HHS Public Access

Author manuscript

Am J Hematol. Author manuscript; available in PMC 2020 November 02.

Published in final edited form as:

Am J Hematol. 2020 July ; 95(7): E166–E169. doi:10.1002/ajh.25803.

Fatigability: A new perspective on and patient-centered outcome measure for patients with anemia

Micah T. Prochaska[1], **Hui Zhang**[2], **Cyrus Alavi**[3], **David O. Meltzer**[1]

[1]Department of Medicine, Section of Hospital Medicine, The University of Chicago, Chicago, Illinois

[2]Center for Health and The Social Sciences, The University of Chicago, Chicago, Illinois

[3]Pritzker School of Medicine, The University of Chicago, Chicago, Illinois

To the Editor:

In patients with anemia there has been a renewed interest in understanding the impact of red blood cell transfusion on patient-reported outcomes,[1] such as fatigue, the primary symptom of anemia.[2] Anemia-related fatigue is a significant concern to patients, effects their quality of life,[1,2] is associated with decreased activity levels, deconditioning, and losses in functional status.[3,4] Nevertheless, transfusion trials in hospitalized patients have largely used mortality alone as a primary outcome. Data from these studies have driven restrictive transfusion policies in which hospitalized patient's hemoglobin (Hb) levels are maintained in ranges associated with high levels of fatigue,[5] with limited data to assess whether transfusion may affect fatigue. Additional transfusion trials using fatigue as an outcome could answer the question of how transfusion affects fatigue. But, prior to initiating costly trials it is first important to consider the limitations of fatigue as an outcome measure in patients with anemia.

One important limitation of fatigue as an outcome measure is that it does not account for patients' activity level, or how activity influences fatigue.[6] This has two significant implications for understanding fatigue and the effect of transfusion on fatigue in patients with anemia. First, differences in functional capacity between patients who report similar fatigue levels cannot be appreciated. For example, two patients with anemia may report similar levels of fatigue, but one patient may be physically active while the other is sedentary. By not accounting for how activity influences fatigue, these patients may be perceived to be the same. Second, not accounting for how activity influences fatigue also makes it difficult to evaluate the effectiveness of transfusion. If transfusion reduces fatigue,

Correspondence: Micah T. Prochaska, University of Chicago, 5841 S. Maryland Avenue, MC 5000, Chicago, IL 60637., mprochas@medicine.bsd.uchicago.edu.

AUTHOR CONTRIBUTIONS

All authors have contributed to the development of this manuscript, including developing the idea, writing, data analysis, and revision.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest relevant to the manuscript submitted.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

it may result in increased activity that could then offset decreases in fatigue. Measuring fatigue alone may make transfusion appear unsuccessful if post-transfusion fatigue levels are the same or higher than pre-transfusion levels, since the changes in patient activity would not have been appreciated. One possible solution to these problems is to measure fatigue in the context of activity, a measure known as fatigability.[6]

Fatigability measures patient's self-reported fatigue in the context of a standardized activity level,[6] with greater fatigability indicating more fatigue at any given level of activity. Since fatigability is standardized it can be used to objectively compare patients with similar fatigue levels but different levels of activity. This makes fatigability potentially clinically useful for identifying patients with anemia at high risk for functional decline due to fatigue interfering with their activity. Fatigability could also better measure the effectiveness of transfusion than fatigue, since it can capture changes in either fatigue and/or activity that may occur after transfusion. Therefore, by accounting for the relationship between fatigue and activity, fatigability addresses a critical limitation of fatigue, suggesting that fatigability could be a useful outcome measure in patients with anemia.

However, despite the potential benefits of fatigability as an outcome measure, it has not been previously used in and/or compared with validated measures of fatigue or activity in studies of patients with anemia. The purpose of this study was to establish the clinical reliability of fatigability in hospitalized patients with anemia by: (a) testing the association between fatigability and increased patient age, comorbidities, and severity of anemia, since these patient characteristics are associated increased fatigue[5] and/or declines in physical function in patients with anemia,[3] and (b) comparing fatigability to validated measures of fatigue and physical function and the strength of their association with demographic (age) and clinical characteristics (comorbidities, Hb) in patients with anemia.

We performed a prospective observational study of hospitalized general medicine patients with a Hb < 10 g/dL during their hospitalization. Patient demographic data including, age, sex, race, ethnicity, comorbidities, and Hb values were obtained from the hospitals administrative database.

Self-reported measures of fatigability, fatigue, and/or physical function were collected through an in-person interview during hospitalization. Fatigability was measured by the pittsburgh fatigability scale (PFS) (primary outcome) and the situational fatigue scale (SFS) physical fatigue subscale. Fatigue was measured by the functional assessment of chronic illness therapy (FACIT) Fatigue subscale and the patient-reported outcomes measurement information system (PROMIS) Fatigue (F) instruments. Physical function was measured by the PROMIS physical function (PF) with mobility aid instrument, which provides a separate score based on patients' ability to ambulate.

Multivariable linear regression models were used to test the association between each measure of fatigability, fatigue, and activity as dependent variables, with patient's age, Charlson Comorbidity Index, and Hb level as independent variables of interest. Comprehensive study methods, including model specification are described in the e-Appendix (Appendix).

The study included 2049 subjects. The mean age was 57 years; 59% were female; 73% were African-American. Table S1 contains the full demographic data of the sample (Table S1).

Higher fatigability was measured by the PFS and SFS and associated with older age, greater number of comorbidities, and anemia severity. On the PFS, the larger fatigability coefficient associated with each increase in age and comorbidity category and each 1 g/dL decrease in Hb, indicate an increasing fatigability level across each of these patient characteristics. Similarly, on the SFS, fatigability levels increased with older age, greater numbers of comorbidities, and lower Hb, although the Hb effect was only statistically significant for patients with a Hb < 7 g/dL (Table 1).

In contrast, neither measure of fatigue (FACIT, PROMIS-F) was consistently associated with patients' age, comorbidities, or severity of anemia. Increased fatigue measured by the FACIT was associated with decreases in patients' Hb levels and having ≥5 comorbidities, but had no association with patient age. Measured by the PROMIS-F, lower fatigue levels were paradoxically associated with older age for patients ≥75, but there were no other associations between fatigue and patient age, comorbidities, or Hb.

The association between physical function and age, comorbidities, and Hb, varied by patients' ambulatory capability. In ambulatory patients lower physical function was associated with each older age and higher comorbidity category, though the association with comorbidities was statistically significant only in patients with ≥3 comorbidities. In ambulatory patients there was no association between physical function and Hb. In non-ambulatory patients decreased physical function was associated only with categories age ≥ 75 and Hb < 7 g/dL.

This study supports the hypothesis that fatigability is strongly associated with expected differences in age, comorbidities, and Hb level in hospitalized patients with anemia. Higher fatigability levels were associated with each increase in age and comorbidity category, and each 1 g/dL decrease in Hb, as measured by our primary outcome, the PFS. Similar associations between fatigability and patient age, comorbidities, and Hb were present when measuring fatigability using the SFS. These results on two different instruments help validate the clinical reliability of fatigability as an outcome measure because older age, comorbidities, and anemia severity are expected to be associated with increased fatigability (greater fatigue at any level of activity).

Our results also highlight the limitations of fatigue as an outcome measure. Measured by the FACIT increased fatigue was associated with lower Hb levels. However, fatigue measured by the FACIT or PROMIS-F had no other associations with patients' age, comorbidities, or Hb. This is perhaps not surprising since fatigue is a subjective self-reported symptom, and measuring it even when with well-validated instruments can produce discrepant and paradoxical results.[6] It is also important to note that in our data older ambulatory patients with more comorbid disease had reduced physical function. This suggests that the effects of age and comorbidities on fatigue may be occurring through the pathway of reduced activity, and these effects would not be captured by measuring fatigue without also understanding changes in patient's activity levels. This is the central limitation of fatigue as an outcome

measure. The significance is that fatigue alone cannot discriminate between older adults with anemia and more comorbid disease that may experience fatigue at lower activity levels (higher fatigability), and younger healthier adults with anemia that may experience a similar fatigue level at higher activity levels (lower fatigability). Fatigability addresses this limitation and our study provides empirical support for using fatigability in future studies of patients with anemia.

Fatigability has several potential uses as an outcome measure in patients with anemia. Fatigability could be used in transfusion trials as a patient-reported outcome. Similarly, fatigability could be used by clinicians to measure the impact of a patient's anemia on their fatigue and activity level, and their response to treatment. Clinicians could also use fatigability to identify high risk patients whose fatigue is interfering with their normal activity, and to target both fatigue as the primary symptom of anemia and activity as the pathway by which anemia-related fatigue is likely to impair functional outcomes.

This study has the limitations of a single site observational study. Additionally, we used self-reported instruments and patient's actual fatigability, fatigue, and activity levels may be different than reported.

Fatigue is limited in capturing the full effect of anemia on patients since it does not account for patient activity. Fatigability, the measure of fatigue in the context of specific activity, addresses this limitation with respect to fatigue, and future studies of patients with anemia should include fatigability as an outcome measure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

FUNDING

This work was supported by a National Heart, Lung, and Blood Institute K23 Patient-Oriented Research Career Development Award. (NIH/NHLBI 1K23HL140132, to M.P.)

This work was also supported by a National Institutes of Health Clinical and Translational Science Award (NIH/NCATS UL1TR0002389, to D.M.)

REFERENCES

1. Lin Y, Buckstein R. Outpatient transfusions: time to study what matters to patients. Transfusion. 2019;59(6):1887–1890. 10.1111/trf.15382. [PubMed: 31161666]
2. Yellen SB, Cella DF, Webster K, Blendowski C, Kaplan E. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. J Pain Symptom Manage. 1997;13(2):63–74. [PubMed: 9095563]
3. Penninx BWJH, Pahor M, Cesari M, et al. Anemia is associated with disability and decreased physical performance and muscle strength in the elderly. J Am Geriatr Soc. 2004;52(5):719–724. 10.1111/j.1532-5415.2004.52208.x. [PubMed: 15086651]
4. den Elzen WPJ, Willems JM, Westendorp RGJ, de Craen AJM, Assendelft WJJ, Gussekloo J. Effect of anemia and comorbidity on functional status and mortality in old age: results from the Leiden 85-plus Study. Can Med Assoc J J Assoc Medicale Can. 2009;181(3–4): 151–157. 10.1503/cmaj.090040.

5. Prochaska MT, Newcomb R, Block G, Park B, Meltzer DO. Association between anemia and fatigue in hospitalized patients: does the measure of anemia matter? J Hosp Med. 2017;12(11):898–904. 10.12788/jhm.2832. [PubMed: 29091977]

6. Eldadah BA. Fatigue and fatigability in older adults. PM&R. 2010;2(5): 406–413. 10.1016/j.pmrj.2010.03.022. [PubMed: 20656622]

Am J Hematol. Author manuscript; available in PMC 2020 November 02.

TABLE 1

Association between fatigability, fatigue, activity, and clinical and demographic characteristics[aa]

	Fatigability						Fatigue						Activity					
	Pittsburgh Fatigability Scale			Situational Fatigue Scale~			FACIT Fatigue			PROMIS Fatigue			PROMIS-PF Ambulatory			PROMIS-PF Non-ambulatory		
	Coef.*	95% CI	*P*	Coef.*	95% CI	*P*	Coef.*	95% CI	*P*	Coef.*	95% CI	*P*	Coef.*	95% CI	*P*	Coef.*	95% CI	*P*
Age (years)																		
18–44		Referent			Referent			Referent			Referent			Referent			Referent	
45–59	2.0	0.66–3.3	<.01	2.1	1.2–3.1	<.01	0.68	−1.5 – 2.9	.54	0.21	−1.5 – 2.0	.82	−2.6	−4.5 – −0.63	.01	−3.3	−7.2 – 0.48	.09
60–74	2.3	1.0–3.7	<.01	2.2	1.3–3.1	<.01	−0.83	−3.1 – 1.4	.47	0.09	−1.6 – 1.7	.92	−3.8	−5.7 – −1.9	<.O1	−3.3	−7.0 – 0.42	.08
≥75	3.2	1.7–4.8	<.01	2.8	1.7–3.8	<.01	1.2	−3.7 – 1.4	.37	−3.1	−5.0 – −1.1	.02	−4.7	−7.1 – −2.4	<.O1	−5.1	−8.9 – −1.2	.01
# of Comorbidities																		
0		Referent			Referent			Referent			Referent			Referent			Referent	
1–2	1.7	0.26–3.1	.02	1.2	0.16–2.2	.02	−0.67	−1.7 – 3.0	.58	0.68	−1.2 – 2.5	.47	−1.5	−3.6 – 0.56	.15	−1.1	−5.2 – 3.0	.61
3–4	2.8	1.2–4.4	<.01	1.5	0.34–2.6	.01	−1.1	−1.6 – 3.9	.41	0.85	−1.2 – 2.9	.41	−3.6	−5.9 – −1.22	<.O1	−0.63	−4.8 – 3.6	.77
≥5	3.5	2.0–5.0	<.01	1.2	0.16–2.2	.02	−2.9	−0.35 – 5.4	.03	1.5	−0.41 – 3.4	.13	−4.2	−6.4 – −2.1	<.O1	−0.41	−4.4 – 3.6	.84
Hemoglobin (g/dL)																		
9 ≤ Hb < 10		Referent			Referent			Referent			Referent			Referent			Referent	
8 ≤ Hb < 9	0.6	−0.59 – 1.9	.31	0.22	−0.65 – 1.1	.63	2.3	0.23–4.3	.03	−0.36	−1.9 – 1.2	.66	−0.50	−2.3 – 1.3	.59	−4.2	−7.2 – −1.1	.08
7 ≤ Hb < 8	1.4	0.07–2.7	.04	0.57	−0.32 – 1.5	.21	2.7	0.49–4.9	.02	0.52	−1.1 – 2.2	.53	0.67	−1.2 – 2.5	.48	−2.2	−5.6 – 1.2	.21
Hb < 7	1.7	0.41–2.9	.01	0.84	−0.01 – 1.7	.05	2.4	0.23–4.5	.03	0.4	−1.2 – 2.0	.62	−0.48	−2.4 – 1.4	.61	−3.5	−6.4 – −0.58	.02

Note: Situational Fatigue Scale Physical Fatigue Subscale, which includes questions that ask about fatigue in the context of activity (ie, fatigability).

Abbreviations: FACIT Fatigue = Functional Assessment of Chronic Illness Therapy Fatigue Subscale score range 0–52; PROMIS Fatigue = Patient Reported Outcome Measurement Instrument System-Fatigue Short Form 8a score range 8–40; PROMIS-PF Ambulatory = Patient Reported Outcome Measurement Instrument System Physical Function with Mobility Aid (patients able to walk 25 ft) score range 11–55; PROMIS-PF Non-Ambulatory = Patient Reported Outcome Measurement Instrument System Physical Function with Mobility Aid (patients NOT able to walk 25 ft) score range 8–40.

[a]Model Controls for: gender, race, SCD, GIBL, and depression.