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Early and sustained improvement in fatigue-related quality of life following red blood cell transfusion in outpatients

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Abstract

PURPOSE—Outpatients with hematologic disease often receive red cell transfusion to treat anemia and fatigue. The effect of transfusion on fatigue-related quality of life and how well this effect is sustained has not been quantified. The study aim was to describe the early and sustained impact over four weeks of red cells on patient-reported fatigue in outpatients age ≥ 50 receiving transfusion as routine clinical care.

METHODS—FACIT-Fatigue scale scores were measured pre-transfusion and at visits targeting 3, 7, and 28 days post-transfusion. Group-based trajectory modeling of patient fatigue scores by study day was used to identify the number of distinct trajectories (*Groups*), then longitudinal mixed-effects modeling of fatigue scores was used to estimate group-specific mean improvements early after transfusion and between days 3 and 28 post-transfusion.

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AUTHOR CONTRIBUTIONS

RB and ESL drafted the manuscript; ZK and JH performed statistical analyses. All other authors contributed significantly to the study design, data acquisition, or critical interpretation of the analyses. All authors reviewed the manuscript for important intellectual content.

CONFLICTS OF INTEREST

No authors declare a conflict of interest

RESULTS—Four distinct fatigue score trajectory groups were identified and were found to be correlated with baseline fatigue scores (means 12, 26, 34, and 47 points). In the three groups with the lowest fatigue trajectories (indicating greater fatigue), improvements in fatigue early after transfusion achieved the established minimum clinically important difference (≥ 3 points, *Group* p=0.0039). In all trajectory groups, mean fatigue levels did not change significantly between 3 and 28 days (± 1 point, *Group* p=0.60).

CONCLUSION—Patient-reported fatigue varies widely among older adult outpatients with hematologic disorders. Nonetheless, trajectory modeling suggests that most anemic patients can expect a noticeable improvement in fatigue in the first few days after transfusion that generally is sustained up to four weeks.

Keywords

patient-reported outcomes; fatigue; fatigue-related quality of life; red blood cells; transfusion practice

INTRODUCTION

Fatigue is a well-known symptom of anemia, and low hemoglobin levels are correlated with worse fatigue and poor quality of life in patients with cancer.[1–3] Recent studies of hospitalized general medical service patients indicate that red blood cell (RBC) transfusion improves short-term fatigue in inpatients,[4,5] but whether transfusion in the hospital is associated with a sustained, clinically important improvement after hospital discharge is not clear. [6,5,7] Similarly, few studies have examined whether RBC transfusion improves fatigue in outpatient transfusion recipients.[8–10]

In the outpatient transfusion setting, older patients with diagnoses such as leukemia or myelodysplastic syndrome frequently receive life-sustaining transfusions to maintain hemoglobin levels above a threshold of 7 or 8 g/dL to treat anemia secondary to chemotherapy or bone marrow failure. Fatigue is a frequent indication for transfusion in these patients, and the goals of care related to transfusion – including improving quality of life and functional status, or reducing symptoms – may differ in this group compared with inpatients.[4,11–13] Several studies have shown that erythropoietin-stimulating agents (ESAs) increase hemoglobin, reduce fatigue and thereby improve quality of life in oncology outpatients.[14–16] However, use of ESAs in this population is now less common due to thrombotic risk and other safety concerns.[17]

In our previous analysis using the RETRO (Red Cells in Outpatients Transfusion Outcomes) study population of older hematology/oncology outpatients receiving RBC transfusion, we demonstrated that transfusion was associated with clinically important (≥3 points) improvement in fatigue scores in many, but not all, participants at one week post-transfusion. [9] In the current analysis, to characterize the longitudinal pattern of fatigue after transfusion, we included additional fatigue scores collected from RETRO participants at timepoints three days after transfusion and up to 28 days post-transfusion.

The aim of the current study was to quantify the early improvement in fatigue post-transfusion and the sustained effect of transfusion at follow up. To this end, we used longitudinal models to quantify early (at three days) and sustained (from three days through up to 28 days) change in fatigue following RBC transfusion. To determine whether patients with a greater fatigue burden respond more favorably to transfusion than patients with relatively less fatigue, as has been seen in other clinical settings,[4,5] we employed trajectory modeling to identify such groups. After identifying four groups of patients experiencing distinct levels of fatigue, we further characterized these groups by clinically important patient and transfusion characteristics.

MATERIALS and METHODS

Study Population

The RETRO study was a prospective, observational study of older adult transfusion recipients before and after RBC transfusion recruited through four outpatient transfusion clinics associated with sites participating in the Recipient Epidemiology and Donor Evaluation Study-III (REDS-III) program funded by the National Heart, Lung and Blood Institute.[18] The study population has been previously described in detail,[9] but briefly, inclusion criteria were: age 50 years 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. Patients with active bleeding or recent myocardial infarction were excluded. Although not an entry criterion, all participants had at least one primary hematologic or cancer-related diagnosis. Patients were classified as having recent cancer treatment if treatment occurred within four weeks either before or after the study transfusion. Cancer treatment was defined as chemotherapy including biological agents, hormonal therapy, or radiation therapy.

The RETRO protocol was approved by the institutional review boards at each participating institution and the data coordinating center (RTI, Research Triangle, NC). Only patients whose medical provider approved their participation in the study were approached for enrollment, and written informed consent was obtained from all participants prior to any study activities.

Study Measures

All transfusions were given as part of standard clinical care, with the decision to transfuse made by the patient's provider. Patients received routine, on-going clinical care including additional RBC transfusions while on study. As previously described,[9] the baseline study transfusion occurred at Visit 1 (V1) and follow-up visits were scheduled for days 3 (V2), 7 (V3), and 28 (V4) post-transfusion. The fatigue questionnaire was administered at the beginning of each study visit; in person at clinic visits (V1, V3) and by telephone at follow-up visits (V2, V4).

Fatigue was measured using the validated, 13-question Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale Version 4. The instrument score range is from 0 to 52 points with a lower score equating to higher fatigue and lower quality of life.[19] The

scale has previously been used to evaluate the effect of blood transfusion in studies of cancer patients,[8] and the minimum clinically important difference (MCID) has been demonstrated to be at least three points.[20]

Baseline hemoglobin was measured the day before or the day of V1 and at 30-minutes after completion of the transfusion. A Karnofsky Performance Status Scale score was assigned to each participant at baseline by a trained study coordinator. The Karnofsky score is a functional status scale with scores in the 80–100 range on a scale of 100 indicating ability to carry on most normal activity.[21] Clinic visits at V1 and V3 included administration of a 6-minute walk test per American Thoracic Society guidelines to further assess functional status.[22] Data on primary diagnosis, recent cancer treatment, additional RBC transfusions given after the baseline transfusion episode, and interim clinical events including emergency department (ED) visits and hospital admissions during the study period were abstracted from the medical record.

Statistical Analyses

In the current analysis, we examined fatigue scores from all four timepoints at which they were collected in order to characterize the longitudinal response to RBC transfusion. To account for the wide variability in the fatigue response to transfusion seen at one-week (V3) and to quantify early (three days/V2) and sustained (up to 28 days/V4) changes in participant fatigue across study visits, we used three analytic approaches.

For comparison with published findings,[9] we summarized individual participants' median (Q1, Q3) changes in FACIT-fatigue score during early (from V1 to V2) and subsequent (from V2 to V4) follow up periods. We illustrate these trends using waterfall plots showing fractions of the sample with changes within one and two MCIDs.

We then used nonparametric group-based trajectory modeling (GBTM) to identify the number of distinct trajectories of substantive interest, without pre-specifying trajectory shapes.[23] Within the GBTM framework we used censored normal models to estimate fatigue trajectories as polynomial functions of days elapsed since the baseline transfusion, from V1 to V4, and to identify groups that explained heterogeneity among the trajectories (*Group*). We summarized the demographic and clinical compositions of each *Group* using descriptive statistics and Kruskal-Wallis and Chi-squared tests.

Finally, we used piecewise-linear random effects maximum likelihood models to estimate mean changes over the "early" and "sustained" periods and tested two *a priori* hypotheses, namely: transfusion confers at least a one-MCID mean improvement in fatigue by V2, and this benefit is sustained through V4. In this model, study participants represent random effects and two covariates (intervals corresponding with early and sustained change) represent the primary fixed effects. We then added the main effect of *Group* (as identified by GBTM), which allows the mean fatigue score to vary at V2 (where early and subsequent periods join), and the interactions of each period with *Group*, to allow the slopes to vary among groups.

Baseline values included sex, age, race, primary diagnosis, recent cancer treatment, number of baseline RBC units (1 or 2) transfused, and 30-minute post-transfusion hemoglobin. In addition, baseline pre-transfusion 6-minute walk test distance and Karnofsky scores were included as measures of functional status. Time-varying follow-up covariates occurring in the interval between V2-V3 or V3-V4 included additional RBC transfusion episodes (none vs any) and a hospitalization or ED visit (none vs any). Additional details of the statistical models and methods and details on the variability of the fatigue trajectories in our sample (Supplement Figure) are presented in the Supplement. Statistical analyses were performed using SAS version 9.4.

RESULTS

Overall Transfusion-Related Changes in Fatigue

The analysis included 204 of 221 enrolled RETRO study patients who completed the fatigue instrument prior to the baseline transfusion at V1. At V1, the overall median (Q1, Q3) fatigue score for participants was 34 (24,40). By V2, 56% of patients experienced a clinically significant early improvement (MCID ≥ 3) in fatigue, 33% had no change (−3 to +3 points), and 11% worsened (Figure 1A). Between V2 and V4, 31% improved, 41% showed no clinically important change in fatigue, and 28% worsened (Figure 1B). Overall median (Q1, Q3) changes were 3.0 (0, 9) in the early period and 1.0 (−3, 3) in the later period. Despite substantial proportions of participants experiencing no change with transfusion, others experienced change >10 times the MCID, demonstrating heterogeneity of responses during both periods. Since this descriptive analysis approach does not pair changes across periods within participants, we next evaluated heterogeneity in longitudinal models incorporating outcomes at all four visits.

Variation in Fatigue Trajectories and Participant Characteristics

Group-based trajectory modeling identified four distinct mean fatigue trajectory groups (*Group*) that included 12 (6%), 53 (26%), 96 (47%), and 43 (21%) of the 204 participants having 1) Low, 2) Moderate, 3) Moderate-High, or 4) High fatigue scores, averaged over the study follow-up (Table 1). Mean fatigue score by trajectory *Group* differed substantially, but within each group observed and predicted score trajectory agreed well (Figure 2). In general, all groups showed early improvements in fatigue and mean fatigue scores at V4 that remained at least as high as at V1 (Figure 2).

Overall and by ascending *Group* assignment, median age was 66, 75, 67, 65, and 66 years, respectively, with males representing 56% of the overall population (Table 1). Although the age of patients in the most fatigued group (Group 1/Low) appeared older compared with the other groups, this difference was not significant ($p = 0.44$).

Primary diagnoses did not significantly differ by fatigue *Group*, with the most prevalent being AML (32%) and MDS (20%). Recent cancer treatment (± 4 weeks) was reported by 92% of the Low score (greater fatigue) group, compared with 62% to 71% of less fatigued groups.

Study participants walked a median distance of 307 meters and assigned fatigue *Group* was associated with timed walk distance as well as Karnofsky Scores. Participants in the three groups with the most fatigue had shorter timed walk distances, and lower Karnofsky Scores were more likely to be recorded for the worse fatigue groups: 42% of the Low and 23% of the Moderate groups vs 9% in the High.

Most patients had pre-transfusion hemoglobin between 7–8 g/dL (74%); 10% of patients overall had hemoglobin <7 g/dL, and 16% had hemoglobin >8.0. The proportional distributions across *Group* did not significantly differ. In addition, median (Q1, Q3) hemoglobin measured 30 minutes post-transfusion was 8.3 g/dL (7.9, 8.9) and was not associated with *Group*, nor was the number of RBC units (1 or 2) transfused at the baseline study visit.

At least one additional RBC unit was transfused to 129 (63%) patients (range 1–7 units, mean 2.3 units per patient, Table 1). The distribution of patients receiving at least one additional RBC across *Group* was not significantly different. In the interval from V1 to V2, only 3% of patients received an additional transfusion. Between V2 and V3 and between V3 and V4, 17% and 60% of patients, respectively, received additional RBC units.

Although all participants were receiving outpatient treatment, some patients (25%) required additional ED visits or hospitalization during the follow-up interval between V2 and V4. However, there was no association between occurrence of an interim hospitalization or ED visit with *Group*.

Early and Sustained Post-transfusion Changes in Fatigue

According to the piecewise-linear longitudinal model, estimated mean fatigue score at V1 was 33 on the 52-point scale. By V2, mean fatigue improved overall by 4.0 points (95% CI, 2.9–5.1; p<0.001) and remained unchanged over the subsequent 3–4 weeks (mean, −0.04; 95% CI, −1.23–1.14; p=0.94) (Table 2).

Mean fatigue scores varied clinically and statistically significantly by *Group*, with baseline means of 12.3, 25.7, 34.1 to 46.7 on the 52-point scale (p < 0.0001; Table 2 and Figure 3). Estimated early mean improvements also varied significantly, with Low through Moderate-High groups all achieving mean improvements exceeding the MCID and the High group achieving <1 MCID (*Group* p=0.0039). Between V2 and V4, fatigue scores worsened slightly in Low and Moderate groups but continued to improve slightly in the higher score lower fatigue groups; however, these effects were neither clinically nor statistically significant (mean changes, ±1 point; *Group* p=0.60).

DISCUSSION

Our analysis shows that RBC transfusion is associated with early and sustained improvement in fatigue-related quality of life in older adult outpatients with hematologic disorders receiving usual-care transfusion therapy. Group-based trajectory modeling allowed us to identify four distinct fatigue trajectories in patients receiving RBC transfusion, associated with relatively low to relatively high fatigue levels over the month-long post-

transfusion follow-up. These modeling results suggest that clinicians could counsel almost all patients to expect noticeable improvement in fatigue (greater than the MCID) in the first few days after transfusion, except those patients with mild fatigue. In addition, most patients can expect their fatigue levels on average to remain at that level over the next few weeks or deteriorate slightly if they fall into a trajectory group with greater fatigue.

Several studies, including our previous analysis using the RETRO population, have demonstrated improvement in fatigue levels a few days to one week after transfusion in anemic patients. [9,4,8] Few studies have measured fatigue in patients for more than a few days after transfusion to examine the time-course of fatigue after RBC transfusion.[5,7] In hospitalized adults, Prochaska et al [5] found that transfusion during an inpatient admission was associated with reduced fatigue at 30 days after discharge. In women with postpartum hemorrhage, subjects randomized to receive RBC transfusion reported less fatigue at 4–6 weeks than women who did not receive transfusions, although the difference was not deemed to be clinically important.[7] These studies, along with the current study, suggest that the effect of transfusion while modest, may persist for several weeks in relatively stable patients.

Our study also looked for associations between fatigue trajectory group and baseline patient characteristics that might help clinicians determine which groups of patients might benefit most from transfusion. Among baseline patient characteristics, fatigue trajectory group was most strongly associated with measures of fitness including timed walk distance and Karnofsky score. This finding suggests that patients with better functional status are more likely to follow the “High” QoL (low level of fatigue) trajectory and show little change in fatigue with transfusion.

In this study, hemoglobin level was not associated with fatigue group, although anemia and fatigue have been associated in patients with cancer.[3] This lack of association might be explained by that fact that most patients were transfused at similar V1 hemoglobin levels and reflects the common provider practice to use hemoglobin of 7 to 8 g/dL as the threshold for outpatient RBC transfusion. Also, fatigue in our study participants may be influenced by clinical factors in addition to anemia.

In a previous study of fatigue and transfusion in hospitalized patients,[5] age <50 years was associated with improved fatigue scores after transfusion. In contrast, in our GBTM-defined groups we detected no association between age and fatigue trajectory (*Group*). Unlike in Prochaska et al,[5] our cohort included only patients 50 or older. It is also possible that the physiologic response to RBC transfusion does not differ in patients across the age span, and that age is less important relative to fatigue burden itself.

It should be emphasized that study patients continued to receive treatment, including additional RBC transfusion, as part of their clinical care. By the end of the month-long study, 63% of participants received at least one additional provider-ordered transfusion after the baseline study transfusion. The frequency of additional RBC transfusion did not vary among the fatigue trajectory groups. Almost all additional transfusions occurred between V3 (one-week post) and V4 (up to four weeks post) during the sustained follow-up period.

However, the timing of assessments did not provide the opportunity to examine changes relative to each transfusion.

A strength of the study is the application of group-based trajectory modeling to help account for the heterogeneity both in patient baseline fatigue scores and in the fatigue response to transfusion (see Supplement Figure).[23] Trajectory modeling has been used to evaluate patient groups showing heterogeneity in an outcome over time, including symptom burden in patients with cancer,[24] frailty in older patients,[25] and fatigue in patients with rheumatoid arthritis.[26] This approach allows visualization of fatigue patterns that transfused patients might be expected to follow over time given existing fatigue burden. For example, trajectory groups with the highest fatigue burden achieved clinically important early gains, whereas gains achieved were sustained by those with lowest fatigue burden.

The study has several important limitations. Scheduling difficulties and the requirement that patients be ambulatory might have led to selection bias against patients with high fatigue burden. We did not distinguish between patients who received transfusion during curative versus palliative treatment; only whether chemotherapy occurred within four weeks of the study transfusion. Finally, as discussed previously, we did not capture individual intervals between the baseline transfusion and subsequent follow-up transfusions during the study period.

CONCLUSION

Patients with hematologic disorders and malignancies, including MDS, report significant levels of fatigue affecting quality of life and in some cases survival.[27–29] Our study patients reported fatigue levels comparable to those published in other studies of cancer patients.[1] Increasingly, patient-centered quality of life indicators, including fatigue, factor in the decision to transfuse and are being included as outcomes in transfusion clinical trials.[30,13,31] Our study indicates that RBC transfusion can have an immediate and moderate-term sustained impact on fatigue and therefore, quality of life, in many patients receiving outpatient transfusion. However, improvements in fatigue with transfusion must be weighed against possible adverse outcomes including acute transfusion reactions, iron overload, and the time and cost-burden associated with outpatient transfusion visits.[32]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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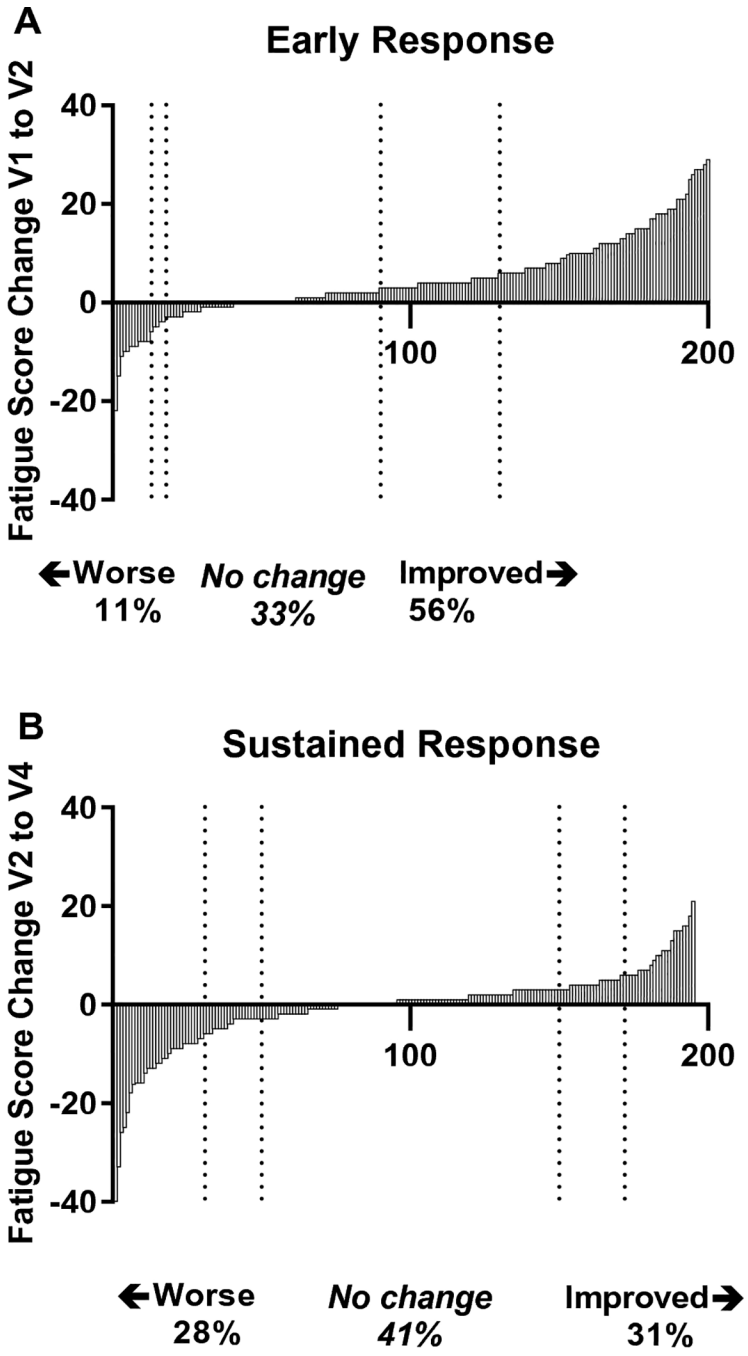

Figure 1.

Waterfall plots show individual participants' changes in fatigue score: (A) between V1 and V2 (mean, 2.4 days; N=201) and (B) between V2 and V4 (mean, 21 days; N=195). Vertical reference lines mark changes of +/− 1 MCID (inner) and +/− 2 MCID (outer). Median (Q1, Q3) fatigue score changes were 3.0 (0, 9) V1 to V2 and 1.0 (−3, 3) V2 to V4.

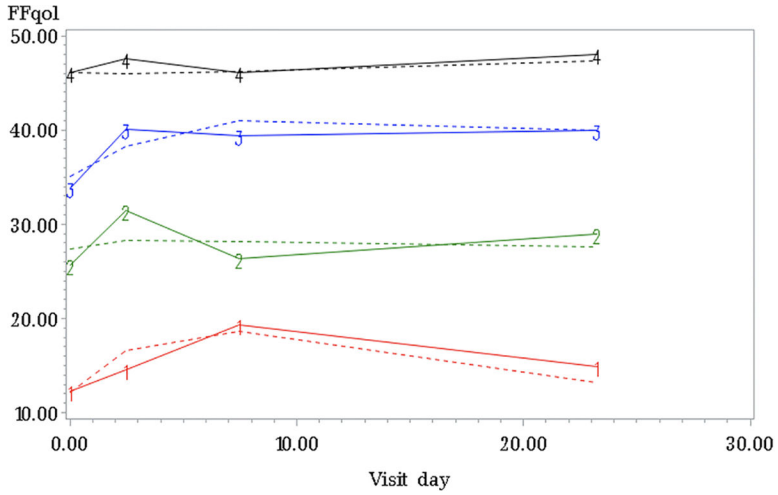

Figure 2.

Group-based trajectory modeling (GBTM) identified four groups with distinct mean fatigue score (FFQoL) trajectories as a function of post-transfusion follow-up day. Observed trajectories (solid lines) and model-based trajectories (dashed lines) are averages of individual group members' trajectories. Lines 1-Low FFQoL; 2-Moderate FFQoL; 3-Moderate-High FFQoL; 4-High FFQoL.

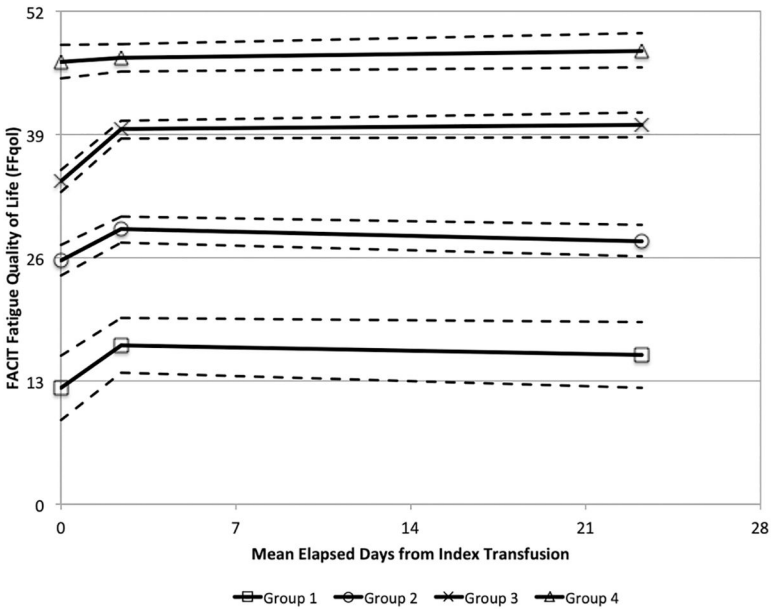

Figure 3.

Estimates of post-transfusion fatigue mean (95% CI) trajectories, by *Group*, based on a piecewise-linear longitudinal model. Groups 1–4, defined via GBTM, include 5.9%, 26.0%, 47.1%, and 21.1% of the cohort of N=204 participants, respectively.

Table 1.

Demographic, clinical, and transfusion characteristics of RETRO study participants by fatigue score trajectory *Group*

	All subjects (N=204)	***Group* 1 Low N=12 (5.7%)**	***Group* 2 Moderate N=53 (26.4%)**	***Group* 3 Moderate-High N=96 (46.9%)**	***Group* 4 High N=43 (21.0%)**	**p**
Characteristics at Baseline Transfusion						
Age (years)	66.0 (59.0 – 73.0)	74.5 (58.0 – 76.5)	67.0 (61.0 – 71.0)	64.5 (59.0 – 71.0)	66.0 (58.0 – 74.0)	0.44
Sex: Male	114 (55.9%)	6 (50.0%)	28 (52.8%)	59 (61.5%)	21 (48.8%)	0.49
Race						0.09
Caucasian/White	163 (79.9%)	11 (91.7%)	45 (84.9%)	74 (77.1%)	33 (76.7%)	
African American	31 (15.2%)	0 (0.0%)	4 (7.5%)	17 (17.7%)	10 (23.3%)	
Other	10 (4.9%)	1 (8.3%)	4 (7.5%)	5 (5.2%)	0 (0.0%)	
Primary Diagnosis						
Acute myeloid leukemia	65 (31.9%)	5 (41.7%)	14 (26.4%)	29 (30.2%)	17 (39.5%)	0.44
Myelodysplastic syndrome	40 (19.6%)	2 (16.7%)	10 (18.9%)	17 (17.7%)	11 (25.6%)	0.74
Lymphoma	24 (11.8%)	0 (0.0%)	8 (15.1%)	9 (9.4%)	7 (16.3%)	0.34
Multiple myeloma	23 (11.3%)	2 (16.7%)	6 (11.3%)	14 (14.6%)	1 (2.3%)	0.12
Acute Leukemia, other	20 (9.8%)	1 (8.3%)	4 (7.5%)	13 (13.5%)	2 (4.7%)	0.40
Recent Cancer Treatment	140 (68.6%)	11 (91.7%)	33 (62.3%)	68 (70.8%)	28 (65.1%)	0.22
6-Minute Walk Distance (m)	307 (212 – 388)	276 (112 – 349)	280 (188 – 356)	284 (212 – 386)	350 (296 – 433)	0.008
Karnofsky Score						0.001
50, 60, 70	33 (16.2%)	5 (41.7%)	12 (22.6%)	12 (12.5%)	4 (9.3%)	
80	113 (55.4%)	6 (50.0%)	31 (58.5%)	58 (60.4%)	18 (41.9%)	
90, 100	58 (28.4%)	1 (8.3%)	10 (18.9%)	26 (27.1%)	21 (48.8%)	
Pre-transfusion Hemoglobin (g/dL)						0.08
< 7	20 (9.8%)	2 (16.7%)	5 (9.4%)	6 (6.3%)	7 (16.3%)	
7–8	151 (74.0%)	6 (50.0%)	42 (79.2%)	71 (74.0%)	32 (74.4%)	
> 8	32 (15.7%)	4 (33.3%)	5 (9.4%)	19 (19.8%)	4 (9.3%)	
RBC Transfused at Baseline (# Units)						0.24
1	149 (73.0%)	7 (58.3%)	39 (73.6%)	75 (78.1%)	28 (65.1%)	
2	55 (27.0%)	5 (41.7%)	14 (26.4%)	21 (21.9%)	15 (34.9%)	
Post-transfusion Hemoglobin (30-min) (g/dL)	8.3 (7.9, 8.9)	8.4 (8.0,9.2)	8.3 (7.9,8.8)	8.3 (7.9,9.1)	8.3 (8.1,8.6)	0.68
Post-baseline Transfusion Events						
≥ 1 RBC Transfusion	129 (63.2%)	7 (58.3%)	34 (64.2%)	65 (67.7%)	23 (53.5%)	0.42
ED/Hospital visit	51 (25.0%)	2 (16.7%)	17 (32.1%)	26 (27.1%)	6 (14.0%)	0.18

Table incudes all participants who completed the fatigue instrument and baseline transfusion at Visit 1. Groups were defined by Group-based trajectory modeling of fatigue scores. 1-Low, 2-Moderate, 3-Moderate-High, and 4-High designations refer to FACIT-Fatigue QoL score. Low score indicates greater fatigue and lower quality of life. Summaries of continuous variables are medians (Q1, Q3), with groups compared via Kruskal-Wallis 3-df tests, and summaries of categorical variables are number and percentages, with groups compared via Chi-square 3-df tests of independence or via Fisher's exact test where cells contain fewer than five values.

Table 2.

Longitudinal estimates of change in fatigue during early and subsequent post-transfusion intervals

FACIT-Fatigue QoL *Group*	FACIT-Fatigue V1	P-value	Change, V1 to V2	P-value	Change, V2 to V4	P-value
All (204)	33.2 (31.8, 34.6)	--	4.0 (2.9, 5.1)	<0.001	−0.04 (−1.23, 1.14)	0.94
1-Low (12)	12.3 (8.9, 15.7)	<0.001	4.5 (0.13, 8.9)	0.0039	−0.93 (−5.61, 3.76)	0.60
2-Moderate (53)	25.7 (24.1, 27.4)		3.3 (1.2, 5.5)		−1.21 (−3.47, 1.05)	
3-Mod-High (96)	34.1 (32.9, 35.3)		5.5 (4.0, 7.1)		0.46 (−1.21, 2.13)	
4-High (43)	46.7 (44.9, 48.4)		0.46 (−1.8, 2.8)		0.73 (−1.75, 3.20)	

Values expressed as mean (95% Confidence Interval). Estimates based on a piecewise-linear longitudinal model, adjusted for trajectory groups identified by GBTM, and Wald tests.