

# Systematic review of health state utility values for acute myeloid leukemia

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**Background:** Cost-utility analyses for acute myeloid leukemia (AML) require health state utility values (HSUVs) in order to calculate quality-adjusted life-years (QALYs) for each health state.

**Aim:** This study reviewed AML-related HSUVs that could be used in economic evaluation studies.

**Materials and methods:** EMBASE, MEDLINE, and Cochrane databases were searched from January 2000 to November 2016 for relevant studies that reported quality of life (QoL) and HSUVs in AML. Identified relevant European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 values were mapped to HSUVs. HSUVs for each health state in the AML treatment pathway were then collated.

**Results:** Ten relevant studies were identified. Six were cost-effectiveness analyses utilizing HSUVs for calculation of QALYs, one was an effectiveness analysis (incremental QALY), and two were QoL studies reporting AML-specific utilities. An additional study reported QoL for patients undergoing stem cell transplantation (SCT). Since no study reported HSUVs for relapse, values from a study of secondary AML patients who failed prior treatment for myelodysplastic syndrome were used. Where multiple HSUVs were available, collected values were given priority over assumed values. AML treatment (induction, consolidation, or SCT) was associated with decreased HSUV, while post-treatment complete remission led to increased HSUV.

**Conclusion:** There are some methodologically robust HSUVs that can be directly used in economic evaluations for AML. Careful interpretation is advised considering significant differences in methodologies and patient population (inclusion, size). We need to develop HSUVs with larger-sized studies, making greater use of condition-specific data.

**Keywords:** acute myeloid leukemia, EQ-5D, health-related quality of life, utility, systematic review, economic analysis, QALY

## Introduction

Acute myeloid leukemia (AML) is an aggressive hematological malignancy that is fatal if left untreated, meriting its designation as a medical emergency.<sup>1,2</sup> In 2014, more than 3,000 people were diagnosed with AML in the UK, while around 2,500 patients died due to this condition.<sup>3</sup> Mortality occurs quickly and is often difficult to prevent. The 5-year survival rate is 26% in the US and 17% in the EU.<sup>4</sup> Treatment should therefore be initiated shortly after diagnosis, ideally within a matter of days. Even with timely intervention, not all patients achieve remission. As many as 50–70% of those who do achieve remission following chemotherapy relapse within 3 years.<sup>5</sup> Bone marrow failure is a defining characteristic of AML. Mortality results predominantly from complications associated with bone marrow failure, such as opportunistic infections or hemorrhage.<sup>6</sup>

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The treatment pathway for AML can be broken down into three phases: induction chemotherapy, consolidation chemotherapy, and stem cell transplantation (SCT) (Figure 1). Intensive induction chemotherapy is the standard of care for most patients with newly diagnosed AML, aimed at inducing complete remission (CR).<sup>1</sup> Should the patient achieve CR, they may continue consolidation chemotherapy or receive high-dose chemotherapy conditioning as a bridge to SCT.<sup>1</sup> Patients often do not reach remission and even if they do, they may still relapse, requiring alternative courses of therapy.<sup>5</sup> Likewise, successful treatment is not without difficulty: the chemotherapeutic agents used to treat this disease are associated with significant toxicities.<sup>7</sup> Even SCT is associated with considerable morbidity and mortality, given the high incidence of graft versus host disease (GVHD).<sup>8</sup>

The diagnosis of AML may be very traumatic for a patient who is given little time to adjust before the initiation of aggressive therapy. In this scenario, short-term and long-term well-being are significantly impacted by the initial choice of therapy, ie, the current standard of care in AML management.<sup>9,10</sup>

Health-related quality of life (HRQoL) is a measurement of well-being. In one application, it is employed during clinical trials when the impact of an investigational treatment on QoL must be quantified. Clinical trials often consider overall

survival or progression-free survival as a primary end point, with HRQoL as a secondary end point. The European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire Core 30 (QLQ-C30) is a frequently used, non-preference based, cancer-specific questionnaire that assesses HRQoL.<sup>11</sup>

For economic evaluation, many health technology assessment bodies require that effectiveness is expressed in terms of quality-adjusted life-years (QALYs). They also commonly prefer health state utility values (HSUVs) that are determined using the EuroQol five-dimensional (EQ-5D) patient preference questionnaire.<sup>12-14</sup> QALYs consider both the quantity of survival and its quality. In each disease setting, HSUVs are used to transform the time patients spend in different health states into QALYs.

The EQ-5D was designed to enable the application of cost-effectiveness analysis; patients contribute to definitions of health utility through population surveys and self-reported health states. EQ-5D scores may then be translated into equivalent QALYs.<sup>15,16</sup> Patients' preference for one health state over another, as in the EQ-5D scale, dictates their assigned value for that health state. However, the use of EQ-5D in cancer clinical trial data collection is not as widespread as the use of non-preference scales such as the QLQ-C30. The QLQ-C30 consists of 30 questions across five functional scales

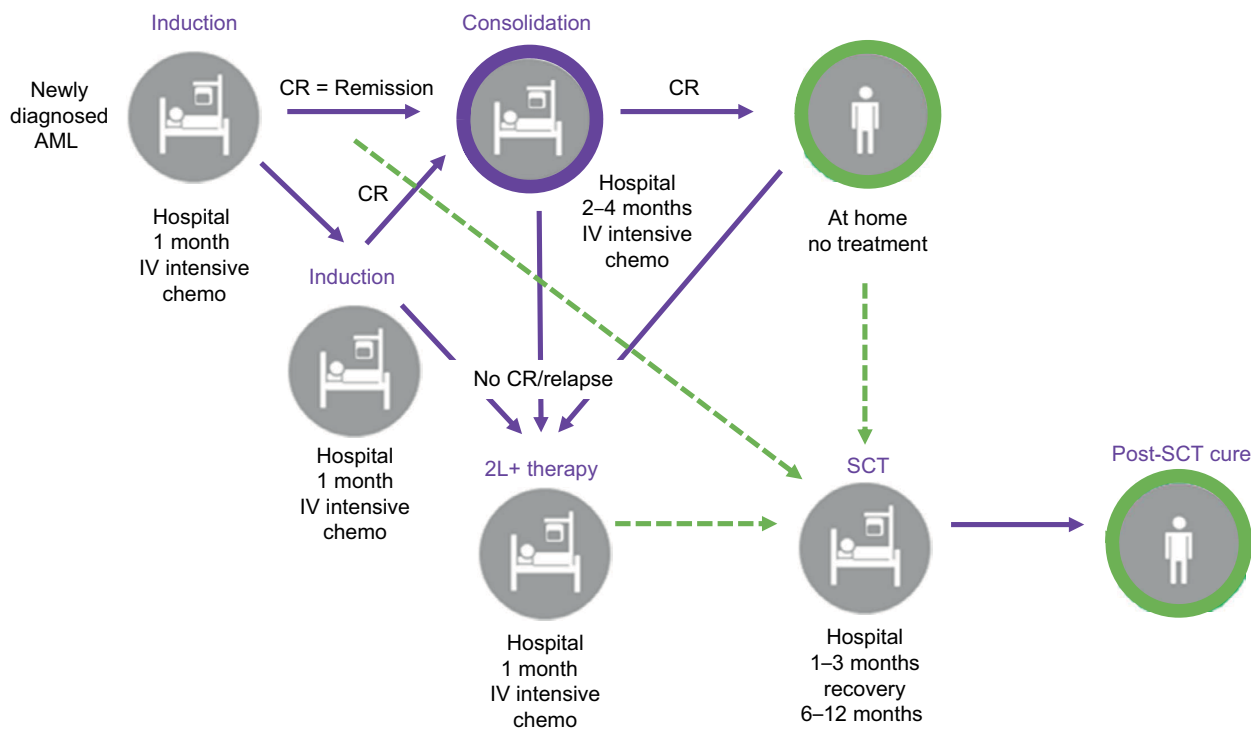


Figure 1 Treatment pathway for acute myeloid leukemia.

Abbreviations: AML, acute myeloid leukemia; CR, complete remission; IV, intravenous; SCT, stem cell transplantation; 2L, second-line.

(cognitive, emotional, physical, social, role), nine symptom scales (appetite loss, constipation, diarrhea, dyspnea, fatigue, financial difficulties, insomnia, nausea and vomiting, pain), and one global health state/QoL scale. Higher scores on the functional and global health state scales correspond to better functioning, whereas high symptom scores correspond to worse symptoms.<sup>11</sup> Where data on health state utilities were not directly collected from patients in clinical trials, utility estimates may be “mapped” from condition-specific HRQoL scales, such as through an algorithmic technique described by Crott et al.<sup>17–18</sup>

Health state utilities for different stages of AML and the toxicities associated with each chemotherapy and SCT regimen are used during the health technology assessment process to estimate the incremental effectiveness of new products versus the standard of care. Most of the previously reported economic analyses have not utilized utilities to describe a range of health states within AML such as pre-relapse versus post-relapse; these studies did not consider the utilities by treatment stage (induction, consolidation, maintenance) or addressed some key health states such as transplantation.<sup>19</sup> This study aimed to review utility values that may be used in economic evaluations of AML. In the process, it aimed to illustrate and critically discuss challenges in creating a comprehensive set of utility values.

## Materials and methods

A list of relevant health states based on the current consensus in AML treatment was selected and reviewed with UK-based clinical experts experienced in treating AML patients. The health states and their characteristics were defined as part of an unpublished time trade-off (TTO) study. The TTO approach, which seeks to determine the length of lifetime a person would hypothetically sacrifice in exchange for a better health state, has been widely used to obtain health state values.<sup>20</sup> In the initial stages of TTO process, health state descriptions were developed and validated in collaboration with key opinion leaders and other specialists.

Disease symptoms, adverse events in treatment, and treatment setting were considered as those that may influence the physical, functional, and emotional health of patients.

Relevant health states identified are as follows (Figure 1):

- Newly diagnosed and undergoing induction treatment
- In remission and undergoing consolidation treatment
- Remission post-chemotherapy – long-term follow-up >1 year
- SCT procedure
- SCT recovery <1 year

- Remission post-SCT, no complications
- Remission post-SCT, GVHD
- Treatment failure/relapse/refractory

A systematic literature review was conducted to identify articles reporting utility data for one or more of the identified health states in AML. In this review, MEDLINE and EMBASE were searched using the Ovid platform, covering nearly 10 years, from January 1, 2006 to November 20, 2016. Systematic reviews and meta-analyses identified were utilized for bibliography searching in order 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 the supplemental results of previously published studies. Abstracts from American Society of Clinical Oncology, European Hematology Society, European Society of Medical Oncology, and American Society of Hematology for the period 2013–2016 were searched. The detailed search strategy is presented in Table S1.

If no studies were identified with data on a specific health state in AML, additional targeted searches were performed to locate studies reporting either utilities or HRQoL related to that specific health state, using a condition that most closely mimics the clinical picture of AML.

Articles were included in the review if they reported utility values for one of the identified health states. Cost effectiveness analyses and health technology assessments were included if utility values were reported. Studies that did not have AML populations and those not reporting utility values were excluded. Only publications written in English and published starting from January 2006 were considered.

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. 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. These methods were adapted from the procedure described by the York Centre for Reviews and Dissemination.<sup>21</sup>

Inclusion and exclusion criteria for the systematic review are presented in Table 1.

## Health state utility derivations

Relevant HRQoL data (EORTC QLQ-C30) for patients undergoing SCT were mapped using a previously published

**Table 1** Study eligibility criteria

Element	Inclusion	Exclusion
Patient population	Patients with acute myeloid leukaemia or myelodysplastic syndrome	Non-human
Intervention and comparators	All, including no interventions	
Outcome measures	<ul style="list-style-type: none"> <li>• Any HRQoL outcomes</li> <li>• Utilities/disutilities/QALYs for health states or adverse events</li> </ul>	Any not listed in the inclusion criteria
Study design	<ul style="list-style-type: none"> <li>• Reports of randomized clinical trials assessing HRQoL</li> <li>• Development and/or validation of HRQoL measures</li> <li>• Observational studies measuring PROs</li> <li>• Retrospective chart audits and database analyses reporting PROs</li> <li>• Patient surveys reporting PROs</li> <li>• Reports of mapping exercises for any outcome measure to utility</li> <li>• Reports of utility elicitation exercises</li> <li>• Reports of utility validation exercises</li> <li>• Reports of economic evaluations using utility measures elicited during the studies</li> <li>• Systematic reviews and meta-analyses (to be used for reference cross-checking only)</li> </ul>	<ul style="list-style-type: none"> <li>• Any not listed in the inclusion criteria</li> <li>• Reviews</li> <li>• Editorials</li> <li>• Notes/Comments/Letters</li> <li>• Systematic reviews of economic evaluations (to be used for bibliography search)</li> </ul>
Restrictions	<ul style="list-style-type: none"> <li>• English language</li> <li>• Year limitation: 2006 to present</li> </ul>	Non-English language studies

**Abbreviations:** HRQoL, health-related quality of life; PROs, patient-reported outcomes; QALYs, quality-adjusted life-years.

algorithm to estimate EQ-5D scores from the EORTC QLQ-C30 scores on the following scales: physical functioning, emotional functioning, social functioning, constipation, diarrhea, pain, and sleep.<sup>17,18</sup>

The algorithm is based on an ordinary least-squares regression algorithm model, which was derived in patients with both the QLQ-C30 questionnaire and the EQ-5D instrument.<sup>18</sup> In this model, the dependent variable was the calculated overall EQ-5D utility decrement, and the explanatory variables were the calculated QLQ-C30 scores using the following formula:

$$\begin{aligned}
 \text{EQ-5D utility} = & 0.85927770 - \\
 & 0.0069693 * (\text{Physical Functioning}) - \\
 & 0.0087346 * (\text{Emotional Functioning}) - \\
 & 0.0039935 * (\text{Social Functioning}) + \\
 & 0.0000355 * (\text{Physical Functioning})^2 + \\
 & 0.0000552 * (\text{Emotional Functioning})^2 + \\
 & 0.0000290 * (\text{Social Functioning})^2 + \\
 & 0.0011453 * (\text{Constipation}) + \\
 & 0.0039889 * (\text{Diarrhea}) + \\
 & 0.0035614 * (\text{Pain}) - \\
 & 0.0003678 * (\text{Sleep}) - \\
 & 0.0000540 * (\text{Diarrhea})^2 + \\
 & 0.0000117 * (\text{Sleep})^2
 \end{aligned}$$

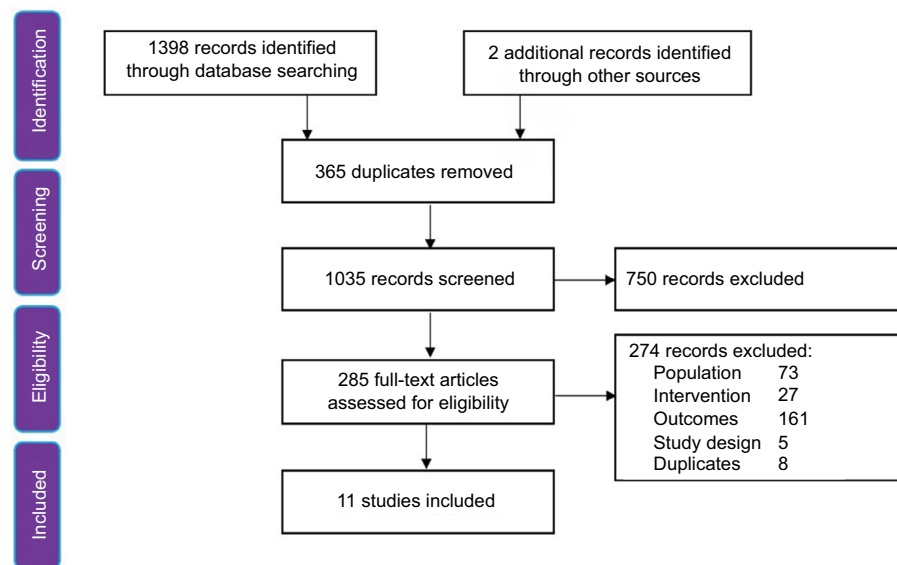
In studies where QLQ-C30 values were already mapped to the EQ-5D, the EQ-5D values were utilized.

## Results

The literature search identified 1398 records (Figure 2). A total of 284 full-text articles were retrieved, with 11 of those meeting all inclusion criteria.

The characteristics of the 11 studies are shown in Table 2.<sup>19,22,24–30,32</sup> Nine studies reported utility values for relevant health states. No studies were identified that reported utility values for patients undergoing SCT treatment. Thus, a targeted search revealed two studies that reported HRQoL (QLQ-C30) for patients undergoing SCT. These were included, with HRQoL data mapped to EQ-5D values as previously described.<sup>25,31</sup>

Table 3 presents the collated utility values, their corresponding AML-relevant health state, and methods of data collection extracted from each study. Many studies measured utility values using the EQ-5D, others employed the QLQ-C30 and mapping or their utilities were assumptions based on studies of similar conditions, and two studies incorporated utilities based on TTO studies. Although there was some variability in the utilities for each health state, they were relatively similar across the identified studies. The lowest utility values were seen in newly diagnosed patients undergoing induction treatment (range 0.524–0.67) and patients in relapse (range 0.50–0.53). Utility values for patients in remission post-chemotherapy ranged from 0.81 to 0.91, while values for patients post-SCT ranged from 0.71 to 0.83. Factors



**Figure 2** PRISMA flow diagram.

**Abbreviation:** PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

leading to disutility in remission were age (0.61 for patients over 60 years old vs 0.71 for all AML patients), history of prior relapse (0.78 with prior relapse vs 0.83 without prior relapse), and GVHD post-SCT (0.864 without GVHD vs 0.691 with GVHD).

The utility values can be used in economic models following the AML treatment pathway. Figure 3 illustrates the fluctuation of utility values as they are matched to each health state in the pathway.

## Discussion

Most of the studies utilized data that were collected directly from patients through the EQ-5D questionnaire or the QLQ-C30 questionnaire. Extrapolation of utilities from other diseases to AML was done for SCT health states (remission and relapse), which identified an area of future research to determine these utilities directly from patients with AML. Based on discussions with the UK-based AML experts, it appears that the utility estimates of the current knowledge base may be fairly representative of health states experienced by AML patients, barring larger and wider-ranging studies on AML utilities in different health states.

The utility values collated show variations in utility across the various health states in AML, with the worst values assigned to both induction and relapse. This finding appears to connote a similarly poor QoL for active AML disease, whether at the beginning of treatment or return of the disease. These low HSUVs in both forms of active AML disease are consistent with findings of a similar systematic

review.<sup>34</sup> More importantly, this stresses the need to focus efforts both on disease reduction and improvement of QoL among patients with active disease.

The transition stage between active disease and remission, ie, the treatment phase, had higher utility values than active disease, which is to be expected given the goal of therapy to reduce disease burden. The values during this stage reflect the complications and side effects that may occur from the therapy itself.<sup>35,36</sup> This finding is consistent with previous studies on the effect of treatment on both the QoL and functional status of patients with AML.<sup>37</sup> The persistent deficits in utility values even during remission also illustrate how patients perceive their own well-being during this health state.<sup>38</sup> As for utility values that exceeded those of the general population, in a TTO approach respondents are not asked to compare their health state to the normal population, but instead to compare their health to the perfect health (utility of 1). As such, the resultant values cannot be compared to the general population. Furthermore, utility scores reported by patients are based on their own individual evaluation of QoL. Thus, patients in remission may report much higher utility scores compared to their diseased health state. The contrast in their QoL between these two health states may lead them to overestimate the QoL of their health state in remission.

EQ-5D utility may depend on the value set used, especially for severe health states. Unfortunately, the identified studies did not report the value sets used in the analyses, which may add uncertainty to the results. Additionally, utility values mapped from the QLQ-C30 instrument should be used with caution



**Table 2** Included studies

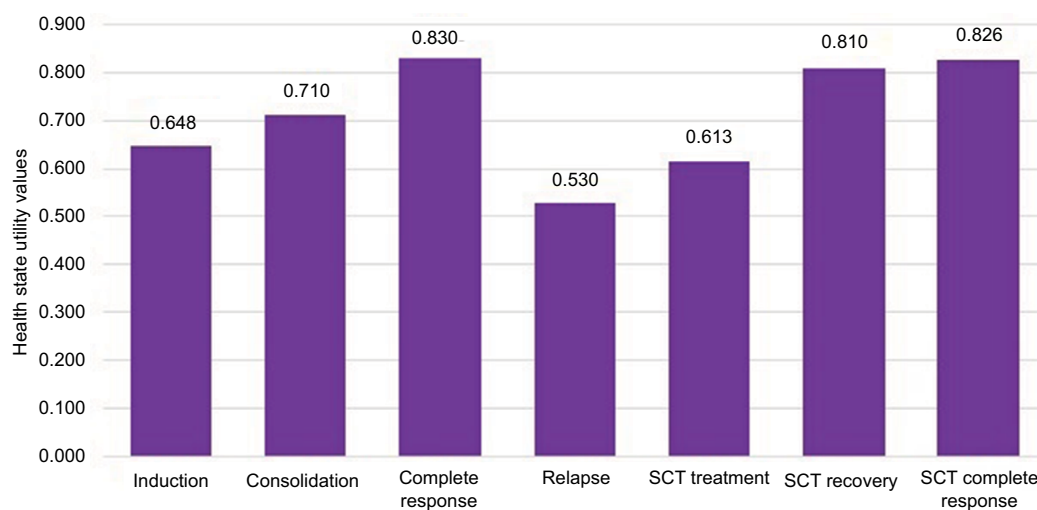
Reference	Type of study/interventions / study population	Utility values
<b>HRQoL studies</b>		
Kurosawa et al, 2014 (Abstract) <sup>22</sup>	Decision analysis Allogeneic HCT vs Chemo	EQ-5D collected: post-SCT overall: 0.74; post-SCT with GVHD (complications): 0.67; post-chemotherapy overall: 0.70. Scale version, values sets, and age of respondents not reported
Pan et al, 2010 <sup>19</sup>	Intermediate/unknown-risk AML CEA Decitabine vs BSC Intermediate/high-risk MDS	Transfusion-independent MDS: 0.84 and transfusion-dependent MDS: 0.60 (both from Szende [2009] <sup>23</sup> TTO study in US, France, Germany, and UK) Secondary AML: 0.53 (QLQ-C30 from Alibhai et al [2007], <sup>35</sup> converted to EQ-5D using mapping algorithm by Kontodimopoulos et al [2009] <sup>38</sup> ) Scale version, values sets, and age of respondents not reported
Leunis et al, 2014 <sup>24</sup>	QOL No current interventions AML survivors post-chemotherapy and HSCT	EQ-5D-5L collected in the Netherlands AML patients, mean age =53 years AML survivors: 0.82; survivors with no relapse: 0.83; survivors after relapse: 0.78
Slovacek et al, 2007 <sup>25</sup>	QOL Autologous HSCT AML and malignant Hodgkin's and non-Hodgkin's lymphoma	EQ-5D-3L collected in Czech AML patients aged 20–69 years, AML: 0.715; AML >60 years old: 0.61
Grulke et al, 2012 <sup>26</sup>	QOL HSCT Variety of cancers (acute leukemia, CML, solid tumors)	Results after mapping to EQ-5D using Crott and Briggs's (2010) <sup>18</sup> algorithm (see "Materials and methods" section), before HSCT: 0.826; during hospitalization for HSCT: 0.613; up to 6 months after HSCT: 0.810; >1 year after HSCT: 0.826
Perić et al, 2016 <sup>27</sup>	QOL HSCT patients with and without GVHD Patients with myeloid malignancies, lymphoid malignancies, and aplastic anemia	QLQ-C30 data collected from HSCT patients 14–70 years old Results after mapping to EQ-5D using Crott and Briggs's (2010) <sup>18</sup> algorithm (see "Materials and methods" section). Patients without GVHD: 0.864; Patients with GVHD: 0.691 QLQ-C30 data collected from Croatian HSCT patients with a mean age =43 years
<b>Cost-effectiveness studies</b>		
Levy et al, 2014 <sup>28</sup>	CEA Azacitidine vs conventional chemotherapy (BSC, lowdose chemotherapy, high-dose chemotherapy) High-risk MDS and low blast AML	AML (>30% blasts): 0.67 EORTC QLQ-C30 data from clinical trial (Kornblith et al, 2002 <sup>35</sup> ) was mapped to EQ-5D using published algorithm (McKenzie and van der Pol, 2009 <sup>41</sup> ). AML utility was assumed to be the same as MDS QLQ-C30 data were collected in patients with a mean age of 74.8 years
Batty et al, 2014 <sup>29</sup>	CEA Decitabine vs conventional induction therapy Elderly, newly diagnosed AML	Active AML: 0.524 (use Gidwani et al's [2012] study <sup>30</sup> ); AML treated with decitabine: 0.71 (assumption); AML in remission and on treatment (consolidation and monotherapy): 0.81 (assumption); AML in remission: 0.91 (based on Goss et al's [2006] study <sup>33</sup> )
Gidwani et al, 2012 <sup>30</sup>	CEA Azacitidine vs decitabine Mixed-risk MDS	AML: 0.524 (using blast stage of CML, Dalziel et al, 2005 <sup>31</sup> ); remission: 0.91 (based on Goss et al, 2006 study <sup>33</sup> )
Uyl de Groot et al, 1998 <sup>32</sup>	CEA and QOL Induction chemo (daunomycin–cytosine arabinoside) + GM-SCF vs induction chemo Elderly AML	EQ-5D (version not reported) collected in Dutch AML patients ≥60 years old: start of Induction: 64.8/70.6; during hospitalization 53.5/67.1; after hospitalization: 68.0/72.7; 6 months post-treatment: 80.6/84.4; 12 months post-treatment: 74.4/75.0 – with GM-SCF vs without, respectively
Goss et al, 2006 <sup>33</sup>	CEA Lenalidomide Low/intermediate-risk MDS	TTO study in the US general population, transfusion-dependent MDS: 0.50; 50% reduced transfusion burden: 0.81; transfusion-independent MDS: 0.91

**Abbreviations:** HRQoL, health-related quality of life; HCT, hematopoietic cell transplantation; AML, acute myeloid leukemia; CEA, cost-effectiveness analysis; BSC, best supportive care; MDS, myelodysplastic syndrome; QoL, quality of life; HSCT, hematopoietic stem cell transplantation; CML, chronic myelogenous leukemia; GVHD, graft versus host disease; EQ-5D, EuroQol five-dimensional; SCT, stem cell transplantation; QLQ-C30, Quality of Life Questionnaire Core 30; EQ-5D-5L, EuroQol 5 dimensions 5-level; EQ-5D-3L, EuroQol 5 dimensions 3-level; EORTC, European Organization for Research and Treatment of Cancer; GM-SCF, granulocyte-macrophage colony-stimulating factor; TTO, time trade-off.

**Table 3** Utility values for reported health states in acute myeloid leukemia

Reported health state	AML-relevant health state	Utility value point estimate	Reference	Data source
Active AML	Induction	0.524	Gidwani et al, 2012 <sup>30</sup>	Assumption based on CML
Newly diagnosed	Induction	0.67	Levy et al, 2014 <sup>28</sup>	Mapped from QLQ-C30
Induction treatment	Induction	0.648	Uyl-de-Groot et al, 1998 <sup>32</sup>	Measured EQ-5D
AML treated with decitabine	Consolidation	0.71	Batty et al, 2014 <sup>29</sup>	Assumption, calculated
After initial hospitalization	Consolidation	0.68	Uyl-de-Groot et al, 1998 <sup>32</sup>	Measured EQ-5D
In remission and on treatment	Maintenance	0.81	Batty et al, 2014 <sup>29</sup>	Assumption, calculated
Six months post-treatment	Remission	0.806	Uyl-de-Groot et al, 1998 <sup>32</sup>	Measured EQ-5D
Transfusion-independent MDS	Remission	0.84	Pan et al, 2010 <sup>19</sup>	TTO Study in MDS
Transfusion-independent MDS	Remission	0.91	Goss et al, 2006 <sup>33</sup>	TTO study in MDS
AML survivors without relapse	Remission, post-1L	0.83	Leunis et al, 2014 <sup>24</sup>	Measured EQ-5D
AML survivors post-relapse	Remission post-relapse	0.78	Leunis et al, 2014 <sup>24</sup>	Measured EQ-5D
Remission prior to SCT	Remission post-chemotherapy	0.826	Grulke et al, 2012 <sup>26</sup>	Mapped from QLQ-C30
Long-term post-chemo	Long-term remission	0.70	Kurosawa et al, 2014 <sup>22</sup>	Measured EQ-5D
Twelve months post-treatment	Long-term remission	0.744	Uyl-de-Groot et al, 1998 <sup>32</sup>	Measured EQ-5D
During SCT treatment	SCT treatment	0.613	Grulke et al, 2012 <sup>26</sup>	Mapped from QLQ-C30
SCT recovery: 6–12 months	SCT recovery	0.810	Grulke et al, 2012 <sup>26</sup>	Mapped from QLQ-C30
Post-SCT: >12 months	Post-SCT	0.826	Grulke et al, 2012 <sup>26</sup>	Mapped from QLQ-C30
Post-SCT	Remission post-SCT	0.71	Slovacek et al, 2007 <sup>25</sup>	Measured EQ-5D
Post-SCT >60 years old	Remission post-SCT, elderly	0.61	Slovacek et al, 2007 <sup>25</sup>	Measured EQ-5D
Post-SCT	Post-SCT	0.74	Kurosawa et al, 2014 <sup>22</sup>	Measured EQ-5D
Post-SCT without GVHD	Post-SCT without GVHD	0.864	Perić et al, 2016 <sup>27</sup>	Mapped from QLQ-C30
Post-SCT with GVHD	Post-SCT with GVHD	0.691	Perić et al, 2016 <sup>27</sup>	Mapped from QLQ-C30
Post-SCT with GVHD	Post-SCT with GVHD	0.67	Kurosawa et al, 2014 <sup>22</sup>	Measured EQ-5D
Secondary AML	Relapse	0.53	Pan et al, 2010 <sup>19</sup>	Mapped from QLQ-C30
Transfusion-dependent MDS	Relapse	0.50	Goss et al, 2006 <sup>33</sup>	TTO Study in MDS

**Abbreviations:** AML, acute myeloid leukemia; MDS, myelodysplastic syndromes; SCT, stem cell transplantation; GVHD, graft versus host disease; CLL, chronic lymphocytic leukemia; TTO, time trade-off; QLQ-C30, Quality of Life Questionnaire Core 30; EQ 5D, EuroQol five-dimensional; 1L, first-line.



**Figure 3** Health state utility values for acute myeloid leukemia.  
**Abbreviation:** SCT, stem cell transplantation.

because of the derivative nature of the values generated.<sup>37</sup> While the validity of mapping techniques has been tested against EQ-5D and other preference-based instruments, such as short form 6 dimensions (SF-6D) and 15 dimensions (SF-15D), it is important to note that primary data for utilities taken directly from patients would still hold priority over these derived values.<sup>38,39</sup> As experience grows with the use of these instruments

and their mapping into QALYs, studies collating and validating this application may be beneficial for future economic analyses, especially when there is a lack of primary studies on utilities focusing on particular diseases such as AML.<sup>39–42</sup>

In our selection of final utility values recommended for use in health economic evaluations, we prioritized values collected directly from patients to those mapped. We, how-

ever, made an exception for the utility values related to SCT. Although Kurosawa et al's publication reported EQ-5D values collected directly from patients, the validity of this research is diminished since it was never published in a peer-reviewed journal.<sup>22</sup> Furthermore, the values reported by Kurosawa et al were considerably lower as compared to other studies, such as those of Uyl-de Groot et al and Leunis et al.<sup>31,24</sup> On the other hand, the mapped values using Grulke et al for remission prior to SCT were more consistent with values reported by other studies.<sup>27</sup> The consistently lower HSUVs reported in the Kurosawa et al's study compared to other studies is the basis for the selection of the HSUVs mapped from Grulke et al. Although the use of mapping applied to mean values versus individual patient level adds potential weakness to resultant utility values, the HSUVs derived from Grulke et al provided a more clinically plausible progression in the improvement of QoL with successful treatment (ie, with SCT), as depicted in Figure 3. Selecting the HSUV provided by Kurosawa et al would have portrayed a significant decline in HSUV following SCT not compatible with known clinical course and prognosis of patients in that health state.<sup>7,43-46</sup>

Overall, this study uncovered a common issue when searching for utility values for rare diseases, such as AML. Studies on rare diseases are relatively rare in themselves and require considerable resources to find.<sup>47</sup> In this study, only 11 have met the inclusion criteria, with many studies excluded mainly because they did not deal with acute hematologic malignancy, and because they did not examine QoL or utility outcomes. One recommendation is to institute a comprehensive policy covering the registration and monitoring of the health status of patients with rare diseases, including their treatment regimens, clinical outcomes, and QoL.<sup>48</sup> With such broad remit, multiple studies may be generated from these datasets and registries, so-called "real-world evidence", enabling the creation of a more complete picture of the disease process, its treatment, and experience living with the disease. TTO studies may likewise be performed to extract further information from existing registries and research.<sup>9,49,50</sup>

More importantly, the determination of HSUVs for rare diseases is particularly challenging, especially since the populations used may be smaller than usual (resulting in wider ranges) and the methodology of determining HSUVs may vary considerably as well.<sup>50</sup> Establishing a set of recommendations to standardize HSUV determination across different diseases and contexts may be valuable in the long term.

## Conclusion

Here we present a broad summary of the available utility scores in AML. There are relatively few methodologically

robust HSUVs that can be directly used in economic evaluations concerned with AML. Careful interpretation of published values is advised considering significant differences in methodologies as well as patient population inclusion and size. There is a need to develop new HSUVs with larger-sized studies which improve on those currently available, either by utilizing TTO studies or by making greater use of condition-specific data and further use of mapping algorithms.

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## Author contributions

AF, GT, SP, and PSB made substantial contributions to the conception and design, analyzed and interpreted the data, and critically revised the article. MD acquired and analyzed the data, and contributed to the revision of the manuscript. APJR contributed to data interpretation and drafting of the article. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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## Supplementary material

**Table S1** Search strategy

1	Acute myeloid leukemia.ti,ab.	60263
2	myelodysplastic syndrome.ti,ab.	23550
3	1 or 2	77788
4	quality adjusted life.ti,ab.	25093
5	qaly\$.ti,ab.	23165
6	qol.ti,ab.	86692
7	quality of life.ti,ab.	564529
8	exp "quality of life"/	579230
9	exp Quality-Adjusted Life Years/	33606
10	Quality adjusted life year\$.ti,ab.	24190
11	Health-related quality of life.ti,ab.	84721
12	hrqol.ti,ab.	31994
13	hrql.ti,ab.	8328
14	health utilit\$ index.ti,ab.	1939
15	HUI.ti,ab.	2335
16	health utilit\$.ti,ab.	4305
17	(hui or hui1 or hui2 or hui3).ti,ab.	3024
18	disutil\$.ti,ab.	970
19	utility.ti,ab.	374317
20	utility analysis.ti,ab.	5699
21	assessment of quality of life.ti,ab.	4109
22	time trade off.ti,ab.	2484
23	TTO.ti,ab.	2226
24	euroqol.ti,ab.	10167
25	(euroqol 5d or EQ-5D or eq-5d or euroqol).ti,ab.	21006
26	eq\$5d.ti,ab.	1648
27	(short form 6d or shortform 6d or sf6d or sf-6d or sf 6d).ti,ab.	1978
28	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27	1123462
29	cost-effectiveness.ti,ab.	128870
30	technology assessment.ti,ab.	11675
31	pharmacoeconomic\$.ti,ab.	10976
32	28 or 29 or 30 or 31	1223333
33	3 and 32	2087
34	limit 33 to human	1860
35	limit 34 to english language	1752
36	limit 35 to yr="2006 -Current"	1398
37	remove duplicates from 36	1033

**Abbreviations:** EQ-5D, EuroQol five-dimensional; HUI, health utility index; TTO, time trade-off.

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