Long-Term Medical Costs and Life Expectancy of Acute Myeloid Leukemia: A Probabilistic Decision Model

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ABSTRACT

Background: Acute myeloid leukemia (AML) can be diagnosed at any age and treatment, which can be given with supportive and/or curative intent, is considered expensive compared with that for other cancers. Despite this, no long-term predictive models have been developed for AML, mainly because of the complexities associated with this disease. Objective: The objective of the current study was to develop a model (based on a UK cohort) to predict cost and life expectancy at a population level. Methods: The model developed in this study combined a decision tree with several Markov models to reflect the complexity of the prognostic factors and treatments of AML. The model was simulated with a cycle length of 1 month for a time period of 5 years and further simulated until age 100 years or death. Results were compared for two age groups and five different initial treatment intents and responses. Transition probabilities, life expectancies, and costs were derived from a UK population-based specialist registry—the Haematological Malignancy Research Network (www.hmrn.org). Results: Overall, expected 5-year medical costs and life expectancy ranged from £8,170 to £81,636 and 3.03 to 34.74 months, respectively. The economic and health outcomes varied with initial treatment intent, age at diagnosis, trial participation, and study time horizon. The model was validated by using face, internal, and external validation methods. The results show that the model captured more than 90% of the empirical costs, and it demonstrated good fit with the empirical overall survival. Conclusions: Costs and life expectancy of AML varied with patient characteristics and initial treatment intent. The robust AML model developed in this study could be used to evaluate new diagnostic tools/treatments, as well as enable policy makers to make informed decisions. Keywords: acute myeloid lymphoma, costs, decision analytic model, life expectancy.

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Introduction

With an annual incidence of approximately 4.0 per 100,000 and a median diagnostic age in the late 60s, acute myeloid leukemia (AML) is a comparatively aggressive cancer that is rapidly fatal if left untreated [1]. There are several different types of AML, with treatment decisions being guided by immunophenotype, cytogenetic, and molecular markers, as well as other prognostic information, including patient’s age and presence of existing comorbidities. Many patients are treated with curative intent, receiving intensive induction chemotherapy followed by consolidation chemotherapy (with or without allograft) and additional chemotherapy if relapse occurs. Others are treated with an approach to care that is nonintensive and also noncurative; in this situation, the focus of care is supportive and palliative, with patients receiving blood transfusions and nonintensive chemotherapy to provide both symptom relief and disease control. The decision to adopt this approach may be taken after intensive induction chemotherapy has been given if there has been no response, or at diagnosis if the patient’s age or comorbidities mean that they would be unlikely to tolerate such intensive treatment. Overall, patient’s age, general fitness, time to remission, and time in remission are considered to be related to prognosis [2–11].

Although AML is not one of the most common cancers, it is often considered to be one of the most expensive to treat, reflecting costly medical interventions (e.g., transplantation), lengthy periods of hospitalization required for the delivery of therapy (curative and supportive), and the treatment of therapy/disease-related complications (e.g., infections) [12,13]. Over the past two decades, however, only a few published studies have attempted to estimate the “long-term economic burden” of treating this complex heterogeneous group of diseases. Furthermore, these studies did not examine cost differences by patient characteristics and/or prognostic factors, and because most of these studies were based on data from a single institution, a clinical trial, or a specific age group, their findings are difficult to extrapolate to the general population [14–20].

With the aim of developing a long-term population-based model for AML, the present study was initiated to predict...
long-term life expectancy and medical costs within a framework reflecting clinical practice, rather than within the predefined and restricted setting of a randomized controlled trial. It was expected that the model could provide an important baseline for evaluating new interventions and diagnostic tools in the future, as well as enable policymakers to make informed decisions. Such predictive models are particularly important for evaluating the cost-effectiveness of new interventions and for allocating health resources efficiently, and as far as we know, no long-term predictive models have previously been developed for AML.

Methods

Study Population

The model was based on data from a specialist UK population-based registry, the Haematological Malignancy Research Network (HMRN; www.HMRN.org), the methods of which have previously been described [21]. Briefly, since September 1, 2004, all patients newly diagnosed with a hematological malignancy (leukemias, lymphomas, and myeloma) in an area with a population of 3.6 million have been prospectively followed. Information is abstracted to clinical trial standards, with details of all treatments, including start dates, end dates, and responses, being accurately recorded. All patients are also linked to data from routine national sources including the National Health Service (NHS) Central Register for death certification and Hospital Episodes Statistics. The HMRN has full ethical approval and Section 251 exemption to collect data for audit and research purposes.

The current study includes all adult (≥18 years) patients newly diagnosed with AML (International Classifications of Diseases for Oncology, 3rd edition: 9861/3, 9895/3, 9920/3, 9897/3) between September 1, 2004, and August 31, 2007, within the HMRN region (N = 352). These patients were followed from the date of diagnosis onwards either to death or to the end of the study period (August 1, 2010); their treatment pathways were individually mapped, and lifetime medical costs were calculated by using a bottom-up costing approach. It is worth noting that in line with national figures, approximately 35% of the patients were enrolled onto one of the national trials open at the time (Medical Research Council 14, 15, 16) [22–24], and the treatment pathways for these patients were mapped according to the chemotherapy they had received. Furthermore, only 50 patients (14.2%) were still alive at the end of the study period (follow-up time range 3–6 years). A more detailed summary of patient characteristics is presented in Table 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2013.12.007.

Overview of Model Structure

The structure of the model was designed to reflect the complexities of treatment strategies, prognosis, and progression of AML based on treatment protocols, relevant literature, and empirical data from HMRN. A decision-analytic model was developed to evaluate the long-term medical costs and life expectancy of AML. This combined a decision tree with eight Markov modes and used a simulated cycle length of 1 month for the time-horizon of 5 years. The model was developed in Microsoft Excel (Microsoft Office Professional Plus 2010 © 2010 Microsoft Corporation).

As shown in Figure 1, the AML model was divided into two parts: a decision tree and a group of Markov models. A hybrid model was selected to capture short-term and long-term effects of both costs and survival [25]. A decision tree structure was used to simulate short-term survival and medical costs until remission was achieved, whereas a number of Markov models were used to simulate long-term and/or postremission outcomes.

Decision Tree

The decision tree structure was built with the following three purposes. First, to allow short-term medical costs and health outcomes to be estimated; second, to allow consideration of prognostic factors (such as age); and third, to allow patients to pass through different treatment pathways and enter different Markov models.

The decision tree structure (Fig. 1) begins with two branches divided according to age (18–59 vs. ≥60 years), with each having a further split categorizing the main initial treatment decision, namely: received or did not receive intensive induction treatment [2,3,10,11]. Within the branches involving the “received induction treatment,” the decision tree is further divided into several branches according to chemotherapy regimens, including cytarabine, daunorubicin, and etoposide (ADE) and daunorubicin and cytarabine (DA). This design was used to allow the model to capture the differences in “costs” and “time to remission/response” between alternative regimens before first remission. It was beyond the scope of the present study, however, to compare the economic impact of different induction regimens.

Time to response is a critical factor that correlates with subsequent outcome, and four types of responses were modeled after each branch of chemotherapy regimens (Fig. 1): early response (achieved remission within 50 days), late response (achieved remission after 50 days), no response (did not achieve remission, including patients who had reinduction but still failed to achieve remission), and early death (died within 3 months from the start of induction treatment) [2,4–8]. This design was important for the purpose of the current work because “time to remission” has a significant impact both on costs and on survival before and after first remission [2,4–8]. Finally, patients classified as “did not receive intensive induction treatment” (i.e., those receiving nonintensive/noncurative treatments only) were assumed to have entered the Markov model directly.

Markov Models

A series of Markov models was developed to estimate long-term medical costs and life expectancy. The rationale behind the development of each Markov model is described below.

Model A and Model B, which could also be considered as “postremission models,” were constructed to simulate outcomes following first remission. Based on disease progression and the response of patients to treatment, Models A and B involve six possible health state scenarios: patients being given intensive treatment with curative intent and achieving remission (First Remission); patients being given treatment and achieving remission followed by relapse of the disease (First Relapse); patients being given second line of treatment and achieving second remission (Second Remission); patients relapsing following their second remission (Second Relapse); patients being given third line of treatment and achieving third remission (Third Remission); patients relapsing and dying (Death). While the structure of Models A and B was the same, the transition probabilities and cost parameters were different. This was because the evidence indicated that patients entering Model A (early response to induction treatment) had different/better prognoses than those entering Model B (late response to induction treatment) [2,3,8,9,26,27]. Although several patients reached a third relapse and/or survived beyond this (based on empirical data), it was decided that third remission would be considered the last health state of AML progression due to limited data. Furthermore, the “tunnel state” structure and an add-on Markov Model E for transplantation were integrated into Model A and Model B (detail nonshown). Model A and Model B were further stratified by age groups, A1 and B1 (18–59 years) and A2 and B2 (≥60 years).

Models C and D simulated patients receiving noncurative treatments. Model C modeled patients who received intensive
induction treatment but failed to respond (i.e., had treatment-resistant disease). Based on empirical data and clinical guidelines [28,29], it was assumed that these patients would subsequently go on to receive nonintensive/noncurative treatment and supportive/palliative care. In contrast, Model D modeled patients who did not receive any induction treatment but solely nonintensive/noncurative and supportive/palliative care. The simulations in both models commenced at the time of diagnosis and continued for 5 years or until death. Both models involved two health states: receiving care and death. This was because the disease (AML) cannot be cured if patients are left untreated or treated with noncurative intent [28,29].

Model E was designed for patients who received bone marrow transplantation and was considered as an add-on Markov model to Models A and B. The rationale behind this was that survival and treatment costs after transplantation differ significantly from those of patients receiving induction and consolidation chemotherapy only. To reflect the actual patient flow, in line with clinical guidelines [28,29], a number of assumptions were made. First, because an individual could receive transplantation at any point in time during remission, it was assumed that for every cycle in remission, there was a likelihood of entering Model E (transplantation model). Second, it was assumed that only those patients who were younger than 60 years were eligible for transplantation. Last, it was assumed that Model E should include the following four health states: transplantation, remission, relapse, and death. Because the probability of relapse decreases the longer a patient remains in remission [2,4–7], all models that contained remission states were further fine-tuned to capture this “time-dependency” feature. Specifically, “tunnel” states were incorporated into all the “remission” states or related states within Models A and B (post-remission models), C and D (noncurative models), and E (transplantation model) [25,30], resulting in 12 tunnels in total. Finally, the time frame for each cycle in all Markov models was fixed and set to a period of 1 month to capture the rapid progression of AML. After each Markov cycle, patients could either move to a different health state or remain in the same health state, with the exception of the tunnel states in which a patient had to exit the current tunnel state, either to enter the next tunnel state or to exit the tunnel.

Model Inputs: Transition Probabilities

To yield a model that reflected the population level, all transition probabilities were derived from empirical HMRN data. Transition probabilities were derived depending on treatments received and outcomes, while the time-dependency transition probabilities were derived from the disease-free survival (DFS) and the time to relapse in remission (TTR) by using the Weibull survival model, defined as follows:

$$S(t) = e^{-\lambda t}$$
Where \( \lambda_i = e^{\beta X_i} \), t is time, \( \lambda_i \) is the scale of the distribution, \( X_i \) is a vector of individual characteristics (age, age-squared, and sex), and \( \beta \) is a coefficient. The detailed calculation processes are described below:

- Probability of staying in remission = DFS = 1 – probability of failure (death, relapse, or transplantation)
- Probability of relapse in remission = TTR
- Probability of receiving transplantation in remission = Time-To-(possible) Transplantation (TTT) in remission
- Probability of death in remission = 1 – DFS – TTR – TTT in remission

Several simplifications, however, were required for certain scenarios. First, when the number of patients was insufficient to estimate the transition probability in a specific health state (such as the small number of patients who achieved a third remission), it was assumed that the transition probability was the same as the previous identical health state (e.g., third remission = second remission). Second, it was assumed that transition probabilities in the remission tunnel states remained constant after 18 months (from cycle 19) because the empirical data suggested that the Kaplan-Meier curve plateaued within 18 months of remission.

The key parameters used in the model are summarized in Tables 1 and 2 and illustrated in Figure 2.

Model Inputs: Medical Costs

The model was built from an NHS perspective, including medical cost only. All cost parameters were calculated by using a bottom-up costing (microcosting) approach within the health care system framework. Unit costs were derived from the British National Formulary, the Personal Social Services Research Unit, and the cost lists of both the NHS Blood and Transplant and Leeds Teaching Hospitals NHS Trust. The NHS Reference Cost 2007 was used only when bottom-up costing was not possible. Therefore, cost parameters used in the current study represent the true costs and include costs for treatments, hospitalizations, diagnostic tests, transfusions, and associated complications. All cost information was further stratified by age group, type of treatment, and health state, so that it could be integrated into the models. For purposes of comparison, all cost results were expressed in 2007 UK sterling. The key cost inputs used in the model are summarized in Tables 1 and 2.

### Outputs

In the model, the health outcome measured was life expectancy, while the economic outcomes were captured by medical costs. Both health and economic outcomes were discounted by using a 3.5% annual discount rate, based on UK guidance recommended by the National Institute for Health and Clinical Excellence [31].

### Assessing Uncertainty

A probabilistic model was implemented to explore the effect of cumulative uncertainty. Each parameter (both transition probabilities and mean costs) was estimated using a distribution that best reflected the available evidence (e.g., Beta, Dirichlet, Gamma, or Normal). The distributions used for the key cost inputs are illustrated in Figure 2.

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**Table 1 – Non-time-dependent transition probabilities and mean costs for individuals during induction (decision tree) conditioned on “received induction treatment” and being aged 18 to 59 years or 60 years or older (in parentheses).**

<table>
<thead>
<tr>
<th>Induction phase (nodes and pathways in the decision tree)</th>
<th>Transition probability</th>
<th>Distribution</th>
<th>Mean costs</th>
<th>£</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>18–59 y</td>
<td>0.2869</td>
<td>Beta</td>
<td>7,843</td>
<td>N/A</td>
<td>Gamma</td>
</tr>
<tr>
<td>Received induction treatment on 18-59 y (≥ 60 y)</td>
<td>0.9307 (0.5060)</td>
<td>Beta</td>
<td>16,623</td>
<td>N/A</td>
<td>Gamma</td>
</tr>
<tr>
<td>ADE</td>
<td>0.2234 (N/A)</td>
<td>Dirichlet</td>
<td>32,953</td>
<td>N/A</td>
<td>Gamma</td>
</tr>
<tr>
<td>DA</td>
<td>0.4681 (0.4567)</td>
<td>Dirichlet</td>
<td>46,426</td>
<td>N/A</td>
<td>Gamma</td>
</tr>
<tr>
<td>FLAG-Ida</td>
<td>0.3085 (0.0866)</td>
<td>Dirichlet</td>
<td>10,856</td>
<td>11,913</td>
<td>Gamma</td>
</tr>
<tr>
<td>DClo</td>
<td>N/A(0.0630)</td>
<td>Dirichlet</td>
<td>15,297</td>
<td>16,145</td>
<td>Gamma</td>
</tr>
<tr>
<td>AraC(LD)</td>
<td>N/A(0.3937)</td>
<td>Dirichlet</td>
<td>37,415</td>
<td>26,686</td>
<td>Gamma</td>
</tr>
<tr>
<td>ADE and early death</td>
<td>0.0476 (N/A)</td>
<td>Dirichlet</td>
<td>44,228</td>
<td>38,369</td>
<td>Gamma</td>
</tr>
<tr>
<td>ADE and late response</td>
<td>0.0952 (N/A)</td>
<td>Dirichlet</td>
<td>15,297</td>
<td>16,145</td>
<td>Gamma</td>
</tr>
<tr>
<td>ADE and no response</td>
<td>0.0476 (N/A)</td>
<td>Dirichlet</td>
<td>37,415</td>
<td>26,686</td>
<td>Gamma</td>
</tr>
<tr>
<td>DA and early death</td>
<td>0.1364 (0.1552)</td>
<td>Dirichlet</td>
<td>17,928</td>
<td>27,825</td>
<td>Gamma</td>
</tr>
<tr>
<td>DA and late response</td>
<td>0.6364 (0.4310)</td>
<td>Dirichlet</td>
<td>10,856</td>
<td>11,913</td>
<td>Gamma</td>
</tr>
<tr>
<td>DA and no response</td>
<td>0.1591 (0.2586)</td>
<td>Dirichlet</td>
<td>15,297</td>
<td>16,145</td>
<td>Gamma</td>
</tr>
<tr>
<td>DClo and early death</td>
<td>0.0682 (0.1552)</td>
<td>Dirichlet</td>
<td>37,415</td>
<td>26,686</td>
<td>Gamma</td>
</tr>
<tr>
<td>DClo and early death</td>
<td>0.0690 (0.1818)</td>
<td>Dirichlet</td>
<td>44,228</td>
<td>38,369</td>
<td>Gamma</td>
</tr>
<tr>
<td>DClo and late response</td>
<td>0.7241 (0.6364)</td>
<td>Dirichlet</td>
<td>17,928</td>
<td>27,825</td>
<td>Gamma</td>
</tr>
<tr>
<td>DClo and no response</td>
<td>0.1724 (0.0909)</td>
<td>Dirichlet</td>
<td>15,297</td>
<td>16,145</td>
<td>Gamma</td>
</tr>
<tr>
<td>ADE and early death</td>
<td>0.7241 (0.6364)</td>
<td>Dirichlet</td>
<td>17,928</td>
<td>27,825</td>
<td>Gamma</td>
</tr>
<tr>
<td>ADE and late response</td>
<td>0.1724 (0.0909)</td>
<td>Dirichlet</td>
<td>15,297</td>
<td>16,145</td>
<td>Gamma</td>
</tr>
<tr>
<td>ADE and no response</td>
<td>0.0476 (N/A)</td>
<td>Dirichlet</td>
<td>37,415</td>
<td>26,686</td>
<td>Gamma</td>
</tr>
<tr>
<td>DClo and early death</td>
<td>N/A(0.1321)</td>
<td>Dirichlet</td>
<td>N/A(27,825)</td>
<td>Gamma</td>
<td></td>
</tr>
<tr>
<td>DClo and late response</td>
<td>N/A(0.0614)</td>
<td>Dirichlet</td>
<td>N/A(37,711)</td>
<td>Gamma</td>
<td></td>
</tr>
<tr>
<td>DClo and no response</td>
<td>N/A(0.3562)</td>
<td>Dirichlet</td>
<td>N/A(56,652)</td>
<td>Gamma</td>
<td></td>
</tr>
<tr>
<td>AraC(LD) and early death</td>
<td>N/A(0.3600)</td>
<td>Dirichlet</td>
<td>N/A(77,953)</td>
<td>Gamma</td>
<td></td>
</tr>
<tr>
<td>AraC(LD) and late response</td>
<td>N/A(0.0800)</td>
<td>Dirichlet</td>
<td>N/A(9,683)</td>
<td>Gamma</td>
<td></td>
</tr>
<tr>
<td>AraC(LD) and no response</td>
<td>N/A(0.1600)</td>
<td>Dirichlet</td>
<td>N/A(14,527)</td>
<td>Gamma</td>
<td></td>
</tr>
<tr>
<td>AraC(LD) and no response</td>
<td>N/A(0.4000)</td>
<td>Dirichlet</td>
<td>N/A(15,674)</td>
<td>Gamma</td>
<td></td>
</tr>
</tbody>
</table>

ADE: cytarabine, daunorubicin, and etoposide; AraC(LD), low-dose cytarabine; DA, daunorubicin and cytarabine; DClo, daunorubicin and clofarabine; FLAG-Ida, fludarabine, cytarabine; G-CSF, (granulocyte colony-stimulating factor), and idarubicin; N/A, not available.
probabilities and cost inputs) was assigned a distribution to reflect sample variability (e.g., beta distributions were used for transition probabilities of binominal events, and gamma distributions were used for medical costs). Then, Monte Carlo simulation was carried out by resampling all distributions simultaneously 500 times. This process was conducted in Excel by using Visual Basic for Applications programming to run the Monte Carlo simulation. All outputs from the iterations were summarized in plots to illustrate the overall uncertainty throughout the current complex model [25].

### Analyses

Cohort life expectancy and costs were derived by model simulation. For comparative purposes, three subgroup analyses were also carried out to investigate the effects of first-line treatment and response, age, and trial participation. In particular, for subgroup analyses of trial and nontrial patients, a subsimulation in the preremission phase and a subanalysis in the postremission phase were conducted to capture differences between these two groups. For exploratory purposes, the model further simulated

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**Table 2 – Non–time-dependent transition probabilities and mean costs for individuals in postremission phases (Markov models) conditioned on being aged 18 to 59 years or 60 years or older (in parentheses).**

<table>
<thead>
<tr>
<th>Postremission phase (transition probabilities in Markov models)</th>
<th>Transition probability</th>
<th>Mean cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Models A1 and A2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First relapse to death</td>
<td>0.2903 (0.8261) Beta</td>
<td>–</td>
</tr>
<tr>
<td>Second relapse to death</td>
<td>0.4286 (0.5000) Beta</td>
<td>–</td>
</tr>
<tr>
<td>Staying in first relapse</td>
<td>0.2963 (0.1739) Beta</td>
<td>7,380 (5,002) 1,589 (885) Gamma</td>
</tr>
<tr>
<td>Staying in second relapse</td>
<td>0.4286 (0.5000) Beta</td>
<td>11,698 (5,002) 5,850 (885) Gamma</td>
</tr>
<tr>
<td>Staying in first remission after month 18</td>
<td>0.9856 (0.9457) Weibull</td>
<td>40 (65) 40 (65) Gamma</td>
</tr>
<tr>
<td>Staying in second remission after month 18</td>
<td>0.9552 (0.4595) Weibull</td>
<td>68 (280) 68 (280) Gamma</td>
</tr>
<tr>
<td>Models B1 and B2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First relapse to death</td>
<td>0.8333 (0.3750) Beta</td>
<td>–</td>
</tr>
<tr>
<td>Second relapse to death</td>
<td>0.8333 (0.9375) Beta</td>
<td>–</td>
</tr>
<tr>
<td>Staying in first relapse</td>
<td>0.1429 (0.3750) Beta</td>
<td>3,450 (2,562) 1,401 (762) Gamma</td>
</tr>
<tr>
<td>Staying in second relapse</td>
<td>0.1667 (0.0625) Beta</td>
<td>3,450 (2,562) 1,401 (762) Gamma</td>
</tr>
<tr>
<td>Staying in first and second remission after month 18</td>
<td>0.9319 (0.957) Weibull</td>
<td>615 (457) 615 (457) Gamma</td>
</tr>
</tbody>
</table>

**Fig. 2 – Time-dependent transition probabilities in the postremission phase (survival curves based on Weibull).**

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life expectancy and costs probabilistically until 100 years of age or death to obtain predictions beyond the 5-year period. The results generated provided a preliminary overview of lifetime medical costs and survival outcomes for treating AML.

The model was validated by means of standard methods, including face, internal, and external validations [32]. Face validation was conducted by consulting clinical experts on the following aspects: model structure, data sources, and results. Internal validation was assessed by comparing predicted costs and survival with empirical estimates obtained from HMRN registry data, and external validation was assessed by comparing predicted results from the model with relevant literature.

**Results**

Based on simulation results of the probabilistic model, the expected 5-year medical cost and life expectancy per patient ranged from £8,170 to £81,636 and 3.03 to 34.74 months, respectively, depending on treatment intent and response (Table 3). This demonstrates the heterogeneity of the AML population. The total economic and health impact of AML across the UK as a whole was also estimated by extrapolation (the expected number of UK AML diagnoses being around 2000 per year), and the results are shown in Table 3.

**Subgroup Analyses**

The effect of initial treatment intent is also demonstrated in Table 3 by breaking down expected medical costs and life expectancy based on initial treatment and response. The expected 5-year medical costs and life expectancy varied widely, from £8,170 (Model D) to £82,281 (Model A) for costs and 0.73 (no response, early death) to 36.81 months (Model A) for life expectancy. The results for Models A and B are, however, relatively similar (£82,281 vs. £79,975 and 36.81 vs. 29.43 months, respectively). A possible explanation for this could be that differences before and after remission even out the overall differences: patients with late response (Model B) take a longer time and incur more costs to achieve remission (£27,367 vs. £17,261), but they have poor prognosis after remission, resulting in shorter survival (26.66 vs. 35.58 months) and less medical costs (£52,609 vs. £65,020) than do patients in Model A.

Figure 3A to D demonstrates the effect of age among the subgroups of different initial treatment intents and responses. As expected, patients younger than 60 years had better survival but incurred more medical costs than did those aged 60 years or older. An exception to this was the subgroup of patients who had no response to induction treatments and died early (Fig. 3C). In this subgroup, expected medical costs and life expectancy were similar between the two age groups, suggesting that the age effect was limited here. It is also worth noting that patients in the same subgroup (Model C and early death) incurred much higher costs but achieved similar survival compared with the subgroup of patients receiving nonintensive/noncurative care (Model D) (Fig. 3C).

Tables 4 and 5 show the trial effect by comparing different features in the phases before and after the first remission. Compared with nontrial patients, trial patients had higher remission rates, shorter time to remission, and significantly higher medical costs in the preremission phase. After achieving remission, the relapse rates were similar in both groups of patients, but the life expectancy was higher among patients younger than 60 years. These results demonstrate that there are significant differences in expected costs and life expectancy between trial and nontrial patients. A detailed comparison, however, could not be carried out because this was outside the
The scope of the current study and the developed model was not designed for this purpose.

**Exploratory Analysis**

To investigate both costs and survival beyond the 5-year time horizon and to test the predictive ability of the model, a lifetime model simulation was conducted probabilistically and is reported in Table 6. Overall, there was no significant difference in expected costs and life expectancy between the 5-year and lifetime horizons. Age at diagnosis, however, played an important role beyond the 5-year time frame. For patients younger than 60 years, life expectancy increased by 69% (from 34.18 to 57.83 months), while the expected medical costs increased by 34% (from £79,483 to £106,814). In contrast, among patients aged 60 years or older, expected medical costs and life expectancy increased only by a small amount beyond the 5-year time frame.

**Model Validation**

Results of the standard model validations are presented below. With respect to face validity, the model structure, data sources, and results were corroborated by clinical experts. For internal validity, the predicted outcomes were compared with empirical estimations derived from HMRN. Results of the survival curves over 5 years are compared in Figure 4. As shown, the model demonstrated good fit with empirical evidence, the predicted survival curve matching the empirical survival curve closely, but dipping slightly beneath it after 20 months, before meeting again at 55 months. With regard to the comparison of medical costs, the 5-years expected cost was £38,720 in the deterministic model and £41,109 in the probabilistic model, the predicted results capturing between 92% and 99% of the empirical estimated cost (£42,307) derived from the study population. Regarding external validity, the cost results predicted by the model were relatively consistent with findings in the relevant literature [19,20]. Overall, the model demonstrated a good capability of predicting both AML medical costs and life expectancy.

**Discussion**

The objective of the current study was to construct an economic baseline model for AML from the UK NHS perspective. This is the first study to develop a model that can simulate and predict life expectancy and long-term medical costs associated with treating patients with AML. Estimations of the 5-year expected medical costs and life expectancy were £41,109 and 16.56 months, respectively. Both expected medical costs and health outcomes varied according to initial treatment intent, age at diagnosis, and trial participation. These results confirmed that AML treatment is resource demanding and that there is considerable variation with respect to patient characteristics, treatments, and prognoses.

In a broader context, the model was found to be reliable, with good predicting ability. More specifically, because the model was predicated on population-based registry data (HMRN), the main treatment pathways and their effects in a real-world clinical setting could be identified and integrated into the model. As a result, the model predictions provide an overview for the general patient population, rather than a restricted trial-based...
perspective. Second, several techniques were incorporated into the model, such as hybrid model structure and tunnel state, allowing key aspects of clinical practice and factors associated with AML prognosis to be properly integrated. Third, results of the subgroup and exploratory analyses conducted in the current study matched initial expectations, implying that the model successfully captured the heterogeneity of AML treatment pathways and disease progression. For instance, the subanalysis results confirmed the effect of initial treatment intent and response, with patients responding to induction treatments (Models A and B) having a longer life expectancy and incurring higher costs than other patient groups (Table 2). The subanalysis results also confirmed the age effect, with patients aged 60 years or older having a lower life expectancy and lower medical costs than patients younger than 60 years (Fig. 3). Finally, internal and external validation of the model demonstrated the reliability and robustness of the results generated by the model. The results were not only close to the empirical data (Fig. 4) but also in line with findings of other relevant studies [19,20].

Although the model appears to be reliable and to reflect the heterogeneity of AML, it is nonetheless subject to some limitations. First, although "minimal residual disease (MRD) level in remission" is an important prognostic factor [2,3,33,34], it was not included in the present model. This was because although MRD results are available for the majority of HMRN patients, they are not universally assessed elsewhere. Incorporation of MRD into the model at this stage would mean that it could not be used in areas where MRD is not routinely assessed. This field can, however, be added at a later date, if appropriate. Second, because of limited data, the third remission was the last health state in the Markov models. This limitation, however, is not likely to undermine the model results because only a small number of patients reached third relapse and beyond. Despite this, the model will be updated with more health states as the overall number of patients, and consequently those with third remission and/or beyond, increases. Third, the cost inputs in the current model were mainly confined to the inpatient and day-case settings due to data constraints. The reliability of cost results, however, was expected to be unaffected because the majority (~85%) of cancer spend is incurred in acute/secondary care setting based on the NHS program budgeting data [35]. Finally, the quality-adjusted life-year (QALY) information was not included in the present model because these data were not collected for patients in our cohort and estimates of relevant preference-based utility information were not available in the existing literature. The introduction of QALY data into the model, however, may have shown a reduction in the quality of life of patients with AML, and because we have not included these, we may have overestimated the effectiveness of some of the health states. Thus, before performing a cost-utility analysis based on this model, QALY data need to be collected. With a view to incorporating this into future models, we are currently undertaking this work by using European Quality of Life - 5 Dimensions questionnaires (EQ-5D) questionnaires.

During the study, three intriguing areas for future research were identified. The first addresses the issue that a large number of patients (especially those aged 60 years or older) tend not to be recruited to clinical trials. Patients outside trials often receive less intensive treatment, such as noncurative care, something that incurs poorer survival and less medical costs compared with trial patients, and this was confirmed by our subgroup analysis (Tables 4 and 5). Taken at face value, this result conflicts with Berman et al.'s study [12], which reported that median costs for nontrial patients were higher than those for trial patients. A possible explanation for this difference is that Berman et al. based their study on data from a single hospital, which excluded patients who were treated with noncurative care at outside institutions; thus, the study did not take into account patients

<table>
<thead>
<tr>
<th>Age group (y)</th>
<th>Cost per month (£)</th>
<th>Time to remission (mo)</th>
<th>Costs (£)</th>
<th>N</th>
<th>CR (%)</th>
<th>Costs (£)</th>
<th>N</th>
<th>CR (%)</th>
<th>Costs (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>97</td>
<td>97</td>
<td>1051</td>
<td>55</td>
<td>2.03</td>
<td>2.03</td>
<td>1051</td>
<td>255</td>
<td>2.03</td>
</tr>
<tr>
<td>16–59</td>
<td>21,371</td>
<td>21,371</td>
<td>1,051</td>
<td>55</td>
<td>2.03</td>
<td>2.03</td>
<td>1051</td>
<td>255</td>
<td>2.03</td>
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<tr>
<td>≥60</td>
<td>47</td>
<td>47</td>
<td>1,035</td>
<td>50</td>
<td>2.03</td>
<td>2.03</td>
<td>1035</td>
<td>250</td>
<td>2.03</td>
</tr>
<tr>
<td>MRC trial (AML, 14, AML, 15, and AML, 16)</td>
<td>2,72 ± 0.44</td>
<td>2,72 ± 0.44</td>
<td>1,813 ± 0.44</td>
<td>863</td>
<td>2.40 ± 0.35</td>
<td>2,72 ± 0.44</td>
<td>1,813 ± 0.44</td>
<td>863</td>
<td>2.40 ± 0.35</td>
</tr>
<tr>
<td>Nontrial</td>
<td>21,371</td>
<td>21,371</td>
<td>1,051</td>
<td>55</td>
<td>2.03</td>
<td>2.03</td>
<td>1051</td>
<td>255</td>
<td>2.03</td>
</tr>
</tbody>
</table>

Table 4: Comparisons in expected medical costs and time to remission in the pretreatment phase among trial and nontrial patients between two age groups (subsimulation with the probabilistic model).
who incurred lower costs because of shorter survival. This, again, demonstrates the importance of population-based data and the need to interpret findings based solely on clinical trials, or from a single institution, with caution because the generalizability of such results to patients with AML as a whole may be inappropriate. Unfortunately, a detailed comparison between trial and nontrial patients could not be carried out in our present study because the model we developed was not designed for this purpose; this is, however, an area that could be explored further in the future. The second area is related to the time horizon. In the current study, a difference between results derived from the 5-year and lifetime horizon simulations was observed, even though most patients with AML would not survive more than 5 years (median survival of 5.2 months). Thus, further explorations of the time horizon effect on expected costs and survival would be an interesting subject for future research. It is worth noting that some parameters of the lifetime model in the current study might need further refinement when more empirical data are observed. This is because only a few cases survived beyond 5 years in our source data, which might have an impact on the accuracy of the model predictions.

Finally, as shown in Table 3 and Figure 3, patients receiving induction treatment with no response had poorer survival and incurred higher costs than did those receiving noncurative treatments (supportive/palliative care) only. If a well-developed prognostic tool/test was available that could predict the likelihood of response before giving induction chemotherapy, it could not only help to prolong the life expectancy of patients but may also have the potential to reduce medical expenses by up to £10,000. In order not to initiate induction treatment, however, the prognostic tool/test would need to have extremely high sensitivity and specificity to enable patients and clinicians to make the decision not to undergo intensive treatment with confidence.

Conclusions

AML life expectancy and costs vary according to patient characteristics and treatment pathways. The population-based model developed in this study, however, demonstrated a good capability of capturing true costs and survival in a real-world clinical setting. Also, it showed a long-term applicability of being able to provide predictions over a 5-year period, and even over the remaining lifetime. We presume that this AML model could be used not only as a baseline for evaluating new diagnostic tools and treatments but also for enabling policymakers to make informed decisions.

Source of financial support: HMRN is funded by Leukaemia & Lymphoma Research. The authors confirm that no additional support was received from any other organization, or activities undertaken that could have influenced the submitted work in any way in the 3 years preceding the study.

Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at http://dx.doi.org/10.1016/j.jval.2013.12.007 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).
REFERENCES