.8 or higher as a reliable and easily applicable marker to predict a cell yield of at least $3 \times 10^8$/kg of recipient weight.

Author Contributions

All authors contributed to the conceptualization and implementation of the research.

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Competing Interests

The authors have declared that no competing interests exist.
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