Journal of Pharmacoeconomics and Pharmaceutical Management

Journal homepage: http://jppm.tums.ac.ir

Cost-Effectiveness of the treatment protocols of pediatrics with Acute Lymphoblastic Leukemia (Decision tree modelling)

Hadi Hayati *[1], **Mohammad Ali Ehsani** [2]

1. *Department of Pharmacoeconomics and Management, School of Pharmacy, Lorestan University of Medical Sciences, Khorramabad, Iran* * ***Corresponding Author:*** Hadihayati88@gmail.com
2. *Department. of Pediatric Hematology and Oncology, Bahrami Hospital, Tehran University of Medical Sciences, Tehran, Iran*

Use your device to scan and read the article online

Citation Hayati.H, Ehsani.M. Cost-Effectiveness of the treatment protocols of pediatrics with Acute Lymphoblastic Leukemia, Journal of Pharmacoeconomics and Pharmaceutical Management. 2024; 10(1):1-10; DOI: 10.18502/jppm.v10i1.15397

Running Title Cost-Effectiveness of the treatment protocols

Article Type Research Paper

Article info:

Received: 15.01.2024
Revised: 01.02.2024
Accepted: 18.02.2024

ABSTRACT

Background: Acute lymphoblastic leukemia (ALL) has a high prevalence at an early age and in children, and with regard to the life expectancy index, this disease causes the loss of many years of life in these patients. Two well-known European protocols called the United Kingdom (UK-ALL) and Berlin-Frankfurt-Munster (BFM-ALL) protocols are used to treat the disease in most countries of the world and in Iran, so the objective of this study is the modeling of the treatment process using both protocols to estimate more cost-effectiveness method.

Methods: A decision tree model was applied to depict the real treatment process to calculate costs per quality-adjusted life-year (QALY). Total costs were included in the model.

Results: The cost-effectiveness ratio of UK-ALL is lower than BFM-ALL (1145.52 USD /3.87 QALY for UK-ALL and 1942.35 USD /3.02 QALY for BFM-ALL). Therefore, the UK-ALL is dominant and BFM-ALL is dominated.

Conclusion: The modeling results showed a double difference between the two studied options, so to better cancer management, policymakers, and oncologists should advocate the economic evaluation methods and modeling to select a real option in the treatment of patients to save resources like UK-ALL.

Keywords: Cancer management, Cost, Acute Lymphoblastic Leukemia, Children, Cost-Effectiveness analysis, Decision Tree Modeling, BFM-ALL, UK-ALL, QALY

Introduction

Acute lymphoblastic leukemia (ALL) has a high prevalence at an early age and in children. With regard to the life expectancy index, this disease causes the loss of many years of life in these patients [1, 2]. Hence, in many countries, due to its high cost and complex and prolonged treatment process, important work has been done to treat this disease, so it was converted from an incurable to a chronic disease like other diseases [3-5]. The childhood treatment of ALL usually involves chemotherapy for 2 to 3 years, and generally, therapies have at least three phases [1, 3, 6]; in this regard the cost issue is an essential factor in the application of these therapeutic protocols and significantly long economic reports and studies have been carried out on easts of these disease, which suggests a huge difference in term of cost between treatments protocols of all indifferent countries and expenses rang in different countries are different with specific protocols and varies from $6000 in China to over $16000 in America and Europe [7-9]. Also, the success of therapy in various studies has been evaluated in terms of various clinical indicators. European well-known protocols called the United Kingdom (UK-ALL) and Berlin-Frankfurt-Munster (BFM-ALL) protocols have been repeatedly examined in long-term clinical trial studies, and their effectiveness has been confirmed in different countries [6, 10-17]. Considering that the main goal of this study is something beyond the clinical outcomes of the clinical trials of these protocols, its details will be omitted, and the reader can refer to the references for more information about the protocols. Therefore, also in Iran, these two protocols are used to treat the disease [4, 18-21]; these protocols generally consist of three phases to treatment: 1) Induction of remission, 2) Consolidation/Intensification and Reinduction and 3) Maintenance [4, 6, 14]. There has never been research of this kind for proper policy-making related to modeling the treatment process and the effectiveness and cost of these two protocols. Therefore, it seemed necessary to model the treatment process of this disease in regard to costs and effectiveness in two protocols [22-24].

On the other hand, decision tree analysis is the application of an analytical method of modeling for systematically comparing different decision options. The decision tree graphically shows selections and facilitates the calculation of values needed to compare these choices. It supports selecting the most cost-effective selection [23, 25]. A decision tree is a tool that has been used for years in many fields. This method of analysis assists in making decisions when the decision is not simple, and there is uncertainty about some of the information. So, we used this method to compare these two protocols [22]. So, the objective of this study is to model the treatment process using the protocols of BFM-ALL and UK-ALL-to estimate a more cost-effective method with the aim of optimal allocation of resources and better policy in the field of expensive and complex cancer treatment.

Methods and Patients

This research is a retrospective study for cost-effectiveness modeling. Data were extracted based on hospital information for two protocols, UK-ALL and BFM-ALL, which are performed for children treatment with ALL in the important medical centers in Tehran, the capital of Iran. By initially reviewing the number of people in the research environment and evaluating the criteria for entry and exit of individuals to study to achieve acceptable results, all patients who had proper conditions to enter the study were selected as samples. The perspective of this study has been society; therefore, all costs are recognized, identified, measured, and valued from this perspective. Three data from a community perspective are required to perform modeling methods.

Transition probability

First, data that involves clinical events, these probabilities are used in different branches of the decision tree. All death, relapse, and recovery rates were determined and calculated in each phase by collecting accurate data in accordance with the treatment process and the options ahead (decision tree). Calculated probabilities are mentioned.

Quality adjusted life *years*

Second, data from the effectiveness of treatment in the form of QALY (quality-adjusted life years) were calculated. So, QALY in all phases of treatment protocols are estimated based on quality-of-life models, which are measured by relating the EQ5D questionnaire. Finally, according to the scores of Iran [26-29], the utility states and QALY were calculated at the end of each phase of treatment [4].

Hayati.H, Ehsani.M. Cost-Effectiveness of the treatment protocols of pediatrics with Acute Lymphoblastic Leukemia, Journal of Pharmacoeconomics and Pharmaceutical Management. 2024; 10(1):1-10; DOI: 10.18502/jppm.v10i1.15397

COSTS

Third, in relation to cost data, the total direct cost of patients (clinical and non-clinical), which includes parent-child costs, is estimated based on all inputs used to treat patients and their prices. Comprehensive medical information was available at the selected hospitals, and the accounting records in the hospitals were collected by referring to patients' files.

Hence, a therapeutic process that takes about 4-5 years to complete recovery is called five years. All the above information was adjusted to the year 2022 according to the discount rate and the official inflation rate of Iran. To analyze the information at the final stage, the Treeage 11 software was used.

Model assumptions

- According to clinical evidence, specialist opinion, and resource review, patients who recover five years after starting treatment are considered perfectly improved people (Remission).
- Considering the decrease in relapsed patients during treatment and the insignificant number of them at the end of the treatment or their complete recovery were eliminated from the model to improve the results.
- The quality of all hospital care and care at home is considered to be the same for all patients. Moreover, excess household expenses and care were excluded from the study.

Treatment process

Figure 1 shows that patients are initially in the initial phase (Induction). After the end of this phase, they will enter the next phase (Consolidation). If the treatment process is performed successfully, they will come to the next stage (Maintenance) and recovery (Remission). However, during treatment, there is a possibility of relapse and death in each phase.

Results

As Table 1 shows, patients under treatment with the BFM-ALL protocol have higher average ages and lengths of hospitalization than those in the UK-ALL protocol group.

And in both treatment groups, there were more male children than female patients.

The results of Table 2 show that the direct cost of treatment of hospitalized patients with the BFM-ALL method is more than the UK-ALL, and accordingly, the BFM-ALL cost components are also more than the UK cost components based on dollars.

The comparisons of the percentage share of each cost component of the total costs of each protocol show that hospitalization (bed) costs in the UK-ALL protocol accounted for a larger share of the total costs, although the dollar amount is less than that of the BFM-ALL method. (Table 1 shows the dollars and their shares.)

According to the results in Table 3, after the end of each phase, patients are confronted with a possible death, recurrence, or success in entering the next phase. In each stage, the probability of success is very high, and only a small number of patients encounter failure, but in the final phase, mortality and recurrence rates are higher than in the previous phases.

Also, Table 3 shows the cost and QALY of each phase of the protocols separately. As seen for UKALL, the total cost is lower than BFMALL, and the QALY is higher.

Figure 3 indicates that the QALY score increased during the treatment process in both protocols. At the end of the treatment, the QALY score of the UK -ALL protocol was higher than that of the BFM-ALL.

Table 4 is the dashboard of all the indicators influencing the treatment process, such as costs and quality of life in the different phases of these two protocols. These data can be used in the decision tree modeling of the treatment process.

Figure 4. shows the results of the decision tree analysis. Finally, the cost-effectiveness ratio of UKALL is lower than that of BFMALL, which means less money per QALY is paid for UKALL than BFMALL. (1145.52/3.87=296 UKALL and 1942.35/3.02=643.2). This indicates a double difference in this ratio between these two methods.

As shown in Figure 5, the UK-ALL is completely dominant, and BFM-ALL is dominant.

Based on the high effects of two variables, BFM maintenance cost (BFMMC) and UK maintenance QALY (UKMQ), on the cost-effectiveness ratio, sensitivity analysis was done. Figure 6 shows up to twice the variables must be changed to change the results. The calculations indicate that the rate of complete recovery five years after the start of treatment in UK-ALL is greater than in BFM-ALL. So, the BFM-ALL protocols have a higher overall cost and a lower impact than UK-ALL; in other words,

the UK-ALL is dominant, and BFM-ALL is dominated. The sensitivity analysis shows that the results can be sensitive in the absence of a 50% QALY BFM protocol and don't show any sensitivity in less than this value.

Discussion

This study is the first study available to comprehensively examine and compare the cost and consequences in terms of quality of life and years of life among children with all UK-ALL BFM-ALL; therefore, the final analysis showed that achievement of 5 years' treatment in UK-ALL is greater than BFM-ALL [30]. Given their somewhat equally similar outcomes, they have a great influence on the dominance of this method. Various studies have made acute childhood lymphoblastic leukemia (ALL) one of the most treatable human cancers [31, 32], and this study approves these results. But in this regard, Rae, who examined the utility cost of all children with two BFM and DFCL protocols in Canada and several European countries in terms of quality of life and calculating QALY for five years, showed that the average direct cost of treatment for patients the BFM method is $88480 also in the BFM protocols the QALY score of 5 years the average QALY between 0.7 to 0.8 was obtained [32, 33]. The QALY of this study is similar to other protocols, but it varied in costs relatively [34, 35]. Similar studies among other worlds countries showed that in European countries and the USA, the cost is much higher than the cost of similar protocols in other Asian and American countries [36]. However, based on the demographic characteristics in Table 1, the average age of the children is about nine years. The incidence and prevalence of the disease in hoys is always more than of girls which is similar in other studies [23]. The average length of hospitalization is an important factor influencing the cost of treatment, as this study indicates a significant difference in the cost difference between the two protocols. The results of this study confirm that, as a general principle, the cost of treatment in developing countries differs from developed countries [4, 23, 32]. Maybe the most important reason refers to the health and economic conditions of these countries. In this study, the costs of hospital services, including catering, food, and cleaning, are the least significant factors affecting total costs. In general, research performed in similar studies among other countries showed that in developed countries, the costs are much higher than the cost of similar protocols in other developing countries. But the remarkable point is the dramatic treatment of this disease, which has changed from an incurable disease to a treatable disease in most protocols [9, 10, 24, 32, 34, 37]. Therefore, the debatable issue is choosing the best option among the existing protocols with the best cost-effectiveness, so economic evaluation methods [34], especially the decision tree, can help to choose the best option for treatment.

Conclusion

Because the BFM-ALL protocol has a higher overall cost and a lower impact than the UK-ALL protocol, the UK-ALL is dominant, and the BFM-ALL is dominant. Considering the significant difference between the cost of these two protocols and even assuming that their consequences are constant and insignificant, we could say that the UK-ALL is the better protocol to use, but an ultimate decision is made by the final decision maker and doctors who make a specific decision based on contingency conditions. So, policymakers and oncologists should advocate the economic evaluation methods in the treatment of patients to save resources besides treating patients like UK-ALL.

Limitations of the study

The most important issue in economic evaluation studies is adjusting of money with consideration of time and high inflation rate in developing countries.

Ethical Considerations

Compliance with ethical guidelines

Funding

No funding was received to assist with the preparation of this manuscript.

Authors' contributions

All authors contributed to obtaining final approval.

Conflict of interest

The authors declare that there is no conflict of Interest.

ACKNOWLEDGMENTS

The authors would like to acknowledge consultants working in the Hepatitis Research Center in Lorestan University of medical sciences.

Tables

Table 1: Demographic variables of the groups under study

Variables		BFM-ALL	UK-ALL
number of patients(N)		255	165
age		10.1	9.3
sex	MALE (%)	0.61	0.65
	FEMALE (%)	0.39	0.35
length of stay(Day)		129	91

Table 2: Cost components of hospitalized patients treated with BFM-ALL and UK-ALL protocols

Cost components	COST-BFM (USD)	%	COST-UK (USD)	%
Bed	679.47	0.33	480.52	0.41
Medicine	617.7	0.3	316.44	0.27
Lab & diagnostic tests	308.85	0.15	105.48	0.09
visit	267.67	0.13	140.64	0.12
Medical supplies	185.31	0.09	128.92	0.11
Total	2059	1	1172	1

Table 3: The transition probabilities between the phases of UK -ALL and BFM-ALL

Phase (UK-ALL)	Success probability To next phase (%)			Death& relapse(%	sum
Induction -start of treatment	Consolidation	UK	97.9	2.1	1
		BFM	92.9	7.1	1
Consolidation-end of 1 month	Maintenance	UK	97.3	2.7	1
		BFM	95.4	4.6	1
Maintenance-end of 2.5 years	Remission	UK	94	6	1
		BFM	94.5	5.5	1

Table 4 The cost and QALY of each phase of UK -ALL and BFM-ALL protocols

Phase	Induction	Consolidation	Maintenance	Total
QALY- BFM	0.05	0.12	3.23	3.40
Cost (USD)	733.00	776.24	549.75	2059
Percent	0.356	0.377	0.267	1
QALY- UK	0.04	0.02	4	4.06
Cost (USD)	460.60	275.42	435.98	1172
Percent	0.393	0.235	0.372	1

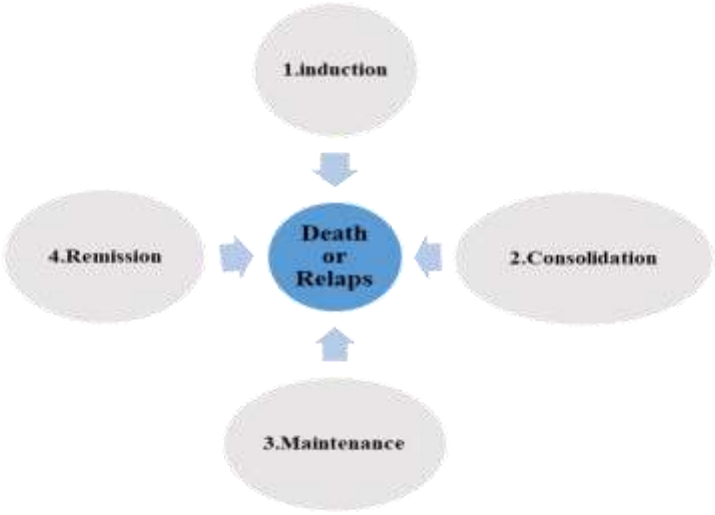

Figure 1. Schematic view of three phases of treatment process

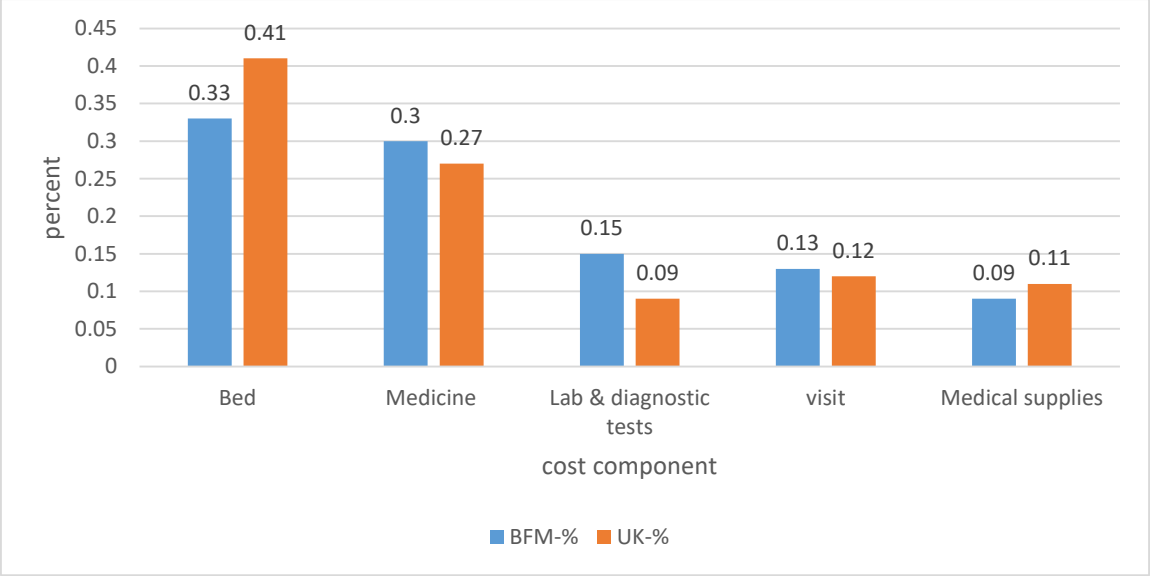

Figure 2. Schematic comparison of cost components of BFM-ALL and UK-ALL protocols

Hayati.H, Ehsani.M. Cost-Effectiveness of the treatment protocols of pediatrics with Acute Lymphoblastic Leukemia, Journal of Pharmacoeconomics and Pharmaceutical Management. 2024; 10(1):1-10; DOI: 10.18502/jppm.v10i1.15397

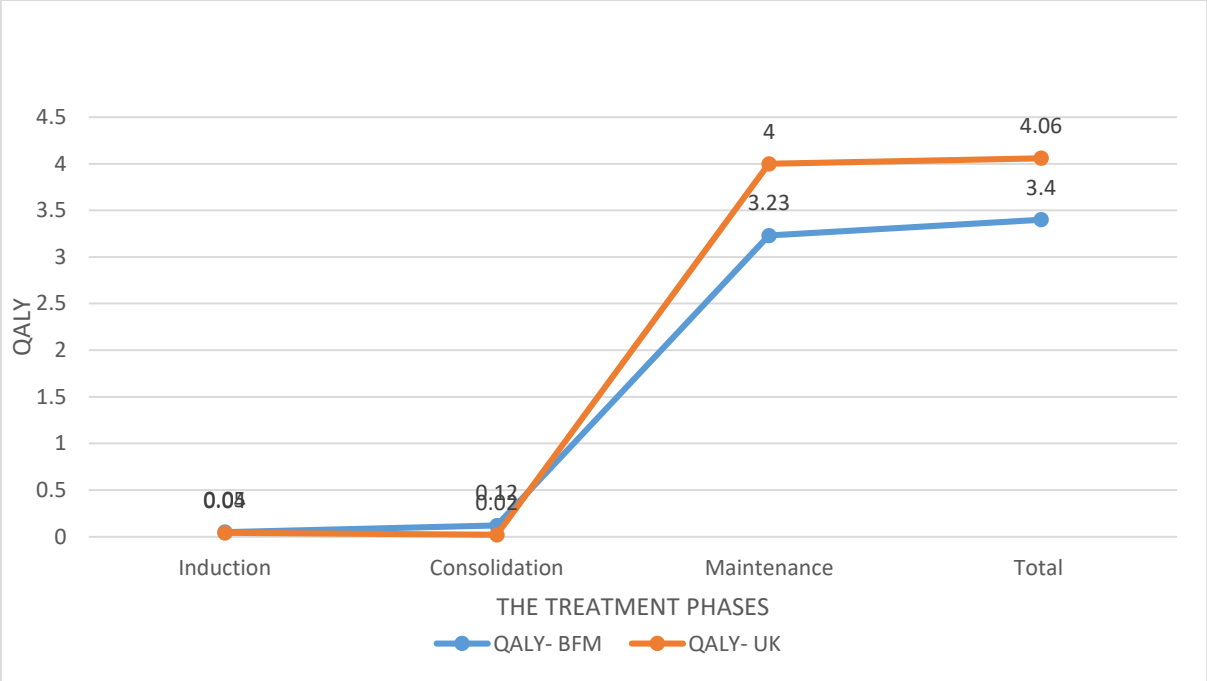

Figure 3. The QALY score at the end of different treatment phases of UK -ALL and BFM-ALL protocols

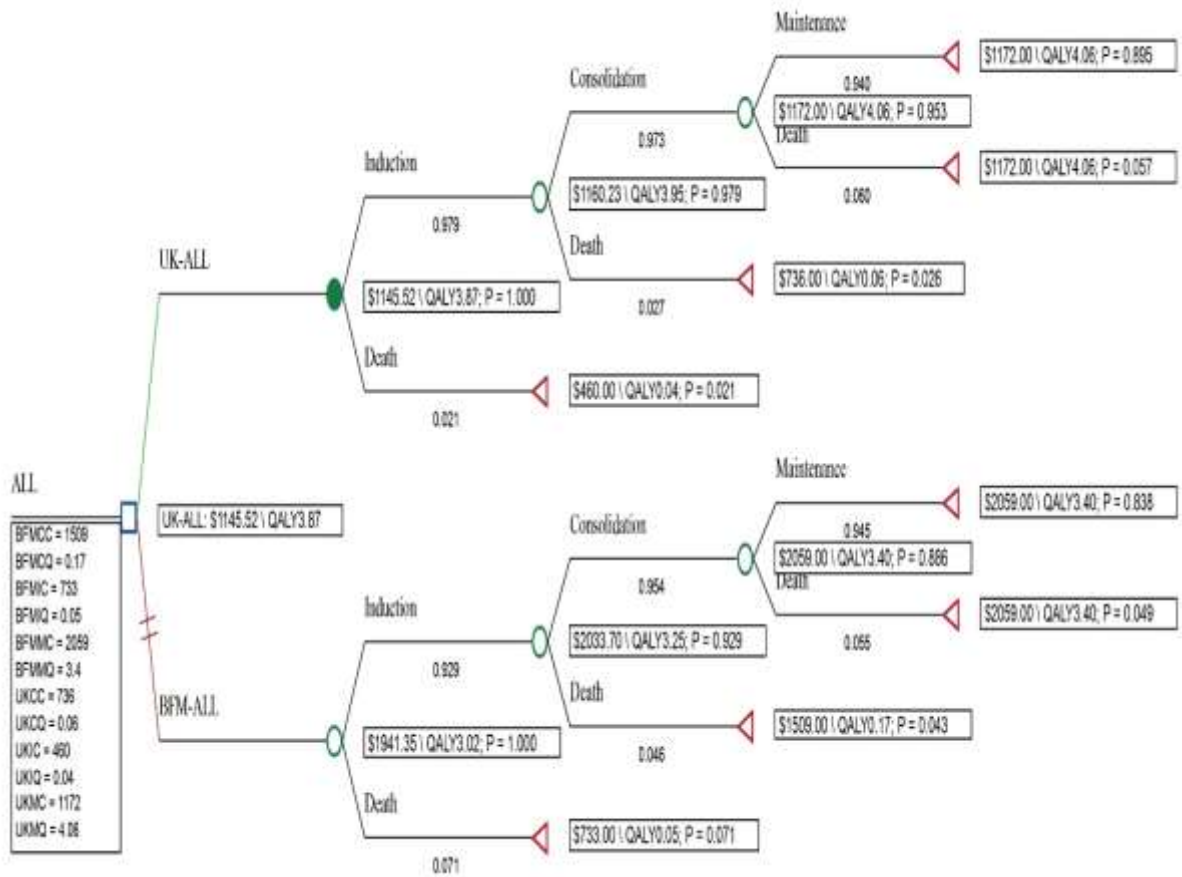

Figure 4. Decision tree modeling of pediatric ALL treatment protocols

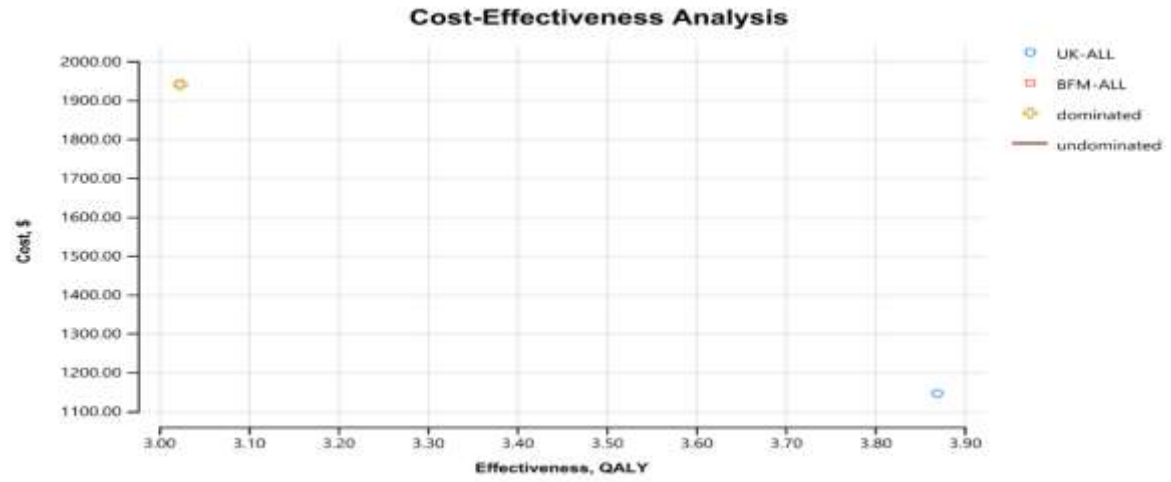

Figure 5. Cost effectiveness analysis of UK-ALL and BFM-ALL

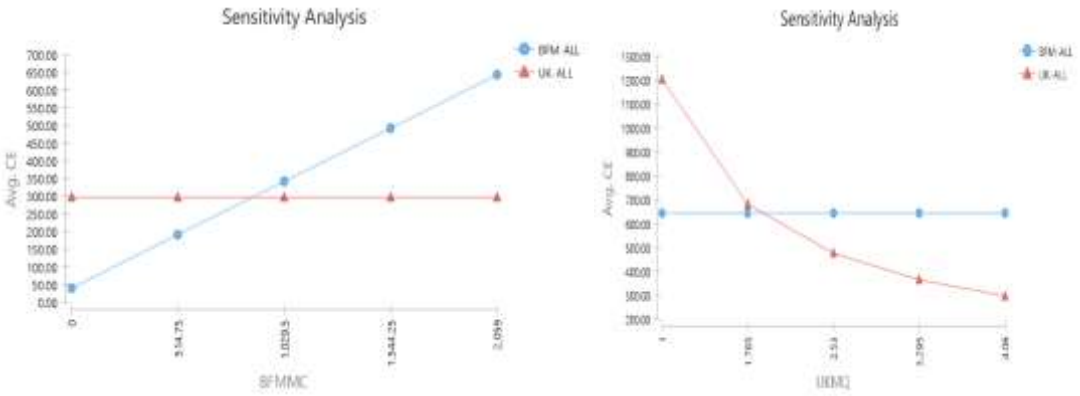

Figure 6. Sensitivity analysis BFM maintenance cost and UK maintenance QALY

Reference

[1] Chen, Si-Liang, et al. 'Toward the Cure of Acute Lymphoblastic Leukemia in Children in China'. JCO Global Oncology, vol. 7, no. 7, American Society of Clinical Oncology (ASCO), July 2021, pp. 1176–1186, https://doi.org10.1200/GO.21.00049.

[2] Hayati, Hadi, Abbas Kebriaeezadeh, Mohammad-Ali Ehsani, et al. 'Cost-Analysis of Treatment of Childhood Acute Lymphoblastic Leukemia Based on UKALL Protocol'. Iranian Journal of Pediatrics, vol. In Press, no. In Press, Briefland, Sept. 2018, https://doi.org10.5812/ijp.7985.

[3] Conter, V., M. Aricò, M. G. Valsecchi, et al. 'Extended Intrathecal Methotrexate May Replace Cranial Irradiation for Prevention of CNS Relapse in Children with Intermediate-Risk Acute Lymphoblastic Leukemia Treated with Berlin-Frankfurt-Münster-Based Intensive Chemotherapy. The Associazione Italiana Di Ematologia Ed Oncologia Pediatrica'. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology, vol. 13, no. 10, American Society of Clinical Oncology (ASCO), Oct. 1995, pp. 2497–2502, https://doi.org10.1200/JCO.1995.13.10.2497.

[4] Hayati, Hadi, Abbas Kebriaeezadeh, Mohammad Ali Ehsani, et al. 'Cost-Utility of Protocols of BFM-ALL and UK-ALL for Treatment of Children with Acute Lymphoblastic Leukemia in Iran'. Iranian Journal of Public Health, vol. 47, no. 3, Mar. 2018, pp. 407–412, https://www.ncbi.nlm.nih.gov/pubmed/29845029.

[5] Hayati, Hadi. 'Comparison of the Unit Cost of Diagnostic Imaging Services before and during the COVID-19 Pandemic Using the Activity-Based Costing (ABC) Method'. Iranian Journal of Radiology: A Quarterly Journal Published by the Iranian Radiological Society, vol. 19, no. 3, Briefland, Oct. 2022, https://doi.org10.5812/iranjradiol-123781.

[6] Schrappe, M. 'A Cost Comparison Analysis of Paediatric Intermediate Care in a Tertiary Hospital and an Intermediate Care Facility in Cape Town'. Plos One, no. 12, South Africa, 2000.

[7] Duncan, Kristal, and Edina Sinanovic. 'A Cost Comparison Analysis of Paediatric Intermediate Care in a Tertiary Hospital and an Intermediate Care Facility in Cape Town, South Africa'. PloS One, vol. 14, no. 4, Public Library of Science (PLoS), Apr. 2019, p. e0214492, https://doi.org10.1371/journal.pone.0214492.

[8] Doshmangir, Leila, et al. 'Correction to: Incidence of Catastrophic Health Expenditure and Its Determinants in Cancer Patients: A Systematic Review and Meta-analysis'. Applied Health Economics and Health Policy, vol. 19, no. 6, Springer Science and Business Media LLC, Nov. 2021, p. 953, https://doi.org10.1007/s40258-021-00686-w.

[9] James, S. L. 'Global, Regional, and National Incidence, Prevalence, and Years Lived with Disability for 354 Diseases and Injuries for 195 Countries and Territories, 1990-2017: A Systematic Analysis for the Global Burden of Disease Study'. The Lancet, vol. 392, 1990, pp. 1789–1858.

[10] ---. 'Prevention of CNS Recurrence in Childhood ALL: Results with Reduced Radiotherapy Combined with CNS-Directed Chemotherapy in Four Consecutive ALL-BFM Trials'. Klinische Padiatrie, vol. 210, no. 4, Georg Thieme Verlag KG, July 1998, pp. 192–199, https://doi.org10.1055/s-2008-1043878.

[11] Conter, V., M. Aricò, G. Basso, et al. 'Long-Term Results of the Italian Association of Pediatric Hematology and Oncology (AIEOP) Studies 82, 87, 88, 91 and 95 for Childhood Acute Lymphoblastic Leukemia'. Leukemia, vol. 24, no. 2, Springer Science and Business Media LLC, Feb. 2010, pp. 255–264, https://doi.org10.1038/leu.2009.250.

[12] Eden, O. B., G. Harrison, et al. 'Long-Term Follow-up of the United Kingdom Medical Research Council Protocols for Childhood Acute Lymphoblastic Leukaemia, 1980–1997'. Leukemia, vol. 14, no. 12, Springer Science and Business Media LLC, Dec. 2000, pp. 2307–2320, https://doi.org10.1038/sj.leu.2401962.

[13] Mitchell, C., et al. 'Long-Term Follow-up of the United Kingdom Medical Research Council Protocols for Childhood Acute Lymphoblastic Leukaemia, 1980-2001'. Leukemia, vol. 24, no. 2, Springer Science and Business Media LLC, Feb. 2010, pp. 406–418, https://doi.org10.1038/leu.2009.256.

[14] Eden, O. B., J. S. Lilleyman, et al. 'Results of Medical Research Council Childhood Leukaemia Trial UKALL VIII (Report to the Medical Research Council on Behalf of the Working Party on Leukaemia in Childhood)'. British Journal of Haematology, vol. 78, no. 2, Wiley, June 1991, pp. 187–196, https://doi.org10.1111/j.1365-2141.1991.tb04415.x.

[15] Shahverdi, E. 'Treatment-Related Complications in Childhood Acute Lymphoblastic Leukemia: Results of Medical Research Council UKALL X'. Middle East Journal of Cancer, vol. 11, no. 2, 2020, pp. 168–173.

[16] Reisi, Nahid, et al. 'The Metabolic Syndrome in Survivors of Childhood Acute Lymphoblastic Leukemia in Isfahan, Iran'. Journal of Research in Medical Sciences: The Official Journal of Isfahan University of Medical Sciences, vol. 14, no. 2, Mar. 2009, pp. 111–116, https://www.ncbi.nlm.nih.gov/pubmed/21772869.

[17] Namazi, Soha, et al. 'Evaluating the Effect of 3 Glucocorticoid Receptor Gene Polymorphisms on Risk of Relapse in 100 Iranian Children with Acute Lymphoblastic Leukemia: A Case-Control Study'. Clinical Therapeutics, vol. 33, no. 3, Elsevier BV, Mar. 2011, pp. 280–290, https://doi.org10.1016/j.clinthera.2011.03.004.

[18] Motaghi, M., et al. 'Comparative Effect of Chamomile Mouthwash and Topical Mouth Rinse in Prevention of Chemotherapy-Induced Oral Mucositis in Iranian Pediatric Patients with Acute Lymphoblastic Leukemia'. Iranian Journal of Blood and Cancer, vol. 9, no. 3, 2017, pp. 84–88.

[19] Myles, Anthony J., et al. 'An Introduction to Decision Tree Modeling'. Journal of Chemometrics, vol. 18, no. 6, Wiley, June 2004, pp. 275–285, https://doi.org10.1002/cem.873.

[20] Liu, Anthony Pak-Yin, et al. 'Treatment Barriers and Clinical Outcome of Children with Medulloblastoma in China: A Report from the Chinese Children's Cancer Group (CCCG)'. Neuro-Oncology Advances, vol. 3, no. 1, Oxford University Press (OUP), Jan. 2021, p. vdab134, https://doi.org10.1093/noajnl/vdab134.

[21] Yang, Wenyu, et al. 'Pulse Therapy with Vincristine and Dexamethasone for Childhood Acute Lymphoblastic Leukaemia (CCCG-ALL-2015): An Open-Label, Multicentre, Randomised, Phase 3, Non-Inferiority Trial'. The Lancet Oncology, vol. 22, no. 9, Elsevier BV, Sept. 2021, pp. 1322–1332, https://doi.org10.1016/S1470-2045(21)00328-4.

[22] Ameri, Hosein, et al. 'Interim Value Set for the EQ-5D-5L in Iran Using the Crosswalk Method'. Medical Journal of the Islamic Republic of Iran, vol. 34, Sept. 2020, p. 121, https://doi.org10.34171/mjiri.34.121.

[23] Goudarzi, Reza, et al. 'Population-Based Preference Weights for the EQ-5D Health States Using the Visual Analogue Scale (VAS) in Iran'. Iranian Red Crescent Medical Journal, vol. 18, no. 2, DoNotEdit,

Feb. 2016, p. e21584, https://doi.org10.5812/ircmj.21584.

[24] Kiadaliri, Aliasghar A. 'A Comparison of Iran and UK EQ-5D-3L Value Sets Based on Visual Analogue Scale'. International Journal of Health Policy and Management, vol. 6, no. 5, Maad Rayan Publishing Company, Sept. 2016, pp. 267–272, https://doi.org10.15171/ijhpm.2016.131.

[25] Bartram, J., et al. 'Improvements in Outcome of Childhood Acute Lymphoblastic Leukaemia (ALL) in the UK-a Success Story of Modern Medicine through Successive UKALL Trials and International Collaboration'. British Journal of Haematology, vol. 191, no. 4, 2020, pp. 562–567.

[26] Pui, Ching-Hon, et al. 'Global Efforts toward the Cure of Childhood Acute Lymphoblastic Leukaemia'. The Lancet. Child & Adolescent Health, vol. 2, no. 6, Elsevier BV, June 2018, pp. 440–454, https://doi.org10.1016/S2352-4642(18)30066-X.

[27] Rae, C., et al. 'Economic Evaluation of Treatment for Acute Lymphoblastic Leukaemia in Childhood'. European Journal of Cancer Care, vol. 23, no. 6, Hindawi Limited, Nov. 2014, pp. 779–785, https://doi.org10.1111/ecc.12173.

[28] Fardell, Joanna E., et al. 'Health-Related Quality of Life of Children on Treatment for Acute Lymphoblastic Leukemia: A Systematic Review'. Pediatric Blood & Cancer, vol. 64, no. 9, Wiley, Sept. 2017, p. e26489, https://doi.org10.1002/pbc.26489.

[29] McGrady, Meghan E., et al. 'Cost-Effectiveness Analysis of an Adherence-Promotion Intervention for Children with Leukemia: A Markov Model-Based Simulation'. Journal of Pediatric Psychology, vol. 43, no. 7, Oxford University Press (OUP), Aug. 2018, pp. 758–768, https://doi.org10.1093/jpepsy/jsy022.

[30] Maser, Brandon, et al. 'Levofloxacin Prophylaxis in Hospitalized Children with Leukemia: A Cost-Utility Analysis'. Pediatric Blood & Cancer, vol. 67, no. 10, Wiley, Oct. 2020, p. e28643, https://doi.org10.1002/pbc.28643.

[31] Gupta, Sumit, et al. 'Health Care Utilisation and Costs Associated with Different Treatment Protocols for Newly Diagnosed Childhood Acute Lymphoblastic Leukaemia: A Population-Based Study in Ontario, Canada'. European Journal of Cancer (Oxford, England: 1990), vol. 151, Elsevier BV, July 2021, pp. 126–135, https://doi.org10.1016/j.ejca.2021.04.006.