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Trajectories of physical well-being among adults with acute myeloid leukemia

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Abstract:
Patients with acute myeloid leukemia (AML) often undergo physical decline leading to negative outcomes. Identification of distinct trajectories may help guide clinical decision making and supportive care interventions. We built group-based trajectory models (GBTM) to find trajectories of change in the Functional Assessment of Cancer Therapy Physical Well-Being sub scale (FACT-PWB, up to 5 timepoints over 0 to 200 days of follow-up) using data from adults with newly diagnosed AML in four supportive care studies. We also estimated the association of baseline characteristics (age, marital status, education, AML risk, baseline FACT-PWB, depression, anxiety) with group membership. Among 343 patients with {greater than or equal to} 2 FACT-PWB scores, mean age was 69.6 (SD 12.1) years; most had intermediate risk AML (178, 51.8%), received intensive treatment (244, 71.1%), and died during follow up (199, 58.0%). The GBTM with four distinct trajectories showed the best fit. The largest group (N=153, 45.0%) showed slight improvement, while the smallest experienced early decline with later improvement (N=8, 2.4%). Baseline FACT-PWB was the only characteristic statistically significantly associated with group membership. Adults with AML show distinct trajectories of physical well-being, and many experience some decline. Exploring trajectories of self-reported and objective physical function may inform decision making and interventions. Clinical trial registration: www.clinicaltrials.gov NCT02975869, NCT03310918, NCT03372291

Conflict of interest: COI declared - see note

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Clinical trial registration information (if any): We conducted a secondary analysis of combined samples from one non-intervention (Study 1) and three U.S. supportive care clinical trials conducted between 2015 and 2019 (clinicaltrials.gov Study 2: NCT02975869,11 Study 3: NCT03310918, Study 4: NCT03372291)

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Key Points

1. Patients with acute myeloid leukemia have distinct trajectories of change in physical well-being after diagnosis which often include decline.

2. More research is needed to identify predictors of trajectory of change in physical well being among patients with acute myeloid leukemia.

Abstract

Patients with acute myeloid leukemia (AML) often undergo physical decline leading to negative outcomes. Identification of distinct trajectories may help guide clinical decision making and supportive care interventions. We built group-based trajectory models (GBTM) to find trajectories of change in the Functional Assessment of Cancer Therapy Physical Well-Being sub scale (FACT-PWB, up to 5 timepoints over 0 to 200 days of follow-up) using data from adults with newly diagnosed AML in four supportive care studies. We also estimated the association of baseline characteristics (age, marital status, education, AML risk, baseline FACT-PWB, depression, anxiety) with group membership. Among 343 patients with ≥ 2 FACT-PWB scores, mean age was 69.6 (SD 12.1) years; most had intermediate risk AML (178, 51.8%), received intensive treatment (244, 71.1%), and died during follow up (199, 58.0%). The GBTM with four distinct trajectories showed the best fit. The largest group (N=153, 45.0%) showed slight improvement, while the smallest experienced early decline with later improvement (N=8, 2.4%). Baseline FACT-PWB was the only characteristic statistically significantly associated with group membership. Adults with AML show distinct trajectories of physical well-being, and many experience some decline. Exploring trajectories of self-reported and objective physical function may inform decision making and interventions.

Clinical trial registration: www.clinicaltrials.gov NCT02975869, NCT03310918, NCT03372291

Keywords: Quality of life, acute myeloid leukemia, survivorship

Introduction:

Acute myeloid leukemia (AML) is the most common myeloid malignancy, with an estimated 20,050 new cases in the United States (U.S.) in 2022 and a five-year relative survival rate of 30.5%.[1] Physical well-being (PWB) is a facet of health-related quality of life (HRQoL) closely associated with physical functioning such as lower extremity function and daily walking.[2,3] Although most adults who have higher risk AML (per Sorror et al composite model) rank HRQoL as less important than cure in their priorities for treatment choice, nearly half indicate quality of life is more important than length of life.[4] In addition to its importance as a patient priority, HRQoL is strongly linked to prognosis including survival, especially among patients over age 60.[4-7]

AML treatment regimens have differing effects on PWB. These regimens can be broadly categorized as intensive chemotherapy, typically administered in an inpatient setting, and lower intensity chemotherapy, often given on an outpatient basis. Several studies have shown that while large proportions (>50%) of adults with newly diagnosed AML report PWB below normative values prior to starting intensive chemotherapy, most recover over several years of follow up.[8,9] While recent studies show overall HRQoL does not differ longitudinally by treatment type (intensive vs. lower intensity) over two years of follow up,[4] historically, patients who received lower intensity treatments have demonstrated better PWB.[10]

Although some studies have reported mean values and within-subject change for HRQoL among adults with AML, the literature lacks analyses exploring trajectories of PWB over time. Further, few studies of PWB have 1) included both patients receiving intensive and lower-intensity chemotherapy and, 2) adequately accounted for mortality-

related loss to follow up. Understanding how PWB changes over time in a sample with these characteristics will better reflect the experiences of patients in real-world practice settings, and may help clinicians identify patients at high risk for adverse trajectories of PWB. In this study, we aimed to identify the trajectories of self-reported PWB among patients with AML and evaluate whether demographic and clinical characteristics (including receipt of intensive vs. lower intensity chemotherapy) are associated with these trajectories.

Methods:

Data source:

We conducted a secondary analysis of combined samples from one non-intervention (Study 1) and three U.S. supportive care clinical trials conducted between 2015 and 2019 (clinicaltrials.gov Study 2: NCT02975869,[11] Study 3: NCT03310918, Study 4: NCT03372291, each approved by their respective institutional review boards). A new diagnosis of AML and ability to provide informed consent were part of inclusion criteria for all studies. All patients in Study 2 and Study 4 were planned for or undergoing intensive chemotherapy treatment at baseline, while Study 1 and Study 3 also included patients on lower intensity treatments. All patients were within the first year of treatment. Detailed inclusion criteria and description of interventions for each trial are provided in Table 1: Study characteristics. We chose to combine patients across studies with similar patient populations and which collected our outcome measure of interest in order to address limitations of previous research such as

insufficient power for longitudinal analyses due to mortality-related loss to follow up and poor generalizability due to single site design.[12]

Measures:

Demographic characteristics: Patient age, race/ethnicity, marital status, educational attainment, and income were obtained using standardized questionnaires at baseline.

Clinical characteristics: European Leukemia Net (ELN) AML risk categories (favorable, intermediate, and adverse-risk) based on the 2010 guidelines were reported by treating oncologists or abstracted from the medical record.[13] Research staff determined whether patients were receiving or planned for intensive vs. lower intensity chemotherapy regimens. Depression and anxiety were measured using the Hospital Anxiety and Depression Scale, a valid and reliable screening tool for adults. This scale includes seven items evaluating anxiety and seven which assess depression, with scores ranging from 0-21 points (<8 points cut score indicates non-cases).[14]

Primary outcome measure: We chose the PWB subscale of the Functional Assessment of Cancer Therapy–General measure (FACT-PWB) as our outcome. The FACT-G and its subscales are valid and reliable self-reported measures of HRQoL among adults with cancer.[15] The FACT-PWB consists of seven questions with a range from 0 to 28 points (higher=better), with two to three points representing a minimal clinically important difference.[16,17]

Analysis:

Missing data: We limited our sample to patients with FACT-PWB measures at two or more follow up time points, who also had non-missing values for baseline demographic and clinical covariates of interest. We compared the distribution of baseline covariates in our analytic sample to those excluded from the analysis due to missing data using chi square or fisher's exact test.

Descriptive statistics: We report descriptive statistics for covariates of interest for the entire sample at baseline and by group as determined by Group Based Trajectory Model (GBTM, see Modeling approach below). Where reported, unadjusted comparisons of covariates by group are tested using a the SAS macro function COMPPROP, which employs a Tukey style multiple comparison of proportions.[18]

Modeling approach: To identify distinct trajectories of change in FACT-PWB over time, we used Group-Based Trajectory models (GBTM) using the SAS macro function PROC TRAJ.[19] GBTM are a class of discrete mixture models that estimate clusters of longitudinal data series and offer a flexible approach for modeling outcome data collected at varying timepoints. Our model specification used a censored normal distribution and an initial cubic polynomial trajectory shape of the curves. We additionally specified a nested model to weight against non-random mortality-related loss to follow up for the FACT-PWB outcome.[20] A priori, we chose patient age, gender, marital status (married vs. non-married), educational attainment (college graduate vs. some college or less), ELN risk category (favorable, intermediate, adverse), receipt of intensive vs. lower intensity chemotherapy, and baseline depression, anxiety, and baseline FACT-PWB as covariates to evaluate for association with group membership.

Model fit: We determined the best fitting model with the ideal number of groups based on several criteria: 1) Bayes Factor (approximated as 2*ΔBIC) improvement between the saturated model (with greater number of groups) and the null model (with fewer), 2) Group size, 3) Average posterior probability of group assignment, and 4) Clinical interpretability.[19,21] This last criteria was determined based on whether identified groups represented patient trajectories recognizable to oncologists in clinical practice. To ensure robust estimation of the Bayes Factor, we used bootstrap with 500 repetitions (resampling with replacement using the SAS macro function BOOT).[22]

Sensitivity analysis: We conducted a sensitivity analysis excluding patients who died before contributing all expected measures of FACT-PWB. We present descriptive statistics for this group and results from GBTM. This analysis eliminated the nested model to weight against non-random mortality-related loss to follow up and repeated the steps described above to select the GBTM model with the best fit. Importantly, we did not restrict this model to the same number of groups selected in the main analysis as 1) the sample size analyzed was substantially smaller, and 2) we do not expect the same groups to be extracted given the distinct (more robust) composition of the patients included in the sensitivity analysis.

For clarity, results relating to groups from the main analysis are designated with prefix “m” (i.e., Group m1), while for those from the sensitivity analysis we use the prefix “s” (i.e., Group s1). All p values are from two-sided hypothesis tests with α=0.05. Analyses were completed using SAS software version 9.4 (SAS Institute, Cary NC).

Results:

Analytic sample:

Pooling patients from the four trials yielded an initial sample size of 405 (Study 1: 99, Study 2: 160, Study 3: 88, Study 4: 58,). After eliminating patients with <2 measures of FACT-PWB during follow up (N=49), and those with missing values for predictor variables of interest (N=13), the final analytic sample consisted of 343 patients. We compared the analytic to the original sample and found they were largely similar, with the exception that a greater proportion of those excluded were from Study 3 (excluded=50.0%; analytic=16.6%, p<.001), were younger (excluded mean=64.6, SD=12.7; analytic mean=69.5, SD 12.1, p=0.005), receiving lower intensity chemotherapy (excluded=62.9%; analytic=28.8%, p<.001), and died during the follow up period (excluded=67.8%; analytic=58.0%, p=0.04) (see Supplemental Table 1).

The 343 patients included in this analysis had a mean age of 69.5 (SD 12.1) years and were primarily male (61.8%, n=212) and white (90.3%, n=310) and had a college degree (52.7%, n=181). Over half (51.8%, n=178) had intermediate risk AML, and 58.0% (n=199) died while on study. Baseline FACT-PWB score was 19.9 (SD 5.8), and patients contributed an average of 113.7 (SD 63.6) days of follow up (range 11, 200). See Table 2 for full results.

Groups and characteristics associated with group membership:

Main analysis (full sample):

Based on our selection criteria (see Table 3), the model with four groups was selected as the best model. The four groups of change in FACT-PWB identified in the final model are shown in Figure 1, and descriptive statistics of group characteristics are presented in Table 4. The largest group (m3: Slight improvement/stable; 153, 45.0%) had the lowest proportion of females (43, 28.1%), the lowest on-study mortality (83, 54.3%), and the second lowest baseline FACT-PWB (mean=18.9, SD 4.3). Conversely the smallest group (m1: Steep decline with recovery; 8, 2.4%) was composed mostly of female patients (5, 62.5%) who died during follow up (6, 75.0%) but started with a higher FACT-PWB (mean=24.0, SD 3.3) and lower depression and anxiety scores at baseline. We also present Group size and average FACT-PWB across timepoints in Table 5. All 343 patients had baseline FACT-PWB scores, but only 53.4% (n=183) of the sample contributed measures of the outcome for the final possible timepoint. Of the 46.6% (n=160) missing data for the final timepoint, 38.1% (n=61) were missing data completely at random simply because this was not part of planned data collection for the participating trial (see Table 1), while the remaining 61.9% (n=99) were missing data due to loss-to-follow up related to death, which was accounted for in the model estimation. When evaluated across groups, a comparison of multiple proportions found the percent of patients missing data due to death did not vary significantly by group. In addition, we trialed excluding the eight patients in m1 from our analytic sample and found the remaining groups (m2, m3, and m4) were largely unchanged (results not shown).

Table 6 displays results from a multinomial logistic regression evaluating the independent association of each baseline factor with group membership. Group m3 was selected as the reference, as it represented the most common trajectory and relative stability of FACT-PWB score from baseline. Higher baseline FACT-PWB score was associated with increased relative odds of membership in Groups m1 (OR=1.57, 95% CI 1.11, 2.22, p=0.01) and m2 (OR=1.43, 95%CI 1.25, 1.62, p<0.01), while higher FACT-PWB at baseline was associated 41% lower odds of membership in Group m4 (OR=0.59, 95%CI 0.43, 0.80, p<0.01), all relative to Group m3. Other baseline factors did not show statistically significant associations with group membership.

Sensitivity analysis (excluding patients missing data due to death):

We also conducted a sensitivity analysis using GBTM to identify distinct trajectories of the outcome in a sample excluding patients with missing FACT-PWB data due to death (n=99, 28.9% of the original analytic sample). The model with the best fit for this data identified three groups as shown in Figure 2: Group s1 (n=90, 37.0%) showed early decline followed by partial improvement; Group s2 (n=137, 55.5%) demonstrated a steady trajectory of slight improvement, and Group s3 (n=17, 7.5%) initially improved and then stabilized as follow up continued. Comparing group membership between the main four group model to the sensitivity analysis three group model, we found the majority (96.7%) of Group s1 corresponded to Group m2, 83.2% of those in Group s2 corresponded to Group m3, and all patients in Group s3 corresponded to Group m4 (see Supplemental Table 2). Supplemental Table 3 shows descriptive demographic and clinical characteristics for Groups s1, s2, and s3.

Interestingly, after excluding those with missing outcome data due to death, similar proportions of patients in all three groups had adverse risk AML (range 35.0-35.6%) and received intensive chemotherapy (range 71.5-76.5%).

In terms of descriptive differences, although Group s1 showed an improving trajectory early in follow up and the highest baseline FACT-PWB score (mean=24, SD 2.9), it also had the fewest patients with favorable risk AML (5.6%, n=5) and the greatest proportion of patients who died during follow up (after contributing all expected FACT-PWB data, 46.7%, n=42). Conversely, Group s3 started with the lowest FACT-PWB (mean=9, SD 3.7), but had the smallest proportion of patients who died during follow up (23.5%, n=4). Patients in Group s3 were primarily female 76.5%, n=13) and had higher levels of depression and anxiety at baseline. FACT-PWB scores are shown for the sensitivity analysis sample and by group over time in Supplemental Table 4. The association of baseline factors with group membership among patients with complete data was largely consistent with results from the main analysis sample. Results from a multinomial logistic regression found baseline FACT-PWB score was the only characteristic independently associated with membership in Group s1 (higher FACT-PWB) or s3 (lower FACT-PWB) relative to Group s2 (see Supplemental Table 5).

Discussion:

This analysis of longitudinal change in PWB among adults with AML identified four trajectories of change in FACT-PWB score over up to 200 days of follow up. The largest group of patients experienced relatively little change in their PWB compared to baseline (Group m3, 45%), followed by those who experienced a slight decline (Group 2, 40.8%),

and smaller proportions who showed improvement (Group m4, 11.8%) and sharp decline (Group m1, 2.4%). These groups differed descriptively; a higher proportion of both those in Groups m1 and m4 were female and were receiving intensive chemotherapy compared to those in the more stable groups. However, a multinomial logistic regression did not find that treatment intensity was significantly associated with group membership. Rather, the only demographic or clinical characteristic associated with group membership was that patients in improving trajectories had lower baseline FACT-PWB scores (Group m4, mean=9.9 SD=3.8), while those who declined began, on average, with better PWB scores (Group m2, mean=24.0, SD=3.2) compared to patients with relatively stable trajectories (Group m3). While the baseline average PWB score (19.9) was only slightly lower than normative values for adults with all cancer types (approx. 21.0),[23,24] the FACT-PWB does exhibit a ceiling effect which may be more pronounced in groups with higher baseline PWB (e.g., Group m2, where 58.2% of scores were ≥24).[25] Another way of interpreting these results would be that we did not find any other baseline characteristics to be independently associated with PWB trajectory after adjusting for baseline PWB.

Existing literature has shown overall HRQoL among patients with AML often declines shortly after treatment initiation, but that most patients demonstrate recovery over time,[9,26] although this recovery may be less robust than that experienced by patients with solid tumors.[27] However, this trend of improvement of overall HRQoL is less clear for PWB. Studies of adults with AML being treated with intensive chemotherapy found that while overall HRQoL as measured by the European Organisation for the Research and Treatment of Cancer scale improved in the years

after diagnosis, the physical functioning sub-scale did not.[8,9] In contrast, Sorror et al reported similar FACT-PWB scores at baseline and improvement of HRQoL over two years in a sample of patients receiving both intensive and less-intensive chemotherapy.[4] Our analysis focused on FACT-PWB similarly did not find treatment intensity to be independently associated with longitudinal trajectory. This may be related to the heterogeneity of disease course for patients receiving palliative, less intensive treatment regimens in that those responding well should demonstrate stable or improving PWB while patients with disease progression may enter a terminal decline during the first six months of treatment.

Distinct from prior work, our analysis adds to the literature by 1) exploring distinct trajectories of change in FACT-PWB, rather than averages for an entire sample over time, and 2) incorporating data from a substantial proportion of patients (58% of our sample) who died while on study. While the largest group (Group m3, n=153, 45.0%) identified showed stable or slightly improving FACT-PWB, we also found a distinct group of patients who slowly declined over the follow up period (Group m2, n=141, 40.8%). This result is complemented by a sensitivity analysis showing the most patients (63.0%) without missing data related to death improved their PWB during follow up (Group s2, n=137, 55.5%, steady slight improvement; Group s3 (n=17, 7.5%), early improvement, then stable). Out of 99 patients missing FACT-PWB measures related to death most (55, 55.6%) were from groups experiencing decline (m2 n=39, m4 n=16). Together these suggest that average improvements in PWB reported among longer-term survivors may obscure underlying heterogeneity in real-world experiences of patients with AML which often include terminal decline.

This secondary analysis is the first study to explore risk factors associated with PWB trajectories among adults with AML. Factors associated with change in PWB have important potential clinical applications in identifying high need patients who may be at risk for future decline. In studies of patients with solid tumors during their last year of life, GBTM have shown that factors such as lower levels of education and higher healthcare utilization are associated with a declining trajectory in overall HRQoL compared to maintaining a high HRQoL until death.[28] However, our analysis found that only baseline PWB was independently associated with trajectory of change. it is likely that predictors of PWB differ from those associated with overall HRQoL, and possible that demographic and clinical characteristics beyond those collected in our study are associated with longitudinal change in PWB. Geriatric assessment (GA), a combination of validated measures that assess specific domains (e.g., function, nutrition) associated with adverse cancer-related outcomes, offers rich source of factors which may be associated with PWB. Although GA was originally developed for use among older adults with cancer, it is increasingly recognized as having applications among adults of all ages with cancer.[29] Measures of physical function often used in GA such as gait speed and as activities of daily living may represent strong candidates for future studies exploring other potential predictors of PWB trajectory.

Our study has several limitations. We chose to pool data from with similar patient populations to address limitations of previous research including insufficient power and poor generalizability due to single site design.[12] While our sample was composed of patients with newly diagnosed AML, heterogeneity in interventions and engagement with study staff for may have influenced FACT-PWB scores, decreasing the

generalizability of these findings to patients who are not participating in supportive care studies. We chose to focus on trajectories of *change* in FACT-PWB rather than trajectories of total FACT-PWB scores, as it may be more clinically relevant to identify which patients are likely to decline regardless of their starting score. However, our findings of baseline PWB as the only significant predictor of trajectory group may be influenced by ceiling or floor effects of the FACT-PWB scale (given that patients with low scores were more likely to belong to a group with improving trajectory and patients with high scores were more likely to be in a group with decline). In addition, we did not have access to validated measures of physical functioning such as activities of daily living or physical performance tests such as gait speed. We were similarly limited in our characterization of socioeconomic status (education, marital status), which has been associated with HRQoL among adults with AML >1 year after diagnosis.[30] Finally, we lacked granular data on how treatment regimens changed over time, and which patients progressed to hematopoietic stem cell transplant, which also may be predictive of longitudinal change in PWB.

Patients excluded from our analytic sample due to missing FACT-PWB measures were more likely to be receiving less-intensive treatments and to die during the study. While we attempted to account for mortality-related loss to follow up in our models, our results may not represent the trajectories of patients receiving less intensive chemotherapies. Future research is needed to confirm these trajectory groups, evaluate a broader set of measures for their association with group membership, and to explore whether such trajectories are associated with other clinical outcomes.

Conclusion:

HRQoL is an important outcome in the treatment of AML due to both its patient-centered nature and its association with other endpoints such as survival. While prior studies have suggested HRQoL improves over time on average, we found this focus on the average HRQoL may obscure largely flat or declining trajectories that are revealed when investigating the subconstruct of PWB using modeling techniques that account for patients who died during follow up. Future research including valid and reliable measures of physical function, such as those used in GA,[31] is needed to identify baseline characteristics which may help predict future declines in PWB and allow clinicians to implement targeted interventions to improve this important patient-reported outcome in this vulnerable population.

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Author Contributions

Marielle Jensen-Battaglia	Analysis and interpretation of Data, Manuscript Writing, Approval of Final Article.
Michael B. Sohn	Statistical analysis plan and interpretation of Data, Manuscript Writing, Approval of Final Article.
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Kah Poh Loh	Statistical analysis plan and interpretation of Data, Manuscript Writing, Approval of Final Article.

Conflict of interest

Dr. El-Jawahri receives support as a Scholar in Clinical Research for the Lymphoma and Leukemia Society. Dr. Loh has served as a consultant to Pfizer and Seagen and has received honoraria from Pfizer. Dr. El-Jawahri has served as a consultant for GSK (GalaxoSmithKline), Incyte, AIM Pathway, as well as Tuesday Health.

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Tables

Table 1: Study characteristics				
	Study 1	***Study 2***	***Study 3***	***Study 4***
Clinicaltrials.gov identifier	***Not applicable***	NCT02975869	NCT03310918	NCT03372291
Inclusion criteria (all studies: ability to provide informed consent and comprehend English)	Patient ≥ 60 years of age with a new diagnosis of AML receiving treatment with either intensive or non-intensive chemotherapy	Hospitalized patients with high risk AML: Newly diagnosed and age ≥60, **or** newly diagnosed with antecedent hematological disorder, **or** newly diagnosed with therapy-related AML, **or** relapsed AML **or** primary refractory AML.	Patients age ≥18 with newly diagnosed, relapsed, or primary refractory AML receiving non-intensive chemotherapy inpatient or outpatient.	Patients age ≥18 with newly diagnosed AML receiving intensive induction chemotherapy requiring 4-6 week hospitalization.
Intervention	Prospective longitudinal observational study	Integrated Palliative and Oncology Care: Standard of care plus collaborative involvement of palliative care clinicians	Integrated Palliative and Oncology Care: Standard of care plus collaborative involvement of palliative care clinicians	Standard of care plus psychological intervention delivered via mobile application focused on educating patients about leukemia and how to cope with its treatment
Control condition	Not applicable	Standard of care	Standard of care	Standard of care
Randomized	Not applicable	Yes	Yes	Yes
Primary outcome	FACT-Leukemia score	FACT-Leukemia score at 2 weeks	Time from documentation of end-of-life care preferences to death	Feasibility based on proportion of subjects enrolled and completing the app modules
FACT-PWB timepoints	Baseline, weeks 2, 4, 8, 12, and 24	Baseline, weeks 2, 4, 12, and 24	Baseline, 1 month, 3 month, 6 month	Baseline, week 2, day 20, day 40
Planned days of follow up	24 weeks	Up to 192 (24 weeks ±7 days)	Approximately 180 (depends on visit ranges)	Up to 50 days (depends on visit ranges)
N contributed to analysis	99	160	88	58
Abbreviations: FACT-PWB=Functional Assessment of Cancer Therapy – Physical Well-Being				

Table 2: Demographic and clinical characteristics		
	Total N=343	
	n	%
Participating study		
Study 1	57	16.6%
Study 2	147	42.8%
Study 3	57	16.6%
Study 4	54	15.7%
Intensive treatment		
Intensive	244	71.1%
Lower-intensity	99	28.8%
White race		
No	33	9.6%
Yes	310	90.3%
Ethnicity		
missing	5	1.4%
Hispanic	17	4.9%
Non-hispanic	321	93.5%
Gender		
Female	131	38.1%
Male	212	61.8%
Married		
No	87	25.3%
Yes	256	74.6%
Educational attainment		
Some college or less	162	47.2%
College graduate	181	52.7%
Annual income		
missing	29	8.4%
<25k	34	9.9%
25-50k	74	21.5%
50-100k	104	30.3%
101-150k	45	13.1%
>=150k	57	16.6%
Acute myeloid leukemia risk score		
Favorable	32	9.3%
Intermediate	178	51.8%
Adverse	133	38.7%
Death at last follow up		
Dead	199	58.0%
Alive or unknown	144	41.9%
	Mean	**SD**
Age in years at baseline	69.46	12.14
HADS depression score at baseline	5.48	3.82
HADS anxiety score at baseline	5.85	4.08
FACT-PWB at baseline	19.91	5.77
Days of follow up for FACT-PWB	113.69	63.56
Abbreviations: HADS=Hospital Anxiety and Depression Scale; FACT-PWB=Functional Assessment of Cancer Therapy-Physical Well-Being		

Table 3: Group Based Trajectory Model Selection

Number of Groups	Group sizes	Probability of group assignment	BIC Lower Confidence Limit*	Bootstrap Bias-Corrected BIC	BIC Upper Confidence Limit*	Bayes Factor/ $2\log_e(B10)$**
1			-4275.24	-4187.38	-4099.52	
	343 (100%)	1.0				
2			-4171.36	-4092.35	-4013.34	190.06
	236 (69.3%)	0.96				
	107 (30.7%)	0.91				
3			-4091.61	-4017.84	-3944.07	149.02
	108 (32.6%)	0.89				
	199 (56.5%)	0.90				
	36 (10.9%)	0.93				
4			-4087.75	-4013.95	-3940.15	7.79
	8 (2.4%)	0.98				
	141 (40.8%)	0.88				
	153 (45.0%)	0.88				
	41 (11.8%)	0.92				
5* **			-4120.00	-4040.92	-3961.84	-53.95
	8 (2.4%)	0.98				
	130 (38.4%)	0.89				
	160 (45.3%)	0.87				
	36 (11.3%)	0.93				
	9 (2.6%)	0.99				

** Confidence limits for bootstrapped BIC reflect one standard deviation from the mean*
***Difference between model with N groups and model with N-1 groups*
****Singular convergence error required respecifying group 3 with linear trajectory shape*
Abbreviations: BIC=Bayesian Information Criterion

Table 4: Demographic and Clinical Characteristics by Group					
Characteristic		**m*1: Steep decline with recovery**	**m2: Slight decline**	**m3: Slight improvement/ stable**	**m4: Early improvement, later decline**
Group size, n (%)		8 (2.4)	141 (40.8)	153 (45.0)	41 (11.8)
Age in years at baseline, mean (SD, range)		69 (6.2, 59.9-80.1)	65 (13.4, 19.7-88.2)	66 (11.0, 35.9-100.3)	58 (15.3, 28.3-82.3)
Gender, n (%)	Female	5 (62.5)	59 (41.8)	43 (28.1)	24 (58.5)
	Male	3 (37.5)	82 (58.2)	110 (71.9)	17 (41.5)
Race, n (%)	Other		16 (11.3)	13 (8.5)	4 (9.8)
	White	8 (100.0)	125 (88.7)	140 (91.5)	37 (90.2)
Marital status, n (%)	Single, divorced or widowed	3 (37.5)	37 (26.2)	34 (22.2)	13 (31.7)
	Married	5 (62.5)	104 (73.8)	119 (77.8)	28 (68.3)
Education, n (%)	Some college or less	3 (37.5)	76 (53.9)	69 (45.1)	14 (34.1)
	College graduate	5 (62.5)	65 (46.1)	84 (54.9)	27 (65.9)
Income, n (%)	missing	2 (25.0)	15 (10.6)	8 (5.2)	4 (9.8)
	<25k	1 (12.5)	16 (11.4)	12 (7.8)	5 (12.2)
	25-50k	2 (25.0)	31 (22.0)	35 (22.9)	6 (14.6)
	50-100k	2 (25.0)	38 (27.0)	50 (32.7)	14 (34.2)
	>100k	1 (12.5)	41 (29.1)	48 (31.4)	12 (29.3)
AML disease risk, n (%)	Favorable risk	0 (0.0)	9 (6.4)	18 (11.8)	5 (12.2)
	Intermediate risk	3 (37.5)	81 (57.4)	77 (50.3)	17 (41.5)
	Adverse risk	5 (62.5)	51 (36.2)	58 (37.9)	19 (46.3)
Treatment regimen, n (%)	Intensive	8 (100.0)	97 (68.8)	107 (69.9)	32 (78.0)
	Lower intensity	0 (0.0)	44 (31.2)	46 (30.1)	9 (22.0)
HADS Depression Score, mean (SD, range)		5 (2.6, 1-8)	4 (3.3, 0-18)	6 (3.7, 0-17)	9 (4.1, 1-17)
HADS Anxiety Score, mean (SD, range)		3 (2.4, 0-7)	5 (4.0, 0-17)	6 (3.8, 0-20)	8 (4.8, 0-17)
FACT-PWB, mean (SD, range)		24 (3.3, 18-28)	24 (3.2, 14-28)	19 (4.3, 8-27)	10 (3.8, 2-17)
Vital status at last follow up, n (%)	Alive	2 (25.0)	54 (38.3)	68 (44.4)	17 (41.5)
	Deceased	6 (75.0)	86 (61.0)	83 (54.2)	24 (58.5)
	Unknown	0 (0.0)	1 (0.7)	2 (1.3)	0 (0.0)
*Abbreviations: *m=main analysis; AML=Acute Myeloid Leukemia; HADS=Hospital Anxiety and Depression Scale; FACT-PWB=Functional Assessment of Cancer Therapy-Physical Well-Being*					

Table 5: Group size and FACT-PWB over time by group						
Group m1						
	N	**N Miss**	**Mean**	**Std Dev**	**Minimum**	**Maximum**
FACT-PWB T1	8	0	24.0	3.3	18.0	28.0
FACT-PWB T2	7	1	9.1	6.8	4.0	20.0
FACT-PWB T3	7	1	8.4	7.9	3.0	24.0
FACT-PWB T4	4	4	8.8	6.7	2.0	18.0
FACT-PWB T5	3	5	18.7	6.8	11.0	24.0
Group m2						
FACT-PWB T1	141	0	23.7	3.2	14.0	28.0
FACT-PWB T2	109	32	18.9	5.5	1.0	28.0
FACT-PWB T3	112	29	19.8	5.5	3.0	28.0
FACT-PWB T4	98	43	20.8	5.2	3.0	28.0
FACT-PWB T5	83	58	19.3	6.0	2.0	28.0
Group m3						
FACT-PWB T1	153	0	18.9	4.3	8.0	27.0
FACT-PWB T2	119	34	18.3	6.1	2.0	28.0
FACT-PWB T3	123	30	20.3	5.4	7.0	28.0
FACT-PWB T4	99	54	21.4	5.0	9.0	28.0
FACT-PWB T5	84	69	22.1	4.8	5.8	28.0
Group m4						
FACT-PWB T1	41	0	9.9	3.8	2.0	17.0
FACT-PWB T2	39	2	16.9	6.7	3.0	27.0
FACT-PWB T3	35	6	20.3	5.4	9.0	28.0
FACT-PWB T4	15	26	22.2	5.2	9.0	27.0
FACT-PWB T5	13	28	21.2	5.7	10.0	28.0
Total						
FACT-PWB T1	343	0	19.9	5.8	2.0	28.0
FACT-PWB T2	274	69	18.1	6.1	1.0	28.0
FACT-PWB T3	277	66	19.8	5.8	3.0	28.0
FACT-PWB T4	216	127	21.0	5.4	2.0	28.0
FACT-PWB T5	183	160	20.7	5.6	2.0	28.0

Abbreviations: m= main analysis; FACT-PWB= Functional Assessment of Cancer Therapy – Physical Well-Being; T1=Time 1 (baseline), T2-5 vary by study, see Table 1

Table 6: Baseline Factors Associated with Group Membership					
Group	**Parameter**	**Odds Ratio**	**95% CI lower**	**95% CI upper**	**P**
m1: Steep decline with recovery	Age	1.08	0.96	1.22	0.21
	Male gender	0.31	0.05	1.79	0.19
	Married	0.63	0.10	3.83	0.62
	Higher education	1.28	0.23	7.10	0.78
	Disease risk	2.23	0.48	10.38	0.31
	Baseline FACT-PWB	1.57	1.11	2.22	0.01
	Baseline HADS depression	1.19	0.90	1.57	0.23
	Baseline HADS anxiety	0.86	0.64	1.15	0.31
	Intensive treatment	-*	-*	-*	0.99
m2: Slight decline	Age	1.00	0.96	1.04	0.86
	Male gender	0.65	0.29	1.47	0.30
	Married	0.97	0.39	2.43	0.95
	Higher education	0.63	0.29	1.34	0.23
	Disease risk	1.07	0.57	2.00	0.83
	Baseline FACT-PWB	1.43	1.25	1.62	<0.01
	Baseline HADS depression	1.03	0.90	1.16	0.70
	Baseline HADS anxiety	1.07	0.95	1.21	0.27
	Intensive treatment	0.80	0.31	2.05	0.65
m3: Slight improvement/stable	REFERENCE	1.0			
m4: Early improvement, later decline	Age	0.97	0.91	1.03	0.32
	Male gender	0.33	0.08	1.33	0.12
	Married	0.52	0.08	3.41	0.49
	Higher education	2.39	0.49	11.53	0.28
	Disease risk	2.14	0.44	10.47	0.35
	Baseline FACT-PWB	0.59	0.43	0.80	<0.01
	Baseline HADS depression	0.97	0.81	1.17	0.76
	Baseline HADS anxiety	0.89	0.71	1.10	0.26
	Intensive treatment	0.52	0.10	2.82	0.45

**Effect estimate unavailable due to complete separation (all patients in Group 1 received intensive treatment)*
Abbreviations: m= main analysis; HADS=Hospital Anxiety and Depression Scale; FACT-PWB=Functional Assessment of Cancer Therapy-Physical Well-Being

Figure Legends

Figure 1: Group Based Trajectory Model for change in Functional Assessment of Cancer Therapy – Physical Well-Being subscale. Dashed lines represent 95% confidence interval for mean value.

Figure 2: Group Based Trajectory Model for change in Functional Assessment of Cancer Therapy – Physical Well-Being subscale (complete cases only). Dashed lines represent 95% confidence interval for mean value.

Figure 1

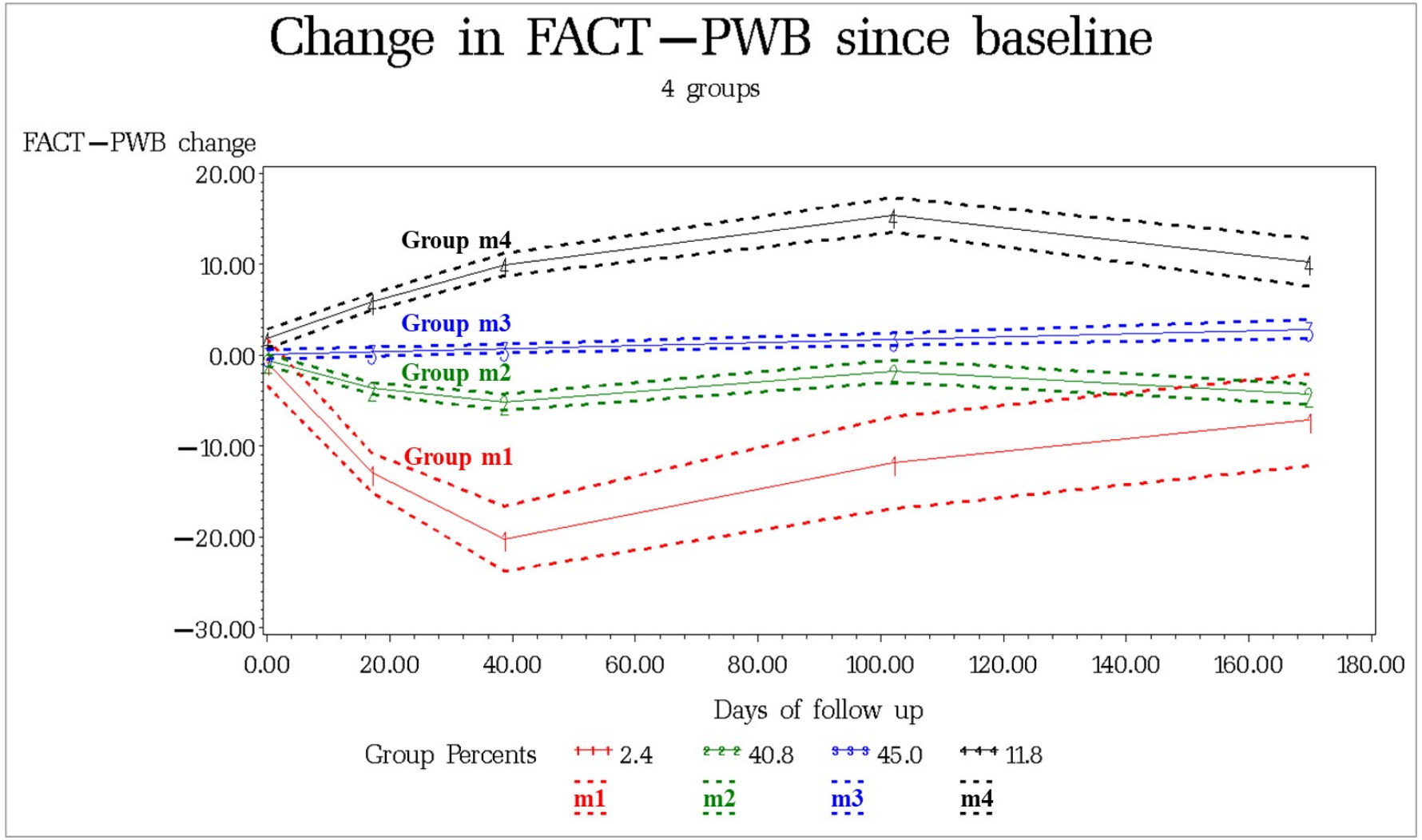

Figure 2