



Fatigue in newly diagnosed acute myeloid leukaemia: general population comparison and predictive factors

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ABSTRACT

Objectives This study compared the burden of fatigue between treatment-naïve patients with newly diagnosed acute myeloid leukaemia (AML) and the general population and investigated patient factors associated with fatigue severity.

Methods Pretreatment patient-reported fatigue was assessed with the Functional Assessment of Chronic Illness Therapy-Fatigue questionnaire in a sample of 463 newly diagnosed patients with AML who were enrolled in a clinical trial. Multivariable linear regression models were used to estimate the adjusted mean differences in fatigue between patients with AML and adults from the general population (n=847) by AML disease risk categories. A clinically meaningful difference in fatigue was defined as ≥ 3 points. Univariable and multivariable linear regression models were used to identify sociodemographic, clinical and molecular correlates of worse fatigue in patients with AML.

Results Patients with AML reported adjusted mean fatigue scores that were 7.5 points worse than the general population (95% CI -8.6 to -6.4, $p < 0.001$). Across AML disease risk categories, adjusted mean differences in fatigue compared with the general population ranged from 6.7 points worse (patients with favourable risk: 95% CI -8.6 to -4.8, $p < 0.001$) to 8.9 points worse (patients with poor risk, 95% CI -10.5 to -7.2, $p < 0.001$). Overall, 91% of patients with AML reported fatigue that was equal to or worse than the general population's median fatigue score. Higher pretreatment fatigue was independently associated with female sex, WHO performance status ≥ 1 and lower platelet levels.

Key messages

What was already known?

► Fatigue is a common symptom reported by patients with AML.

What are the new findings?

► Treatment-naïve AML patients reported worse fatigue than the general population.
► Differences in fatigue were largest between patients in the poor disease-risk category and the general population.

What is their significance?

► Patients with AML are vulnerable to fatigue before treatment and may benefit from supportive care.

Conclusions Patients with newly diagnosed AML reported worse fatigue than the general population, and mean differences exceeded twice the threshold for clinical significance. Our findings may help to identify patients with AML most likely to benefit from supportive care interventions to reduce fatigue.

INTRODUCTION

Acute myeloid leukaemia (AML) is a heterogeneous cancer that starts in the bone marrow and is characterised by the clonal expansion of myeloid blasts in the blood, bone marrow and/or other tissues.¹ AML is the one of most common leukaemias affecting adults in the USA, accounting for 32% of leukaemia incidence and second only to chronic lymphocytic leukaemia (37%).² This translates to almost 20 000 expected new cases of AML

in the USA in 2020 alone. AML is also a leading cause of leukaemia-related deaths, with more than 11 000 AML-related deaths expected in 2020.² The National Comprehensive Cancer Network (NCCN) has defined risk categories to describe the prognostic patterns of AML (ie, *favourable*, *intermediate* and *poor* risk categories).¹ NCCN risk categories are based on molecular mutations and cytogenetic abnormalities (eg, chromosomal deletions, translocations and duplications), and better outcomes are expected for patients who fall in the *favourable* risk category compared with others. Clinicians use the current NCCN risk categories to inform risk-adapted treatment plans for individual patients with AML. Thus, NCCN risk categories are important for maximising clinical outcomes.

A recent review concluded that fatigue is the most common symptom reported by patients with AML, regardless of treatment status (ie, active treatment vs post-treatment).³ Studies of patients with AML undergoing intensive and prolonged treatments, such as induction chemotherapy, found that fatigue is more strongly related to health-related quality of life (HRQOL) than other treatment side effects (eg, nausea, emesis, appetite loss).⁴ In addition, patients with AML consistently rate fatigue as moderate to severe throughout treatment.⁵ Post-treatment, long-term and severe fatigue is a significant concern affecting the HRQOL of many patients.^{3,6} Moreover, a recent study showed that greater patient-reported fatigue in treatment-naïve patients with AML predicted shorter survival.⁷ Therefore, understanding and alleviating fatigue early in the trajectory of AML diagnosis and treatment may be a critical component to promoting favourable patient outcomes.

Given fatigue's prevalence and persistence, researchers have attempted to identify factors that predict fatigue in patients with AML, including socio-demographic characteristics, clinical characteristics⁸ and biological factors (eg, proinflammatory cytokines).^{9–12} However, previous studies have not distinguished patients with AML by NCCN risk categories, possibly due to small sample sizes limiting the statistical power to do so. Further characterisation of fatigue among subgroups of patients with AML using common clinical categorisations will provide important information about variations in the burden of fatigue in this patient population. These nuances may be particularly important in light of research showing that patient-reported fatigue in patients with untreated AML is associated with overall survival.⁷ Moreover, although fatigue is generally accepted as a hallmark of AML and its treatments, studies have not yet determined the severity of fatigue among patients with newly diagnosed AML relative to the general population.

To address these limitations, the primary objective of this analysis was to compare the burden of fatigue between a cohort of treatment-naïve patients with newly diagnosed AML and a cohort representing the

general population. The secondary objectives were to investigate fatigue severity by NCCN risk categories and to investigate sociodemographic, clinical and molecular correlates of worse pretreatment fatigue among patients with AML.

METHODS

Between January 2012 and May 2015, 515 treatment-naïve patients with AML were registered to participate in a single-arm study to determine whether a risk-adapted, minimal residual disease-directed therapy could positively affect overall survival.¹³ For the purpose of these analyses, we considered 508 participants who were eligible and had an available risk category. Patient-reported HRQOL was a secondary endpoint of the trial, and all patients were invited to complete a baseline assessment (ie, before starting therapy) with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30¹⁴ and the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale.^{15,16} The trial was originally designed in 2010, and thus all patients were stratified according to contemporary classifications (ie, NCCN 2009 version 1).¹⁷ Eligibility criteria for participants were an unequivocal diagnosis of untreated, *de novo* AML according to WHO diagnostic criteria,¹⁸ age 18–60 years old, no prior treatments for AML and a WHO performance status of 0–3.¹⁹ Additional details related to the study inclusion and exclusion criteria are reported elsewhere.¹³

All participants provided written informed consent.

Sample of adults from the general population

Data for the general population were collected by a marketing information and decision support system titled Knowledge Networks (Menlo Park, California). Knowledge Networks drew a random sample of individuals at least 18 years old in the USA from an internet-based survey panel including more than 100 000 demographically representative adults. Participants on the panel responded to one survey per month in exchange for free installation of WebTV internet service. In total, 1075 individuals from the general population completed the FACIT-Fatigue questionnaire. Of those individuals, 61 were excluded from these analyses because they reported a current or historical cancer diagnosis, and 167 were excluded because they were older than 61 years old (ie, the maximum age in the AML sample). Thus, 847 participants (49.6% male, mean of 39.8 years old) were retained for these analyses. These participants are a largely overlapping subset of participants that have been used as a general population reference group to compare other patient populations' fatigue (eg, patients with myelodysplastic syndromes²⁰ and patients with anaemic cancer²¹).

Measures

Fatigue

Self-reported fatigue was assessed using the 13-item FACIT-Fatigue scale.^{15 16} Participants rated statements about fatigue in the past week on a Likert-type scale from *not at all* (0) to *very much* (4). Consistent with other FACIT measures, negatively worded items were reverse-scored and responses were summed so that higher total scores indicated better functioning (possible range 0–52). Thus, lower total scores indicated worse fatigue.¹⁵ Consistent with previous work, a difference of at least 3 points was considered clinically meaningful.^{15 16} For these analyses, only the baseline fatigue scores of patients with AML were compared with fatigue in the general population, so that scores were not confounded by factors such as active AML treatments.

Statistical analyses

Frequencies, proportions, means, SD, medians and IQR were used to describe the main characteristics of patients with AML. χ^2 and Wilcoxon-Mann-Whitney tests were used to assess possible systematic differences between patients with AML who did versus did not complete the FACIT-Fatigue questionnaire at baseline. For these analyses, patients with intermediate risk were merged with patients with intermediate risk and no leukaemia-associated immunophenotypes (previously identified in the main clinical paper¹³). Multivariable linear regression analyses were performed to estimate the overall mean difference in fatigue scores between patients with AML and the general population, adjusting for age and sex and including a binary status indicator (AML vs general population). The multivariable linear regression model was repeated separately by patients' NCCN risk category (ie, *favourable*, *intermediate* and *poor* risk). For descriptive purposes, the cumulative distribution of FACIT-Fatigue scores was computed for patients with AML and the general population, and the proportions of patients with AML who reported a fatigue score equal to or worse than the mean and median fatigue scores in the general population were reported. To determine independent correlates of fatigue among patients with AML, univariable linear regression analyses were conducted with sociodemographic, clinical and molecular variables as independent variables. The following sociodemographic and clinical variables were considered: sex (male vs female), age, WHO performance status (0 vs ≥ 1), presence of comorbidities (yes vs no), haemoglobin levels, white cell count, percentage of blast cells and platelet count. The following molecular variables were considered: presence (yes vs no) of FLT3-ITD, RUNX1-RUNX1T1, CBF β -MYH11 and NMP1 gene mutations. Then, a multivariable linear regression model was estimated to explain fatigue among patients with AML, including the significant sociodemographic, clinical and molecular predictors

of fatigue identified from the univariable analyses. All statistical tests were two-sided, and statistical significance was determined with $\alpha=0.05$. Analyses were performed with SAS V.4 software.

RESULTS

Of the 508 patients with AML considered for these analyses, 463 (91%) completed the baseline FACIT-Fatigue questionnaire. There were no differences between patients who did (n=463) and did not complete the questionnaire (n=45) with regard to key sociodemographic and clinical characteristics. Details are reported in the online supplemental materials.

Table 1 describes the characteristics of patients with AML overall and by NCCN risk categories. There were roughly equivalent proportions of male (n=264, 52.0%) and female (n=244, 48.0%) patients, and patients were a median of 49 years old (IQR 40.0–55.0). Most patients had a WHO performance status of 0 (n=289, 58.6%) and no comorbidities (n=402, 84.1%).

Fatigue in patients with AML compared with the general population

The average fatigue score in the general population was 40.5 (SD=10.2, median 44.0), and the average fatigue score among patients with AML was 33.1 (SD=8.7, median 33.8) (**table 2**). After adjusting for age and sex, fatigue among patients with AML across NCCN risk categories was an average of 7.5 points worse than the general population (95% CI –8.6 to –6.4, $p<0.001$), which is more than twice the 3-point threshold for a clinically meaningful difference. The largest difference in fatigue scores was observed between the general population and patients in the NCCN *poor* risk category; fatigue among patients with AML and *poor* risk was an average of 8.9 points lower than the general population (95% CI –10.5 to –7.2, $p<0.001$), almost three times the threshold for a clinically meaningful difference.

The cumulative distribution of fatigue scores in patients with AML and the general population is shown in **figure 1**. Overall, 84% (n=389/463) and 91% (n=422/463) of patients with AML reported fatigue that was equal to or worse than the mean and median fatigue scores in the general population, respectively. For descriptive purposes, the mean differences between patients with AML by NCCN risk category and the general population are graphically depicted in **figure 2**.

Independent correlates of fatigue in patients with AML

Worse fatigue among patients with AML was associated with female sex ($\beta=-2.11$, 95% CI 3.70 to –0.53, $p=0.009$), WHO performance status of at least 1 ($\beta=-3.15$, 95% CI –4.79 to –1.52, $p<0.001$), lower haemoglobin levels ($\beta=0.56$, 95% CI 0.12 to 0.99, $p=0.013$), greater percentage of blast cells ($\beta=-0.05$,

Table 1 Characteristics of patients with acute myeloid leukaemia and by NCCN risk category

Variable	NCCN risk category			
	Total (N=508)	Favourable (n=139)	Intermediate (n=175)	Poor (n=194)
Sex, n (%)				
Male	264 (52.0)	72 (51.8)	92 (52.6)	100 (51.5)
Female	244 (48.0)	67 (48.2)	83 (47.4)	94 (48.5)
Age, years				
Median	49.0	50.0	48.0	48.0
IQR	40.0–55.0	43.0–55.0	40.0–55.0	38.0–55.0
WHO performance status, n (%)				
0	289 (58.6)	80 (59.3)	100 (59.2)	109 (57.7)
1	143 (29.0)	43 (31.8)	50 (29.6)	50 (26.5)
2	59 (12.0)	11 (8.2)	19 (11.2)	29 (15.3)
3	2 (0.4)	1 (0.7)	0 (0)	1 (0.5)
Missing	15 (–)	4 (–)	6 (–)	5 (–)
Presence of comorbidities, n (%)				
No comorbidities	402 (84.1)	106 (80.9)	136 (82.9)	160 (87.4)
At least one comorbidity	76 (15.9)	25 (19.1)	28 (17.1)	23 (12.6)
Missing	30 (–)	8 (–)	11 (–)	11 (–)
Haemoglobin level, g/dL				
Median	8.9	8.9	9.2	8.6
IQR	8.1–10.0	8.2–10.0	8.2–10.5	8.0–9.8
White cell count, cells ×10 ⁹ /L				
Median	14	17.4	5.7	27.3
IQR	3.4–50.0	5.6–57.0	2.0–22.5	6.1–70.9
Blast cells, %				
Median	54.0	54.5	40.0	62.0
IQR	20.0–80.0	20.0–74.0	10.0–77.0	39.0–90.0
Platelet count, ×10 ⁹ /L				
Median	55.0	56.0	55.0	50.0
IQR	29.0–94.0	28.0–94.0	30.0–108.0	28.0–82.0

NCCN, National Comprehensive Cancer Network.

95% CI –0.08 to –0.02, $p < 0.001$), higher white cell counts ($\beta = -0.35$, 95% CI –0.51 to –0.19, $p < 0.001$) and lower platelet counts ($\beta = 0.18$, 95% CI 0.08 to 0.28, $p = 0.001$). The only significant molecular correlate was the FLT3-ITD mutation ($\beta = -2.08$, 95% CI –3.90 to –0.26, $p = 0.025$). All univariable linear regression models are described in [table 3](#).

In multivariable analysis, the following variables were significantly associated with worse fatigue above and beyond other predictors: female sex ($\beta = -2.30$, 95% CI –4.01 to –0.59, $p = 0.009$), WHO performance status of at least 1 ($\beta = -2.55$, 95% CI –4.30 to –0.81, $p = 0.004$) and lower platelet count ($\beta = 0.22$, 95% CI 0.08 to 0.37, $p = 0.002$). Additional

Table 2 Distribution of fatigue scores and adjusted mean differences between patients with acute myeloid leukaemia and the general population (n=463)

Sample	Distribution of fatigue scores			Adjusted mean difference from general population* (95% CI)	P value
	Mean (SD)	Median	Range		
General population	40.5 (10.2)	44.0	2–52	NA	NA
AML total sample	33.1 (8.7)	33.8	0–52	–7.5 (–8.6 to –6.4)	<0.001
NCCN risk category					
Favourable	33.9 (7.8)	34.7	13–52	–6.7 (–8.6 to –4.8)	<0.001
Intermediate	34.0 (8.3)	34.3	8–51	–6.8 (–8.5 to –5.1)	<0.001
Poor	31.8 (9.4)	31.9	0–50	–8.9 (–10.5 to –7.2)	<0.001

*Mean differences were adjusted for age and sex.

NA, not applicable; NCCN, National Comprehensive Cancer Network.

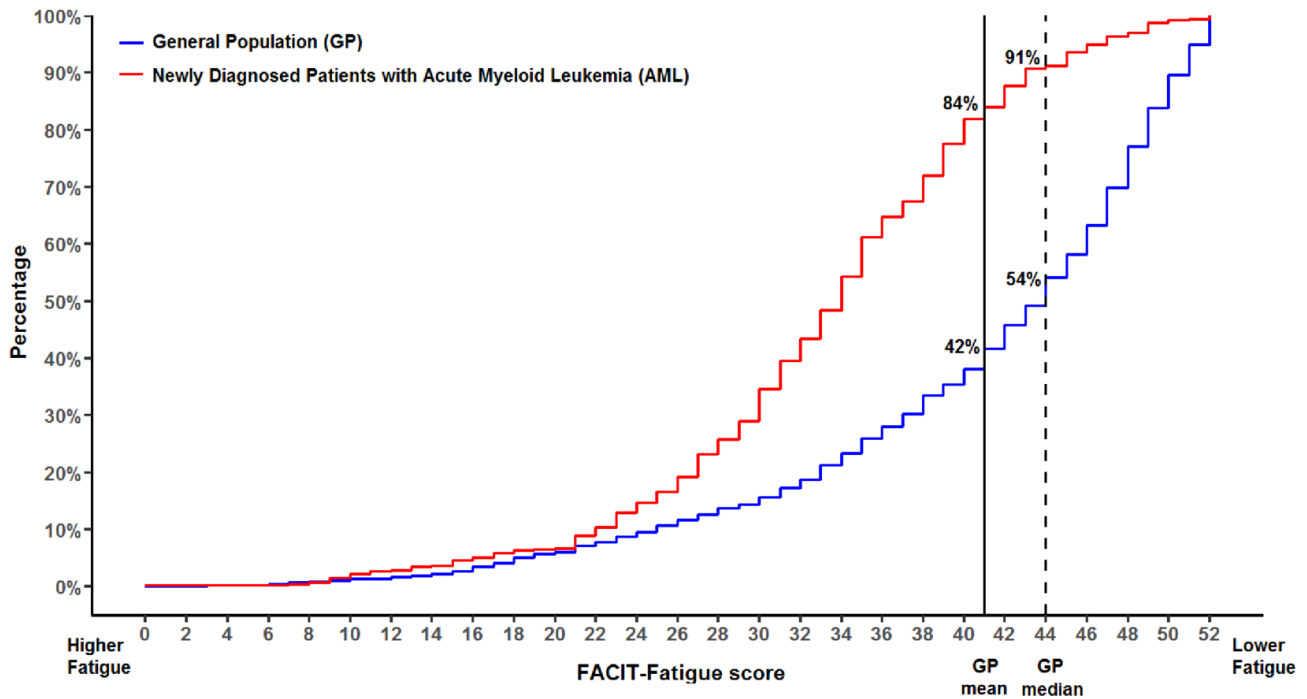


Figure 1 Cumulative distribution of FACIT-Fatigue scores in patients with acute myeloid leukaemia and the general population. From left to right, the height of the curve represents the overall proportion of patients reporting fatigue equal to or worse than the corresponding FACIT-Fatigue score. The vertical line represents the mean FACIT-Fatigue score in the general population. FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue.

information on the multivariable analysis is shown in table 3.

DISCUSSION

This was the first study to compare fatigue between newly diagnosed, treatment-naïve patients with AML with the general population, overall and by disease risk categories. Findings indicated that most patients with AML had worse fatigue than the general population, and differences in fatigue were clinically meaningful

across NCCN risk categories. Analyses by individual risk categories showed that the burden of fatigue in both *favourable* and *intermediate* risk categories was nearly identical and exceeded twice the magnitude of a clinically meaningful difference with the general population. Patients in the NCCN *poor* risk category reported worse fatigue than the general population at a magnitude of almost three times the clinically meaningful threshold. The sizeable differences in fatigue observed across the three risk categories highlight how vulnerable patients with AML are to fatigue, even before initiating treatment.

Prior work has established that fatigue is a highly prevalent symptom among patients with AML³ and persists well beyond diagnosis.²² Studies suggest that fatigue improves for patients who achieve remission with treatment,²³ and fatigue improvement appears to be unrelated to treatment intensity (ie, intensive vs non-intensive chemotherapy).²⁴ Moreover, fatigue severity appears to be similar among younger (<60 years old) and older patients with AML (≥60 years old).²⁵ Recently, Buckley and colleagues²⁶ interviewed 82 patients with AML at various disease stages to determine the most prevalent symptoms associated with AML. Fatigue was one of the most prevalent symptoms, second only to fear/anxiety, and fatigue was reported by more than three-quarters of the sample (76%). Moreover, almost half of the sample (44%) reported that fatigue was ‘very impactful’ for HRQOL.

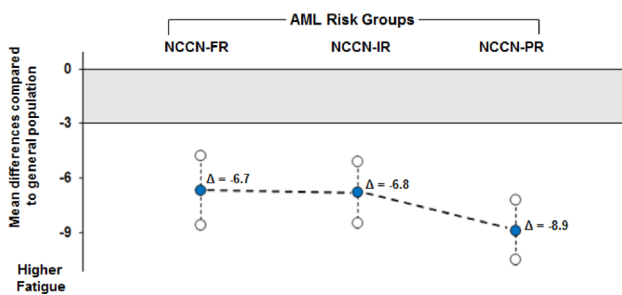


Figure 2 Mean differences in FACIT-Fatigue scores between patients with acute myeloid leukaemia (AML) and the general population by National Comprehensive Cancer Network (NCCN) risk category (FR, favourable risk; IR, intermediate risk; PR, poor risk). Mean differences were adjusted for age and sex. Lines between the adjusted mean differences were plotted for descriptive purposes. Mean differences plotted outside the grey shaded area indicate that the mean difference exceeded the 3-point clinically meaningful difference threshold. FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue.

Table 3 Results of univariable and multivariable regression models relating sociodemographic, clinical and molecular variables to fatigue among patients with acute myeloid leukaemia

	Univariable analysis			Multivariable analysis		
	Estimate	95% CI	P value	Estimate	95% CI	P value
Sociodemographic variables						
Female sex	-2.11	3.70 to -0.53	0.009	-2.30	-4.01 to -0.59	0.009
Age	-0.03	-0.11 to 0.05	0.437	NA	NA	NA
Clinical variables						
WHO performance status ≥ 1	-3.15	-4.79 to -1.52	<0.001	-2.55	-4.30 to -0.81	0.004
≥ 1 comorbidity	-1.26	-3.47 to 0.95	0.262	NA	NA	NA
Haemoglobin level, g/dL	0.56	0.12 to 0.99	0.013	0.06	-0.43 to 0.54	0.815
White cell count, $\times 10^9/L$	-0.35	-0.51 to -0.19	<0.001	-0.15	-0.34 to 0.04	0.125
Blast cells, %	-0.05	-0.08 to -0.02	<0.001	-0.02	-0.05 to 0.02	0.314
Platelet count, $\times 10^9/L$	0.18	0.08 to 0.28	0.001	0.22	0.08 to 0.37	0.002
Molecular variables						
FLT3-ITD	-2.08	-3.90 to -0.26	0.025	-0.05	-2.05 to 1.95	0.961
RUNX1-RUNX1T1	0.20	-3.27 to 3.68	0.908	NA	NA	NA
CBF β -MYH11	-0.14	-3.21 to 2.93	0.928	NA	NA	NA
NMP1	-0.17	-1.83 to 1.49	0.839	NA	NA	NA

Only significant univariable predictors of fatigue were included in the multivariable analysis.

NA, not applicable.

While the prevalence and trajectory of fatigue in AML have been fairly well studied, far fewer studies have identified independent factors that could help clinicians identify patients at risk for worse fatigue burden early in the diagnostic work-up. The current study addresses this gap in the literature by focusing on fatigue among patients with AML before receiving any treatments. In addition, patients in this sample were younger than those reported in other work (median age was 49 years old). In a multivariable analysis, worse fatigue was correlated with female sex, WHO performance status of at least 1 and lower platelet counts. These characteristics could aid clinicians in identifying subgroups of patients at greater risk of worse fatigue as well as worse outcomes that are associated with fatigue, such as shorter survival.⁷ The finding that female sex was associated with worse fatigue is consistent with previous studies of patients with other haematological malignancies, either newly diagnosed²⁷ or undergoing treatment,²⁸⁻³⁰ and should be explored more in future work. In addition, the finding that lower platelet counts were associated with worse fatigue is consistent with a recent study by Zhang and colleagues,³¹ who showed that platelet count at the time of diagnosis was an independent prognostic factor for survival in patients with AML, thereby lending important insights about the relevance of this variable for capturing overall disease burden.

This was the first study to evaluate molecular mutations as correlates of fatigue in AML. However, it is not the first study to investigate biological correlates more generally. There is a small body of work evaluating the relationships between fatigue and cytokines in patients with AML,^{7 9-11} which is driven by

the sickness behaviour model. This model posits that behavioural symptoms of illness, such as fatigue, may be determined by sickness-associated inflammation and cytokine activity.³² However, a recent study of more than 200 patients with AML concluded that cytokines explained only a small amount of the variance in cancer-related fatigue.¹² In recent years, advances in the use of genomic sequencing have allowed researchers and clinicians to determine how specific molecular mutations relate to outcomes among patients with AML.³³ Yet, until now, no studies have investigated how molecular mutations relate to fatigue in this population. Our univariable analyses showed that the presence of the FLT3-ITD mutation was associated with worse fatigue, although this relationship did not persist in multivariable models. The FLT3-ITD mutation is one of the most common AML-related mutations, observed in almost one-third of patients with AML.³³ Previous work indicates that patients with the FLT3-ITD mutation are at risk of worse treatment outcomes, including greater risk of disease relapse and mortality.³⁴ Consistent with the sickness behaviour model, it is possible that the relationship between worse fatigue and FLT3-ITD mutation observed in this study reflects greater overall disease burden. This possibility and other clinical implications of the FLT3-ITD mutation should be explored in future work to inform better management of fatigue and to promote better clinical outcomes. In addition, given that sickness behaviours typically present in clusters (eg, fatigue, pain, depression),³⁵ future work should also consider the role of other patient-reported outcomes and symptom clusters.

Limitations of this study include a cross-sectional design, and thus the direction of causality could not be determined in the reported relationships. In addition, data related to other common symptoms that have been previously associated with fatigue in patients with cancer, such as pain and depression, were not available.³⁵ Large-scale prospective studies are needed to better elucidate factors associated with fatigue among patients with AML. Finally, while the NCCN classification system used in this study was current at the time of study design, this classification system has since been refined. However, this did not affect the primary objective of this work.

This study has notable strengths. To the best of our knowledge, this was the largest study of fatigue among newly diagnosed and treatment-naïve patients with AML. It used a well-validated patient-reported measure of fatigue which allowed for evaluations of both the statistical and clinical significance of the reported differences in fatigue between patients with AML and the general population. In addition, the majority of patients had no significant medical comorbidities that could account for the reported burden of fatigue, strengthening the clinical implications of these results. Finally, as previously noted, this was the first study to compare pretreatment fatigue in newly diagnosed patients with AML with the general population and assess the burden of fatigue in AML by NCCN risk categories. It was also the first to evaluate molecular mutations as correlates of fatigue in this population. In conclusion, our findings represent a step towards better understanding the burden of fatigue among newly diagnosed patients with AML.

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REFERENCES

- 1 Tallman MS, Wang ES, Altman JK, *et al.* Acute myeloid leukemia, version 3.2019, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2019;17:721–49.
- 2 American Cancer Society. Cancer Facts & Figures 2020. Atlanta: American Cancer Society, 2020. Available: <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2020/cancer-facts-and-figures-2020.pdf> [Accessed : January 28, 2021].
- 3 Korol EE, Wang S, Johnston K, *et al.* Health-Related quality of life of patients with acute myeloid leukemia: a systematic literature review. *Oncol Ther* 2017;5:1–16.
- 4 Schumacher A, Wewers D, Heinecke A, *et al.* Fatigue as an important aspect of quality of life in patients with acute myeloid leukemia. *Leuk Res* 2002;26:355–62.
- 5 LeBlanc TW, Wolf SR, El-Jawahri A, El-Jawahri A, *et al.* Symptom burden, quality of life, and distress in acute myeloid leukemia patients receiving induction chemotherapy: results of a prospective electronic patient-reported outcomes study. *Blood* 2015;126:1.
- 6 Crossnohere N, Richardson DR, Smith BD, *et al.* Understanding the collateral damage of treating acute myeloid

- leukemia: an estimate of patient-reported side effect rates from a national survey. *Blood* 2018;132:1.
- 7 Lacourt TE, Kavelaars A, Ohanian M, *et al.* Patient-Reported fatigue prior to treatment is prognostic of survival in patients with acute myeloid leukemia. *Oncotarget* 2018;9:31244–52.
 - 8 Alibhai SMH, Leach M, Kowgier ME, *et al.* Fatigue in older adults with acute myeloid leukemia: predictors and associations with quality of life and functional status. *Leukemia* 2007;21:845–8.
 - 9 Panju AH, Danesh A, Minden MD, *et al.* Associations between quality of life, fatigue, and cytokine levels in patients aged 50+ with acute myeloid leukemia. *Support Care Cancer* 2009;17:539–46.
 - 10 Fung FY, Li M, Breunis H, *et al.* Correlation between cytokine levels and changes in fatigue and quality of life in patients with acute myeloid leukemia. *Leuk Res* 2013;37:274–9.
 - 11 Khosravi M, Taghvaye Masoumi H, Gholami K, *et al.* The relationship between fatigue and cytokine levels in patients with acute myeloid leukemia. *Int J Hematol Oncol Stem Cell Res* 2018;12:318–21.
 - 12 Alibhai SMH, Breunis H, Matelski J, *et al.* Age-Related cytokine effects on cancer-related fatigue and quality of life in acute myeloid leukemia. *J Geriatr Oncol* 2020;11:402–9.
 - 13 Venditti A, Piciocchi A, Candoni A, *et al.* Gimema AML1310 trial of risk-adapted, MRD-directed therapy for young adults with newly diagnosed acute myeloid leukemia. *Blood* 2019;134:935–45.
 - 14 Aaronson NK, Ahmedzai S, Bergman B, *et al.* The European organization for research and treatment of cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;85:365–76.
 - 15 Yellen SB, Cella DF, Webster K, *et al.* Measuring fatigue and other anemia-related symptoms with the functional assessment of cancer therapy (FACT) measurement system. *J Pain Symptom Manage* 1997;13:63–74.
 - 16 Cella D. The functional assessment of cancer Therapy-Anemia (FACT-An) scale: a new tool for the assessment of outcomes in cancer anemia and fatigue. *Semin Hematol* 1997;34:13–19.
 - 17 NCCN Clinical Practice Guidelines in Oncology. Acute myeloid leukemia, version 1.2009. Available: https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf [Accessed 6 may 2018].
 - 18 Arber DA, Orazi A, Hasserjian R, *et al.* The 2016 revision to the world Health organization classification of myeloid neoplasms and acute leukemia. *Blood* 2016;127:2391–405.
 - 19 Oken MM, Creech RH, Tormey DC, *et al.* Toxicity and response criteria of the eastern cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649–56.
 - 20 Steensma DP, Heptinstall KV, Johnson VM, *et al.* Common troublesome symptoms and their impact on quality of life in patients with myelodysplastic syndromes (MDS): results of a large Internet-based survey. *Leuk Res* 2008;32:691–8.
 - 21 Cella D, Zagari MJ, Vandoros C, *et al.* Epoetin alfa treatment results in clinically significant improvements in quality of life in anemic cancer patients when referenced to the general population. *J Clin Oncol* 2003;21:366–73.
 - 22 Alibhai SMH, Leach M, Gupta V, *et al.* Quality of life beyond 6 months after diagnosis in older adults with acute myeloid leukemia. *Crit Rev Oncol Hematol* 2009;69:168–74.
 - 23 Alibhai SMH, Breunis H, Timilshina N, *et al.* Quality of life and physical function in adults treated with intensive chemotherapy for acute myeloid leukemia improve over time independent of age. *J Geriatr Oncol* 2015;6:262–71.
 - 24 El-Jawahri A, Abel GA, Traeger L, *et al.* Quality of life and mood of older patients with acute myeloid leukemia (AML) receiving intensive and non-intensive chemotherapy. *Leukemia* 2019;33:2393–402.
 - 25 Mohamedali H, Breunis H, Timilshina N, *et al.* Older age is associated with similar quality of life and physical function compared to younger age during intensive chemotherapy for acute myeloid leukemia. *Leuk Res* 2012;36:1241–8.
 - 26 Buckley SA, Jimenez-Sahagun D, Othus M, *et al.* Quality of life from the perspective of the patient with acute myeloid leukemia. *Cancer* 2018;124:145–52.
 - 27 Efficace F, Gaidano G, Breccia M, *et al.* Prevalence, severity and correlates of fatigue in newly diagnosed patients with myelodysplastic syndromes. *Br J Haematol* 2015;168:361–70.
 - 28 Heinonen H, Volin L, Uutela A, *et al.* Gender-Associated differences in the quality of life after allogeneic BMT. *Bone Marrow Transplant* 2001;28:503–9.
 - 29 Hahn EA, Glendenning GA, Sorensen MV, *et al.* Quality of life in patients with newly diagnosed chronic phase chronic myeloid leukemia on imatinib versus interferon alfa plus low-dose cytarabine: results from the iris study. *J Clin Oncol* 2003;21:2138–46.
 - 30 Efficace F, Baccarani M, Breccia M, *et al.* Health-Related quality of life in chronic myeloid leukemia patients receiving long-term therapy with imatinib compared with the general population. *Blood* 2011;118:4554–60.
 - 31 Zhang Y, Gu H, Chen Q, *et al.* Low platelet counts at diagnosis predict better survival for patients with intermediate-risk acute myeloid leukemia. *Acta Haematol* 2020;143:1–10.
 - 32 Dantzer R. Cytokine, sickness behavior, and depression. *Immunol Allergy Clin North Am* 2009;29:247–64.
 - 33 DiNardo CD, Cortes JE. Mutations in AML: prognostic and therapeutic implications. *Hematology Am Soc Hematol Educ Program* 2016;2016:348–55.
 - 34 Ravandi F, Kantarjian H, Faderl S, *et al.* Outcome of patients with FLT3-mutated acute myeloid leukemia in first relapse. *Leuk Res* 2010;34:752–6.
 - 35 Kirkova J, Walsh D. Cancer symptom clusters--a dynamic construct. *Support Care Cancer* 2007;15:1011–3.

Supplemental Table. Comparison of patients with AML who did and did not complete the FACIT-Fatigue questionnaire pretreatment.

Variable	Patients Who Did Not Complete the FACIT-Fatigue Questionnaire (N=45)	Patients Who Completed the FACIT-Fatigue Questionnaire (N=463)	<i>p</i> -value
Sex, n (%)			0.665
Male	22 (48.9)	242 (52.3)	
Female	23 (51.1)	221 (47.7)	
Age, years			0.255
Median	51.0	48.0	
IQR	39.0-56.0	40.0-55.0	
WHO Performance Status, n (%)			0.400
0	24 (54.6)	265 (59.0)	
1	17 (38.6)	126 (28.0)	
2	3 (6.8)	56 (12.5)	
3	0 (0.)	2 (0.5)	
Missing	1 (-)	14 (-)	
Presence of comorbidities, n (%)			0.459
No comorbidities	37 (88.1)	365 (83.7)	
At least 1 comorbidity	5 (11.9)	71 (16.3)	
Missing	3 (-)	27 (-)	
Hb level, g/dL			0.923
Median	8.9	8.9	
IQR	8.3-10.0	8.0-10.0	
WBC count, cells x 10 ⁹ /L			0.182
Median	25.5	13.0	
IQR	5.4-48.3	3.4-50.9	
Blast cells, %			0.772
Median	55.0	54.0	
IQR	18.0-80.0	20.0-80.0	
Platelet count, x10 ³ /L			0.069
Median	66.0	54.0	
IQR	40.0-109.0	28.0-87.0	

Abbreviations. AML, acute myeloid leukemia; dL, deciliter; g, grams; Hb, hemoglobin; IQR, interquartile range; n, frequency; L, liter; NCCN, National Comprehensive Cancer Network; WBC, white blood cell; WHO, World Health Organization.