

Health-related quality of life in acute myeloid leukemia patients not eligible for intensive chemotherapy: results of a systematic literature review

Anna Forsythe¹
Christina S Kwon¹
Timothy Bell²
T Alexander Smith³
Bhakti Arondekar⁴

¹Purple Squirrel Economics, New York, NY, USA; ²Pfizer Inc, New York, NY, USA; ³Pfizer Ltd, Walton Oaks, UK; ⁴Pfizer Inc, Collegeville, PA, USA

Background: AML is a rapidly progressing bone marrow cancer, with poor survival rates compared to other types of leukemia. IC and NIC as well as BSC treatment options are available; however, there is scant published literature on the impact of disease and treatment on the HRQoL in patients receiving NIC.

Aim: This study determined the HRQoL among NIC AML patients.

Materials and methods: Embase, Medline, Cochrane database, and conference abstracts were searched using the prespecified PICOS criteria from January 2000 to November 2017 for studies reporting HRQoL and patient preference utilities in NIC AML. Studies on patients with RAEB-t MDS, randomized clinical trials (RCTs), prospective observational studies, and patient surveys were included, while systematic reviews and meta-analyses were used for bibliographic searching.

Results: Thirteen records from 12 original studies were identified. These included five records from four RCTs, three prospective studies, four patient survey studies, and one cost-effectiveness analysis. At baseline, NIC AML patients had poor HRQoL scores especially in fatigue (33) and GHS (50) on a 0–100 scale, with higher scores indicating better health. Low baseline HRQoL scores, especially PF and fatigue (<50) were shown to be significant independent predictors of poor survival. Clinical responders demonstrated meaningful improvements, especially in PF and fatigue, along with other health domains after being treated with NIC agents across several studies.

Conclusion: HRQoL is poor for patients with NIC AML; measures such as fatigue and PF at baseline have been identified as independent prognostic factors for overall survival with several studies showing improvement in both domains with treatment. RCTs should incorporate evaluation of treatment impact on patients' PF and fatigue as important measures of effectiveness.

Keywords: acute myeloid leukemia, hematology, unfit, low intensity, hypomethylating agents, myelodysplastic syndrome

Introduction

AML is generally a disease of older people and is uncommon before the age of 45 years.^{1,2} Within USA, the average age of a patient with AML is 68 years, with about 19,520 new cases of AML patients and 10,670 deaths from AML.³ AML is an aggressive disease with an unfavorable prognosis and accounts for 25% of acute leukemias in adults worldwide, with an estimated 5-year survival of 26% in USA.^{3,4} Prior epidemiological research has shown that age >70 years was the strongest predictor to receive

Correspondence: Anna Forsythe
Purple Squirrel Economics, 4 Lexington
Avenue, Suite 15K, New York, NY
10010, USA
Tel +1 646 478 8213
Email annaforsythe@pshta.com

nonintensive treatment compared to IC in patients newly diagnosed with AML based in an academic population-based registry study, whereas younger age (<60 years) was inversely associated with IC.⁵ Treatments for these patients are limited, particularly for those with poor performance status, comorbidities, and unfavorable cytogenetic abnormalities.^{6–8}

The standard of care for fit patients with AML is IC, which includes the “7+3” regimen, comprising 7 days of treatment with cytarabine combined with 3 days of treatment with an anthracycline.^{7,9,10} For unfit patients with AML who are not eligible for IC, the NCCN guidelines include therapy with HMA such as decitabine, azacitidine, and low-dose cytarabine (LDAC); similarly, the ELN guidelines state that treatment alternatives for unfit patients are limited to BSC, low-intensity treatment, or clinical trials with investigational drugs.^{11,12} Low-intensity options are either LDAC or therapy with HMA. LDAC is generally well tolerated and produces complete remission rates in the order of 15–25%; however, overall survival (median, 5–6 months) is unsatisfactory.¹² Even though AML is primarily a disease of older adults,^{1,2,7,13} age is not the only factor for determining treatment with intensive or NIC or BSC. Treatment decisions for patients with AML may be impacted by patient-specific factors such as cytogenetics, initial blood counts, performance status, comorbidities, daily life activities that have led to the changes in chemotherapy regimens, treatment-related mortality, and toxicity risk.¹³

It has also become increasingly important to assess the impact of AML and its treatments on HRQoL since not all patients are eligible for IC. The awareness of HRQoL is a broad concept that covers different domains such as physical, mental, social, and role functioning.^{14,15} Information about the impact on HRQoL can be used for different purposes. First, this information is useful for treatment allocation; currently, treatment allocation in AML depends largely on the effectiveness of the different treatments in terms of survival.^{14,16,17} Furthermore, HRQoL information provides insight into specific health problems and treatment needs of patients with AML. The identification of these health problems can help in the effort to improve current treatments and develop new treatment modalities.^{14,18,19} For example, results from a prospective evaluation indicated that negative effects of treatment on MDS patient's quality of life were limited to the time in the hospital, specifically intensively treated patients spent 79% of their remaining lifetime in hospitals, whereas nonintensively treated patients spent 14%.^{20,21} The HRQoL of these patients and their ability to function improved since they

left the hospital and scores after discharge were similar as to pretreatment scores.^{20,21} The symptom burden for AML patients is significant and involves some of the following: general (weight loss/loss of appetite, fever); low count of red blood cells (anemia); tiredness/fatigue, weakness, and dyspnea (shortness of breath); low count of white blood cells (leukopenia/neutropenia): infections, fever; low count of blood platelet counts (thrombocytopenia): excess bruising/bleeding; increase in blast counts; disturbed sleep; and dry mouth.^{6–8} To the authors' knowledge, there are no prior systematic reviews published evaluating the impact of disease and treatment on the HRQoL in AML patients who are not eligible for IC. The aim of this study was to conduct a SLR to determine the reported HRQoL among patients with AML receiving NIC.

Materials and methods

A SLR of evidence was conducted on HRQoL reported in patients with AML receiving NIC using matches on prespecified PICOS approach. In addition, the PRISMA was used as a guide to ensure that the current standard for systematic review methodology was met.²² In this review, Embase, Medline, and the Cochrane collaboration databases were searched using the Ovid platform, covering ~10 years, from January 2007 to November 2017 to identify relevant studies reporting HRQoL and patient preference utilities and to ensure that all relevant studies included the HMA regimens used in NIC AML. Systematic reviews and meta-analyses were utilized for bibliography searching to identify additional relevant studies. In addition, conference abstracts were searched to retrieve studies that had not yet been published as full-text articles and to supplement results of previously published studies. Abstracts from the American Society of Clinical Oncology, European Hematology Society, European Society of Medical Oncology, and American Society of Hematology for the period 2014–2017 were searched. The detailed search strategy is presented in Table S1. For disease, “LEUKEMIA, MYELOID”, “ACUTE/”, “LEUKEMIA, MYELOID/”, and ACUTE DISEASE/” were the MeSH terms we used. For the quality of life, we used “quality of life/” and “quality adjusted life year/” as MeSH terms.

Study designs that were likely to report HRQoL and utility data for AML were included in this review. Based on the WHO AML criteria, studies on patients with RAEB-t MDS (≥20% bone marrow blast) also were included. Studies that did not have NIC AML populations and those not reporting

HRQoL were excluded. Only publications written in English and published starting from January 2007 were considered since evidence older than 10 years may not be relevant as treatment practice may have changed. Shortlisted articles were initially assessed based on title and abstract. Publications not meeting inclusion criteria were excluded and listed along with the reason for study exclusion. Full-text publications were then retrieved and assessed based on the full text. Publications identified through the systematic review were evaluated in a three-step process (abstract review, full text review, and data extraction) to assess whether they should be included for data extraction. The inclusion and exclusion criteria used against the publications were developed using the PICOS format (Table 1). All steps were conducted by two independent reviewers, and any discrepancies in article selection were reassessed by a third reviewer. After the full-text review, all papers meeting inclusion criteria were retained for data extraction. Papers that were excluded in each step were listed, along with their reason for exclusion

was documented for use in the PRISMA flow diagram (Figure 1).

The quality assessment for the HRQoL studies was assessed using the Efficace framework, which aims to determine the robustness, consistency, and relevance of such studies to support decision-making.²³ The search for this SLR was conducted in December 2017, and the search strategy is provided in Table S1.

Results

A total of 13 records from 12 original studies were identified, which are listed in Table 2. These included five records from four original randomized clinical trials (RCTs), three prospective studies, four patient survey studies, and one cost-effectiveness analysis reporting utility values. Ten studies utilized the EORTC QLQ-C30 and five studies reported EQ-5D values. Other scales used included HRQoL questionnaire for patients with hematological diseases (QoL-E), QoL Cancer Survivor, FACT-leukemia, FACT-fatigue, global fatigue scale,

Table 1 Study eligibility criteria

Element	Inclusion	Exclusion
Patient population	<ul style="list-style-type: none"> • Adults (≥18 years) • Newly diagnosed with AML or high risk MDS • Not eligible for IC 	<ul style="list-style-type: none"> • Nonhuman • Refractory/relapsed AML • AML treated with IC
Intervention and comparators	<ul style="list-style-type: none"> • Glasdegib • Azacitidine • Decitabine • Cytarabine (low dose) • Hydroxycarbamide • 6-Mercaptopurine • Etoposide • BSC 	<ul style="list-style-type: none"> • Studies not including any therapies of interest • Stem cell transplantation studies • Surgery studies • Radiotherapy studies
Outcomes measures	<ul style="list-style-type: none"> • Any HRQoL outcome • Utilities/disutilities/QALYs for health states or adverse events 	<ul style="list-style-type: none"> • Studies not including at least one of the outcomes listed in the inclusion criteria
Study design	<ul style="list-style-type: none"> • Reports of randomized clinical trials assessing HRQoL • Development and/or validation of HRQoL measures • Observational studies measuring PROs • Retrospective chart audits and database analyses reporting PROs • Patient surveys reporting PROs • Reports of mapping exercises for any outcome measure to utility • Reports of utility elicitation exercises • Reports of utility validation exercises • Reports of economic evaluations using utility measures elicited during studies • Studies that present data via a validated scale • Systematic reviews and meta-analyses (to be used for reference cross-checking only) 	<ul style="list-style-type: none"> • Reviews • Editorials • Notes/comments/letters
Restrictions	<ul style="list-style-type: none"> • Published in the English language • Year limitations: 2007 to present 	<ul style="list-style-type: none"> • Published in a non-English language

Note: ^aUtility studies were not limited to AML noneligible for IC.

Abbreviations: PROs, patient-reported outcomes; QALY, quality-adjusted life year.

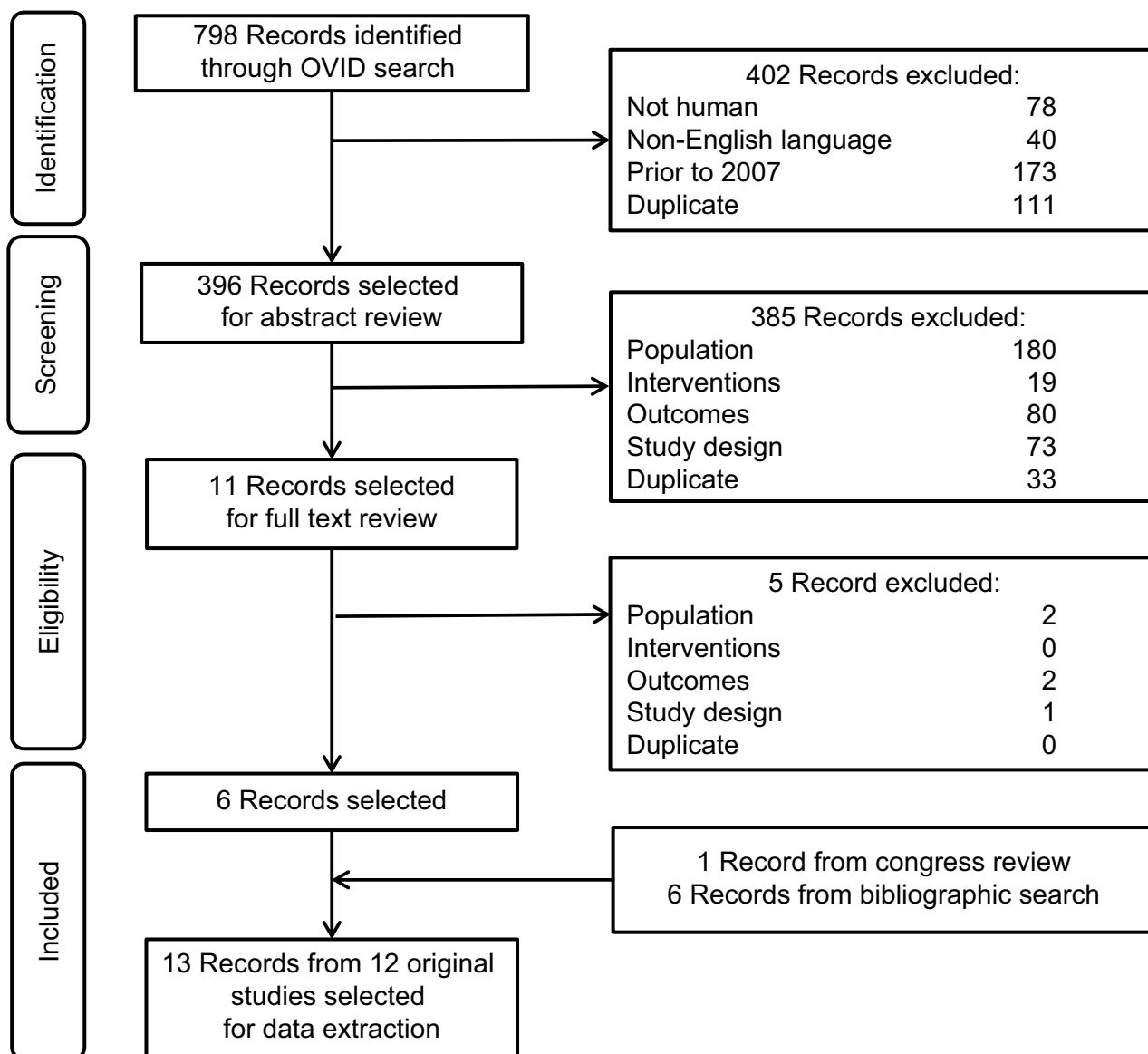


Figure 1 PRISMA flow diagram

FACIT Fatigue, activities of daily living index, and Hospital Anxiety and Depression Scale. The following four QLQ-C30 domains were considered most relevant: fatigue, PF, GHS, and dyspnea.⁹ A 10-point minimally important difference threshold on a 100-point scale was assumed by the majority of studies to represent meaningful change.⁹

The HRQoL results from the four original RCTs informed the reviewers that some NIC treatments achieved a meaningful improvement in the fatigue of EORTC QLQ-C30, while other patients achieved meaningful improvement in both fatigue (cycles 7 and 9) and GHS.^{9,17,24–26} Patients aged ≥60 years with MDS or chronic myelomonocytic leukemia

(intermediate 1/2, or high risk), who were ineligible for intensive treatment, showed a significant improvement in their PF and borderline improvement in GHS of EORTC QLQ-C30.¹⁷

There were similar findings from HRQoL prospective studies, of which one study conducted a longitudinal, observational prospective assessment of the EORTC QLQ-C30, FACT-fatigue, EQ-5D, and global fatigue scale in patients with MDS treated with azacitidine. The results informed the reviewer that responders to therapy had significantly superior EQ-5D scores ($P=0.0002$) and lower scores in FACIT-fatigue ($P<0.0001$) vs patients who did not respond to therapy.²⁷ Another longitudinal study with MDS patients

Table 2 Included studies

References	Interventions	Type of study/study population	Scales used	QoL summary
Minden et al ²⁶ (abstract); Dombret et al ⁹	AZA vs CCR (standard induction chemotherapy, low-dose cytarabine, or supportive care only)	RCT, N=488; age ≥65 years, newly diagnosed AML, not eligible for HSCT	EORTC QLQ-C30	157 AZA patients and 134 CCR patients were evaluable for HRQoL. AZA or CCR showed general improvement in the four relevant domains. No HRQoL detriment was seen with AZA or CCR at the group level during treatment. "Few" statistically significant ($P<0.05$). "Fewer" met the MID threshold. CCR achieved meaningful improvement in fatigue (cycles 7 and 9) and GHS/QoL (cycle 9). Patients receiving AZA achieved meaningful improvement in fatigue (cycle 9). Scores varied substantially among individual patients in both treatment groups
Oliva et al ²⁴ (abstract)	AZA vs BSC after conventional induction (3+7) and consolidation chemotherapy	RCT, N=99; age >60 years, newly diagnosed or secondary AML (>30% myeloid marrow blasts), ECOG PS <3	EORTC QLQ-C30, QoL-E (ver 3)	After first "3+7" regimen; QoL-E: no changes; QLQ-C30: deterioration in PF (median 80, IQR 60–93, to 67, IQR 52–87, $P=0.008$), role function (median 83, IQR 67–100, to 67, IQR 33–83, $P=0.023$), and GHS (median 50, IQR 33–69, to 67, IQR 50–75, $P=0.002$) and improvement in dyspnea ($P=0.023$). After consolidation therapy, among patients obtaining a CR QoL-E: improvement in median physical scores (56, IQR 41–72, to 63, IQR 50–84, $P=0.033$), disease-specific domain scores (59, IQR 48–67, to 74, IQR 67–85, $P=0.003$), and treatment outcome index scores (55, IQR 32–77, to 79, IQR 41–86, $P=0.026$); QLQ-C30: improvement in emotional function (83, IQR 67–92, to 92, IQR 77–100, $P=0.015$), GHS (median 50, IQR 33–65, to 67, IQR 58–83, $P=0.002$). Dyspnea and insomnia regressed while financial problems increased
Lübbert et al ¹⁷	DEC + BSC vs BSC	RCT, N=233; Age ≥60, MDS or CMML, int-1, int-2, or high-risk, ineligible for intensive treatment, ECOG ≤2	EORTC QLQ-C30	Patients on the DEC arm showed a significant improvement in their physical functioning and borderline improvement in GHS. No apparent effect was seen on dyspnea. Trends of most of QoL scales favors DEC
Sekeres et al ²⁵	LDAC + lintuzumab vs LDAC	RCT, N=211; age ≥60 years, de novo AML, exposed to chemotherapy for different malignancies, ECOG PS ≤2	FACT-Leu	No consistent pattern of change in FACT-Leu score was observed. The median change in FACT-Leu score was similar in both arms where the range of scores overlapped considerably
Tseng et al ²⁷ (abstract)	AZA	Prospective observational, N=56; MDS, treated with AZA	EORTC QLQ-C30, FACT-fatigue, EQ-5D, and a global fatigue scale	50 were evaluable for QoL. Clinically important differences were seen in physical, role, cognitive, and social functioning. GHS between responders and nonresponders (all higher in responders). Responders had significantly superior GHS ($P=0.001$) and EQ-5D scores ($P=0.0002$) and lower levels of fatigue ($P<0.0001$)
Ingber et al ²⁸ (abstract)	AZA	Prospective observational, N=20; MDS, treated with AZA	EORTC QLQ-C30, EQ-5D, global fatigue scale	The only clinically significant improvements were observed with the EORTC physical functioning and fatigue subscales but constipation scores were higher and GHS/QoL deteriorated over time.
Oliva et al ²⁹	Intensive therapy vs palliative treatment	Prospective observational, N=113; age ≥60, newly diagnosed de novo AML	EORTC QLQ-C30 (ver. 3) and QoL-E (ver. 2)	At diagnosis, the median QoL-E general standardized score 54 (IQR 46–70)/median EORTC QLQ-C30 global score decreased 50 (IQR 41–66) Fatigue in QoL-E median 45 (IQR 32–53)/QLQ-C30 median 33 (IQR 22–66) Loss of appetite was perceived by 75% of patients
Deschler et al ³⁰	BSC vs (HMA vs IC + HCT	Patient survey, N=195	EORT QLQ-C30 and ADL (Barthel index)	At baseline, median EORTC QLQ-C30 fatigue (BSC vs HMA vs IC/HCT vs total): 53.3 vs 66.6 vs 44.3 vs 53.3, median ADL (Barthel index) (BSC vs HMA vs IC/HCT vs total): 100 vs 100 vs 100

(Continued)

Table 2 (Continued)

References	Interventions	Type of study/study population	Scales used	QoL summary
Pandya et al ³¹ (abstract)	NA	Patient survey, N=75; AML, IL or R/R (75% [n=56] first line vs 25% [n=19] relapsed/refractory AML)	FACT-Leu and EQ-5D-3L	First-line patients may have a directionally better QoL scores than those on later lines of therapy IL vs R/R: EQ-5D = 0.75 vs 0.71 (P=0.51) and the FACT-Leu = 103.7 vs 92.5 (P=0.098). R/R patients were significantly more likely than first-line patients to be affected physically by their AML condition IL vs R/R: FACT-Leu-physical well-being sub-domain = 13.0 vs 17.6, P=0.005
Cheng et al ³⁴ (abstract)	NA	Patient survey, N=18; AML, achieved the first CR	EORTC QLQ-C30, QoL-CS, FACIT-fatigue, and HADS	Participants scored well on the EORTC QLQ-C30. The FACIT-fatigue (worst 0 to best 52) mean score was 28.7 and the median score was 33.5 (normal ≥30). On the HADS anxiety scale, two participants scored in the abnormal range. On the QoL-CS, participants scored above 6/10 in all domains, with exceptions of the psychological subscales of distress and fear (physical 8.7/psychological 7.9/distress 4.7/fear 4.5/social 7.1/spiritual 7.4)
Leunis et al ¹⁴	NA	Patient survey, N=92; AML survivors vs general population	EQ-5D and EORTC QLQ-C30	The majority of the patients with AML reported problems on the five functioning scales of the QLQ-C30. The average scores on all functioning scales were significantly lower in patients with AML compared to adjusted general population scores. The differences in physical, role, cognitive, and social functioning were also clinically relevant. Despite these differences, no significant difference was found for the global quality of life
Levy et al ³³	AZA vs CCR (BSC alone, low-dose chemotherapy + BSC, and standard-dose chemotherapy + BSC)	Utility, CEA; AML survivors vs general population	EQ-5D mapped from EORTC QLQ-C30 and SF-6D mapped from SF-12	The utility analysis results show that, compared with patients receiving BSC, patients treated with AZA had a better quality of life and the difference increased with increasing length of treatment

Note: SF-6D and SF-12, short form health surveys.

Abbreviations: ADL, activities of daily living; AZA, azacitidine; CEA, cost-effectiveness analysis; CCR, conventional care regimens; CMML, chronic myelomonocytic leukemia; CR, complete response; DEC, decitabine; ECOG PS, The Eastern Cooperative Oncology Group performance status; EQ-5D-3L, EuroQoL 5-dimensions 3-levels; FACIT-fatigue, Functional Assessment of Cancer Therapy-fatigue; FACT-Leu, Functional Assessment of Cancer Therapy-leukemia; HADS, Hospital Anxiety and Depression Scale; HCT, hematopoietic cell transplantation; HSCT, hematopoietic stem cell transplantation; MID, minimally important difference; NA, Not applicable; QoL, quality of life; QoL-CS, quality of life cancer survivor; RCT, randomized clinical trials; R/R, relapsed/refractory.

found that clinically significant improvements were achieved in the physical functioning and fatigue subscales of EORTC QLQ-C30.²⁸ The final reviewed prospective study evaluated the relationship between HRQoL and survival where it was found that HRQoL scores at diagnosis discriminated patients according to overall survival.²⁹ Patients with low scores including functional, PF, role function, and fatigue scores (<60) had shorter survival compared to those with higher scores: QOL-E functional score (median 15 weeks, 95% CI 12–17 weeks vs 55 weeks, 95% CI 42–69 weeks; $P=0.002$), QOL-E physical score (median 18 weeks, 95% CI 0–37 weeks vs 60 weeks, 95% CI 34–87 weeks; $P=0.038$), EORTC QLQ-C30 PF (median 14 weeks, 95% CI 5–24 weeks vs 60 weeks, 95% CI 44–77 weeks; $P<0.0001$), EORTC QLQ-C30 role function (median 21 weeks, 95% CI 7–36 weeks vs 55 weeks, 95% CI 32–79 weeks; $P=0.015$), and EORTC QLQ-C30 fatigue score (median 14 weeks, 95% CI 13–15 weeks vs 55 weeks, 95% CI 46–65 weeks; $P=0.004$).²⁹

The HRQoL results from the four patient survey studies presenting the median fatigue scores of EORTC QLQ-C30 were 53.3, 66.6, and 44.3 in newly diagnosed MDS and AML patients (aged ≥ 60 years) receiving BSC, HMAs, and IC, respectively. The score in all patients was 53.3.³⁰ Relapsed/refractory patients were significantly more likely to be affected physically than patients with first-line disease;³¹ the utility value for first-line patients were higher (EQ-5D = 0.75) vs relapsed/refractory patients (EQ-5D = 0.71) suggesting that first-line patients may have had better HRQoL scores than those on later therapies.³¹ Fatigue and distress (followed by pain) were the symptoms reported most often among patients with AML and MDS.³² According to Leunis et al,¹⁴ fatigue was the most frequently reported symptom in patients with AML (78%) and other frequently reported symptoms were pain, dyspnea, insomnia, and financial difficulties. Patients with AML had significantly more problems with fatigue, pain, dyspnea, and appetite loss than the general population.¹⁴ The utility value for the overall population was 0.82, patients with relapse had lower utility values vs those without a relapse (0.78 vs 0.83) and there was no much difference seen in the utility values between patients receiving high-dose chemotherapy plus hematopoietic stem cell transplantation (HSCT) vs HSCT alone.¹⁴ Overall, at baseline, NIC AML patients had poor HRQoL scores especially in fatigue (33) and GHS (50) on a 0–100 scale, with higher scores indicating better health. Low baseline HRQoL scores, especially PF and fatigue (<50) were shown to be significant independent predictors of poor survival. Clinical responders demonstrated meaningful improvements in QLQ-C30 physical, role, cognitive, and

social functioning, GHS, fatigue, and EQ-5D scores from baseline after being treated with chemotherapy. Clinically meaningful and significant improvements in fatigue and PF were observed with nonintensive chemotherapeutic agents across several of these studies.

The single cost-effectiveness analysis compared an HMA with conventional care regimens, including BSC, and low or standard-dose chemotherapy plus BSC in the treatment of higher risk AML with 20–30% of blasts. The utility analysis results show that, compared with patients receiving BSC, patients treated with the HMA had a better quality of life with the utility values increasing from day 0 onward to day 183, and the difference increased with increasing length of treatment; the utility values for patients treated with the HMA were 0.67 at baseline and increased to 0.80 at day 182 vs BSC with the utility value of 0.67 at baseline and increased to 0.72 at day 182.³³

Interestingly, we found that baseline factors such as fatigue, gender, comorbidities, bone marrow blasts, and secondary AML were not related to HRQoL in one study.²⁴ However, other studies showed these factors along with others to be correlated to HRQoL, such as baseline hemoglobin (Hb) levels and scores of QOL-E functional ($r=0.0216$, $P=0.14$), fatigue ($r=0.256$, $P=0.002$), and disease specific ($r=0.247$, $P=0.010$) were shown to be statistically correlated. Furthermore, scores from the EORTC QLQ-C30 of GHS ($r=0.270$, $P=0.001$), physical ($r=0.304$, $P<0.0001$), role ($r=0.281$, $P=0.001$), cognitive ($r=0.262$, $P=0.003$), social ($r=0.229$, $P=0.010$), functions and fatigue ($r=-0.280$, $P=0.001$), dyspnea ($r=-0.287$, $P=0.001$), and appetite loss ($r=0.244$, $P=0.007$) were statistically related to HRQoL. Age was also found to be correlated with QOL-E disease-specific scores ($r=0.242$, $P=0.012$). Finally, higher scores in HRQoL can be seen over time if transfusion dependence status is collected at the time of HRQoL assessments, displaying a possible strong HRQoL relationship between response and transfusion dependence, which could be a factor for NIC AML patients (Figure 2).²⁷

Discussion

HRQoL is a multi-dimensional concept encompassing the patient's perception of functioning and well-being. To account for this complexity, HRQoL instruments capture certain domains, at a minimum, physical, emotional, and social functioning. Collecting and publishing HRQoL data are very important to both understand the patient's perspective and evaluate any impact or correlation of treatment that may have on a patient's condition. Currently, there are no prior SLRs

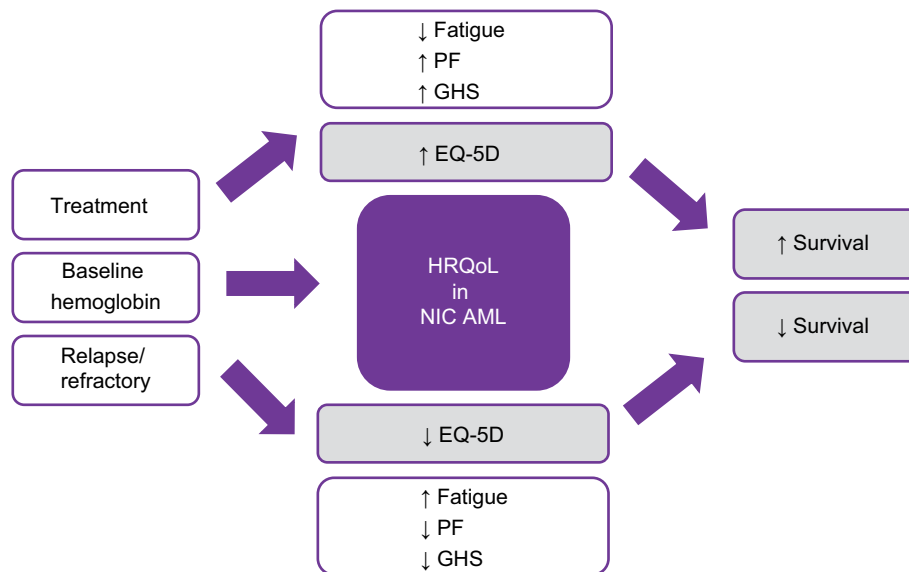


Figure 2 Impact of HRQoL in NIC AML

focusing on HRQoL data in NIC AML patients; therefore, the need for this information is valuable. In this SLR, we identified only 12 studies reporting HRQoL and patient preference utilities in NIC AML patients; this clearly demonstrates that there is scant published literature on the impact of disease and treatment on the HRQoL in NIC AML patients. Having an instrument that succinctly and reliably captures the impact of AML disease and treatment in the NIC AML population would help investigators incorporate HRQoL endpoints into clinical trials and help inform health care decision makers to make better treatment plans. Helping people to maintain or have improvement in HRQoL and to live longer is clearly a goal of AML therapy, even for patients not eligible for IC. Failing to understand the HRQoL implications of different treatments may mean that it could be difficult to provide this information to future AML patients facing decisions who are not eligible for IC.

Although there is scarcity of published HRQoL reported data in the NIC AML patients, from the few studies that were reviewed, we found that HRQoL was correlated with better overall survival.^{9,17,26,33} Survival was independently predicted by the QoL-E scores of PF when controlling for factors such as age, concomitant diseases, and treatment options.²⁹ Patients with short MDS duration had worse outcomes and was shown to be an independent adverse prognosticator.¹⁷ Even though HRQoL is highly subjective, this subjectivity can be alleviated since majority of these studies were randomized controlled trials. It has become clear that the role of

HRQoL in the elderly AML patients has value at diagnosis as a prognostic factor for overall survival and, thus, a potential variable that may be integrated in the process of decision-making for treatment allocation.²⁵

Understanding baseline factors can assist with individual patient treatment allocation and can provide additional information to a physician's assessment. For example, older age, impairments in activities of daily living, Karnofsky index <80%, and HRQoL/fatigue ≥ 50 are likely to have poor outcomes.³⁰ Also, NIC AML patients had poor HRQoL scores (<50) on a 0–100 scale, especially in fatigue (33) and GHS (50), which were shown to be significant independent predictors of poor survival.³⁰ Prior studies, as Deschler et al, have found patient characteristics such as fatigue, PF, gender, comorbidities, bone marrow blasts, and secondary AML to be highly related to HRQoL outcomes; however, we found additional baseline HRQoL parameters to be possible independent prognostic factors in AML patients such as Hg level, age, and transfusion dependence. Including these additional baseline parameters when collecting HRQoL assessment could facilitate decision makers to assist with better treatment outcomes for NIC AML patients.

Patients diagnosed with AML are older and generally have poor prognosis. While treatment may extend overall survival for patients with AML, it may also cause significant toxicity and impairment of HRQoL;^{17,26,34} therefore, using less IC agents has shown to be associated with general improvement in HRQoL in the relevant domains of fatigue, PF, and

GHS.^{14,24} Other studies observed clinically meaningful and significant improvements in fatigue and PF with nonintensive chemotherapeutic agents.¹⁷ These studies discussed how clinical responders demonstrated meaningful improvements in QLQ-C30 physical, role, cognitive, and social functioning, GHS, fatigue, and EQ-5D scores from baseline after being treated with nonintensive chemotherapeutic agents.

Finally, AML patients who have relapsed or become refractory to first-line treatment report worse HRQoL than those still on first-line treatments.³¹ These observational data showed a need for effective and tolerable treatments that can maintain or improve patients' HRQoL, especially for patients with relapsed or refractory disease. Thus, it is important to understand the impact of AML on patients receiving first-line treatment vs those who were relapsed/refractory to first-line treatment.³¹ Although there is heterogeneity of data reporting across published studies, there is a consistent message that the HRQoL is poor, worsened by comorbidities, disease progression, or relapse in disease. Utility values and HRQoL have shown improvement with successful treatment; therefore, therapies that can help control symptom burden without negative adverse events and prevent relapses are needed.

Conclusion

HRQoL plays a crucial role in the treatment of AML patients. Currently, there are no prior SLRs conducted in evaluating HRQoL within NIC AML patients and from this SLR exercise, we found very scant literature assessing this information. Fatigue and PF at baseline have been identified as independent prognostic factors for overall survival with several studies showing improvement in both domains with treatment. Alongside the evaluation of treatment-related efficacy and safety, randomized controlled studies should also incorporate and assess the impact of treatment on patient's PF and fatigue with the aim to improve overall HRQoL.

Abbreviations

AML, acute myeloid leukemia; BSC, best supportive care; ELN, European LeukemiaNet; EORTC QLQ, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D, EuroQOL-5 Dimensions; FACIT, Functional Assessment of Chronic Illness Therapy; FACT, Functional Assessment of Cancer Therapy; GHS, global health status; HMA, hypomethylating agents; HRQoL, health-related quality of life; IC, intensive chemotherapy; LDAC, low-dose cytarabine; MDS, myelodysplastic syndrome; NCCN, National Comprehensive Cancer Network;

NIC, nonintensive chemotherapy; PF, physical function; PICOS, population, intervention, comparator, outcome and study design; RAEB-t, refractory anemia with excess blasts in transformation; SLR, systematic literature review.

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Parts of this study were previously published in an abstract submitted to the 2018 Congress of the European Hematology Association (<https://learningcenter.ehaweb.org/eha/2018/stockholm/215952/anna.forsythe.health.related.quality.of.life.28hrqol29.in.acute.myeloid.leukemia.html>). Editorial support was provided by Nazia Merritt at Purple Squirrel Economics. This study was funded by Pfizer.

Author contributions

AF, CSK, and TB made substantial contributions to the conception and design of the study, analyzed and interpreted the data, and critically revised the article. TAS analyzed and interpreted the data and critically revised the article for important content. BA contributed to data interpretation and drafting of the article. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

TB, TAS, and BA are employees of Pfizer. AF and CSK are the employees of Purple Squirrel Economics who were paid consultants to Pfizer in connection with the conduct of the study and development of this article. The authors report no other conflicts of interest in this work.

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Supplementary material

Table S1 Search strategy

1	exp LEUKEMIA, MYELOID, ACUTE/	79,787
2	exp LEUKEMIA, MYELOID/	180,001
3	exp ACUTE DISEASE/	323,400
4	2 and 3	9,745
5	LEUKEMIA, MYELOID/	33,612
6	ACUTE DISEASE/	323,400
7	5 and 6	7,711
8	(acut\$ or akut\$ or agud\$ or aigu\$).tw,kf,ot.	2,725,487
9	((myelo\$ or mielo\$ or nonlympho\$ or granulocytic\$) and (leuk?em\$ or leuc\$)).tw,kf,ot.	233,145
10	8 and 9	136,561
11	aml.tw,kf,ot.	82,861
12	(Acute Myeloid Leukemia\$ or Leukemia\$, or Leukaemia\$ or Acute Myeloid or Myeloid Leukemia\$, Acute).af.	787,634
13	(Leukemia\$, Laukaemia\$, Myelo\$, Acute or Myelo\$ Leukemia\$, Acute or Acute Myelo\$ Leukemia\$).af.	100,183
14	(Leukemia\$, Nonlympho\$, Acute or Nonlympho\$ Leukemia\$, Acute or Acute Nonlympho\$ Leukemia\$).af.	5,775
15	(Leukemia\$, Leukaemia\$, Granulo\$, Acute or Granulo\$ Leukemia\$, Acute or Acute Granulo\$ Leukemia\$).af.	53,759
16	or/12–15	787,634
17	1 or 4 or 7 or 10 or 11 or 16	798,957
18	(glasdegib or azacitidine or decitabine or low dose cytarabine or LDAC or hydroxycarbamide or 6-mercaptopurine or etoposide or best supportive care).ti,ab	72,222
19	17 and 18	16,693
20	Quality of Life/	573,654
21	(QOL or HRQL or HRQOL).ab,ti	139,382
22	(patient adj2 reported adj2 outcome adj2 measure\$).ti,ab	139,382
23	(utility or utilities).ti,ab	425,239
24	utility measure\$.ti,ab	1,380
25	"quality of life".de	573,654
26	"quality adjusted life year".de	20,701
27	quality adjusted life year/	36,275
28	(quality adj4 life).ti,ab	651,934
29	(qol or "disability adjusted life").ti,ab	103,635
30	(qaly* or qald* or qale* or qtime* or daly*).ti,ab	32,294
31	(euroqol or eq5d or "eq 5d" or "eq5d" or "euro qual" or "euro qol" or euroqual).ti,ab	26,629
32	(EORTC\$ or European Organi\$ation for Research and Treatment of Cancer).ti,ab	7,383
33	(willingness adj4 pay).ti,ab	11,776
34	(standard adj1 gamble*).ti,ab	2,015
35	((("time trade" adj1 off*) or (time adj1 tradeoff*)) or tto or timetradeoff).ti,ab	4,369
36	(TTO or SG or WTP).ti,ab	27,036
37	((valu* or measur*) adj4 (health or outcome or outcomes or effect or effects or change* or state*)).ti,ab	1,088,035
38	(preference* adj4 (patient* or public or valu* or measur*)).ti,ab	51,709
39	(multiattribute* adj1 (health or theor* or analys* or utilit*)).ti,ab	356
40	((multi adj1 attribute*) and (attribute* adj1 theor*)).ti,ab	3
41	((multi adj1 attribute*) and (attribute* adj1 analys*)).ti,ab	17
42	((multi adj1 attribute*) and (attribute* adj1 utilit*)).ti,ab	391
43	(utilit* adj4 (valu* or measur* or health or life or estimat* or elicit* or disease)).ti,ab	32,190
44	((symptom or symptoms) adj5 (score* or scale* or instrument* or measur*)).ti,ab	179,539
45	(FACT-G or "EORTC QLQ-C-30" or FLIC or QLI-CV).tw.	4,589
46	functional assessment of cancer therapy.tw.	5,456
47	or/20–46	2,411,950
48	19 and 47	809
49	(letter or editorial or comment or news or newspaper article).pt.	3,485,218
50	animals/not (humans/and animals/)	35,974
51	case reports/	2,029,566
52	in vitro.pt	3
53	or/49–52	11,256,953
54	48 not 53	798
55	limit 54 to Humans	720
56	limit 55 to English	680
57	limit 56 to 2007–present	507
58	Deduplicate	396

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