

Bone marrow derived CD 34+ cells and leukocytes in 729 children and adults with non-malignant diseases

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Abstract

Background: To our knowledge, no large studies reporting bone marrow (BM) derived cell counts of children and adults with non-malignant diseases have been published so far. Thus, the primary objective was to evaluate BM-derived CD34+ and leukocyte cell counts in 729 female and male patients of different age groups who underwent autologous cell-based therapy for non-malignant diseases.

Methods: For this study, a retrospective data analysis of laboratory parameters including BM-aspirated and post-centrifuge concentrated CD34+ cells and leukocytes was performed. Associations and differences of cell counts between age groups, gender, and diagnose related group were evaluated.

Results: Included were data of 187 female and 542 male patients aged between 2 and 75 years, who underwent autologous cell-based therapy for various non-malignant diseases. The median percentage of CD34⁺ cells of leukocytes was 1.10% in BM-aspirate (BMA) and 0.96% in post-centrifuge BMA concentrate (BMAC). Significant moderate positive correlations were observed between CD34+ cells (count/ μ l) and leukocytes (count/ μ l) in BMA and in BMAC. Significant strong negative correlations were detected between age (years) and CD34+ cells (count/ μ l/kg) in BMA and in BMAC. No significant differences regarding CD34+ cells (count/ μ l) in BMA were detected between adults, while significant differences regarding cell counts were detected between diagnose related groups, but not between females and males.

Conclusions: This study demonstrated BM-derived CD34+ and leukocyte cell counts in BMA and BMAC of 729 patients with various non-malignant diseases. While BM-derived CD34+ cells were significantly higher in younger patients, similar cell counts were detected within adults.

Introduction

In the past decade, bone marrow (BM)-derived cell-based therapies have been performed in various fields of regenerative medicine. In spite of the fact that BM contains hematopoietic stem cells, the CD34 + cells are an essential part in therapy and are known as indirect indicators for progenitor cells and thus, are considered as the gold standard for stem cell quantifications.¹ Yet, little is known about standard values of these cells in the BM. CD34 + cell counts are still not routinely reported in therapeutic studies with autologous BM. Thus, crucial knowledge of what we are doing in regenerative medicine is at least in part lacking. The reason for this discrepancy may be that hematooncologist, who have the best knowledge in BM physiology, rarely engage in regenerative medicine, while on the other side, specialists (mainly surgeons) engaged in regenerative medicine have little access to hematology.

Flow cytometry analysis for quantifying single-cells such as the hematopoietic surface marker CD34 has been widely used in clinical practice, especially in peripheral blood of patients with malignant diseases.² To our knowledge, comprehensive studies reporting on typical amounts of CD34 + cells in BM are sparse. Sutherland et al.³ stated that approximately a range of 1 to 3% of BM cells express CD34 + antigen

(without reporting a sample size) and Brooimans et al.⁴ detected 1.4% of CD34 + in BM-aspirate (BMA) in a small series of patients.

Stem cell counts are important, since it is assumed that better clinical results can be achieved with a higher donor-site stem cell count.⁵ The volume of a graft required for hematopoietic stem cell transplantation is commonly based on either the number of CD34 + cells or the number of total nucleated BM cells.⁶

Furthermore, the impact of age is well documented for cell-based procedures, but controversial. On the one hand, grafts from older donors did not adversely affect outcomes of allogeneic hematopoietic cell transplantation as compared to grafts from younger donors in hematooncology, while on the other hand, lower CD34 + cell counts were reported in older donors,^{7–9} and older age correlated with inferior results¹⁰ or lower CD34 + cell counts in some specific diagnoses.¹¹ Thus, it seems clear that BM cell counts are deteriorating with increased age. However, the majority of studies reported data of patients with malignant diseases or their healthy donors,^{6–8,10} but little is known about patients with non-malignant pathologies.

With the present study, we are reporting counts of CD34 + cells and leukocytes in BMA and centrifuged BMA-concentrate (BMAC) in a large number of patients who underwent autologous stem cell transplantation for various non-malignant diseases. Cell counts were analyzed regarding influences of age, gender and diagnose related groups.

Material And Methods

For this retrospective study, all laboratory data of patients who underwent stem cell transplantation for non-malignant diseases up to 2019 were evaluated. The respective diagnoses of patients treated at the institute for regenerative medicine were spinal cord injury, amyotrophic lateral sclerosis, autism, cerebral palsy, neurodegenerative diseases (e.g. multiple sclerosis, Parkinson, ataxia), muscle dystrophy, and neurological diseases (e.g. traumatic brain injury, stroke). Included were female and male patients aged between 2 and 75 years with available BM-derived CD34⁺ cells (count/ μ l and count/ μ l/kg body weight) and leukocytes (count/ μ l and cells/ μ l/kg body weight) of the BMA and post-centrifuged BMAC.

Percentages of CD34⁺ cells of leukocytes and concentrations of BMAC of BMA were calculated. Data from procedures with missing or invalid cell counts were excluded.

The study was approved by the ethics committee of the Medical University of Graz (31–152 ex 18/19, Ethikkommission der Medizinischen Universität Graz, Auenbruggerplatz 2, 1.OG, 8036 Graz, Austria / EU). All methods were carried out in accordance with relevant guidelines and regulations.

All procedures were performed as point-of-care method in a laminar air flow operating room. Aspiration of BM was performed by the same experienced surgeon (G.S.K.) from the posterior and anterior iliac crest. Stem cells were harvested with a Yamshidi Needle (15ga x 2.688in MAX Bone Marrow Aspiration Needle,

ARGON Medical devices, Athens, USA) under sedoanalgesia. BMA was retrieved using 10ml syringes and changing direction repeatedly as published by Oliver et al.¹². Following, BMA was processed in the operating room according to the SmartRedux protocol (Biosafe, Eysins, Switzerland) using a fully automated cell separator system (Sepax® S-100; Cytiva Europe GmbH, Vienna, Austria).

One ml of the total BMA sample was immediately transferred to the same laboratory and analyzed with fluorescence activated cell sorter (FACS) using a stem cell kit from Beckman Coulter and the ISHAGE protocol (<https://www.bc-cytometry.com/PDF/DataSheet/IM3630.pdf>).

Statistical analysis

Demographic details were presented using descriptive statistics. Data distribution was assessed by visual inspection of histograms and the Kolmogorov-Smirnov test. Qualitative data were expressed by numbers and percentages and quantitative data as means with standard deviation or median with range. CD34 + concentrations (in times) after centrifugation were calculated as CD34 + cells (count/ μ l) in BMAC divided by CD34 + cells (count/ μ l) in BMA. For continuous and normal distributed data, independent t-tests were applied and Mann-Whitney U or Kruskal-Wallis tests were used for non-parametric data to determine differences between two or more groups, respectively. Bonferroni adjustments served for multiple testing. Spearman's rank correlation coefficients (rho) were used to assess the correlation between parameters. Statistical significance level was set at $P < .05$ (2-sided). Statistical analyses were performed using SPSS Statistics 25 (IBM Corporation, Armonk, NY).

Results

A total of 729 laboratory datasets were evaluated. There were significantly more children ($n = 445$, 61.0%) than adults ($n = 284$, 39.0%; $p < 0.001$) and males than females ($p < 0.001$) treated with autologous stem cell transplantation. Frequencies of CD34 + cells (count/ μ l) and leukocytes (count/ μ l) in BMA are presented in Supplement file Figure S1 and S2. The median percentage of CD34 + cells of the leukocytes in BMA as well as in BMAC was 1.1%. All demographic data are presented in Table 1.

Table 1
Demographic data

Characteristics	TOTAL (n = 729)
Age (years) at time of procedure	21.1 ± 19.6
Mean ± SD	11.0 (2–75)
Median (range)	
Age groups (n, %)	169 (23.2)
Children	231 (31.7)
Preschool (2–5 years)	45 (6.2)
School (6–12 years)	124 (17.0)
Adolescent (13–18 years)	120 (16.5)
Adults	40 (5.5)
Young (19–39 years)	
Middle-aged (40–59 years)	
Elderly (≥ 60 years)	
Gender (n, %)	187 (25.7)
Female	542 (74.3)
Male	
Diagnose related group (n, %)	151 (20.7)
spinal cord injury	97 (13.3)
amyotrophic lateral sclerosis	263 (36.1)
autism	149 (20.4)
cerebral palsy	37 (5.1)
neurodegenerative diseases	19 (2.6)
muscle dystrophy	13 (1.8)
neurological diseases	

Abbreviation:

Characteristics	TOTAL (n = 729)
Bone marrow aspirate (median, IQR)	15800 (10200, 23300)
Leukocytes (count/ μ l)	416 (192.7, 879.5)
Leukocytes (count/ μ l/kg body weight)	146 (75, 274)
CD34 $^{+}$ cells (count/ μ l)	4.47 (1.22, 12.90)
CD34 $^{+}$ cells (count/ μ l/kg body weight)	1.10 (0.66, 1.55)
Percentage of CD34 $^{+}$ cells of leukocytes (%)	
Post centrifuge concentrate (median, IQR)	85000 (46600, 137350)
Leukocytes (count/ μ l)	2174 (1124.3, 4024.3)
Leukocytes (count/ μ l/kg body weight)	800 (374.5, 1392.5)
CD34 $^{+}$ cells (count/ μ l)	18.46 (7.69, 43.48)
CD34 $^{+}$ cells (count/ μ l/kg body weight)	0.96 (0.58, 1.47)
Percentage of CD34 $^{+}$ cells of leukocytes (%)	
Abbreviation:	

IQR, interquartile range.

CD34 $^{+}$ cells (count/ μ l) and leukocytes (count/ μ l) in BMA (Fig. 1) and in BMAC showed moderate positive correlations ($\rho = 0.687$; $p < 0.001$ and $\rho = 0.663$; $p < 0.001$, respectively).

The median percentage of CD34 $^{+}$ cells of the leukocytes in BMA was significantly higher in children aged between 2 and 18 years (1.38%; IQR 1.03, 1.77) than in adults (0.62%; IQR 0.38, 0.88; $p < 0.001$). In BMAC the median percentage of CD34 $^{+}$ cells of the leukocytes was also significantly higher in children (1.28%; IQR 0.90, 1.74) than in adults (0.60%; IQR 0.41, 0.88; $p < 0.001$).

Very strong and strong negative correlations were detected between age (years) and CD34 $^{+}$ cells (count/ μ l/kg) in BMA (Fig. 2; $\rho = -0.827$, $p < 0.001$) and in BMAC ($\rho = -0.712$, $p < 0.001$), respectively. The negative relationship between age (years) and CD34 $^{+}$ cells (count/ μ l) in BMA ($\rho = -0.601$; $p < 0.001$) was moderate and weak in BMAC ($\rho = -0.285$; $p < 0.001$). All correlations between age and cell counts are presented in Supplement file Table S1.

Comparisons between age groups, gender, and diagnose related groups regarding BMA and BMAC showed significant differences between children and adults and between diagnose related groups, but not between females and males (Supplement file Table S2).

A comparison of CD34 + cells (count/ μ l/kg) in BMA between age-gender stratified groups showed significant differences between girls (9.3, range 0.8–42.9) and women (1.3, range 0.3–7.1; $p < 0.001$), boys (10.0, range 0.5–127.3) and men (1.0, range 0.2–7.7; $p < 0.001$), as well as between women and men ($p = 0.012$), but not between girls and boys ($p = 0.513$).

Comparison regarding CD34 + cells (count/ μ l) in BMA showed significant differences between age groups ($p < 0.001$), while no significant differences were detected between adults' age groups (19-39years vs. 40-59years: $p = 0.326$; 19-39years vs. 60-79years: $p = 0.874$; 40-59years vs. 60-79years: $p = 0.999$).

Percentages of CD34 + cells of the leukocytes in BMA of children and adults according to their non-malignant diseases are presented in Fig. 3.

Density gradient separation using a centrifuge-based system showed that the lower the CD34 + cells (count/ μ l) in BMA, the higher the concentration (times) of CD34 + cells (count/ μ l) in BMAC after centrifugation (Fig. 4) and thus, the system was able to increase the concentration of nucleated cells by a median of 4.59 (IQR 2.53, 8.85) times. Significant lower median concentration increase regarding CD34 + cells was detected in children (3.82, IQR 2.18, 6.81) than in adults (6.92, IQR 3.39, 13.8; $p < 0.001$).

Discussion

The present study investigated leucocytes and CD34 + cell counts in BMA and BMAC in the largest number of subjects with non-malignant diseases so far and included all ages ranging from 2 to 75 years. One major finding of 729 cell counts was that approximately 1% of leucocytes were CD34 + cells in BMA and in BMAC with slight variations according to age. Second, BM-derived CD34 + cells were significantly higher in children as compared to adults, whereas comparable cell counts were detected within the respective age groups of adults. Cell counts were independent of gender.

Results of a previous study reporting only a weak inverse relationship ($r=-0.4$) between age and the number of CD34 cells seem opposed to our findings on the first site. However, they mainly included a small series of elderly patients with chronic heart failure.¹¹ Indeed, we not only reported a mix of DRGs, we also showed differences regarding various age groups in a much larger sample size. Furthermore, our findings (higher cell counts in younger patients) support a previous study with a smaller sample size.⁶

Autologous BM-derived cell-based therapies in regenerative medicine are on the rise. While it is generally known that BMA contains a mix of nucleated cells and other biologics such as growth factors and exosomes¹³, comprehensive information regarding normal ranges of leucocytes and/or CD 34 + cell counts in BMA and BMAC in a large series of patients of all age groups was missing.

We found a significant positive linear correlation ($CD34+ = 8.3 \times 10^{-3} \text{ leukocytes} + 61.2$) between CD34 + cells and leucocytes ($\rho = 0.687$; $p < 0.001$). This finding add further knowledge to the findings of a study by Terstappen et al.¹⁴ ($0.96 \pm 0.30\%$ (range, 1.47–0.62%) in 10 adults) and Brooimans et al.⁴ ($1.5 \pm 0.7\%$ in 134 healthy donors).

Stem cells are mononuclear cells and therefore, a fraction of the bone marrow derived leukocytes. Surprisingly, to our knowledge no prior study described the positive and strong correlation between both parameters, which might be of use in future clinical practice. Since stem cells can only be identified using specific CD antigen sets (CD34, CD90, CD45, CD107,...), which is costly and laborious, this correlation can be utilized, to predict the amount of stem cells based on the number of bone marrow derived leukocytes alone, which is much easier. As a matter of fact, only a negligible share of publications reports the absolute number of stem cells used per patient.¹⁵ Using the newly described correlation, a much cheaper possibility exists, to assess, if a specific patient has a high or low stem cell number. It has to be assessed in the future, if patients with a higher leukocyte- and stem cell - count will have better outcomes and might therefore be better suitable for stem cell operations.

According to our data stem cell counts do not deteriorate in adults (18–75 years); this supports the work by Povsic et al.¹⁶ who reported that ageing is not associated with BM-resident progenitor cell depletion (18–85 years).

Yet, we are unaware of any study reporting data of cell counts in children (2-18years). Despite the fact that cell counts of our large group of children had several different diagnoses, leucocytes and CD 34 + cell counts were significantly lower in adults. It remains speculative, if the higher cell count in children is necessary for growth and differentiation up to the age of puberty. However, since cell counts remained stable in adults (18-75years), increasing age might not necessarily be a contraindication for autologous stem cell therapy.

Furthermore, lower cell counts may also be due to specific diseases, as for example reported by Terstappen et al.¹⁴ reporting lower stem cell counts to be indicative for unfavorable outcome.

It is also not clear yet, if heterogeneous clinical results are linked to heterogeneous bone marrow derived stem cell counts. One could assume, that a higher yield of stem cells might result in a superior clinical outcome. Anyway, the possible predictive value of stem cell counts needs further investigations, especially linking donor-site cell counts to clinical outcome and thus, to sort out patients with unfavorable cell counts to avoid unnecessary interventions.

Since the onset of regenerative medicine several centrifuges are available on the market for mononuclear cell concentration.^{17,18} The concentration factor in our data showed a negative correlation to the number of leukocytes in BMA. Thus, a higher degree of concentration is found in patients with a lower bone marrow leukocyte count. This in part counteracts the dilution occurring in any aspirate higher than 2ml, which is due to the inflow of peripheral blood into bone marrow during the aspiration process.¹⁹

Despite the large sample size reporting cell counts, there are some limitations: Cell counts were quantified at an extern laboratory and therefore, measurement accuracy could be influenced by transport, however serial tests with the laboratory found no significant difference between one to 12 hours of transport in ethylenediaminetetraacetic acid (EDTA) tubes. Furthermore, our data are probably not comparable to

individuals with other diagnoses than those of our study group. Severity of illness, not reported in this study, might also contribute to cell count variations and hence, can influence our data. Due to the retrospective study design, we are not able to provide data on other cells (e.g. red blood cell count) nor are we able to compare BM-derived cell counts with peripheral blood cells. Cell counts might also be influenced by BMA volume, which we did not measure in this study. Further studies of different age groups are needed (a) to evaluate typical BM-derived cell counts of individuals with other diagnoses than ours, (b) to report cell count related outcome, and (c) to link cell count data to epigenetic variables (e.g. smoking habits, body mass index, etc.) However, this large study provides baseline data for further evaluations regarding autologous BM-derived cell therapies.

Conclusion

This study demonstrated BM-derived CD34 + and leukocyte cell counts in BMA and BMAC of 729 patients with various non-malignant diseases. While BM-derived CD34 + cells were significantly higher in younger patients, similar cell counts were detected within adults.

Declarations

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Authors' contributions

CP: Conception and design, manuscript writing, and final approval of manuscript

BL: Collection and/or assembly of data, data analysis and interpretation, manuscript writing, and final approval of manuscript

PRH: Manuscript writing and final approval of manuscript

GSK: Conception and design, provision of study material or patients (As an experienced general and cardiac surgeon, he performed all stem cell procedures), collection and/or assembly of data, data analysis and interpretation, and final approval of manuscript

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Availability of data and materials

Datasets supporting the conclusions of this article are included within the article and its additional file.

Ethics approval and consent to participate

The protocol for this retrospective study, including a waiver of the informed consent requirement, was approved by the ethics committee of the Medical University of Graz (31-152 ex 18/19, Ethikkommission der Medizinischen Universität Graz, Auenbruggerplatz 2, 1.0G, 8036 Graz, Austria / EU). All methods **were carried out in accordance with relevant guidelines and regulations.**

Consent for publication

Not applicable.

Competing interests

The authors indicate no potential conflicts of interest.

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Figures

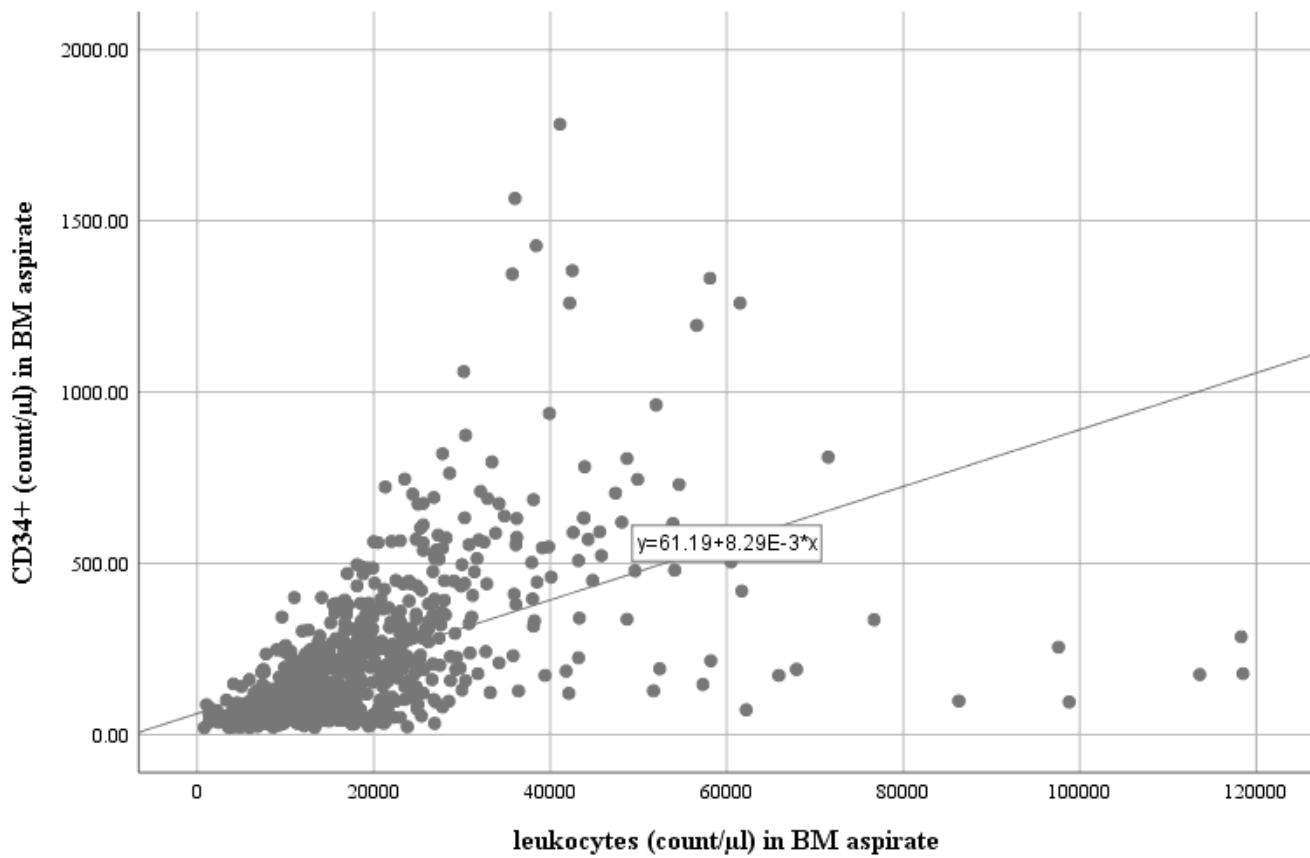


Figure 1

CD34+ cells and leukocytes. Scatter plot showing positive linear relationship between CD34+ cells (count/μl) and leukocytes (count/μl) in bone marrow (BM) aspirate.

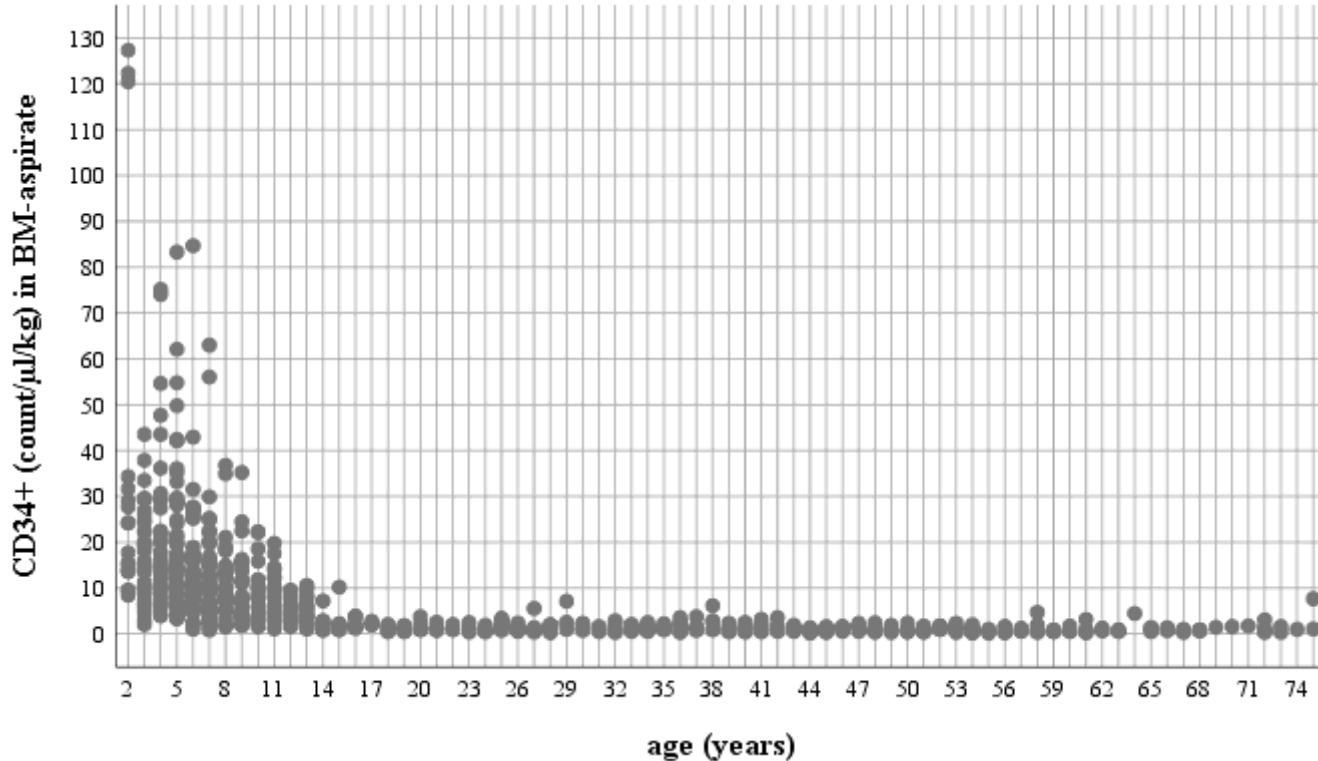


Figure 2

CD34+ cells and age. Scatter plot showing the relationship between CD34+ cells (count/ μ l/kg body weight) and age (years) in bone marrow (BM) aspirate.

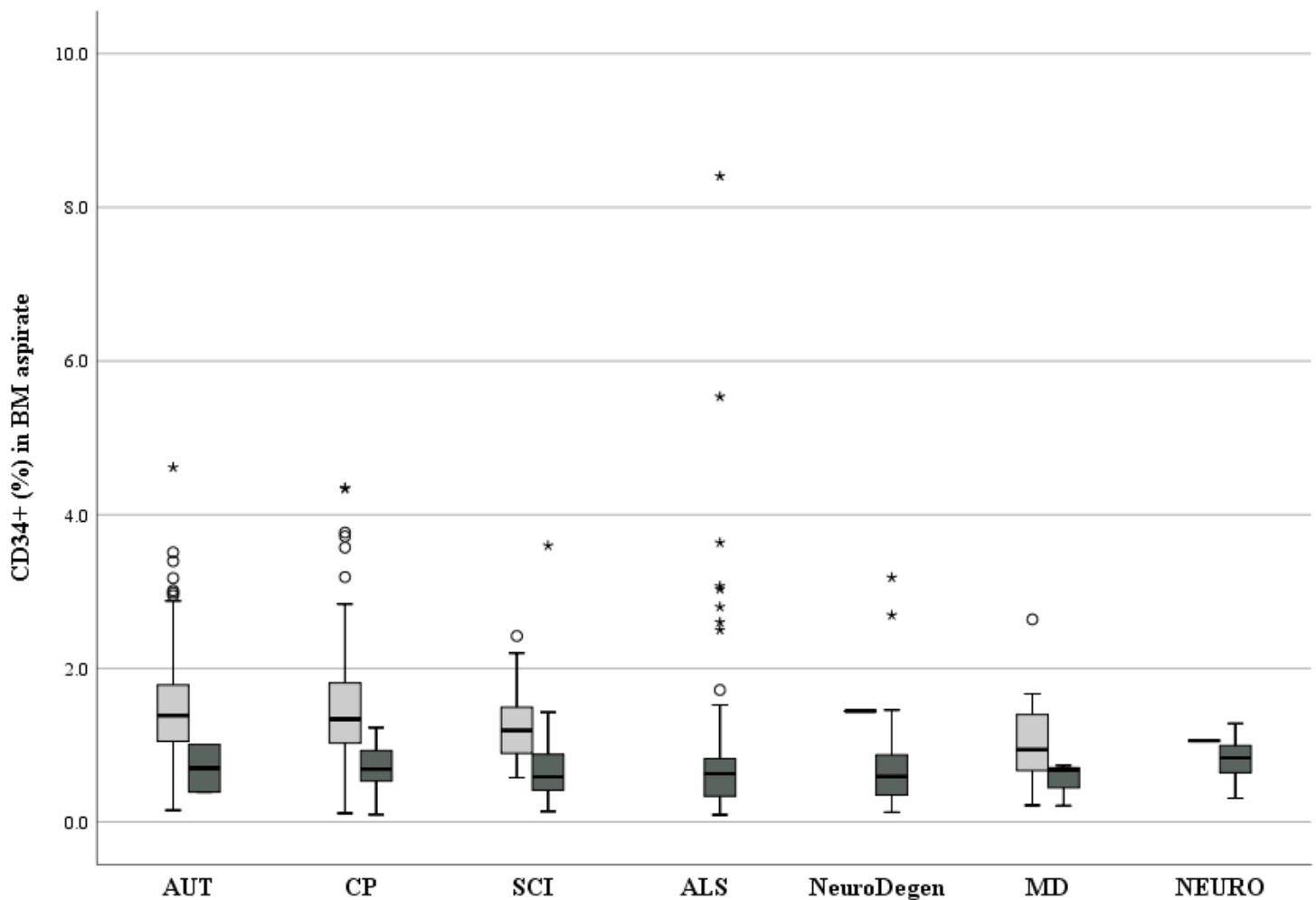


Figure 3

CD34+ cells of patients with non-malignant diseases. Percentage of CD34+ cells of the leukocytes (count/ μ l) in bone marrow (BM) aspirate according to the non-malignant diseases including autism (AUT), cerebral palsy (CP), spinal cord injury (SCI), amyotrophic lateral sclerosis (ALS), neurodegenerative diseases (NeuroDegen), muscle dystrophy (MD), and neurological diseases (NEURO) of children (2-18 years, light grey) and adults (dark grey).

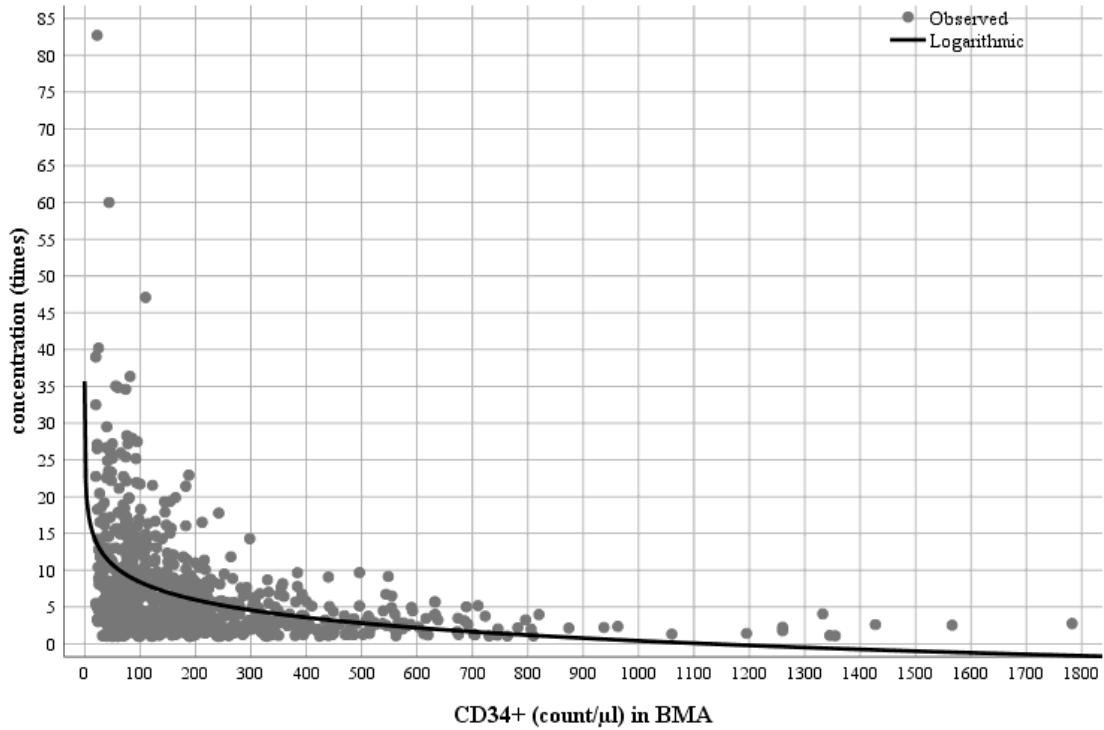


Figure 4

CD34+ cells in bone marrow aspirate (BMA) and bone marrow aspirate concentrate (BMAC). Scatter plot showing that the lower the CD34+ cells (count/ μ l) in BMA the higher the concentration (times) of CD34+ cells (count/ μ l) in BMAC after centrifugation.

Supplementary Files

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