Title

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Therapeutic Impact of Red Blood Cell Transfusion on Anemic Outpatients: the RETRO Study

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Abstract

BACKGROUND—Patients with cancer or other diagnoses associated with chronic anemia often receive red blood cell transfusion as outpatients, but the effect of transfusion on functional status is not well-demonstrated.

STUDY DESIGN AND METHODS—To estimate the effect of transfusion on functional status and quality of life, we measured 6-minute walk test distance, and fatigue- and dyspnea-related quality of life scores before and one-week after red cell transfusion in 208 outpatients age 50 with at least one benign or malignant hematology/oncology diagnosis. To account for potential confounding effects of cancer treatment, patients were classified into two groups based on cancer treatment within 4 weeks of the study transfusion. Minimum clinically important improvements over baseline were 20 meters in walk test distance, 3 points in fatigue score, and 2 points in dyspnea score.

RESULTS—The median improvement in unadjusted walk test distance was 20 meters overall, and 30 meters in patients not receiving recent cancer treatment. Fatigue scores improved overall by a median 3 points, and by 4 points in patients without cancer treatment. There was no clinically important change in dyspnea scores. In multiple linear regression analysis, patients who maintained hemoglobin levels 8 g/dL or greater at one-week post-transfusion, had not received recent cancer treatment, and who did not require hospitalization during the study showed clinically important increases in mean walk test distance.

CONCLUSIONS—Red cell transfusion is associated with a modest, but clinically important improvement in walk test distance and fatigue score outcomes in adult hematology/oncology outpatients.

Keywords

INTRODUCTION

Patients with hematological malignancies frequently receive red blood cell (RBC) transfusion as outpatients. In many cases, transfusion is required to maintain hemoglobin (Hgb) levels in patients with bone marrow failure due to underlying disease or chemotherapy. Often the decision to transfuse is based primarily on a pre-determined Hgb level. Increasingly, however, clinicians and patients consider functional status or quality of life indicators such as fatigue in the decision to transfuse, and these measures are incorporated into clinical trials that evaluate optimal transfusion thresholds.[1–3]

A recent study in a general medical population suggests that RBC transfusion improves patient-reported outcomes including fatigue and other quality of life measures.[4] However, the impact of RBC transfusion on physical performance or functional capacity is less certain. Trials in post-surgical patients did not show improvement in ability to walk

independently when RBC transfusion was used to keep Hgb at 10 versus 8 g/dL.[5,6] While anemia is associated with fatigue in cancer patients,[7,8] few studies have examined whether RBC transfusion in hematology/oncology patients has an impact on both fatigue and functional status measures such as timed-walk test performance.[9]

To characterize the effects of RBC transfusion on the functional status and quality of life in older adult hematology/oncology patients in the outpatient setting, we measured 6-minute walk test distance, and fatigue-related and dyspnea-related quality of life scores in over 200 patients before and one-week after RBC transfusion.

METHODS

Study Design and Participants

The Red Cells in Outpatients Transfusion Outcomes (RETRO) study was a prospective, observational study. Participants were recruited through outpatient clinics associated with 4 sites participating in the Recipient Epidemiology and Donor Evaluation Study-III (REDS-III) program funded by the National Heart, Lung and Blood Institute. Patient inclusion criteria were: age 50 or older, ambulatory, and anemic with a current order for RBC transfusion and at least one prior RBC transfusion administered within six months of study entry. Exclusion criteria included active bleeding, transfusion during dialysis, and unstable angina or myocardial infarction within 30 days prior to study enrollment. Only patients whose medical provider approved their participation in the study were enrolled.

To account for potential confounding effects of concurrent or recent chemotherapy on study outcomes,[10] patients were classified into two groups: The Cancer Treatment group was defined as those who received cancer treatment within 4 weeks either before or after the study transfusion; the No Cancer Treatment group did not. Cancer treatment was defined as chemotherapy including biological agents or hormonal therapy, or radiation therapy.

The study protocol was approved by the institutional review boards at each participating institution and the data coordinating center (RTI, Research Triangle, NC). Written informed consent was obtained from all participants.

Study Protocol

All transfusions were given as part of standard clinical care, and the decision to transfuse was made by the patient's physician. The pre-transfusion 6-minute walk test and fatigue and dyspnea questionnaires were administered on the day of the study transfusion. The walk test and questionnaires were repeated at 5–10 days after transfusion at a second clinic visit. A schedule of study visits is in Supplemental Table S1.

Hemoglobin was measured within a day prior to the study transfusion episode, at 30 minutes post-transfusion, and at 5–10 days post-transfusion at the time of the second walk test. N-terminal pro B-type natriuretic peptide (NT-proBNP) was measured in samples collected immediately before and 30 minutes after transfusion.

Additional RBC transfusions and interim clinical events defined as emergency department (ED) visits or hospital admissions occurring between the study transfusion and the second clinic visit were recorded. The sum of the RBC units transfused on the day of the study and after the study day but before the second walk test was designated as the "total RBC dose."

Outcomes

The two primary outcomes were change from before to one-week after transfusion in 6-minute walk test distance and fatigue score. Additional outcomes were change in dyspnea score and NT-proBNP levels with RBC transfusion. The minimum clinically important difference (MCID) for 6-minute walk test distance was 20 meters,[11–13] for the fatigue score was 3 points,[14] and for the dyspnea score was 2 points.[15]

Study Procedures

6-minute walk test.—The 6-minute walk test is self-paced and assesses submaximal functional capacity used for most activities of daily living.[16] The 6-minute walk test was performed indoors in a hospital corridor away from other foot traffic. A 25-meter distance with turnaround points was marked with cones. Patients rested for 10 minutes prior to testing and were instructed to walk as far as possible for 6 minutes per American Thoracic Society guidelines.[17]

Fatigue-related quality of life.—Fatigue-related quality of life was measured using the 13-question Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale Version 4. Scores range from 0 to 52 points with a higher score corresponding to less fatigue and better quality of life.[18] The FACIT-Fatigue scale has been used to evaluate the effect of blood transfusion in studies of cancer patients.[19]

Dyspnea-related quality of life.—Dyspnea-related quality of life was measured using the FACIT-Dyspnea scale short form. This 10-question scale has been validated in chronic obstructive pulmonary disorder and chronically ill patients[15,20,21] and is scored from 27–75 points. A lower score indicates less dyspnea and better quality of life.

Karnofsky performance status scale.—The Karnofsky Performance Status Scale is used to quantify the functional status of cancer patients and is a predictor of survival and other outcome measures.[22,23] The Karnofsky score ranges from normal functioning (score 100) to death (score 0). Karnofsky scores in the 80–100 range indicate ability to carry on normal activity with no special care needed. A Karnofsky score was assigned by a study coordinator to each patient at baseline as an overall measure of functional status.

Laboratory/Biomarkers—Complete blood counts (CBCs) were performed on an EDTA specimen using automated hematology analyzers in each hospital's clinical laboratory. Serum ferritin was measured using samples frozen and batch tested at a reference clinical laboratory (ARUP Laboratories, Salt Lake City, UT). The REDS-III Central Laboratory performed the NT-proBNP analyses on frozen samples using one lot of reagents with the Ortho Clinical Diagnostics VITROS ECi/ECiQ Immunodiagnostic Systems NT-proBNP assay.

Statistical Analysis

Transfusion recipients were analyzed as a total population and stratified by whether the patient received cancer treatment (primarily chemotherapy) within four weeks of transfusion. Study size (N=200) was based on the ability to detect at minimum a 20-meter difference in walk test distance before and after transfusion with 80% power. Absolute changes in walk test distance, fatigue scores, and dyspnea scores were computed for each participant as the difference between pre-transfusion and one-week post-transfusion measurements. In univariate analyses of subject-level change in each outcome, we performed Wilcoxon signed-rank tests for the null hypothesis that median change is equal to zero.

Three separate multiple linear regression analyses were performed for change in each outcome (walk test, fatigue, and dyspnea) using the backward elimination technique to identify significant clinical variables. The initial models for each outcome included the following covariates: demographics (age, sex, body mass index), Karnofsky score, cancer treatment status, ED visits or hospitalizations (interim events), number of RBC units transfused in the last 12 months, total RBC dose, pre-transfusion Hgb, post-transfusion Hgb, change in one-week Hgb, pre-transfusion fatigue scores, pre-transfusion NT-proBNP levels, and change in NT-proBNP level at 30 minutes. For the model of change in dyspnea, we also included baseline dyspnea and total volume transfused (volume of RBC and other fluids including saline). A set of clinically meaningful covariates identified prior to analysis were retained in each model regardless of statistical significance to adjust for known factors for that outcome. Supplemental tables S3A-S3C show all the covariates included in the final models. Interaction effects between cancer treatment status and other significant covariates were evaluated to select the final models. Final models were assessed by examining the residuals plotted against the predicted values for model fit and probability plots of the residuals to confirm the normality assumption. Two-sided p-values less than 0.05 were considered statistically significant. Analyses were conducted using SAS/STAT software, Version 9.4 (Cary, NC).

RESULTS

Study Recruitment and Participant Characteristics

Between November 2014 and January 2017, 750 patients age 50 or greater were screened for eligibility, primarily by reviewing clinic appointments. Of 467 candidates, 246 were not evaluated, ineligible, or declined to participate (Figure 1). A total of 221 participants enrolled, underwent pre-transfusion outcome assessments, received the study transfusion, and were classified as being in either the Cancer Treatment (n=149) or No Cancer Treatment group (n=72). Post-transfusion outcomes were available in 208 participants: 200 completed walk tests, 208 completed fatigue questionnaires, and 168 completed dyspnea questionnaires.

There were no major differences in baseline characteristics among patients receiving and not receiving recent cancer treatment (Table 1). Median patient age was 66 (IQR 59 to 74 years). The oldest participant was age 89 years. All patients had at least one primary benign

hematologic or cancer-related diagnosis; more than one primary diagnosis was possible. The most common primary diagnoses were hematologic malignancies including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), lymphoma, multiple myeloma and other leukemias. Solid tumors accounted for 6% of the primary diagnoses (13 patients). Non-malignant hematologic diagnoses included aplastic anemia (5 patients), and sickle cell disease (3 patients). At least one comorbidity (most commonly hypertension or depression) was present in 62% of patients. The median baseline Karnofsky score was 80 (IQR 80–90). The median number of RBC units transfused in the previous 12 months was 7 (Table 2).

Pre-transfusion Hgb was similar in Cancer Treatment and No Cancer Treatment groups (median for all subjects was 7.7; IQR 7.4 to 7.9 g/dL) and consistent with a transfusion trigger of <8.0 g/dL for most patients. On the day of the study transfusion episode, patients received either one unit (74%) or two units of RBCs (26%). There were no acute transfusion reactions reported. During the week-long period between the baseline and follow-up walk tests, 35 of 200 patients (17.5%) received one to three additional RBCs as ordered by their medical provider and 10% of patients had at least one ED visit or hospitalization. At the one-week visit, Hgb was similar in the Cancer Treatment and No Cancer Treatment groups (median for all subjects 8.7; IQR 8.1 to 9.4 g/dL). At that visit, 21% of subjects had Hgb levels <8.0 g/dL, 45% had Hgb between 8.0 and 9.0 g/dL, and 34% had Hgb levels >9.0 g/dL.

Unadjusted Change in Outcomes

Baseline 6-minute walk test distance was 266 m (IQR 187 to 379 m) in the No Cancer Treatment group and 323 m (IQR 213 to 392 m) in the Cancer Treatment group (Table S2). Overall, the median within-subject change in walk test distance was 20 m (IQR −6 to 47 m; p<0.001; Figure 2A, Table S2). For the No Cancer Treatment group, unadjusted median change in walk test distance was 30 m (IQR 0 to 50; p<0.001; 62% had MCID   20m). In the Cancer Treatment group, median change in walk test was 16 m (IQR −11 to 45; p<0.001; 45% had MCID   20m).

Median improvement in fatigue in all patients combined was 3 points (IQR −2 to 9; p<0.001; Figure 2B, Table S2). In the No Cancer Treatment group, the median fatigue score increase was 4 points (IQR 0 to 11; p<0.001; 54% had MCID   3 points) compared with 2.5 points (IQR −3 to 7.5; p<0.003; 50% had MCID   3 points) in the Cancer Treatment group.

For the two primary outcomes considered together, 70% of patients (146 of 208) showed clinically important improvement equal to MCID or greater in walk test distance only (but not fatigue), in fatigue score only, or in both walk test and fatigue score. In the No Cancer Treatment group, 78% (52 of 67 patients) improved in walk test distance and/or fatigue score. In the Cancer Treatment group, 67% (94 of 141 patients) improved in at least one or both outcomes.

Median improvement in dyspnea score at one-week for all patients was −0.1 points (IQR −6 to 2; p<0.01; Figure 2C, Table S2); for the No Cancer Treatment group was −1.9 points (IQR −6 to 0.4; p<0.05; 49% had MCID   −2 points); and for the Cancer Treatment group was 0.0 points (IQR −5 to 2.6; p=0.048; 38% had MCID   −2 points).

Pre-transfusion NT-proBNP levels ranged from 27.5 to >35,000 pg/mL (median 438.5 pg/ml, IQR 197.0 to 1065.0, Table 2). NT-proBNP levels did not change significantly immediately after transfusion (post-transfusion median 430.0 pg/ml, IQR 167.0 to 999.0). Baseline NT-proBNP level was not associated with change in dyspnea score (Pearson correlation coefficient [r] <0.08).

Regression Analyses of Changes in Walk Test, Fatigue, and Dyspnea

In the multivariable analysis of change in walk distance, larger improvements were predicted by no recent cancer treatment, absence of interim events, post-transfusion Hgb 8 g/dL, and total RBC dose (all p<0.05; Table 3, Table S3A). Patients with no recent cancer treatment had an estimated adjusted change in walk test distance of 25.3 m greater on average than patients who had received recent cancer treatment (p=0.02); patients without interim events had an average improvement of 44.5 m (p=0.01). Patients with post-transfusion Hgb 8 g/dL showed improvement 32 meters greater than those with Hgb <8 g/dL (p=0.01). Each RBC unit predicted improvement in walk distance of 17.1 meters per unit (p=0.04). However, in a separate analysis, we found no additional improvement in walk test distance in patients with post-transfusion Hgb levels over 9 g/dL versus 8–9 g/dL.

In the regression analysis of change in fatigue score, no recent cancer treatment and lack of interim events were associated with significant improvement in fatigue scores (both p<0.05; Table 3, Table S3B). In addition, lower baseline fatigue score (indicating worse fatigue) was associated with greater improvement in fatigue with transfusion (p<0.001).

For the regression model of change in dyspnea, only pre-transfusion fatigue and dyspnea scores were significantly associated with change in dyspnea, such that patients with worse baseline scores showed greater improvement in dyspnea (p<0.05 and p<0.001 for baseline fatigue and dyspnea, respectively; Table 3). None of the other variables used to adjust for change in dyspnea score, including cancer treatment group and NT-proBNP levels, was statistically significant in the dyspnea model (Table S3C).

DISCUSSION

The RETRO study demonstrated that on average, RBC transfusion improves short-term 6-minute walk test distance and fatigue in outpatients. Although some patients did not improve, most patients (including 78% of those not on any recent cancer treatment) showed clinically important improvement in either walk test performance (20 meters) or fatigue score (3 points) or in both measures one week after RBC transfusion. For both fatigue and walk test performance, improvement with RBCs was most apparent in clinically stable patients not on recent chemotherapy. There was no clinically important change in dyspnea scores.

RETRO is one of few studies to demonstrate a benefit of RBC transfusion on functional status, specifically 6-minute walk test distance. This benefit is consistent with the results of a small study demonstrating improved physiologic measures of exercise capacity with RBC transfusion in hematology patients.[9] However, in a study of patients post hip surgery, RBC transfusion did not have a significant impact on subjects' ability to walk independently 10

feet or across the room at 30- or 60-day follow-up.[5] Similarly, in older patients recovering from orthopedic surgery, 6-minute walk test performance was not affected by moderate post-operative anemia.[6,24]

Because of limited previous studies measuring 6-minute walk test distance in the hematology/oncology population, we evaluated the effect of transfusion on change in walk test using the MCID of 20 meters used to evaluate change in 6-minute walk test in patients with chronic medical conditions.[11–13] In addition, a 6-minute walk test distance of 20 meters converts to a gait speed of 0.056 m/sec, which falls squarely within the range (0.04 – 0.06 m/sec) that defines a small but clinically meaningful improvement for both community-dwelling and mobility-disabled elders.[12]

The observed improvement in unadjusted fatigue scores also is consistent with a small, but clinically important change in quality of life. Previous studies have shown that transfusion helps to mitigate the symptoms associated with anemia, an independent predictor of fatigue in oncology and palliative care patients.[19,25–30] The RETRO study provides further evidence that RBC transfusion is associated with short-term, modest improvement in fatigue in hematology/oncology patients.

Within both the Cancer and No Cancer Treatment groups, participants showed variable responses to RBC transfusion. Our model of change in walk test distance identified two other factors associated with improvement: Hgb 8 g/dL at one week and more units of RBC transfused. However, we have insufficient evidence to conclude that Hgb levels over 9 or 10 g/dL would provide additional benefit. Our study does suggest the possibility that more RBC units per transfusion or more frequent transfusions may further improve functional status in some patients. Randomized clinical trials to maintain higher Hgb levels in older, or other anemic cancer patients treated with chemotherapy may be needed to establish the optimal RBC transfusion trigger in this population.[2,31]

For both primary study outcomes, some participants did not improve. In the adjusted models, patients receiving recent cancer treatment and patients with intercurrent illnesses requiring hospitalization or ED visits responded less well to transfusion. RBC transfusion, while necessary and life-sustaining in patients with cancer, may not overcome the effect of underlying poor health on the quality of life and functional performance outcomes measured in the study. The finding that the effect of transfusion was limited in patients with increased disease burden may be especially important in transfusion decisions at the end of life in the palliative care setting.[29,32]

Shortness of breath can be an indication for RBC transfusion or a sign of a possible transfusion complication if from fluid overload or lung injury. In the RETRO study, the change in dyspnea score was statistically significant, but not large enough to be clinically important. Therefore, we found no evidence for exacerbation of dyspnea with transfusion in this outpatient population. Similarly, NT-proBNP levels were measured to address the hypothesis that study subjects with high baseline NT-proBNP levels or large transfusion-associated increases in NT-proBNP levels might be less likely to benefit from transfusion or might even be harmed by transfusion due to fluid overload. We found that NT-proBNP levels

did not change appreciably with transfusion and were not statistically significantly associated with any of the three study outcomes.

A significant strength of the RETRO study is that each patient served as his or her own control. This design reduces the risk of confounding by controlling for age, gender, and underlying disorder, and permits an efficient evaluation of the impact of transfusion. The study was limited by not including some patients because of scheduling difficulties, which might have led to selection bias or reduced generalizability. We did not distinguish between patients who received transfusion during curative versus palliative treatment. Finally, we did not collect information on the timing of chemotherapy relative to transfusion.

The participants in the RETRO study are reflective of a growing trend for older, adult hematology/oncology patients to receive transfusions as outpatients.[33] In the REDS-III study of current transfusion practice in the United States, over 58% of all outpatient red cell transfusion encounters had either blood disorders or malignancy as their primary diagnosis, and 75% of these outpatients were over age 50.[34] Similar to our own cohort and other studies, most outpatient red cell transfusion encounters in the REDS-III study (92%) involved one or two units.[34,35]

Patient-centered outcome measures of functional status and quality of life are increasingly important in evaluating treatments and interventions, including RBC transfusion, in cancer patients. The RETRO study used change in three outcome measures to evaluate the effect of transfusion: 6-minute walk test, FACIT-Fatigue score, and FACIT-Dyspnea score. We showed that transfusion is associated with clinically important improvement in two of these outcomes: walk test distance and fatigue. To define which patients might benefit from transfusion, future studies could include data from wearable monitors to capture effect of RBC on vital signs and physical activity,[36] or non-invasive measurement of oxygen saturation to capture tissue response to transfusion.[37] Such data, combined with pre-transfusion Hgb levels and results of patient-centered outcome studies like RETRO, will help clinicians personalize the decision to transfuse oncology patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

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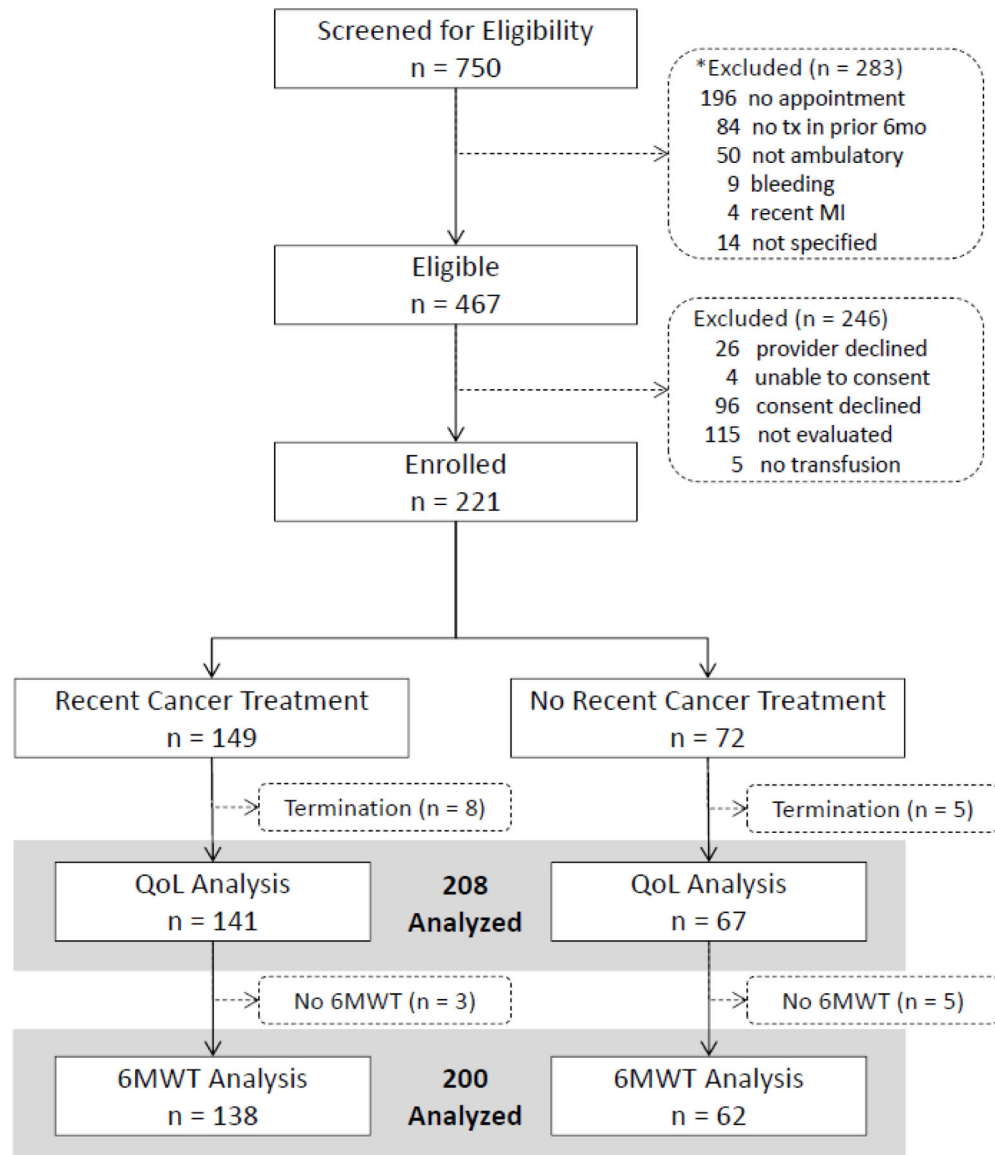
Figure 1. RETRO Subject Enrollment.
Subject flow chart showing screening for eligibility and classification to Cancer Treatment or No Cancer Treatment groups for the analysis of change in 6-minute walk test and quality of life. Termination indicates that the subject withdrew from the study and no outcome data was available for analysis. Reasons for termination were death (2 subjects, one each in the No Cancer Treatment or Cancer Treatment groups), change in the underlying medical condition (2 subjects), or lack of follow up due to scheduling difficulty. Eight patients completed quality of life questionnaires but lacked the second walk test due to hospitalization (3 patients), clinic schedule, or unrelated medical condition, and were excluded from the analysis of change in walk test. *Some subjects had more than one reason for exclusion at screening.
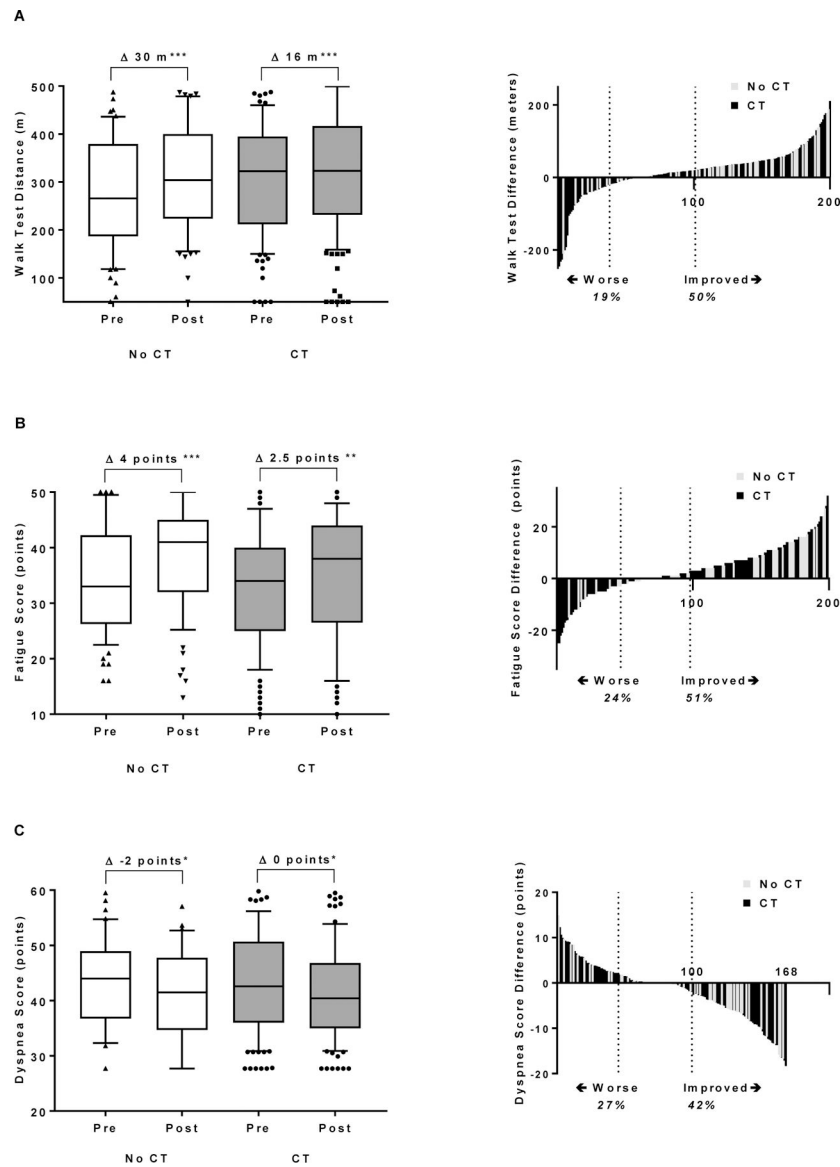
Figure 2. Change in Outcome Measures with RBC Transfusion.
Unadjusted pre- and post-transfusion findings based on three outcomes: (A) 6-minute walk
test distance, in meters; (B) FACIT-Fatigue scale score, in points; (C) FACIT-Dyspnea scale
score in points. Results for the No Cancer Treatment group are shown in light boxes or bars;
for the Cancer Treatment group results are shown in shaded boxes or black bars. (See also
Table S2.) *Left plots*: Central bar of boxplot displays median outcome and box shows values
between the 25th and 75th percentiles. Result above paired boxplots reports median change
in outcome and its statistical significance via signed-rank test (*p<0.05; **p<0.01;
***p<0.001). *Right plots*: Waterfall plot displays change for each subject (y-axis), ordered
from worst to best (x-axis). Vertical lines mark minimum clinically important differences
(MCID†) in worse and improved directions, with clinically unimportant changes falling
between the reference lines. Percentages indicate proportion of all subjects (No Cancer
Treatment and Cancer Treatment) worse or improved. MCID definitions of improvement:

(A) 6-minute walk test, increase by 20 meters or more; (B) FACIT-Fatigue score, increase by at least 3 points; (C) FACIT-Dyspnea score, decrease at least 2 points. MCID definitions of worse: As above but in opposite direction.

Table 1.

Study Population Demographics and Clinical Characteristics

Characteristic	All PatientsN=208	No Cancer Treatment N=67	Cancer Treatment N=141
Demographics			
Age	66 (59–74)	67 (60–75)	66 (58–73)
Sex – Male	116 (56%)	36 (54%)	80 (57%)
Race			
Caucasian/White	166 (80%)	52 (78%)	114 (81%)
African American	32 (15%)	13 (19%)	19 (13%)
Asian/Pacific Islander	1 (0.5%)	0 (0%)	1 (1%)
Native American	2 (1%)	1 (1.5%)	1 (1%)
Other/not stated	7 (3.5%)	1 (1.5%)	6 (4%)
Ethnicity			
Non-Hispanic	187 (90%)	61 (91%)	126 (89.5%)
Hispanic/Latino	8 (4%)	2 (3%)	6 (4%)
Other/not stated	13 (6%)	4 (6%)	9 (6.5%)
Primary Diagnosis[*]			
Acute myeloid leukemia	68 (33%)	21 (31%)	47 (33%)
Myelodysplastic syndrome	40 (19%)	13 (19%)	27 (19%)
Lymphoma	24 (12%)	5 (7%)	19 (13%)
Multiple myeloma	23 (11%)	5 (7%)	18 (13%)
Leukemia, other	20 (10%)	5 (7%)	15 (11%)
Solid tumor	13 (6%)	2 (3%)	11 (8%)
Other heme non-malignant	12 (6%)	8 (12%)	4 (3%)
Chronic lymphocytic leukemia	11 (5%)	2 (3%)	9 (6%)
Myeloproliferative neoplasm	11 (5%)	7 (10%)	4 (3%)
Other heme malignant	7 (3%)	2 (3%)	5 (4%)
Aplastic anemia	5 (2%)	4 (6%)	1 (1%)
Bone marrow transplant	2 (1%)	2 (3%)	0 (0%)
Sickle cell disease	3 (1%)	2 (3%)	1 (1%)
Body Mass Index	26.0 (23.5–30.2)	25.7 (22.5–28.4)	26.4 (23.8–30.6)
Karnofsky Score	80 (80–90)	80 (80–90)	80 (80–90)
Comorbidities			
Number of patients with at least one comorbidity[†]	129 (62%)	40 (60%)	89 (63%)
Hypertension	81 (39%)	21 (31%)	60 (43%)

Characteristic	All PatientsN=208	No Cancer Treatment N=67	Cancer Treatment N=141
Depression	29 (14%)	7 (10%)	22 (16%)
Diabetes	28 (13%)	7 (10%)	21 (15%)
Cardiovascular	22 (11%)	11 (16%)	11 (8%)
Laboratory			
Creatinine, mg/dL[‡]	1.0 (0.8–1.3)	1.1 (0.9–1.5)	1.0 (0.8–1.2)
Ferritin, ng/mL[§]	1383 (827–2206)	1256 (764–2201)	1456 (867–2211)
Medications			
Iron therapy[∥]	2 (1%)	1 (1%)	1 (1%)
Erythropoiesis stimulating agent	15 (7%)	7 (10%)	8 (6%)

Values expressed as median (interquartile range) or number (% group total). Table includes all patients with at least partial walk test or quality of life data (for the change in walk test analysis, 200 patients completed both pre- and post-transfusion 6-minute walk tests).

[*] All patients had at least one primary hematologic or cancer-related diagnosis; multiple diagnoses possible.

[†] More than one comorbidity possible, only top 4 comorbidities listed.

[‡] Most recent value prior to study transfusion.

[§] Reference range 30–530 ng/mL for males and 18–340 ng/mL for females age 50 years and older (ARUP Laboratories).

[∥] Oral or intravenous.

Table 2.

Baseline Transfusion Characteristics of the Study Population

Characteristic	All Subjects N=208	No Cancer Treatment N=67	Cancer Treatment N=141
Transfusion History			
Number of RBC units Transfused previous 12 months	7 (3– 17)	7 (4 – 15)	7 (3 – 17)
Number RBC Units Day of Study Transfusion			
1 RBC unit	153 (74%)	54 (81%)	99 (70%)
2 RBC units	55 (26%)	13 (19%)	42 (30%)
Total RBC Dose [*]	1 (1–2)	1 (1–2)	1 (1–2)
Pre-transfusion Hgb, g/dL			
< 7.0	21 (10%)	8 (12%)	13 (9%)
7.0–8.0	152 (74%)	47 (70%)	105 (75%)
> 8.0	33 (16%)	12 (18%)	21 (15%)
NT-proBNP, pg/mL [†]	438.5 (197.0–1065.0)	422.0 (163.0–1110.0)	440.0 (211.0–1050.0)

Values expressed as median (interquartile range) or number (% group total).

[*] Includes study transfusion (1 or 2 RBC units) plus additional RBC units transfused between walk tests (some patients as part of their clinical care received an additional 1–3 units of RBCs between walk tests).

[†] As a reference, in individuals age 65–74 without congestive heart failure, median NTproBNP is 98.3 pg/mL (Vitros, package insert).

Table 3.

Factors Predicting Change in Outcomes with RBC Transfusion using Multiple Linear Regression Analysis

Outcome Change Pre- to Post-transfusion	Cancer Treatment Group No CT vs CT	Interim Hospitalization or ED Visit No vs Yes	Post Transfusion Hgb 8 g/dL vs <8 g/dL	Total RBC Dose per RBC unit	Baseline Fatigue Score per fatigue scale point at baseline	Baseline Dyspnea Score per dyspnea scale point at baseline
6-Minute Walk Test, meters	25.3 (4.5, 46.2)	44.5 (9.0, 80.0)	32.0 (7.7, 56.2)	17.1 (1.1, 33.1)	NS	--
Fatigue-related Quality of Life, points	3.2 (0.6, 5.9)	5.3 (1.1, 9.4)	NS	NS	−0.4 (−0.5, −0.3)	NS
Dyspnea-related Quality of Life, points	NS	NS	NS	NS	−0.1 (−0.2, −0.02)	−0.4 (−0.5, −0.2)

Numbers represent the regression coefficient (estimated effect size) of each predictor's significant (P<0.05 or greater) association with the change in outcome. Confidence intervals (95%) are shown in parentheses. Complete model outputs are available in Table S3A-S3C.

NS indicates a predictor remained in the model but was not significant; -- indicates the predictor was not tested in the final model. For the Fatigue-related QoL scale, higher scores indicate better QoL and less fatigue; for the Dyspnea-related QoL scale, lower scores indicate better QoL and less dyspnea.

Total RBC Dose – for definition see Table 2. CT indicates cancer treatment, ED Emergency Department, and QoL Quality of Life.