

Long-term health-related quality of life and lifestyle behavior of patients with acute myeloid leukemia

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Abstract

Background: Despite improvements in survival outcomes for acute myeloid leukemia (AML), limited evidence is available on health-related quality of life (HRQoL) and health problems experienced by long-term survivors.

Patients and methods: This international, cross-sectional study evaluated HRQoL, comorbidities, and lifestyle behaviors among long-term AML survivors enrolled from 24 centers across 6 countries. Health-related quality of life was assessed using the SF-36 and the EORTC QLQ-C30 questionnaires, while comorbidities were measured with an adapted version of the validated self-administered comorbidity questionnaire. Lifestyle factors, including physical activity, diet, smoking, alcohol consumption, and body mass index, were also assessed.

Results: Overall, 225 AML survivors were enrolled, with a median time since diagnosis of 8.8 years (IQR 6.4–11.9) and a median age of 58.9 years (IQR 49.0–67.0). Compared with the general population, AML survivors exhibited clinically relevant impairments in SF-36 physical functioning ($\Delta = -8.09$, $P < .001$) and role physical scales ($\Delta = -11.09$, $P < .001$), as well as clinically relevant lower physical component summary scores ($\Delta = -3.94$, $P < .001$). Survivors treated with alloSCT reported worse HRQoL profiles compared with those treated with autoSCT or chemotherapy only. Comorbidities were highly prevalent (88.5%), with impaired vision, back pain, and arthrosis/arthritis being the most frequent. Analysis of lifestyle behaviors showed that 66.2% of AML survivors were physically inactive, 80.2% did not meet dietary recommendations, and 55.3% were overweight/obese. Multivariate analysis identified physical inactivity as the only independent factor associated with worse HRQoL ($\beta = -6.3$, $P < .001$).

Conclusion: Our study shows that AML survivors experience physical limitations and a high comorbidity burden even many years after diagnosis, and it provides insights to better inform survivorship care programs. Further research examining the relationship between physical activity and HRQoL in long-term AML survivors is warranted.

Key words: acute myeloid leukemia; patient-reported outcome; health-related quality of life; quality of life; hematologic neoplasms; long-term cancer survivors.

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Implications for Practice

Our results indicate that long-term AML survivors experience physical limitations and a high comorbidity burden even many years after diagnosis. There is an important association between physical activity and HRQoL and this element should be highly considered in AML survivorship care programs.

Introduction

Acute myeloid leukemia (AML) accounts for 19% of all leukemia cases worldwide, with an estimated incidence of 124,330 new cases in 2019.¹⁻³ The age-standardized incidence and mortality rates of AML were 1.58 and 1.19, respectively, per 100,000 population in 2019,¹ with a high burden observed in individuals over 70 years of age and in regions with high level of socioeconomic development (ie, North America, Australasia, Western and Central Europe).²⁻⁴ Despite global increases in AML incidence and mortality,⁵ 5-year survival has improved over time, particularly in patients younger than 70 years,⁶⁻⁹ likely due to better risk stratification, supportive care, and patient selection for allogeneic hematopoietic stem cell transplantation (alloSCT).^{7,10} As the continuous approval of novel targeted therapies^{11,12} and advances in transplantation¹³ expand treatment options for older, unfit, and molecularly defined AML patients,^{11,14,15} further improvements in survival are expected with their progressive adoption in clinical practice.^{8,16}

With an increasing number of AML survivors, it is critical to better understand the long-term impact of the disease and its treatments on the health-related quality of life (HRQoL). While substantial evidence exists regarding long-term outcomes in survivors of solid tumors and lymphomas,^{17,18} data on AML survivors remain limited.

Retrospective studies have thus far suggested that long-term AML survivors are at risk of developing comorbidities, late relapses, second malignancies, and both physical and psychological late effects, underscoring the need for targeted survivorship care.^{19,20} Moreover, the association between comorbidity burden and poorer HRQoL observed in AML and other cancer populations²¹⁻²⁴ highlights the potential benefit of understanding modifiable factors that could help to improve survivors' well-being, develop adequate prevention, and inform survivorship care.

To address these gaps, we conducted a real-life study of long-term AML survivors representing a broad range of clinical and demographic characteristics. We collected data on HRQoL, comorbidities, and lifestyle behaviors to provide a comprehensive description of survivorship outcomes. The main objective of this study was to compare the HRQoL profile of long-term AML survivors with that of their peers from the general population. Secondary objectives were to describe the prevalence of comorbidity and lifestyle behaviors and to examine the association between lifestyle behaviors and HRQoL outcomes.

Methods

Patients and study design

This was a cross-sectional multicenter long-term survivorship study performed by the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) and the European Organisation for

Research and Treatment of Cancer (EORTC). Patients were recruited from 24 centers across 6 countries (Belgium, France, Italy, North Macedonia, Turkey, and Slovenia). Eligible participants had a confirmed diagnosis of AML ($\geq 20\%$ blast in bone marrow), excluding acute promyelocytic leukemia, were aged ≥ 18 years at diagnosis, were at least 5 years post-diagnosis at the time of enrollment, and were in AML-free status. Exclusion criteria included any major cognitive deficits or psychiatric disorders precluding completion of self-reported measures, age > 75 years at study inclusion, or receipt of any active treatment for AML at the time of participation. Individuals aged over 75 years at study entry were excluded to reduce the potential responder burden among older patients. For this study, long-term survivors were defined as individuals alive > 5 years after diagnosis.²⁵

The study was approved by the ethics committees of each participating center and was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent. The study was registered at ClinicalTrials.gov (NCT03755856).

Study logistic and data collection

Eligible patients were invited to participate by their treating hematologist either during a clinic visit or via mailed invitations. All eligible patients received an explanation of the purpose of the study, and those who consented to participate were given a Survey Booklet, including a set of patient-reported outcomes (PRO) questionnaires and sociodemographic data. Due to the observational, multicenter design of the study and operational challenges faced by study sites during the COVID-19 pandemic, it was not feasible to systematically capture the total number of potentially eligible long-term AML survivors approached for participation across sites. Patients were asked to complete the survey and to return it either personally or by mail to the clinic. Investigators provided information on the full medical history of the patients and entered the returned surveys into a web-data collection system (<https://redcap.gimema.it>). For the purpose of this study, patients were classified into one of three mutually exclusive treatment groups based on treatment history: (1) alloSCT; (2) autologous stem cell transplantation and no allogeneic SCT (autoSCT); and (3) intensive chemotherapy only (ie, chemo-only).

Health-related quality of life

General HRQoL was evaluated with the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) (version 1)²⁶ and cancer-specific HRQoL was assessed using the EORTC Quality of Life Questionnaire-Core30 (EORTC QLQ-C30).²⁷ The SF-36 consists of 36 items yielding eight scales: physical functioning (PF), role limitations due to physical problems (RP), bodily pain (BP), general health perceptions (GH), vitality (VT), social functioning (SF), role limitations due to emotional

problems (RE), and mental health (MH). Each SF-36 scale ranges from 0 to 100, with higher scores indicating better outcomes. Two summary scores, namely the physical component summary (PCS) and the mental component summary (MCS), are also derived from a weighted combination of the 8 scales.²⁸ This questionnaire was successfully used in previous studies comparing HRQoL of long-term survivors with the general population.^{29,30} The EORTC QLQ-C30 consists of 5 functioning scales (physical, role, emotional, cognitive, and social functioning); 3 symptom scales (fatigue, nausea/vomiting, and pain); 6 single-item scales (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial difficulties); and the global health status/quality of life (GHS/QoL) scale. The items were scaled and scored using the recommended EORTC procedures.³¹ Raw scores for each EORTC QLQ-C30 scale were transformed to a 0-100 scale; higher scores indicate better functioning and GHS/QoL or higher symptom severity. This questionnaire was widely adopted in HRQoL studies in AML patients.^{32,33} The EORTC QLQ-C30 summary score was also computed, being previously validated in patients with hematologic malignancies.³⁴

Comorbidity/health problems and second malignancy

Comorbidity/health problems were assessed with an adapted version of the validated Self-Administered Comorbidity questionnaire (SCQ).³⁵ An adapted version of SCQ list of 14 comorbid conditions (including heart disease, hypertension, asthma/chronic bronchitis/chronic obstructive pulmonary disease, diabetes, ulcer or stomach disease, kidney disease, liver disease, anemia or other blood cell disorders, cancer other than AML, depression, back pain, arthrosis/arthritis, rheumatoid arthritis, and other comorbidities) was extended with the following 11 health problems relevant to cancer survivorship according to consensus-based recommendations or AML survivorship evidence^{32,36,37}: allergies, impaired vision, cataract surgery, thyroid disorders, chronic skin disorders, impaired hearing, impaired extremities, gut disease other than ulcer or stomach disease, chronic genitourinary diseases, hormonal disorders, and obesity. Patients were asked whether they experienced these health problems in the last 12 months. Second malignancy was defined as any new primary malignant neoplasm diagnosed after the initial diagnosis of AML, excluding non-melanoma skin cancers, in situ neoplasms, and other benign tumors.

Lifestyle behaviors

Lifestyle behaviors included 5 modifiable lifestyle factors—physical activity (PA), diet, smoking, alcohol consumption, and body mass index (BMI). Physical activity was measured with the Godin Leisure-Time Exercise Questionnaire (GLTEQ).³⁸ Using only moderate and strenuous exercise scores, survivors were classified as active (score ≥ 24) or insufficiently active (score ≤ 23).^{39–41} Dietary information was collected with a single question on usual consumption (0 to ≥ 7 days per week) of at least 5 portions a day of fruits and vegetables.⁴² Participants reporting 7 days were classified as meeting the WHO nutrient intake goal (5-A-Day); those reporting 0 to 6 days as not meeting 5-A-Day (no 5-A-Day).⁴¹ We adopted the same cut-off used in previous population-based survivorship research employing this single-item dietary measure.⁴² The threshold of 7 days is

considered the most accurate way to identify individuals consistently meeting the WHO recommendation of daily fruit and vegetable intake. Self-reported smoking status was measured via a single item (“Do you currently smoke cigarettes on a regular basis”) rated on a yes/no scale.⁴² Alcohol consumption was captured using a pragmatic self-reported item, as in previous work.⁴³ Participants were asked: “Do you at any time drink wine, strong beer or liquor? If yes: Is it usually more than a glass or two?”, and response categories were: 0 (never), 1 (yes, usually not more than a glass or two), and 2 (yes, usually more than a glass or two). Alcohol consumption was analyzed as a binary variable: “limited alcohol intake” (categories 0-1) versus “current drinker” (original category 2). The BMI was calculated as self-reported weight (kilograms) divided by height (meters squared). Respondents were grouped into underweight/normal weight (BMI <25) or overweight/obese (BMI ≥ 25).

Statistical methods

Descriptive statistics were conducted for the demographic and clinical characteristics of long-term AML patients. Continuous variables were summarized using the mean, standard deviation (SD), median, and interquartile range (IQR), with categorical variables presented as frequency and percentage. Health-related quality of life profile of AML patients was compared with the Italian general population,⁴⁴ differences in mean scores and corresponding 95% confidence intervals (CI) of SF-36 scales were reported. To account for possible confounders in HRQoL outcomes, samples were previously matched by age, sex, education, and comorbidity/health problems (ie, heart disease, asthma/chronic bronchitis/COPD, diabetes, depression, arthrosis/arthritis, and rheumatoid arthritis). Namely, a 1:2 optimal pair matching was implemented, using the difference in propensity scores as the distance measure. Mean differences were also adjusted by the same variables used for the matching. An 8-point difference on the eight SF-36 scales was considered a clinically relevant between-group difference,⁴⁵ whereas a difference of 2 points was considered clinically relevant for the PCS and MCS scores.^{46,47} Mean scores obtained from the EORTC QLQ-C30 scales were reported overall and by type of treatment. Clinical relevance of mean differences between groups were evaluated according to previously published guidelines.⁴⁸ The prevalence of lifestyle behaviors in long-term AML survivors was reported. To further examine whether each lifestyle behaviors was independently associated with HRQoL outcomes, univariate and multivariate linear regression model analysis, using the EORTC QLQ-C30 summary score (0-100) as the dependent variable, were performed including a selection of clinical and sociodemographic variables based on their potential impact on HRQoL (ie, age at study entry, sex, time since diagnosis, level of education, living arrangement, presence of at least one comorbidity/health problem, inclusion in a RCT as first-line treatment, AML treatment type, occurrence of relapse). After having checked for multicollinearity, a stepwise multivariable regression analysis was performed on the same outcome variable. The prevalence of comorbidity/health problem was reported overall and by type of treatment. All statistical tests were two-sided with type I error $\alpha=0.05$. Given the exploratory nature of this study, we did not adjust for multiple testing. All analyses were performed using R software.

Results

Overall, 225 AML survivors were enrolled between May 2019 and February 2022. Most participants completed the survey using the paper questionnaire (n=196, 87%) and 13% (n=29) completed the survey online. The median time since diagnosis was 8.8 years (IQR 6.4-11.9 years), and the median age of patients at study participation was 58.9 years (IQR 49.0-67.0 years). The median time since the end of treatment was 7.9 years (IQR 5.5-11.1 years). One-hundred seventy-six (78.9%) patients were in first complete remission, and 70 (31.1%) were treated in the setting of an RCT (during first-line treatment). One hundred twenty-two (54.7%) patients received alloSCT, 58 (26%) chemo-only, and 43 (19.3%) autoSCT. Patients' characteristics are reported in Table 1.

Health-related quality of life profile of AML survivors compared with the general population

Patients with AML reported a statistically and clinically relevant worse score in the SF-36 PF scale ($\Delta=-8.09$; 95% CI, -11.47 to -4.72, $P<.001$) and RP scale ($\Delta=-11.09$; 95% CI, -17.04 to -5.14, $P<.001$) compared with their peers in the general population. There were no other clinically relevant differences between the 2 groups across the other SF-36 scales. Regarding the 2 summary scores, AML survivors had a statistically significant and clinically relevant worse PCS score than the general population ($\Delta=-3.94$; 95% CI, -5.47 to -2.40, $P<.001$) while no difference was found in the MCS score ($\Delta=0.09$; 95% CI, -1.67 to 1.85, $P=.921$). Details are reported in Table 2. We did not observe statistically significant differences in the SF-36 scores of Italian patients (63.1% of the study sample) compared to those from other countries (data not shown).

Health-related quality of life profile by type of treatment

Patients who received alloSCT tended to report a worse HRQoL profile, as measured by the EORTC QLQ-C30, than those who received autoSCT or chemo-only. For example, compared with patients who received alloSCT, those who received chemo-only and autoSCT reported, respectively, small ($\Delta=7.6$) and medium ($\Delta=13.3$) clinically relevant better outcomes in social functioning. In symptoms scales, survivors who were treated with autoSCT reported clinically relevant better fatigue ($\Delta=-7.4$), dyspnea ($\Delta=-7.1$), insomnia ($\Delta=-5.5$), diarrhea ($\Delta=-3.8$), and financial difficulties ($\Delta=-9.4$) than those treated with alloSCT. Survivors treated with chemo-only reported clinically relevant better fatigue ($\Delta=-5.0$), dyspnea ($\Delta=-7.5$), constipation ($\Delta=-6.4$), and financial difficulties ($\Delta=-10.4$) than survivors treated with alloSCT. Details are reported in Table 3. Significant differences in clinical characteristics were observed across treatment groups. For example, relapse since first complete remission was more frequent among survivors with alloSCT compared to those treated with autoSCT or chemotherapy alone. Detailed sociodemographic and clinical characteristics by treatment group are presented in Table S1.

Prevalence of comorbidity/health problems

There were 193 (88.5%) of 218 survivors reporting at least one comorbidity/health problem. The most frequently reported comorbidity/health problem in all AML survivors was impaired

Table 1. Demographic and clinical characteristics of long-term AML patients (N=225).

Characteristic	N=225
Age at study entry (years)	
Mean (SD)	57.1 (12.5)
Median (IQR)	58.9 (49.0-67.0)
Sex, n (%)	
Female	119 (52.9%)
Male	106 (47.1%)
Country	
Italy	142 (63.1%)
France	27 (12%)
Turkey	24 (10.7%)
Belgium	16 (7.1%)
Macedonia	11 (4.9%)
Slovenia	5 (2.2%)
Time since diagnosis (years)	
Mean (SD)	10.0 (4.7)
Median (IQR)	8.8 (6.4-11.9)
Level of education, n (%)	
Low (up to compulsory school)	68 (30.9%)
Intermediate (high school)	102 (46.4%)
High (university degree or higher)	50 (22.7%)
Missing	5
Living arrangements, n (%)	
Not living alone	187 (85.4%)
Living alone	32 (14.6%)
Missing	6
Comorbidity at study entry, n (%)	
0	25 (11.4%)
≥ 1	195 (88.6%)
Missing	5
Inclusion in a RCT as first line treatment, n (%)	
Yes	70 (31.1%)
No	155 (68.9%)
Type of treatment, n (%)	
Allogeneic transplant	122 (54.7%)
Intensive chemotherapy	58 (26.0%)
Autologous transplant	43 (19.3%)
Missing	2
Number of relapses since first complete remission, n (%)	
0	176 (78.9%)
≥ 1	47 (21.1%)
Missing	2

Abbreviations: AML, acute myeloid leukemia; IQR interquartile range; RCT, randomized clinical trial; SD, standard deviation.

vision (48.2%), followed by back pain (36.2%), arthrosis/arthritis (34.4%), and hypertension (31.2%). Second malignancy was reported by 11 (5.0%) of 218 AML survivors. Statistically significant differences in the prevalence of arthrosis/arthritis, liver disease, and allergies by AML treatment history were observed. For example, the prevalence of arthrosis/arthritis was lower in patients who received autoSCT (16.3%) than in those who were treated with alloSCT (37.3%) or chemo-only (42.1%). Prevalence of allergies was higher in AML survivors who received chemo-only (24.6%) than in those who received autoSCT (14.0%) or alloSCT (9.3%). Details are reported in Table 4. As a complementary analysis, SF-36 PF was evaluated according to the number of comorbidities, and no statistically significant differences were observed (data not shown).

Table 2. SF-36 scores and adjusted mean differences between the overall AML population and the matched control group.

SF-36 scales	AML patients Mean (SD)	Matched control group Mean (SD)	Mean difference	CI 95%	P-value
Functional scales					
Physical functioning	91.42 (3.02)	99.51 (3.02)	-8.09 ^a	-11.47; -4.72	<.001
Role physical	85.52 (5.65)	96.61 (5.32)	-11.09 ^a	-17.04; -5.14	<.001
Bodily pain	78.02 (4.12)	82.78 (3.89)	-4.76	-9.11; -0.42	.032
General health perceptions	70.78 (3.38)	76.51 (3.17)	-5.73	-9.29; -2.17	.002
PCS	52.34 (1.45)	56.28 (1.37)	-3.94 ^a	-5.47; -2.40	<.001
Mental health					
Vitality	65.87 (3.23)	69.15 (3.05)	-3.28	-6.69; 0.14	.060
Social functioning	77.75 (3.50)	82.35 (3.30)	-4.60	-8.29; -0.91	.015
Role emotional	81.56 (5.75)	87.72 (5.42)	-6.16	-12.23; -0.09	.047
Mental health index	71.67 (3.17)	70.11 (3.00)	1.56	-1.79; 4.92	.359
MCS	47.98 (1.67)	47.89 (1.57)	0.09	-1.67; 1.85	.921

Abbreviations: AML, acute myeloid leukemia; CI, confidence interval; MCS, mental component summary; PCS, physical component summary; SD, standard deviation.

Mean differences adjusted for age, sex, education, and comorbidities (heart disease, asthma/COPD, diabetes, depression, arthrosis/rheumatoid arthritis).

^aExceeds minimally important difference (ie, 8 points for the SF-36 scales and 2 points for the PCS and MCS scores).

Table 3. Health-related quality of life profile by the EORTC QLQ-C30 for long-term AML survivors (N=219).

Characteristic	Overall, mean (SD) N=219	Allogeneic transplant, mean (SD) n=121	Autologous transplant, mean (SD) n=42	Intensive chemotherapy, mean (SD) n=56
Functional scales				
Physical functioning	84.33 (17.56)	82.33 (18.61)	86.98 (16.26)	86.67 (15.83)
Role functioning	87.14 (21.49)	87.47 (22.08)	86.51 (19.90)	86.90 (21.72)
Social functioning	80.52 (27.25)	76.03 (29.73)	89.29 (16.80) ↑↑	83.63 (26.30) ↑
Emotional functioning	78.46 (22.56)	76.58 (24.49)	81.75 (18.79)	80.06 (20.64)
Cognitive functioning	82.50 (22.30)	83.20 (22.72)	80.16 (22.76) ↓	82.74 (21.31)
Global health status/QoL	75.00 (19.06)	75.21 (19.08)	74.40 (20.11)	75.00 (18.53)
Symptoms profile				
Fatigue	23.74 (23.84)	26.45 (23.76)	19.05 (19.68) ↑	21.43 (26.37) ↑
Pain	16.06 (20.99)	15.56 (20.15)	14.29 (19.33)	18.45 (23.93)
Nausea/vomiting	3.50 (11.75)	3.99 (13.27)	3.17 (9.90)	2.68 (9.42)
Dyspnea	14.92 (22.37)	18.18 (23.96)	11.11 (19.01) ↑	10.71 (20.21) ↑
Insomnia	22.98 (29.68)	24.52 (32.71)	19.05 (22.26) ↑	22.62 (27.78)
Appetite loss	5.63 (16.40)	7.44 (18.00)	3.97 (15.09)	2.98 (13.15)
Constipation	11.26 (22.00)	13.50 (25.67)	10.32 (17.25)	7.14 (15.19) ↑
Diarrhea	8.37 (19.05)	8.54 (20.43)	4.76 (11.81) ↑	10.71 (20.21)
Financial difficulties	18.42 (30.64)	22.87 (33.62)	13.49 (23.35) ↑	12.50 (27.39) ↑↑
Summary score	85.11 (13.57)	83.65 (14.04)	87.61 (11.57)	86.41 (13.72)

Abbreviations: AML, acute myeloid leukemia; SD, standard deviation.

↑, ↑↑, indicates respectively a small, or medium clinically relevant better outcome (ie, higher score in the functional scales or global QoL scale and lower score in symptom scales) compared with the allogeneic transplant group, based on the previously defined criteria for the EORTC QLQ-C30.⁴⁸

↓ indicates a small clinically relevant worse outcome (ie, lower score in the functional scales or global QoL scale and higher score in symptom scales) compared with the allogeneic transplant group, based on the previously defined criteria for the EORTC QLQ-C30.⁴⁸

Prevalence of lifestyle behaviors and association with health-related quality of life

Overall, 145 (66.2%) of 219 survivors were considered insufficiently active, 174 (80.2%) of 217 AML survivors had a no 5-A-Day dietary pattern, 184 (83.6%) of 220 survivors were non-smokers, 209 (95.9%) of 218 reported limited alcohol intake, and 121 (55.3%) of 219 were overweight/obese (BMI ≥25) (Table 5).

In univariate analysis the following variables were significantly associated with the EORTC-QLQ C30 summary score: high level of education ($\beta=6.1$; 95% CI 1.1 to 11; $P=.016$), being a non-smoker ($\beta=5.2$; 95% CI 0.38 to 10; $P=.035$), and being insufficiently active ($\beta=-6.6$; 95% CI -10 to -2.9; $P<.001$).

In multivariate analysis, the only factor that remained independently associated with a lower EORTC-QLQ C30 summary score was being insufficiently active ($\beta=-6.3$; 95% CI -10 to -2.6; $P<.001$) (Table 6).

Discussion

We found that, even after a median time of 9 years since diagnosis, AML survivors reported a clinically relevant worse physical health status compared with their peers from the general population. Almost 90% of participants reported at least one comorbidity, while nearly half experienced impaired vision, and around one-third suffered from back pain, arthrosis/arthritis,

Table 4. Prevalence of comorbidities in long-term AML survivors, overall and by type of treatment (N=218).

Characteristic	Overall N=218	Allogeneic trans-plant n=118	Autologous trans-plant n=43	Intensive chemo-therapy n=57	P-value
Comorbidity at study entry, n (%)					.115
0	25 (11.5%)	14 (11.9%)	8 (18.6%)	3 (5.3%)	
≥1	193 (88.5%)	104 (88.1%)	35 (81.4%)	54 (94.7%)	
Type of comorbidities					
Impaired vision, n (%)	105 (48.2%)	62 (52.5%)	17 (39.5%)	26 (45.6%)	.311
Back pain, n (%)	79 (36.2%)	41 (34.7%)	15 (34.9%)	23 (40.4%)	.754
Arthritis, n (%)	75 (34.4%)	44 (37.3%)	7 (16.3%)	24 (42.1%)	.017
Hypertension, n (%)	68 (31.2%)	37 (31.4%)	11 (25.6%)	20 (35.1%)	.596
Impaired hearing, n (%)	37 (17.0%)	24 (20.3%)	4 (9.3%)	9 (15.8%)	.246
Impaired extremities, n (%)	36 (16.5%)	20 (16.9%)	6 (14.0%)	10 (17.5%)	.872
Chronic skin disorders, n (%)	35 (16.1%)	18 (15.3%)	4 (9.3%)	13 (22.8%)	.179
Diabetes, n (%)	34 (15.6%)	22 (18.6%)	3 (7.0%)	9 (15.8%)	.196
Ulcer or stomach disease, n (%)	33 (15.1%)	19 (16.1%)	5 (11.6%)	9 (15.8%)	.772
Thyroid disorders, n (%)	33 (15.1%)	17 (14.4%)	3 (7.0%)	13 (22.8%)	.087
Depression, n (%)	32 (14.7%)	20 (16.9%)	5 (11.6%)	7 (12.3%)	.587
Rheumatoid arthritis, n (%)	32 (14.7%)	16 (13.6%)	5 (11.6%)	11 (19.3%)	.502
Cataract surgery, n (%)	32 (14.7%)	19 (16.1%)	6 (14.0%)	7 (12.3%)	.790
Allergies, n (%)	31 (14.2%)	11 (9.3%)	6 (14.0%)	14 (24.6%)	.022
Asthma/chronic bronchitis/COPD, n (%)	29 (13.3%)	15 (12.7%)	6 (14.0%)	8 (14.0%)	.962
Obesity, n (%)	23 (10.6%)	13 (11.0%)	2 (4.7%)	8 (14.0%)	.277
Liver disease, n (%)	23 (10.6%)	14 (11.9%)	0 (0.0%)	9 (15.8%)	.012
Heart disease, n (%)	19 (8.7%)	12 (10.2%)	1 (2.3%)	6 (10.5%)	.246
Anemia or other blood disorders, n (%)	19 (8.7%)	7 (5.9%)	4 (9.3%)	8 (14.0%)	.184
Gut disease other than ulcer or stomach disease, n (%)	18 (8.3%)	11 (9.3%)	2 (4.7%)	5 (8.8%)	.754
Chronic genitourinary diseases, n (%)	16 (7.3%)	5 (4.2%)	4 (9.3%)	7 (12.3%)	.134
Other comorbidities, n (%)	16 (7.3%)	6 (5.1%)	3 (7.0%)	7 (12.3%)	.228
Kidney disease, n (%)	15 (6.9%)	7 (5.9%)	3 (7.0%)	5 (8.8%)	.771
Hormonal disorders, n (%)	12 (5.5%)	4 (3.4%)	3 (7.0%)	5 (8.8%)	.288
Cancer (other than AML), n (%)	11 (5.0%)	6 (5.1%)	1 (2.3%)	4 (7.0%)	.589

Abbreviations: AML, acute myeloid leukemia; COPD, chronic obstructive pulmonary disease.

Table 5. Prevalence of lifestyle behaviors in long-term AML survivors

Lifestyle behaviors	
Eating pattern (n = 217/225)	
No 5-A-Day	174 (80.2%)
5-A-Day	43 (19.8%)
Smoking status (n = 220/225)	
Non smoker	184 (83.6%)
Smoker	36 (16.4%)
Alcohol consumption (n = 218/225)	
Limited alcohol intake	209 (95.9%)
Current drinker	9 (4.1%)
Body mass index (n = 219/225)	
Overweight/obese (BMI ≥25)	121 (55.3%)
Underweight/Normal weight (BMI <25)	98 (44.7%)
Physical activity (n = 219/225)	
Insufficiently active	145 (66.2%)
Active	74 (33.8%)

AML, Acute Myeloid Leukemia

or hypertension. Similar results were observed in a study conducted on survivors of acute promyelocytic leukemia, a subtype of AML, where more than 80% of patients reported at least one comorbid condition.²⁴ The high comorbidity burden observed in our cohort may therefore have contributed to the reduced physical health status. Indeed, in a German cohort of

AML survivors with a follow-up period of eight years, Messerer and colleagues found that the presence of comorbid conditions was a significant independent factor associated with worse global health status.³²

Our findings are consistent with previous evidence from Japanese⁴⁹ and Dutch⁵⁰ cohorts of patients with a shorter time since the end of treatment, which similarly reported physical limitations and a worse HRQoL profile among AML survivors compared to the general population.^{49,50} Similar findings have also been described in lymphoma survivors, showing poorer physical but comparable mental HRQoL relative to population norms.^{51,52} More recently, evidence from a German cohort observed higher HRQoL but worse physical well-being in long-term AML survivors compared with matched reference cohorts.⁵³

Our results suggest that treatment modalities might differently affect long-term HRQoL. Survivors who received alloSCT reported clinically relevant lower social functioning and higher symptom severity, such as fatigue and dyspnea, compared with those treated with either autoSCT or chemotherapy. Previous studies have similarly reported lower HRQoL in AML survivors who underwent alloSCT as compared with those who received autoSCT or chemotherapy.^{33,50,54} However, these studies had shorter follow-up periods. Interestingly, one study with a similar follow-up duration to ours also found worse HRQoL in survivors treated with alloSCT compared to those treated

Table 6. Univariate and multivariate linear regression model on the EORTC QLQ-C30 summary score.

Characteristic	Univariate			Multivariate		
	Beta	95% CI	P-value	Beta	95% CI	P-value
Age at study entry (years)	0.03	-0.11, 0.18	.634	NA	NA	NA
Sex						
Male	—	—		NA	NA	NA
Female	-1.3	-4.9, 2.3	.476	NA	NA	NA
Time since diagnosis (years)	0.15	-0.23, 0.53	.426	NA	NA	NA
Level of education						
Low (up to compulsory school)	—	—		NA	NA	NA
Intermediate (high school)	3.5	-0.64, 7.7	.097	NA	NA	NA
High (university degree or higher)	6.1	1.1, 11	.016	NA	NA	NA
Living arrangements						
Living alone	—	—		NA	NA	NA
Not living alone	1.5	-3.7, 6.7	.581	NA	NA	NA
Presence of any comorbidities						
≥1	—	—		NA	NA	NA
0	-1.1	-6.5, 4.2	.673	NA	NA	NA
Inclusion in a RCT as first line treatment						
No	—	—		NA	NA	NA
Yes	2.0	-1.9, 5.9	.307	NA	NA	NA
Type of treatment, <i>n</i> (%)						
Allogeneic transplant	—	—		NA	NA	NA
Intensive chemotherapy	2.8	-1.6, 7.1	.103	NA	NA	NA
Autologous transplant	4.0	-0.81, 8.7	.103	NA	NA	NA
Number of relapses since first complete remission, <i>n</i> (%)						
≥1	—	—		NA	NA	NA
0	2.0	-2.4, 6.5	.367	NA	NA	NA
Eating pattern						
No 5-A-Day	—	—		NA	NA	NA
5-A-Day	2.4	-2.2, 6.9	.308	NA	NA	NA
Smoking status						
Smoker	—	—		—	—	
Non smoker	5.2	0.38, 10	.035	4.5	-0.27, 9.2	.064
Alcohol consumption						
Limited alcohol intake	—	—		NA	NA	NA
Current drinker	0.43	-8.7, 9.6	.926	NA	NA	NA
Body Mass Index						
Underweight/normal weight (BMI <25)	—	—		NA	NA	NA
Overweight/obese (BMI ≥25)	3.1	-0.57, 6.7	.098	NA	NA	NA
Physical activity						
Active	—	—		—	—	
Insufficiently active	-6.6	-10, -2.9	<.001	-6.3	-10, -2.6	<.001

Abbreviations: CI, confidence interval; NA, not applicable (not selected by stepwise regression).

with chemotherapy,³² although the comparison did not include patients receiving autoSCT.

Another finding from our study shows that a substantial proportion of long-term adult AML survivors do not adopt healthy lifestyle behaviors. For instance, two-thirds of participants were physically inactive, and more than half were overweight or obese. These findings are consistent with a previous study reporting that few survivors of solid tumors adhered to recommendations for PA and fruit/vegetables consumption.⁴² Direct comparison with prior evidence in adult AML survivors is difficult, as only limited data exist, often from single-country cohorts or combined populations. For example, in a Korean cohort, Suh and colleagues reported that 6% of participants had smoked and 42% had consumed alcohol in the past year. However, this study included survivors of several acute leukemias, not exclusively AML.⁵⁵

Population-based data indicate that suboptimal lifestyle behaviors are also common among individuals without a cancer history. Current evidence shows persistently low adherence to dietary and activity recommendations across several countries, with high levels of insufficient physical activity in Europe and clustering of unhealthy behaviors.^{56,57} Based on recent global pooled analyses, nearly a third of adults worldwide do not meet the recommended levels of physical activity.⁵⁸ Future longitudinal population-based studies may help to elucidate potential lifestyle changes associated with a diagnosis of AML.

In our multivariate analysis, physical inactivity emerged as the only factor independently associated with worse HRQoL. Prior research on the role of PA in AML patients suggested that exercise interventions are feasible and may improve HRQoL and reduce symptom burden.^{59–63} However, most of this evidence derives from studies conducted on patients during

treatment or with shorter time since diagnosis. In a pilot phase II RCT of 40 AML patients with a mean time since diagnosis of two years, Alibhai and colleagues showed that a home-based exercise intervention could be safely delivered, although adherence rates to this program were poor.⁶¹ While our findings add to this body of evidence by documenting an association between physical inactivity and HRQoL in long-term AML survivors, causal conclusions cannot be drawn. For example, this association may reflect reverse causation, whereby survivors with better overall physical health may generally have better HRQoL and be more likely to engage in physical activity. These results highlight the relevance of further longitudinal research to determine whether promoting PA may contribute to improved survivorship outcomes.

This study has limitations. The cross-sectional design does not allow us to establish causal relationships, and the absence of a denominator, largely due to COVID-19-related disruptions during the study period, prevented assessment of participation rates and possible selection bias. Also, HRQoL comparisons with the general population were based on Italian normative data. Finally, a questionnaire specific to patients with AML could have provided additional insights. However, the two PRO questionnaires used in this study are widely employed in AML research.⁶⁴

A key strength of our study is its large and international sample, including survivors from diverse countries and health-care systems, thus enhancing the generalizability of our findings. Moreover, as most participants were treated outside the context of clinical trials, the results may reflect the real-life experiences of AML survivors.

Our study indicates that long-term AML survivors experience physical limitations and a high comorbidity burden even many years after diagnosis, and it provides insights to enhance survivorship care programs in this setting. Our findings also underscore the importance of further research examining the relationship between physical activity and HRQoL in long-term AML survivors.

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Author contributions

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Supplementary material

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Conflicts of interest

F.E. had a consultancy or advisory role for AbbVie, Incyte, Novartis, FibroGen, GlaxoSmithKline (GSK), and JAZZ Pharmaceuticals and research support (institution) from Daiichi Sankyo and Otsuka, all outside the submitted work. M.V. reports honoraria from AbbVie, Amgen, AstraZeneca, Dephaforum Srl., Incyte Corporation, and Novartis; and personal fees from Amgen outside the submitted work. N.F.: Speaking bureau for Gilead, Pfizer, Amgen, Jazz, Abbvie; outside the submitted work.

Data availability

The raw data supporting the conclusions of this article are available upon reasonable request to the corresponding author.

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