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Effect of Aging and Predonation Comorbidities on the Related Peripheral Blood Stem Cell Donor Experience: Report from the Related Donor Safety Study

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A B S T R A C T

The development of reduced-intensity approaches for allogeneic hematopoietic cell transplantation has resulted in growing numbers of older related donors (RDs) of peripheral blood stem cells (PBSCs). The effects of age on donation efficacy, toxicity, and long-term recovery in RDs are poorly understood. To address this we analyzed hematologic variables, pain, donation-related symptoms, and recovery in 1211 PBSC RDs aged 18 to 79 enrolled in the Related Donor Safety Study. RDs aged > 60 had a lower median $CD34^+$ level before apheresis compared with younger RDs (age > 60, 59×10^6/L; age 41 to 60, 81×10^6/L; age 18 to 40, 121×10^6/L; $P < .001$). This resulted in older donors undergoing more apheresis procedures (49% versus 30% ≥ 2 collections, $P < .001$) and higher collection volumes (52% versus 32% > 24 L, $P < .001$), leading to high percentages of donors aged > 60 with postcollection thrombocytopenia $<50 \times 10^9$/L (26% and 57% after 2 and 3 days of collection, respectively). RDs aged 18 to 40 had a higher risk of grades 2 to 4 pain and symptoms pericollection, but donors over age 40 had more persistent pain at 1, 6, and 12 months (odds ratio [OR], 1.7; $P = 0.02$) and a higher rate of nonrecovery to predonation levels (OR, 1.7; $P = .01$). Donors reporting comorbidities increased significantly with age, and those with comorbidities that would have led to deferral by National Marrow Donor Program unrelated donor standards had an increased risk for persistent grades 2 to 4 pain (OR, 2.41; $P < .001$) and failure to recover to predonation baseline for other symptoms (OR, 2.34; $P = .004$). This information should be used in counseling RDs regarding risk and can assist in developing practice approaches aimed at improving the RD experience for high-risk individuals.

INTRODUCTION

Over the past decade registries such as the National Marrow Donor Program (NMDP) have published detailed data describing the unrelated donor (URD) experience, identifying individuals at increased risk for pain and collection-related symptoms, slower recovery, need for placement of a central venous line (CVL), and severe adverse events [1–6]. In spite of the fact that roughly half of allogeneic hematopoietic cell donations come from related donors (RDs), data describing details of early toxicities and longer-term outcomes in these individuals are scarce, with only 1 large study focusing mainly on severe adverse events [7]. A possible explanation for the paucity of RD outcome studies is that URDs are handled by large registries that have a mandate to report detailed safety data, whereas in many countries RDs are treated by local transplant centers that are primarily focused on care of the recipient and rarely collect data on RD experiences.

Inadequate data regarding RDs is concerning for a number of reasons. Although URD registries have specific guidelines regarding donor clearance [8], there are not generally accepted guidelines about when to reject a RD, although a publication from the Worldwide Network for Blood and Marrow Transplant advocates for transplant centers to adopt standards similar to URD registries [9]. In addition, RDs vary tremendously in age (from infants to individuals in their seventies) and are often willing to donate to family members in spite of significant comorbidities or potentially increased donor risk.

With these concerns in mind a group of North American investigators teamed with the NMDP and the Resources for Clinical Investigators in Bone Marrow Transplantation at the Center for International Blood and Marrow Transplant Research (CIBMTR) to conduct a prospective observational trial of RDs of all ages collected at 53 transplant centers in the United States. The trial design included a primary comparison of RDs with URDs between ages 18 and 60 years (subject of a separate manuscript) as well as detailed study of the outcomes of pediatric donors (separate manuscript) and those over age 60. This report focuses on the effect of age and the presence of comorbidities on the adult peripheral blood stem cell (PBSC) RD experience from their predonation baseline through 1 year after donation, including recovery to predonation health. We also focus on the donation experience of PBSC RDs above age 60, comparing their outcomes with younger

donors, because safety data on this potentially more frail population are scarce [10–13].

METHODS

A total of 1211 RDs ≥ age 18 participated in the study. Before donation RDs underwent a comprehensive medical evaluation including a detailed history, physical examination, blood tests, and further workup as necessary per center standards. If approved for donation, RDs were approached for consent for this Institutional Review Board–approved study if they were willing and able to complete symptom reviews at 1, 6, and 12 months after donation administered by the CIBMTR Survey Research Group. The trial was registered at ClinicalTrials.gov (ID NCT00948636).

Data Collection

A predonation form including history of pre-existing medical conditions (comorbidities) was completed at the time of donor clearance. Details on collection-related symptoms and pain were gathered at 5 time points: predonation, peridonation (just before the first day of apheresis), and 1, 6, and 12 months after donation. Toxicity was defined by common toxicity criteria measures (grades 0 to 4) for symptoms commonly noted during PBSC and bone marrow collection (fever, fatigue, skin rash, local reactions to an injection, nausea, vomiting, anorexia, insomnia, dizziness, and syncope) and is called the modified toxicity criteria (MTC). This approach has been extensively validated by the NMDP and published previously [2,3,14,15]. Pain was assessed for the back, bones, head, hip, i.v. site, joints, limbs, muscles, neck, throat, or other. Pain was graded on a scale of 0 to 4 as none, mild, moderate, severe, or disabling. Pain and toxicity measures were assessed by the transplant center at predonation and peridonation time points, and the CIBMTR Survey Research group was responsible for follow-up assessments.

A product-specific collection form detailed information on the collection procedure. Donors were also followed to assess long-term psychological recovery (reported previously [16–18]).

Endpoints

Skeletal pain represented pain in at least 1 of the following sites: back, bone, head, hip, joints, limbs, and neck. Severity of skeletal pain was defined as the maximum grade among these pain sites. Body symptoms were assessed using the MTC outlined above, and the peak toxicity level across symptoms was analyzed. Recovery to predonation levels by 1 year was defined as a pain or symptom score less than or equal to the score at predonation.

Predonation comorbidity ascertainment included assessment for a history of bleeding and gastrointestinal, genitourinary, hematologic, hepatic, pulmonary, cardiovascular, psychiatric, central nervous system, endocrine, autoimmune, or other significant coexisting disorders or diseases. For the purposes of analysis we divided comorbidities into 3 categories: (1) comorbidities that would not result in URD deferral according to NMDP standards [19,20], (2) comorbidities that clearly would have resulted in NMDP deferral, and (3) comorbidities that could possibly have led to a deferral, but more detailed donor clinical data would be needed to make that judgment.

Statistical Methods

Chi-square tests or Fisher's exact tests as appropriate were used to compare the incidences of skeletal pain and MTC symptoms as well as recovery to predonation levels in univariate analyses of donor age groups. Because event rates were substantially different on the first day of collection before apheresis versus at postcollection time points, separate multivariate analyses were done for these different time periods. Multivariate analyses using logistic regression models were conducted to examine impact of age on pain and MTC symptoms on the first day of collection before apheresis and for nonrecovery to predonation baseline pain and symptom levels at 1 year, while adjusting for other donor characteristics. Generalized estimating equations were used to compare age groups on pain and MTC symptoms across subsequent longitudinal time points of 1 month, 6 months, and 1 year, while adjusting for the correlation within subjects using a sandwich variance estimate.

All effects were estimated via odds ratios (ORs). Donor age was a main effect forced into all models; stepwise model selection was used to determine additional donor characteristics to be included. The following donor and donation characteristics were considered for inclusion in the multivariate model: donor race/ethnicity, sex, body mass index, comorbidity classification, predonation baseline counts (WBCs, hemoglobin, platelets, neutrophils, and mononuclear cells), $CD34^+$ cell counts just before the first apheresis procedure, collection parameters (number of days of apheresis, volume of blood processed, CVL placement, granulocyte colony-stimulating factor [G-CSF] dose, and year of donation), and predonation symptoms (skeletal pain and maximum MTC grade). Interactions between donor age and other factors were assessed, but none was significant. For the generalized estimating equations model we additionally considered a time after collection effect and assessed the interaction between other factors and time point; no significant interactions with time were found.

RESULTS

Age Effect on Demographics, Collection, and Comorbidities

Table 1 shows characteristics of related PBSC donors in 3 age categories, 18 to 40 years (n = 261), 41 to 60 years (n = 695), and >60 years (n = 255) at donation. Notably, younger donors were more diverse in racial background. Older donors were at higher risk for requiring multiple days of collection (8% with ≥3 collections versus 3% in both younger groups, $P < .001$) and had higher volumes of blood processed during their collection procedures (32%, 40%, and 52% of younger, middle aged, and older donors, respectively, had >24 L processed; $P < .001$). Rates of CVL placement did not vary with age, but women were 2 to 3 times more likely to require CVL placement (37% of female RDs had a CVL placed).

Comorbidities increased significantly with age, with 45%, 63%, and 77% of RDs reporting at least 1 comorbidity in the younger, middle, and older age groups, respectively ($P < .001$, Table 1). Notably, in men over age 60, there was a significant increase in donors who would have definitely been deferred by NMDP standards (20%, compared with 3% and 8% in the younger cohorts, $P < .001$). Looking at specific categories of comorbidities, as might be expected, there was a notable increase between the youngest and oldest groups in almost all categories, but the increase was most prominent and statistically significant in cardiovascular (9% to 53%, $P < .001$), endocrine (8% to 25%, $P < .001$), and genitourinary conditions (2% to 8%, $P = .003$; Figure 1 and Supplemental Table 1). More than half of the donors above age 60 had cardiovascular comorbidities, mainly hypertension.

Age Effect on Hematologic Parameters and $CD34^+$ Mobilization

Table 2 shows key hematologic measures at predonation baseline, preapheresis on collection day 1, and postapheresis on collection days 1 and 2. Figure 2 illustrates ranges of WBC, hemoglobin, and platelets from precytokine administration through the mobilization and collection process by age group. Older donors (>60) had a trend toward lower WBCs ($P = .07$) and platelets ($P = .09$) before donation. A significantly lower predonation hemoglobin was noted in older male RDs (versus younger men, $P = .004$) and higher hemoglobin in older female RDs (versus younger women, $P = .001$). Cytokine mobilization resulted in lower median WBC values in older donors (46.3, 42.0, and 41.6×10^9/L in younger, middle age, and older donors, respectively; $P < .001$). Apheresis decreased hemoglobin by a mean of 1.56 to 1.86 g/dL from predonation (significantly more in women > 40 years old, $P = .01$) and decreased platelets a mean of 120 to 129×10^9/L, but most hematologic changes before and after individual apheresis procedures were not clinically meaningful. One important potential hematologic risk was noted, however, with significant thrombocytopenia occurring after multiple and larger volume apheresis procedures in older donors (26% of donors aged > 60 postapheresis day 2 and 57% postapheresis day 3 had platelet counts $<50 \times 10^9$/L).

In line with the lower median WBC counts in older donors noted above, there was a dramatic decrease in $CD34^+$ cell concentrations just before apheresis in older donors. Donors aged 18 to 40 had a median preapheresis $CD34^+$ count of 121×10^6/L (range, 17 to 1342 [see Table 2 for interquartile ranges]), whereas donors aged 41 to 60 had a median of 81×10^6/L (range, 7 to 1001) and donors > 60 years old had a median less than half of the youngest donor group (59×10^6/L [range, 3 to 1761];
$P < .001$).

Table 1
Characteristics of Adult PBSC RDs by Age at Donation

Variable	Age 18-40	Age 41-60	Age ≥ 61	P*
Number of donors	261	695	255	
Number of transplant centers	35	38	33	
Donor related				
Donor age at donation				<.001
18-30	115 (44)	0	0	
31-40	146 (56)	0	0	
41-50	0	267 (38)	0	
51-60	0	428 (62)	0	
61-70	0	0	228 (89)	
71 or older	0	0	27 (11)	
Median (range)	32 (18-41)	53 (41-61)	65 (61-79)	<.001
Donor sex				.52
Male	145 (56)	392 (56)	126 (49)	
Female	116 (44)	303 (44)	129 (51)	
Donor race/ethnicity				<.001
Non-Hispanic white	184 (70)	604 (87)	225 (88)	
Hispanic	29 (11)	34 (5)	10 (4)	
Black/African American	23 (9)	35 (5)	10 (4)	
Asian/Pacific Islander	17 (7)	12 (2)	7 (3)	
American Indian/Alaska Native	2 (1)	4 (1)	0	
Other/multiple race	3 (1)	4 (1)	2 (1)	
Decline/unknown	3 (1)	2 (<1)	1 (<1)	
Donor body mass index, kg/m^2				.061
Underweight (<18.5)	1 (<1)	2 (<1)	0	
Normal (18.5-24.9)	73 (30)	136 (21)	50 (20)	
Overweight (25-29.9)	75 (30)	250 (38)	85 (34)	
Obese (≥30)	98 (40)	270 (41)	112 (45)	
Unknown	14 (N/A)	37 (N/A)	8 (N/A)	
Median (range)	28.2 (18.5-57.0)	28.7 (17.8-57.9)	29.3 (18.7-48.5)	.212
Donor comorbidity, male				<.001
Absent	84 (58)	148 (38)	29 (23)	
Present-accept	23 (16)	75 (19)	12 (10)	
Present-indeterminate	34 (23)	137 (35)	60 (48)	
Present-defer	4 (3)	32 (8)	25 (20)	
Donor comorbidity, female				<.001
Absent	60 (52)	111 (37)	29 (22)	
Present-accept	21 (18)	52 (17)	15 (12)	
Present-indeterminate	28 (24)	98 (32)	68 (53)	
Present-defer	7 (6)	42 (14)	17 (13)	
Mobilization related				
Number of days agent administered				<.001
1	2 (1)	0	1 (<1)	
2	0	3 (<1)	1 (<1)	
3	2 (1)	12 (2)	4 (2)	
4	130 (50)	281 (41)	95 (37)	
5	97 (37)	322 (47)	105 (41)	
6	28 (11)	71 (10)	42 (16)	
7	1 (<1)	1 (<1)	5 (2)	
8	0	1 (<1)	2 (1)	
10	1 (<1)	0	0	
Unknown	0 (N/A)	4 (N/A)	0 (N/A)	
Mobilizing agents				.233
G-CSF	260 (>99)	692 (>99)	253 (99)	
G-CSF+granulocyte-macrophage-CSF	1 (<1)	0	0	
G-CSF+plerixafor	0	3 (<1)	2 (1)	
G-CSF average daily dose, μg/day				
Number assessable	252	666	249	
Median (range)	960 (480-1920)	912 (300-2040)	900 (480-1764)	.562
G-CSF average daily dose per donor weight, μg/kg/day				
Number assessable	252	662	247	
Median (range)	10.3 (4.7-21.1)	10.3 (4.7-22.1)	10.5 (4.7-22.8)	.404
Collection related				
Year of donation				.744
2010	35 (13)	78 (11)	27 (11)	
2011	83 (32)	218 (31)	79 (31)	
2012	92 (35)	283 (41)	103 (40)	
2013	51 (20)	116 (17)	46 (18)	
Number of days of apheresis				<.001
1	184 (70)	462 (66)	131 (51)	
2	69 (26)	214 (31)	103 (40)	
3	5 (2)	11 (2)	17 (7)	
4	3 (1)	7 (1)	1 (<1)	

(*continued*)

Table 1 (*Continued*)

Variable	Age 18-40	Age 41-60	Age ≥ 61	P*
5	0	1 (<1)	3 (1)	
Volume of whole blood processed, L				<.001
<18	124 (48)	255 (37)	64 (25)	
18-24	53 (20)	164 (24)	59 (23)	
≥24	84 (32)	275 (40)	132 (52)	
Unknown	0 (N/A)	1 (N/A)	0 (N/A)	
Median (range)	18.0 (.3-56.1)	20.0 (.4-112.6)	24.0 (.6-100.8)	<.001
CVL placement, male				.365
No	131 (90)	339 (86)	107 (85)	
Yes	14 (10)	53 (14)	19 (15)	
CVL placement, female				.738
No	70 (60)	189 (62)	84 (65)	
Yes	46 (40)	114 (38)	45 (35)	
CVL site				.569
Femoral	1 (2)	7 (4)	2 (3)	
Internal jugular	54 (90)	154 (92)	59 (92)	
Subclavian	5 (8)	6 (4)	3 (5)	

Values are n (%) unless otherwise defined.

* The Pearson chi-square test was used for comparing discrete variables; the Kruskal-Wallis test was used for comparing continuous variables.

The lower precollection $CD34^+$ levels in older donors had clinical consequences, because lower $CD34^+$ cell concentrations before collection had strong associations with numbers of procedures and risk of low platelet counts after collection. Median precollection $CD34^+$ cell concentration for donors undergoing a single apheresis procedure was 92×10^6/L, whereas those for those undergoing 2 and 3 or more procedures it was 46×10^6/L and 29×10^6/L, respectively (Supplemental Table 2). Donors experiencing platelet counts below 50×10^9/L after day 1 of collection had a median precollection $CD34^+$ level of 37×10^6/L, whereas those not going below platelet counts of 50×10^9/L after day 1 of collection had a median $CD34^+$ level of 92×10^6/L.

Finally, it is well understood in the mobilization literature that donors with precollection $CD34^+$ counts $< 20 \times 10^6$/L or especially $<10 \times 10^6$/L are highly likely to fail collection. The likelihood of this occurring significantly increased with age in our cohort: In the youngest cohort only 1% versus 11% in the oldest cohort had $CD34^+$ cell concentrations $< 20 \times 10^6$/L before collection, whereas 0 versus 4% had $CD34^+$ cell concentrations $< 10 \times 10^6$/L ($P < .001$ and .002, respectively; Supplemental Table 3).

Age Effect on Pain, MTC Toxicities, and Recovery to Predonation Health: Univariate Analysis

Table 3 and Figure 3A,B show an unexpected finding, with the highest overall level and intensity of pain associated with PBSC collection reported by the youngest age group (aged 18 to 40) and progressively lower levels of pericollection pain reported by older donor groups (grades 2 to 4 pain and 3 to 4 pain 52% and 20% in donors aged 18 to 40 versus 31% and 11% in donors aged > 60; $P < .001$ and .007, respectively). This observation was also true in pericollection for grades 2 to 4 MTC symptoms (24% in the youngest and 15% in the oldest group; $P = .012$). Specific locations of pain and a types of symptoms noted by age are shown in Figure 4A, B.

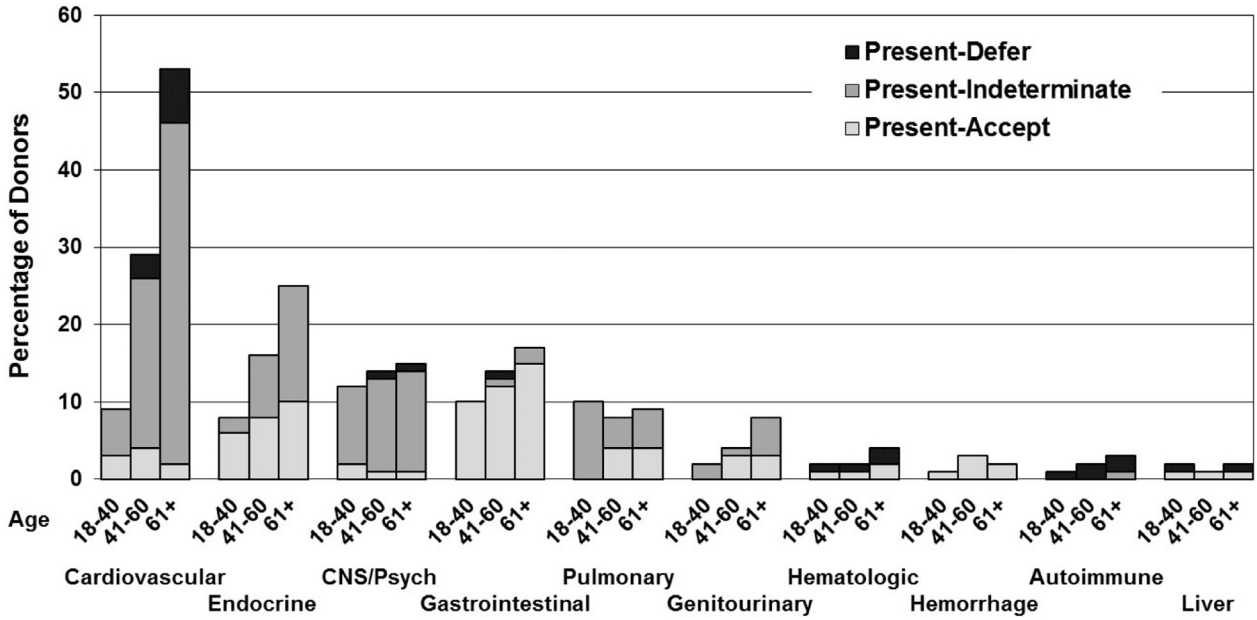

Figure 1. Classification of comorbidities in adult PBSC RDs by age at donation. Note that a donor can have more than 1 comorbidity. The *orange fill* represents donors who would have been deferred by NMDP standards, the *green fill* indicates donors with comorbidities that were indeterminate regarding deferral, and the *blue fill* represents comorbidities that would not have resulted in deferral.

Table 2
Hematologic Parameters in Adult PBSC RDs by Age at Donation

Variable	Age 18-40	Age 41-60	Age ≥ 61	*P**
Number of donors	261	695	255	
Predonation baseline				
WBC, $\times 10^9$/L				
Number assessable	259	689	253	
Median (range)	6.5 (2.7-13.6)	6.4 (2.9-15.3)	6.2 (2.9-12.3)	.073
Hemoglobin, male, g/dL				
Number assessable	144	389	124	
Median (range)	15.4 (11.5-17.6)	15.1 (10.2-18.6)	14.8 (11.4-17.3)	.004
Hemoglobin, female, g/dL				
Number assessable	115	300	129	
Median (range)	13.2 (10.8-15.7)	13.6 (9.8-16.8)	13.7 (11.1-15.9)	.001
Platelets, $\times 10^9$/L				
Number assessable	259	688	253	
Median (range)	242 (136-445)	237 (128-435)	233 (124-410)	.092
Collection day 1 preapheresis				
WBC, $\times 10^9$/L				
Number assessable	256	680	246	
Median (range)	46.3 (9.9-97.3)	42 (14.2-103.4)	41.6 (8.4-94.8)	<.001
Hemoglobin, male, g/dL				
Number assessable	139	376	120	
Median (range)	14.9 (11.3-16.6)	14.6 (11.3-17.7)	14.2 (11.2-17.2)	<.001
Hemoglobin, female, g/dL				
Number assessable	113	288	122	
Median (range)	12.7 (11.0-15.1)	13 (9.5-15.4)	13 (10.1-15.9)	.108
Platelets, $\times 10^9$/L				
Number assessable	256	680	246	
Median (range)	225 (97-438)	215 (79-564)	208 (83-336)	<.001
CD34 cells, $\times 10^6$/L				
Number assessable	147	392	124	
Median (range) [interquartile range]	121 (17-1342) [68-194]	81 (7-1001) [47-136]	59 (3-1761) [31-111]	<.001
Collection day 1 postapheresis				
WBC, $\times 10^9$/L				<.001
<30	31 (21)	142 (41)	46 (43)	
30-49.9	96 (64)	184 (53)	55 (51)	
≥50	22 (15)	23 (7)	7 (6)	
Unknown	112 (N/A)	346 (N/A)	147 (N/A)	
Median (range)	37.6 (11.6-75.4)	32.5 (12.8-74.1)	31.5 (16.1-70.2)	<.001
Hemoglobin, male, g/dL				.002
<10	0	1 (1)	0	
10-11.9	4 (5)	12 (6)	12 (24)	
12-13.9	46 (56)	119 (61)	28 (56)	
≥14	32 (39)	64 (33)	10 (20)	
Unknown	63 (N/A)	196 (N/A)	76 (N/A)	
Median (range)	13.7 (10.3-15.7)	13.4 (8.9-16.3)	13.2 (10.5-15.8)	.070
Hemoglobin, female, g/dL				
<10	2 (3)	8 (5)	1 (2)	.549
10-11.9	47 (70)	92 (60)	34 (59)	
12-13.9	18 (27)	52 (34)	22 (38)	
≥14	0	1 (1)	1 (2)	
Unknown	49 (N/A)	150 (N/A)	71 (N/A)	
Median (range)	11.4 (8.9-13.4)	11.6 (8.5-14.6)	11.6 (9.5-14.5)	.134
Platelets, $\times 10^9$/L				<.001
<50	2 (1)	7 (2)	3 (3)	
50-79	12 (8)	59 (17)	23 (21)	
80-99	20 (13)	64 (18)	26 (24)	
100-149	65 (44)	163 (47)	39 (36)	
≥150	50 (34)	56 (16)	16 (15)	
Unknown	112 (N/A)	346 (N/A)	148 (N/A)	
Median (range)	129 (18-277)	113 (39-244)	101 (44-233)	<.001
Collection day 2 postapheresis				
WBC, $\times 10^9$/L				.563
<30	10 (25)	48 (37)	23 (37)	
30-49.9	25 (63)	68 (53)	35 (56)	
≥50	5 (13)	13 (10)	4 (6)	
Unknown	37 (N/A)	104 (N/A)	62 (N/A)	
Median (range)	37.2 (7.9-55.9)	34 (12.1-77.9)	32.4 (17.4-82.5)	.252
Hemoglobin, male, g/dL				.203
<10	0	0	0	
10-11.9	3 (18)	4 (7)	7 (23)	
12-13.9	8 (47)	32 (57)	18 (58)	
≥14	6 (35)	20 (36)	6 (19)	
Unknown	20 (N/A)	48 (N/A)	28 (N/A)	

(*continued*)

Table 2 (*Continued*)

Variable	Age 18-40	Age 41-60	Age ≥ 61	P*
Median (range)	13.7 (11.4-15.5)	13.4 (10.5-15.2)	12.7 (10.1-15.0)	.028
Hemoglobin, female, g/dL				.870
<10	2 (9)	9 (12)	3 (10)	
10-11.9	16 (70)	40 (55)	20 (65)	
12-13.9	5 (22)	23 (32)	8 (26)	
≥14	0	1 (1)	0	
Unknown	17 (N/A)	56 (N/A)	34 (N/A)	
Median (range)	11.2 (9.5-13.3)	11.5 (8.1-14.3)	11.2 (8.7-13.3)	.368
Platelets, $\times 10^9$/L				.685
<50	9 (23)	28 (22)	16 (26)	
50-79	13 (33)	49 (38)	23 (37)	
80-99	5 (13)	24 (19)	13 (21)	
100-149	11 (28)	20 (16)	8 (13)	
≥150	2 (5)	8 (6)	2 (3)	
Unknown	37 (N/A)	104 (N/A)	62 (N/A)	
Median (range)	77 (31-157)	75 (14-209)	66 (21-165)	.254

Values are n (%) unless otherwise defined.

For pain at other time points, however, older donors fared worse. Older donors had higher predonation levels of pain versus younger donors, and a higher percentage of older donors reported pain at 1 year after collection (7% versus 17% versus 18% of donors in the youngest to oldest age groups reported grades 2 to 4 pain at 1 year; $P = .002$). Older donors were also more likely than younger donors to fail to return to their predonation pain levels (18% of 18- to 40-year-olds failed to return to predonation levels of pain at 1 month versus 27% of 41- to 60-year-old and 32% of >60-year-old donors [$P = .005$]; differences persisted at 1 year, although the P value fell short of significance, $P = .07$). As opposed to pain, MTC symptoms reported by RDs of all ages gradually returned to predonation baseline over the first year after donation (Figure 3B).

Age Effect on Pain, MTC Toxicities, and Recovery to Predonation Health: Multivariate Analysis

Pericollection pain and symptoms

Table 4 shows a multivariate analysis of factors contributing to risk for pericollection grades 2 to 4 pain and MTC symptoms. Older donors were less likely to experience pain (OR .41 for >60-year-olds versus the youngest donors; $P < .001$), whereas women, donors with predonation baseline pain, Hispanic donors, donors undergoing a single day of apheresis, and donors receiving a daily dose of G-CSF > 960 μg were more likely to experience grades 2 to 4 pain on the first day of collection before apheresis. For grades 2 to 4 MTC symptoms, again, older donors had a lower risk (OR .53 for >60-year-olds versus the youngest donors; $P = .006$). Donors with predonation baseline pain and Hispanic donors had an increased risk, whereas black donors had a lower risk for MTC toxicities.

Postcollection pain and symptoms at 1 month, 6 months, and 1 year

Table 5 shows that donors over age 40 had a 65% to 71% increase in risk for grades 2 to 4 pain after collection when measured at 1 month, 6 months, and 1 year. This persistent pain did not improve over time (Table 5 and Figure 3A). Female donors and donors with predonation baseline pain were also at increased risk for persistent grades 2 to 4 pain. Of note, donors who reported no comorbidities and those who reported acceptable comorbidities had the lowest risk for postcollection pain, whereas donors who had comorbidities that were indeterminate or who would have been deferred by NMDP standards had significantly increased risk for postcollection pain (OR versus no comorbidities, 1.39 and 2.41; $P = .054$ and $P < .001$, respectively). Postcollection MTC symptoms were not affected by age; however, women were at highest risk (OR, 2.37; $P < .001$) followed by donors with predonation baseline levels of pain (OR, 1.67; $P = .007$).

Nonrecovery to predonation baseline pain and symptom level at 1 year

Table 6 shows multivariate analysis of risks associated with the inability of individual donors to return to their predonation baseline pain and MTC symptom status. Age again had an important effect, with donors ages 41 to 60 and >60 having 1.75 and 1.66 ORs of nonrecovery to predonation pain levels ($P = .003$ and .022, respectively). Women were also at increased risk (OR, 1.46; $P = .006$). Of note, those who started with pain at predonation baseline were more likely to return to their predonation level of pain, pointing out that most pain reported in donors at 1 year occurred in donors who did not report pain at predonation baseline. Age did not appear to affect the risk of nonrecovery to predonation levels of MTC symptoms; however, donors reporting comorbidities that warranted more investigation to know if NMDP deferral would have occurred were at increased risk (OR, 1.74; $P = .012$) and those who would have been deferred by NMDP standards were at even higher risk of nonrecovery to predonation baseline MTC symptoms (OR, 2.34; $P = .004$). Skeletal pain at predonation baseline increased risk of nonrecovery to predonation levels of MTC symptoms. In addition, the presence of MTC symptoms at predonation baseline increased the likelihood of recovery to that predonation value. Of note, for both pain and MTC symptoms, donors entering the study during the later years of enrollment had an improved chance of recovering to predonation baseline.

DISCUSSION

Previous studies of the experience of PBSC collection and recovery in RDs have made only limited comments on the effect of aging [7,21–27]. Although a number of studies have shown a decline in the number of $CD34^+$ cells mobilized with older age, donor numbers assessed have been small [10–13]. Additionally, previous studies have not looked at how this decrease in donor $CD34^+$ yield influenced the overall experience of older donors. Our study shows that the median yield in donors over age 60 is half that of donors ages 18 to 40; additionally, 11% of older donors are very poor mobilizers, with preapheresis $CD34^+$ levels $< 20 \times 10^6$/L. This leads to older donors undergoing both more

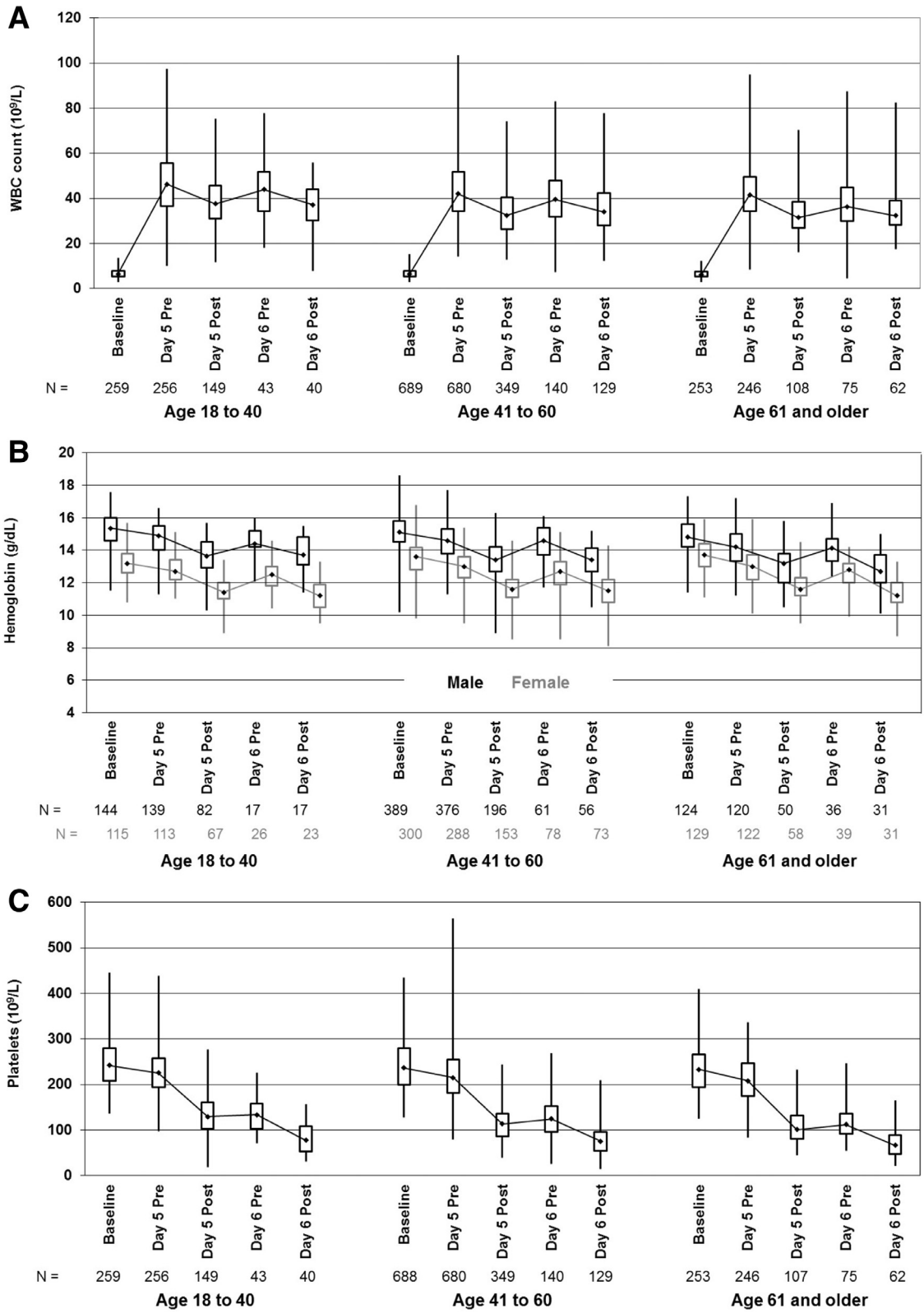

Figure 2. Adult PBSC RD hematology at baseline and collection by age at donation. Graphs show Minimum, Lower quartile, Median, Upper quartile, and Maximum. Day 5 is the first day of apheresis; Pre and Post refer to the apheresis procedure. (A) WBC counts. (B) Hemoglobin level. (C) Platelet counts.

Table 3
Univariate Analysis of Skeletal Pain and Body Symptoms Experienced by Adult PBSC RDs at Predonation, on the First Day of Collection before Apheresis, and at 1 Month, 6 Months, and 1 Year Postdonation, by Age at Donation

	Age 18-40			Age 41-60			Age ≥ 61			
Event and time point	No. of Patients	No. of Events (%)	95% CI*	No. of Patients	No. of Events (%)	95% CI*	No. of Patients	No. of Events (%)	95% CI*	P†
Skeletal pain										
Predonation, grades 2-4	261	14 (5)	(3-9)	695	65 (9)	(7-12)	255	23 (9)	(6-13)	.122
First day of collection, grades 2-4	260	134 (52)	(45-58)	690	281 (41)	(37-44)	254	78 (31)	(25-37)	<.001
First day of collection, grades 3-4	260	52 (20)	(15-25)	690	86 (12)	(10-15)	254	29 (11)	(8-16)	.007
At 1 month, grades 2-4	207	14 (7)	(4-11)	626	70 (11)	(9-14)	244	39 (16)	(12-21)	.009
At 6 months, grades 2-4	200	18 (9)	(5-14)	616	99 (16)	(13-19)	243	33 (14)	(10-19)	.039
At 1 year, grades 2-4	191	14 (7)	(4-12)	584	98 (17)	(14-20)	234	42 (18)	(13-23)	.002
Nonrecovery at 1 month	207	38 (18)	(13-24)	626	170 (27)	(24-31)	244	77 (32)	(26-38)	.005
Nonrecovery at 6 months	200	49 (25)	(19-31)	616	176 (29)	(25-32)	243	75 (31)	(25-37)	.327
Nonrecovery at 1 year	191	49 (26)	(20-32)	584	201 (34)	(31-38)	234	79 (34)	(28-40)	.071
Body symptoms										
Predonation, grades 2-4	255	13 (5)	(3-9)	678	10 (1)	(1-3)	250	7 (3)	(1-6)	.009
First day of collection, grades 2-4	260	62 (24)	(19-30)	691	110 (16)	(13-19)	255	39 (15)	(11-20)	.012
At 1 month, grades 2-4	207	10 (5)	(2-9)	627	40 (6)	(5-9)	244	14 (6)	(3-9)	.756
At months, grades 2-4	200	12 (6)	(3-10)	615	40 (7)	(5-9)	243	11 (5)	(2-8)	.575
At 1 year, grades 2-4	192	10 (5)	(3-9)	585	38 (6)	(5-9)	235	13 (6)	(3-9)	.813
Nonrecovery at 1 month	202	44 (22)	(16-28)	610	125 (20)	(17-24)	239	51 (21)	(16-27)	.897
Nonrecovery at 6 months	195	39 (20)	(15-26)	598	109 (18)	(15-22)	239	42 (18)	(13-23)	.793
Nonrecovery at 1 year	187	25 (13)	(9-19)	569	102 (18)	(15-21)	232	34 (15)	(10-20)	.271

Skeletal pain represents pain in at least 1 of the following sites: back, bone, headache, hip, joints, limbs, and neck. The severity of skeletal pain is defined as the maximum grade among these pain sites. Body symptoms include fever in absence of infections, fatigue, skin rash, injection site reaction, nausea, vomiting, anorexia, insomnia, dizziness, and syncope. The toxicity level is defined as the maximum grade among these symptoms. CI indicates confidence interval.

* Exact confidence interval.

† Fisher's exact test *P* value.

episodes of apheresis and higher volumes of apheresis compared with younger donors. This then means that a much higher percentage of older donors are experiencing significant thrombocytopenia associated with the collection process (26% of donors aged > 60 postapheresis day 2 and 57% postapheresis day 3 had platelet counts $< 50 \times 10^9$/L).

Previous studies have also looked at serious adverse events, and some have assessed pain [7,23,24]. These studies have shown that most donors have mild to moderate pain, and the process is generally well tolerated. They have not, however, shown the effect of age on pain and symptoms and also have not followed donors closely for these symptoms for an extended time period afterward. The analysis we report allows us to have a much more comprehensive understanding of the RD experience and to individualize how we counsel RDs. Knowing a donor's age, gender, and ethnicity, we can explain individually their risk of pain and other symptoms as well as their risk of having lingering mild discomfort as long as a year after the collection process.

It is important to note that although PBSC donors aged > 60 are at lower risk of significant acute pain compared with younger donors, they are less likely to recover to their predonation level of pain. It should be noted that older and younger donors who had pain at predonation baseline actually recovered to that predonation level more often. This means that the older donors who have some mild to moderate pain and have not recovered to their predonation level are generally donors who start with no predonation pain. Of note, in spite of this finding we showed in an earlier publication that RDs aged > 60 have equivalent health-related quality of life outcomes compared with donors aged 18 to 60 [16]. Lack of recovery to baseline pain and symptoms varied over the study period, with donors enrolled during the later part of the study having a better chance of recovery. Study methodology did not change, so the reason for this observation is unclear. Possible explanations include center changes in donor management because of closer attention paid to donors because of study participation or changes over time in the types of donors collected by the centers. Analysis of our data did not reveal a clear answer to why recovery changed over time.

Although we show that age is an important criterion in assessing risk of a donor for significant pain or MTC symptoms, our study is also the first to show that the presence of reported comorbidities in a donor has an effect on their likelihood of reporting pain at 1, 6, and 12 months after the collection and their likelihood of nonrecovery to their predonation baseline level of symptoms. Likely because of numbers we were not able to find associations of worse outcomes with a specific comorbidity or category of comorbidities, but we do note that donors who had no comorbidities or those who had comorbidities that would have been acceptable according to NMDP screening standards [19,20] were at lower risk than donors who clearly would have been rejected as an NMDP donor or for whom it was unclear whether they would have been rejected. This categorization of comorbidities is a broad way of determining the seriousness of a given reported comorbidity and indicates that comorbidities matter and should be important in the assessment and counseling of related PBSC donors. It also suggests that RD centers should consider adopting screening recommendations similar to those of URD registries, as suggested and outlined in a consensus paper from the Standing Committee on Donor Issues of the Worldwide Network for Blood and Marrow Transplantation [9]. This recommendation should be assessed in the context of understanding what donor options are available for a given recipient and the willingness of a given RD to assume some level of increased risk for their family member.

In summary, age matters with the process of RD PBSC collection. Older donors have more chronic pain at predonation

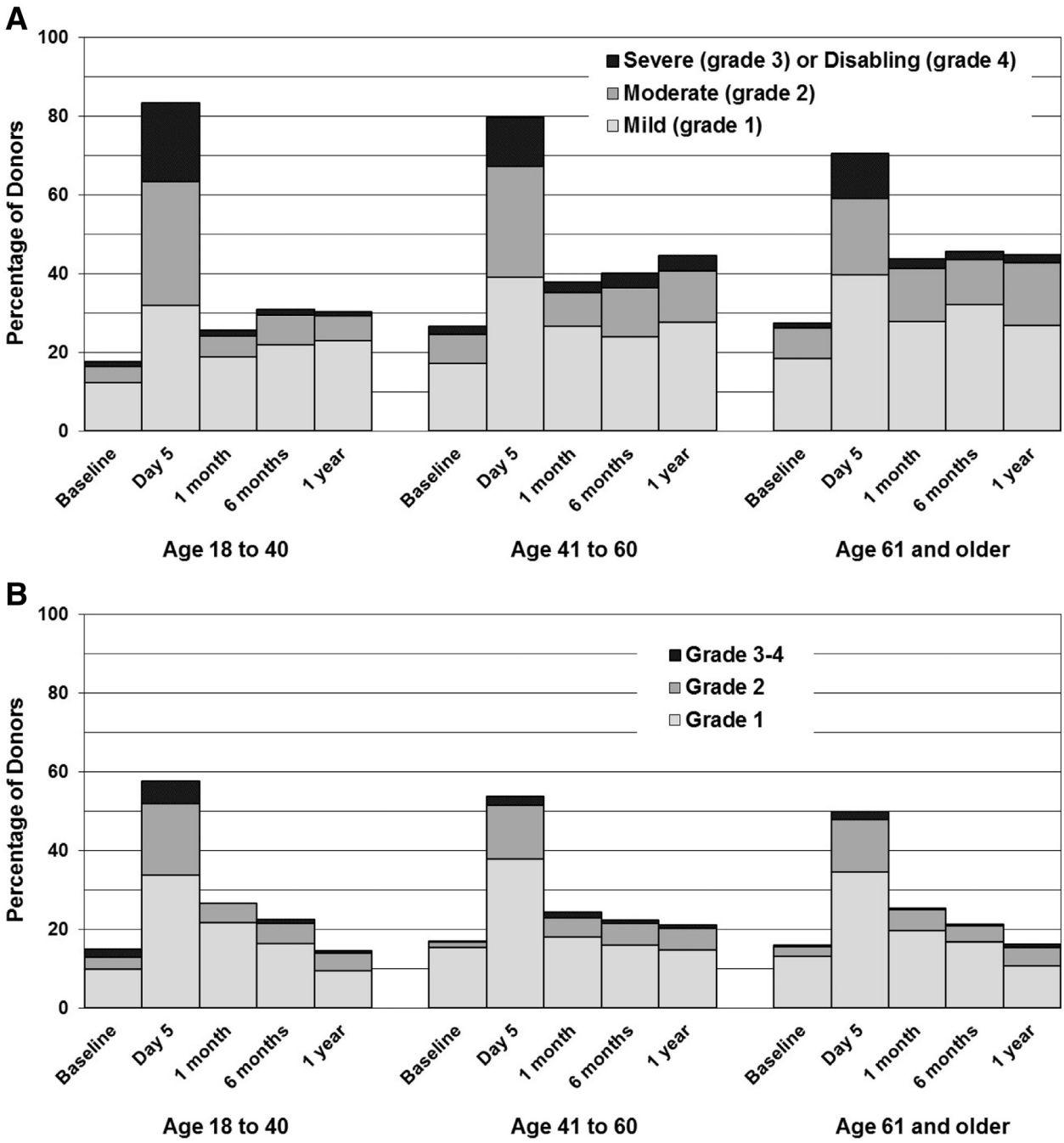

Figure 3. Skeletal pain and body symptoms experienced by adult PBSC RDs at predonation baseline, on the first day of collection before apheresis, and at 1 month, 6 months, and 1 year after donation, by age at donation. (A) Skeletal pain. Skeletal pain represents pain in at least 1 of the following sites: back, bone, headache, hip, joints, limbs, and neck. The severity of skeletal pain is defined as the maximum grade among these pain sites. (B) Highest toxicity level across all body symptoms. Body symptoms include fever in absence of infections, fatigue, skin rash, injection site reaction, nausea, vomiting, anorexia, insomnia, dizziness, and syncope. The toxicity level is defined as the maximum grade among these symptoms.

baseline and a higher number of and more significant comorbidities. After G-CSF mobilization older donors have lower levels of preapheresis $CD34^+$ cells, leading to a higher likelihood of multiple apheresis procedures or higher volume procedures. This in turn leads to a higher risk of postapheresis thrombocytopenia. Most significantly, even though donors over age 60 are less likely to report significant pain and symptoms during the collection than younger donors, they are more likely to have nonrecovery to predonation baseline up to 1 year after the procedure. These findings should be considered by RDs during the consent process, and studies or center practices aimed at preventing or improving the donor experience should be encouraged.

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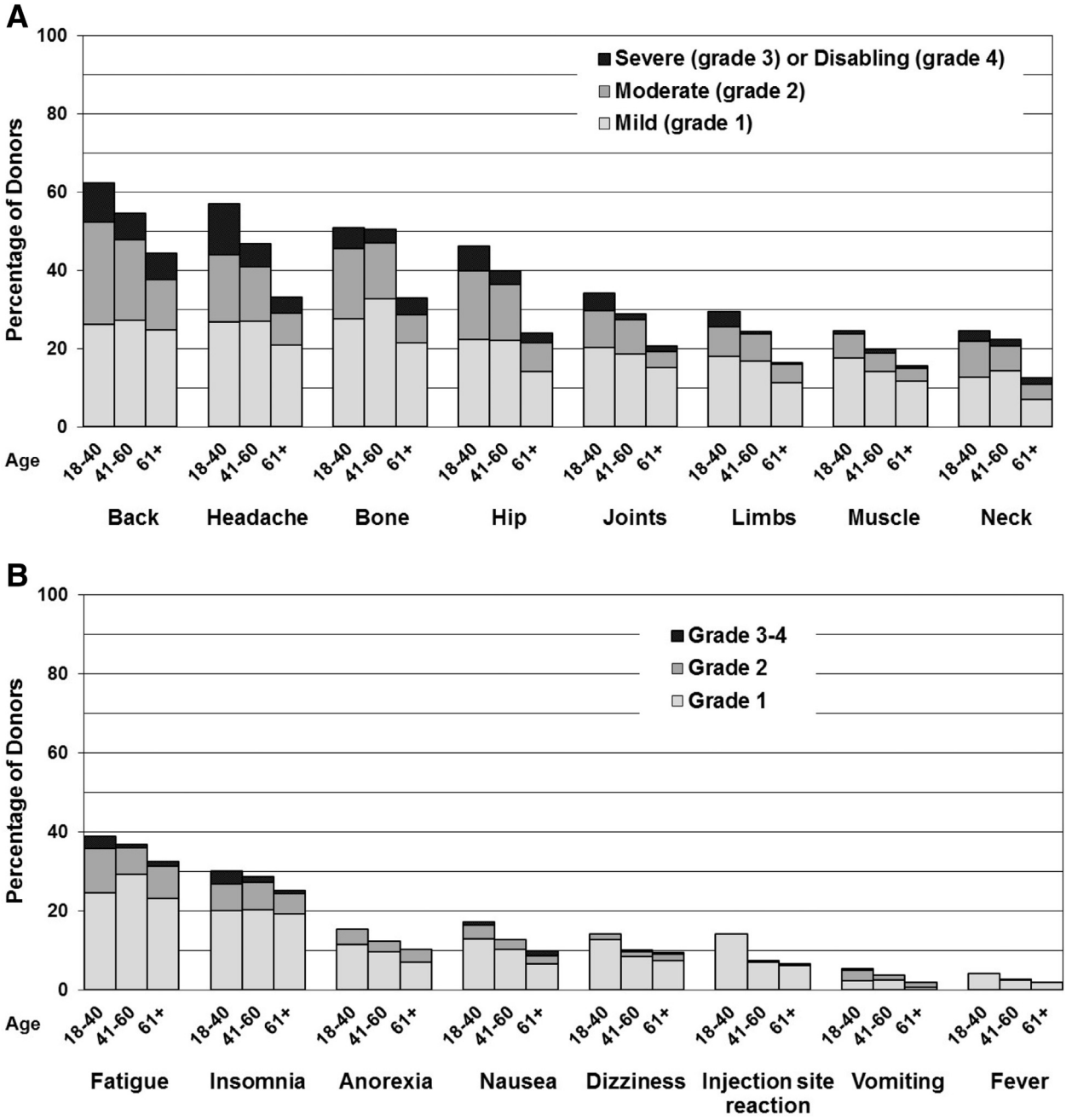

Figure 4. Severity of pain at various sites and body symptoms experienced by adult PBSC RDs on the first day of collection before apheresis, by age at donation. (A) Pain sites. (B) Body symptoms.

Table 4
Logistic Regression Model for Grades 2-4 Skeletal Pain and Grades 2-4 Body Symptoms on the First Day of Collection before Apheresis

Variable	OR	95% CI	*P*
Skeletal pain grades 2-4			
Donor age at donation			<.001
18-40	1.00		
41-60	.64	(.47-.87)	.004
≥61	.41	(.28-.60)	<.001
Donor sex			
Male	1.00		
Female	1.48	(1.15-1.90)	.002
Donor race/ethnicity			.009
Non-Hispanic white	1.00		
Hispanic	2.34	(1.39-3.91)	.001
Black/African American	1.05	(.62-1.76)	.863
Other/unknown	1.44	(.82-2.51)	.203
Predonation skeletal pain			
Grade 0	1.00		
Grades 1-4	2.19	(1.66-2.89)	<.001
Number of days of apheresis			
1	1.00		
>1	.72	(.56-.94)	.014
G-CSF average daily dose, μg/day			.007
0-960	1.00		
>960	1.54	(1.18-2.02)	.002
Unknown	1.07	(.54-2.11)	.844
Body symptoms grades 2-4			
Donor age at donation			.003
18-40	1.00		
41-60	.56	(.39-.81)	.002
≥61	.53	(.33-.83)	.006
Donor race/ethnicity			.023
Non-Hispanic white	1.00		
Hispanic	1.70	(.99-2.92)	.054
Black	.35	(.14-.90)	.030
Other/unknown	.76	(.35-1.66)	.493
Predonation skeletal pain			
Grade 0	1.00		
Grades 1-4	1.94	(1.40-2.70)	<.001

Skeletal pain represents pain in at least 1 of the following sites: back, bone, headache, hip, joints, limbs, and neck. The severity of skeletal pain is defined as the maximum grade among these pain sites. Body symptoms include fever in absence of infections, fatigue, skin rash, injection site reaction, nausea, vomiting, anorexia, insomnia, dizziness, and syncope. The toxicity level is defined as the maximum grade among these symptoms.

Table 5
Generalized Estimating Equations Model for Longitudinal Binary Data of Grades 2-4 Skeletal Pain and Grade 2-4 Body Symptoms at 1 Month, 6 Month, and 1 Year Post-Donation

Variable	OR	95% CI	*P*
Skeletal pain			
Donor age at donation			.022
18-40	1.00		
41-60	1.71	(1.12-2.60)	.013
≥61	1.65	(1.03-2.66)	.038
Donor sex			
Male	1.00		
Female	1.51	(1.16-1.96)	.002
Comorbidity			.005
Absent	1.00		
Present-accept	1.19	(.78-1.81)	.419
Present-indeterminate	1.39	(.99-1.93)	.054
Present-defer	2.41	(1.55-3.75)	<.001
Predonation skeletal pain			
Grade 0	1.00		
Grades 1-4	2.89	(2.21-3.79)	<.001
Time postdonation			.006
1 month	1.00		
6 months	1.30	(1.05-1.61)	.016
1 year	1.43	(1.14-1.80)	.002
Body symptoms			
Donor age at donation			.331
18-40	1.00		
41-60	1.19	(.75-1.89)	.455
≥61	.89	(.51-1.55)	.687
Donor sex			
Male	1.00		
Female	2.37	(1.66-3.39)	<.001
Predonation skeletal pain			
Grade 0	1.00		
Grades 1-4	1.67	(1.15-2.41)	.007

Skeletal pain represents pain in at least 1 of the following sites: back, bone, headache, hip, joints, limbs, and neck. The severity of skeletal pain is defined as the maximum grade among these pain sites. Body symptoms include fever in absence of infections, fatigue, skin rash, injection site reaction, nausea, vomiting, anorexia, insomnia, dizziness, and syncope. The toxicity level is defined as the maximum grade among these symptoms.

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Table 6
Logistic Regression Model for Nonrecovery to Predonation Skeletal Pain and Body Symptoms at 1 Year

Variable	OR	95% CI	*P*
Skeletal pain			
Donor age at donation			.013
18-40	1.00		
41-60	1.75	(1.20-2.55)	.003
≥61	1.66	(1.08-2.56)	.022
Donor sex			
Male	1.00		
Female	1.46	(1.12-1.92)	.006
Predonation skeletal pain			
Grade 0	1.00		
Grades 1-4	.39	(.28-.55)	<.001
Year of donation			
2010-2011	1.00		
2012-2013	.72	(.55-.94)	.016
Body symptoms			
Donor age at donation			.233
18-40	1.00		
41-60	1.24	(.76-2.03)	.382
≥61	.87	(.48-1.56)	.639
Comorbidity			.018
Absent	1.00		
Present-accept	1.51	(.89-2.57)	.126
Present-indeterminate	1.74	(1.13-2.68)	.012
Present-defer	2.34	(1.31-4.20)	.004
Predonation skeletal pain			
Grade 0	1.00		
Grades 1-4	1.77	(1.19-2.64)	.005
Predonation body symptoms			
Grade 0	1.00		
Grades 1-4	.22	(.11-.44)	<.001
Year of donation			
2010-2011	1.00		
2012-2013	.65	(.46-.92)	.014

Skeletal pain represents pain in at least 1 of the following sites: back, bone, headache, hip, joints, limbs, and neck. The severity of skeletal pain is defined as the maximum grade among these pain sites. Body symptoms include fever in absence of infections, fatigue, skin rash, injection site reaction, nausea, vomiting, anorexia, insomnia, dizziness, and syncope. The toxicity level is defined as the maximum grade among these symptoms.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2018.11.004.

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