

# Quantitative cost-effectiveness index of cancer treatments

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**Abstract.** In spite of advancements being made in technology and treatment strategies, which have markedly improved the survival rate of patients, the cost of cancer care worldwide has increased over the past decades. The presence of several cost-effectiveness ratios has provided significant indexes to assess the balance between cost and effectiveness. However, the currently available indexes still fail to provide a comprehensive and objective evaluation of cancer treatment. Therefore, the present study developed a novel approach, namely a quantitative cost-effectiveness index of cancer treatment, based on the calculation of the hospitalization expense index and efficacy evaluation index. The present study used the data of 16 patients with childhood acute myeloid leukemia who received the high-dose chemotherapy as an example, and the quantitative cost-effectiveness index was used to evaluate the value of this approach. As the increasing prevalence of cancer and the rising cost of pharmaceuticals have contributed to the expenditure, the development of this index may help to solve the current dilemma of cancer treatment and may prove to be essential for the development of an effective approach which may be accessible to and affordable by common persons; thus would then lead to a higher cure rate.

## Introduction

Innovative interventions in cancer treatment may improve the survival rate of patients; however, such improvements may bear a substantial economic cost (1). Thus far, the evaluation of cancer therapeutic efficacy is only dependent on medical indicators (2-5). In some cases, the high-cost treatment may reach the same goal as the low-cost regimen. The assessment of treatment efficacy is mainly based on the opinions of the medical doctors. However, there are numerous subjective and objective factors affecting the judgement of experts; thus,

the current assessment criteria are not comprehensive and objective, and are perhaps against the principles of fairness and impartiality. Therefore, it is necessary to comprehensively and objectively assess the quality of cancer care as the concept of value must be incorporated into cancer care (6).

The present study designed a quantitative cost-effectiveness index (QCEI) of cancer treatments, which may be a more objective and impartial indicator to assess the effectiveness of available options for malignancies.

## Patients and methods

*Hospitalization expense index (HEI).* Though hospitalization expense is frequently discussed by various researchers (7,8), there is no a specific index to assess it. The HEI, a novel economic index which can be used to evaluate the efficacy of malignancy treatment, was calculated as follows:  $HEI = \text{individual expense in the first year} / \text{average expense of all patients in the first year (hospital expense)}$ . As regards the total hospitalization expense index (THEI) of cooperative hospitals, it can be calculated using following formula:  $THEI = \text{individual hospital HEI in the first year} / \text{average hospital HEI in the first year}$ . The larger value of the index indicates a better economic value with a mean value of 1.0.

*Efficacy evaluation index (EEI).* The EEI is an index to evaluate the curative effects on malignancies (9,10) and was calculated using the following formula:  $EEI = (\text{individual survival time within three or five year}) / (\text{average survival time of all patients with the same disease from a center or hospital within three year or five year})$ . As such, the EEI for cooperative hospitals was calculated as follows:  $EEI = (\text{average survival time of patients from a hospital within three year or five year}) / (\text{mean survival time of hospitals within three year or five year})$ . A higher EEI demonstrates a better curative effect with an average value of 1.0. This is the relative ratio, which should also include the number of cases and consider the ratio of the survival to the number of cases. The following example is 4.265:25 of EEI (the international reference value is 3.845: large sample).

EEI is crucial for assessing efficacy when reflecting the basis of medical care. Normally, the ratio of HEI and EEI will be 1/2. For example, in acute myeloid leukemia (AML), when calculating the HEI, refractory secondary AML, mixed AML and tractable subtypes such as M3 AML and myeloid leukemia associated with Down syndrome should be excluded.

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In cases of <20 patients, the HEI and EEI can be calculated regardless of the risk difference of disease. HEI and EEI are relative evaluation indexes (absolute indexes should include other factors).

**Risk distribution.** AML can be simplified into the favorable, intermediate and adverse-risk categories (11,12). The favorable-risk group requires the following conditions: M2 AML patients (age,  $\geq 10$  years) hardly achieving remission after two courses of therapy, with a white blood cell count  $\geq 100 \times 10^9/l$ . The intermediate risk group includes patients achieving remission after two courses of induction therapy. The adverse-risk group includes those achieving remission after one course of induction therapy.

**Innovation, improvement and inheritance.** Innovation herein refers to the development of a new method or regimen. It tends to significantly improve the efficacy of clinical treatment in clinical practice (13). Improvement refers to making changes to existing treatments to improve clinical diagnosis and patient prognosis. Inheritance refers to the application of currently advanced therapeutics and chemotherapeutics to achieve international standards for the treatment.

**Retrospective and prospective studies.** A prospective study usually contains double-blind and placebo-controlled trial with complete record data from no <20 patients who receive the same regimen. Each subtype of AML varies in risk, and high-risk and ultra-high-risk categories are the main targets of researches. In a prospective study on AML, the cases of curable M3 and myeloid leukemia associated with Down syndrome, as well as refractory secondary leukemia (14) including chronic granulocytic leukemia and Langerhans cell histiocytosis (15), juvenile myelomonocytic leukemia (16), and hybrid AML should be excluded.

A retrospective study, also known as a case control study, looks backwards and examines potential factors in relation to an outcome. A prospective study looks for outcomes and usually involves taking a cohort of subjects and examining them over a long period of time (17,18).

**Assessment of innovation under specific conditions.** Some innovative studies are published as retrospective analyses due to various reasons (19). Their findings with statistically reliable data are still considered as innovative or beneficial. If no study has ever reported the finding at home, the study belongs to domestic innovation. If no study has reported the finding worldwide, the outcome should be considered as an international innovation or improvement. During calculation, some patients with recurrence and treatment-related mortality should also be included in the formula.

**Data collection.** The present examined the HEI and EEI of 16 cases of childhood AML who received high-dose chemotherapy (HDCT) with cytarabine (Table I) from January, 2010 to December, 2020 through the Hospital Information Systems of the First Affiliated Hospital of Guangzhou Medical University. All cases were diagnosed as AML according to the 2008 WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues (20). Of note, some cases were included in

a trial of HDCT by Wu *et al.* (21), with an 80% 5-year survival rate. Prior to data collection, written informed consents were obtained from the legal guardians of each participant and approval was obtained from the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (Guangzhou, China).

## Results

**Complete formula of the QCEI.** Based on the sum of HEI (1.2 point) and EEI (1 point), the measurement of the QCEI of cancer treatments takes the following factors into consideration: i) Follow-up duration of  $\geq 18$  months +0.02,  $\geq 3$  years +0.05,  $\geq 5$  years +0.08; ii)  $\geq 20$  cases +0.03; 5-year event-free survival (EFS)  $> 1\%$  +0.03 (75% of international level); 3-year EFS  $> 1\%$  +0.05; iii) prospective innovative study, +1.3; retrospective innovative study, +1.2; iv) prospective study with improvement in treatment +0.8, retrospective study with improvement +0.6; v) prospective study using an inherited regimen +0.4, retrospective study using an inherited regimen +0.2; vi) recurrence:  $\geq 1/10$  -0.01,  $\geq 2/10$  -0.02; vii) mortality rate:  $\geq 1/10$  -0.015. The complete formula is demonstrated in Table II.

The retrospective analysis developed a new treatment for AML with a  $> 5$ -year follow-up and a low rate of recurrence (12.5%) and mortality ( $< 10\%$ ); thus, it obtained a high score of 4.265. Based on the factors in the study, the overall score of all types of studies is demonstrated as follows: i) The total score of a prospective innovative study, 4.345 points; ii) a retrospective innovative study, 4.245; iii) a prospective study making a contribution to treatment, 3.845; iv) a retrospective study promoting developments in treatment, 3.645; v) a prospective study using an advanced approach, 3.215; vi) a retrospective study using a previous approach with a score of 2.2 is also an advanced study, as the average QCEI of studies worldwide is 2.0. The above scores, compared in different ranges, are the highest local level.

## Discussion

The efficacy of the HDCT approach has reached an international leading level. Our study pioneered treatment with chemotherapy alone. As an innovative retrospective study, its score of quantitative cost-effectiveness index was 4.265. The prospective innovative study on childhood AML at the front line has achieved a QCEI score of 3.845.

Of the 16 cases included in the example, there were 4 cases of adverse-risk AML, 9 cases of intermediate-risk AML, and 2 cases of favorable-risk AML (risk ratio, (adverse:intermediate:favorable risk=4:9:2). Among the adverse-risk AML cases, 1 case of M2a AML was generally considered more manageable. The intermediate risk groups included 2 cases of M4a, and 2 cases of M2. The favorable risk group consisted of 2 cases of M6. Therefore, the difference in risk degree among three categories of AML was not noteworthy.

With the measurement of EEI and HEI, the QCEI of cancer treatment may effectively reflect the value of therapies and thereby warrants further investigation and application. However, since this is the first version of the QCEI of cancer

Table I. General information of the 16 patients with pediatric acute myeloid leukemia.

Patient no.	Age (years)	Typing	Risk	Total cost (\$)	First year expense (\$)	Prognosis	Survival time (days)
1	7	M2a	Intermediate	51,600	38,360	Survival	3,260
2	8	M2a	Data loss	35,000	25,710	Survival	3,155
3	12	M4a	Adverse	39,500	27,930	Survival	2,868
4	7	M1	Intermediate	43,500	31,090	Survival	2,591
5	8	M2/M3	Adverse	35,100	35,070	Relapse	392
6	2	M5	Intermediate	32,000	31,970	Relapse	311
7	7	M4a	Intermediate	51,600	44,900	Death	511
8	5	M4a	Intermediate	139,900	88,300	Survival	798
9	4	M2a	Intermediate	60,500	31,050	Survival	746
10	4	M6	Favorable	63,700	40,270	Survival	634
11	3	M6	Favorable	82,700	58,300	Survival	543
12	4	M2a	Intermediate	77,400	55,760	In treatment	395
13	1	M5	Intermediate	64,700	40,580	In treatment	414
14	11	M0	Intermediate	98,600	83,530	In treatment	246
15	11	M4a	Adverse	61,700	61,650	In treatment	253
16	11	M4a	Adverse	74,900	67,050	In treatment	135
Mean value				63,275	47,595		1,078.25

Of note, there were a total of 15 cases of favorable, intermediate, adverse risk. In those with adverse-risk, there were 4 cases of M2a, M2/M3, M4a and M4a; in those with intermediate risk, there were 9 cases of M2a, M1, M2, M5, M0, Ma and Ma; in those with favorable risk, there were 2 cases of M6. One case was lost. In total, 4 cases had an age ≥10 years.

Table II. Formula used for the indexes.

Index	Denominator	Numerator	Formula
Hospitalization expense index (HEI)	Individual hospitalization expense in the first year (individual expense)	Average expense of all patients in the first year (hospital expense)	HEI=individual expense/hospital expense
Efficacy evaluation index (EEI)	Individual survival time within three or five years	Average survival time of all patients	EEI=individual survival time/Average survival time
Quantitative cost-effectiveness index (QCEI)			QCEI=HEI + EEI + score (follow-up) + (degree of innovation) + score (case) + score (EFS)-score (mortality and recurrence rate)

For the measurement of QCEI, apart from HEI and EEI, it was calculated considering factors including follow-up duration, EFS, the type of analysis (retrospective, prospective), the degree of innovation, recurrence rate, mortality rate and risk categories of the disorders. i) Follow-up duration, ≥18 months +0.02; ≥3 years +0.05; ≥5 years, +0.08; ii) ≥20 cases, +0.03; 5-year EFS >1% +0.03 (75% of international level); 3-year EFS >1% +0.05; iii) prospective innovative study +1.3; retrospective innovative study +1.2; iv) prospective study with improvement in treatment +0.8, retrospective study with improvement +0.6; v) [rospective study using an inherited regimen +0.4, retrospective study using an inherited regimen +0.2; vi) recurrence rate: ≥1/10 -0.01, ≥2/10 -0.02; vii) mortality rate: ≥1/10 -0.01. EFS, event-free survival.

treatment, further studies are required. The index potently provides an available method for the assessment of treatments for cancer, which may also contribute to the development of health and medical publishing. Cost-effectiveness analysis (CEA) is used to support health sector decisions about the allocation of limited resources and contribute to policy management and inequality aversion (22). A recent study

performed CEA to assess cost-effectiveness by comparing diagnostic test results, coronary revascularization, incident major adverse cardiovascular event, and costs during 60 days and 2 years (23). Compared with this approach and other CEAs, the QCEI in the present study clearly indicates the effectiveness when tailoring the benefits of treatment and focuses on cancer patients. In this case, QCEI may directly

recommend suitable and economical treatment options to patients and policy makers.

AML is a relatively rare, yet costly type of cancer, currently characterized by high-cost intensive treatments that often require hospitalization. Currently, in the USA, the total mean episode costs are highest in relapsed/refractory (R/R) episodes (\$439,104), followed by hematopoietic stem cell transplantation (\$329,621) and high-intensity chemotherapy (\$198,657) (24,25). Such an economic burden is too heavy for numerous families, particularly those in developing countries (26). The comprehensive evaluation of the treatment efficacy and expense is crucial to therapy treatment. Only when the treatment efficacy is ensured and the treatment costs are reduced, can more AML patients be able to receive first-line treatments (27). Moreover, as cancer survival rates rise, so does the cost of life-saving treatments (28). Over the past two decades, health spending on cancer has increased more rapidly than the increase in cancer incidence (29). There is no single strategy that would be optimal for all patients with a given disease. It is essential to find a strategy to assess the cost and effectiveness of treatments against cancer. In recent years, with regard to cancer, precision medicine is often advocated, combined with gene-targeted therapy and immune-targeted approaches (30). In this manner, health care providers can offer and plan specific care for their patients, based on financial condition, behaviors, habits and genes.

In conclusion, the QCEI of cancer treatment developed in the present study might help policy makers, physicians, and the society to share the decision making for cancer management, contributing to the development of precision medicine as well.

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### Availability of data and material

The datasets generated and/or analyzed during the current study are not publicly available due to the privacy of patients, but are available from the corresponding author on reasonable request.

### Authors' contributions

ZW proposed and created the quantitative cost-effectiveness index of cancer treatment; wrote the draft of the manuscript, and calculated the data of each patient. YY recorded the patient data regarding pediatric acute myeloid leukemia and calculated the cost of treatment for each patient together with ZW. DC supervised the study for years and applied for ethics approval to the hospital, and was also involved in data collection. All authors have read and approved the final manuscript. DC and YY confirm the authenticity of all the raw data.

### Ethics approval and consent to participate

Prior to data collection, written informed consents were obtained from the legal guardians of each participant and approval was obtained from the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (Guangzhou, China).

### Patient consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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