



The Economic Burden of Acute Myeloid Leukemia in Iran

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Abstract

Background: Cancer imposes a significant economic burden on the health system and society. Acute myeloid leukemia (AML) is the third deadliest leukemia and is one of the leading health problems worldwide. The present study aimed to estimate the economic burden of AML in Iran for 2020.

Methods: In this study, we estimated a prevalence-based on the cost-of-illness of the AML in Iran. A societal perspective was considered, in which the direct costs and productivity losses with the adoption of the human capital approach in the AML cases were estimated for 2020. Moreover, in the present study, several resources including national cancer registry reports, hospital records, occupational data, and interviews with experts were cited.

Results: Approximately 98% of patients with AML received induction therapy. The AML economic burden was \$33,243,107.39. Indirect costs accounted for 60% (21,593,764.4\$) of this amount, and direct medical costs and direct non-medical costs make up for 19% (6,359,380.88\$) and 16% (5,289,962.11\$) of this estimated economic burden, respectively

Conclusion: The economic burden of AML in Iran is very remarkable and due to the increasing prevalence of this disease, it is expected to increase gradually. Having insights into the costs associated with the disease provide an excellent opportunity for health policymakers and managers to effectively improve resource allocation.

Keywords: Acute myeloid leukemia; Consolidation therapy; Iran; Economic burden

Introduction

AML is the most common type of acute leukemia in adults, accounting for 15% to 20% of all childhood cancer, and is the leading cause of

death among various types of leukemia worldwide (AML is the third leading cause of leukemia). These characteristics make it one of the



most important health problems in the world (62%). According to the US and European registry system, the age-adjusted incidence rate of AML varies from 4.3 to 5.4 per 100,000 person-year (1-3).

AML is more prevalent in the elderly, and reports indicate that the age-adjusted incidence rate for patients 65 yr and older is 20.1 per 100,000 patients per year, while in younger patients it is 2.0 per 100,000 patients per year. The registry data showed that there was no difference in the prevalence of AML between men and women up to 65 yr of age, while in older patients there was a lower prevalence for women (0.03 v vs. 0.06, $P < .001$) (1-3).

In Iran, AML is the second prevalent type of leukemia, which accounts for 15.66% and 12.24% of total leukemia cases in women and men, respectively (4).

Not only AML affects the patients' health and their quality of life, but it inflicts a huge cost on households and also on the health system. The increasing number of patients seeking expensive drugs and economic challenges are the probable reasons for cost increments. Therefore, it is important for the health care system, the community, patients, and their families to be aware of the costs and economic burden of AML (5).

On the other hand, having the right information about the obvious costs of cancer enables policymakers to allocate the appropriate resources to the health care system, as well as insurance companies to decide on payment methods.

Thus, evaluating the economic burden of the disease provides valuable information for policymakers to develop appropriate health programs for the health sector, manage population health research, and make decisions on human and financial resource management.

This ultimately increases the capacity of the health care system to advance cost-effective policies for prevention, treatment, and rehabilitation (6, 7). Therefore, this study was conducted to estimate the costs of AML based on the prevalence of this disease from a social perspective in Iran for 2020.

Materials and Methods

In estimating the economic burden of diseases, two main methods are used, including "prevalence-based" and "incidence-based". In the incidence-based method, the patient's costs are calculated from the time of diagnosis to a specific time, for example, one year after diagnosis or the final stage of the disease leads to death or recovery. In the prevalence-based approach, the costs of the disease are calculated over a period of time, for example over a one-year period. This procedure is an appropriate method for evaluating the economic burden of disease (8). In the present study, the economic burden of AML in Iran for 2020 is estimated from a social perspective using the prevalence-based method. Cost analysis included direct medical, non-medical, and indirect costs.

Estimating the prevalence of AML in Iran

The Cancer Registration Program in Iran was established in 2003 and its reports have been published annually. Therefore, these national data were used to calculate the incidence and prevalence of AML in Iran. Then, by modifying the incidence and mortality rates from their underestimating data, we estimate the prevalence of AML in Iran based on registry system data using the annual percentage change (APC) and survival rate in 2019. Finally, the AML survival rate was achieved from published reports (9).

Data were collected from inpatients or outpatients at Shariati Hospital, one of the most prestigious medical, research, and educational centers in Tehran, Iran. This center is under the supervision of the Tehran University of Medical Sciences and is the largest referral center for AML patients in Iran. Patient records, demographic and pathological information (for disease staging) were used to extract direct medical costs.

Data on direct non-medical and indirect costs were obtained from telephone interviews with patients or their families. To access patients' records, the necessary authorization was obtained from the Vice-Chancellor of Research and Tech-

nology of Iran University of Medical Sciences. Moreover, the purpose of the study was explained in a telephone interview and the verbal consent of the interviewees was obtained.

Direct medical costs

Therapeutic approaches in AML vary based on patient risk stratification such as patient age, blast percentage, cytogenetic and molecular studies. These treatments include chemotherapy regimens (induction and consolidation steps) and autologous or allogeneic hematopoietic stem cell transplantation (10).

We calculated direct costs for Induction therapy, salvage chemotherapy, consolidation chemotherapy, and hematopoietic stem cell transplantation. Induction therapy has 7+3 chemotherapy protocols. Patients who had no response to the induction protocol or had recurrence after the first remission and also were receiving high-dose chemotherapy (FLANG, FLAG, CLANG, and CLAG protocols) were nominated to receive salvage chemotherapy. Evaluation of response to treatment at +14 and +28 d of the protocol is also done by studying bone marrow and flow cytometry and supportive therapies (11,12).

Consolidation chemotherapy has been dependent on risk stratification after the first remission. The low-risk patients were treated with HIDAC or 5+2 chemotherapy protocols, and moderate or high-risk patients were treated with allogeneic hematopoietic stem cell transplantation (Allo-HSCT). Recent treatment costs included pre-transplant evaluation tests, CT scans, and consultations, cell separation, transplant chemotherapy protocol, and initial supportive care (11,12). Finally, patient records were used to extract the average cost of each diagnostic and therapeutic scale at different stages of the disease.

Direct non-medical costs

Since there were no non-medical cost studies or data from cancer patients such as AML, transportation costs and home care costs were estimated. A questionnaire was used to assess non-medical direct costs, then the information was obtained

through telephone interviews with patients or their families (13).

Indirect costs

Indirect costs of AML include loss of productivity due to disability, job loss, and early death. The indirect costs were calculated by using the human capital approach, assuming that the monetary value of the production loss due to a disability or untimely death of the patient is equal to the patient's wages before disability and death.

To calculate the cost of productivity lost due to disability, the number of days of disability due to AML was extracted by interviewing patients and their families. The average number of the lost days was multiplied by the patient's average daily wage. Different daily wages were used for employed and unemployed patients.

The minimum daily wage approved by the Ministry of Labor Cooperation and Social Welfare of Iran in 2019 was considered for unemployed patients (14). Since usually a family member accompanies the patient at the time of referral. Therefore, these time costs were estimated for a family member as a patient, and assuming that family members are unemployed, the minimum wage rate was considered.

To estimate the cost of productivity lost due to early death in AML, the number of deaths due to AML was calculated and adjusted based on age groups and gender from data obtained from the Ministry of Health. Then, the number of years lost in each age group was provided by subtracting the average age group from the life expectancy rate in 2019, published in WHO database (15). Finally, the years lost in different age groups were calculated by multiplying the number of deaths in the age groups by the corresponding life expectancy. The minimum annual cost and the average annual cost were used for employed and unemployed patients, respectively. Information on the employment rate in each age group based on gender, as well as the average annual wage and the minimum annual wage was obtained from the Ministry of Labor Cooperation and Social Welfare of Iran (14). All costs of this study are based on the Purchasing Power Parity index and have

been converted to US dollars in 2020 (US dollars) (16).

Results

Most of the patients in the present study were men (58.4%) with a mean age of 47.82. The average monthly income was \$89.45(±18) dollar and 94.3% of the patients were insured.

Overall, 98% of patients received induction therapy, which accounted for 39% of direct medical expenses, and 75% of patients with relapse accounted for 31% of direct medical expenses. Although only 36% of patients received consolidation treatment, the cost per patient (\$961.91) was higher than the other components. In addition, the cost of transplantation after salvage therapy had the lowest share of direct medical costs (\$59481414.28) and also the cost per patient (\$358.52) (Table 1).

Table 1: The direct medical costs of AML management in Iran in 2020(\$)

<i>Cost type</i>	<i>Direct medical costs</i>				
	Per patient	Percentage of patient	Number of patients	Total	Percentage of direct medical cost
Induction	908.10	98	2755.76	2502510.24	0.39
Consolidation	961.91	36	1012.32	973770.43	0.15
BMT	358.52	59	1659.08	594814.28	0.09
Relapse	942.35	75	2109	1987430.50	0.31
Salvage	289.16	37	1040.44	300855.43	0.05
Total cost	3460.04			6359380.88	

According to the interview was done by telephone, most of the patients' required home care during or after being discharged from the hospital.

The average home care days were 64 days. In more than 90% of cases, patients care was conducted by a spouse or family member, whereas in less than 10% care was provided by a trained nurse, nurse or practical nurse. Moreover, the average transportation for patients consisted of approximately 21 trips. The average cost of travel per patient was \$ 153.46 and of patient care at

home was \$647.2; for a total of \$3,470,028.51 and \$1,819,933.59 respectively. The direct non-medical fee was \$5,289,962.11.

The average days of disability and absence from work for patients and their companions were 92 and 23 d, respectively. And, the average monthly wage for each employed and unemployed person was \$252.96 and \$151.20, orderly. The average cost of disability and absence from job was \$758.89 per patient. We estimated that the total cost of disability and job absence was approximately \$2,323,779 in 2020 (Table 2).

Table 2: The indirect costs of disability and absence from work due to AML in Iran in 2020(\$)

<i>Status</i>	<i>Mean of missed work days</i>	<i>Mean Cost per patient, \$US</i>	<i>Total cost, \$US</i>
Patients	92	758.89	2134021.17
Accompanies	23	202.95	189758.25
Total	115	961.84	2323779.42

There were 267 deaths due to AML. The mean number of years lost due to early death of AML per patient was 19 years. The highest death rates occurred in the age groups of 65 ± 69 yr and 55 ± 59 yr, respectively. In addition, the highest

mortality rate was calculated for the age group of 50 ± 54 (\$3,998,200.29). The economic burden of AML in Iran in 2020 was \$33,243,107.39 and its main components were indirect costs (Table 3).

Table 3: The indirect costs of AML due to premature mortality in Iran in 2020(\$)

<i>Age group (yr)</i>	<i>Number of death</i>		<i>Number of years lost</i>	<i>mortality cost</i>		<i>Total mortality cost</i>
	Men	Women		Men	Women	
15-19	1	0	116	180238.35	164876.09	345114.44
20-24	2	4	320	442279.19	678307.52	1120586.71
25-29	3	3	288	674982.05	485087.32	1160069.37
30-34	4	2	256	829015.65	289115.60	1118131.25
35-39	7	5	454	1283076.31	634052.21	1917128.52
40-44	4	3	230	632869.09	330424.79	963293.88
45-49	21	10	857	2715660.67	912794.48	3628455.15
50-54	32	12	992	3133487.80	864712.49	3998200.29
55-59	39	10	510	1595359.42	346948.56	1942307.98
60-64	24	18	540	1060412.94	713966.70	1774379.64
65-69	42	21	483	786038.40	516279.35	1302317.75
Total	179	88	5046			19269984.98

Discussion

Our work is the first study that evaluates the economic burden of acute myeloid leukemia (AML) in Iran. AML has a significant economic burden for the Iranian medical system and patients. The economic burden of AML in Iran was \$33,243,107.39, of which 65% was related to indirect costs (\$21,593,764.4) and part of direct medical expenses was 19% (\$6,359,380.88). Although it is difficult to compare total costs of economic burden among studies conducted in other countries due to differences in their study

approaches, estimated costs, different treatment patterns in their countries and health systems, it seems by comparing the AML economic burden among different countries with different health systems, we could provide a better understanding of the economic consequences of health policies and programs.

Although more than 50% of patients (59%) had transplant therapy, the cost of the other two methods (recurrent and consolidated) was higher than that chosen in each case (\$358.52). Almost all patients (98%) are induced with a definitive diagnosis. Therefore, the highest portion of med-

ical direct costs was due to induction treatment (39%). Since after early diagnosis of the disease, patients who receive this kind of treatment, often encountered to a numerous chemical complications of the treatment at the early phases of the treatment. Therefore, it is required to assign many of resources and allocate a high range of costs at the first steps of this treatment course. In addition, 75% of patients developed relapse which its portion out of total direct medical costs was 0.31%. Chemotherapy in treatment of AML patients, has lots of complications which lead to increase in frequency of hospitalization in hospital and as well a remarkable increase in costs (17). The total direct medical costs of the consolidated method were very small (0.15) while 36% of patients used it. This probably came from using fewer surplus treatments & resources or a delay in hospitalization following the induction method, due to the reduction of side effects of this method.

According to studies in the United States and the United Kingdom, the cost of transplantation is higher than other interventions, followed by the cost of induction and then consolidation chemotherapy (18).

The cost of transplant in the United Kingdom and the United States was the highest direct medical cost at \$177,187 (259314.64\$) and 352,682\$ (516153.02\$), respectively in 2019. About 80% of direct medical costs in the UK are set at the cost of transplants, while in Iran due to the acceptance of treatment costs by patients and hidden subsidies for these patients, transplant costs have been lower than in the UK and other countries and the cost is about \$358.52 and \$594814.28 respectively for all patients. And, it costs less because of the reduced risk of recurrence.

In the long run, transplantation costs less because of the reduced risk of recurrence. In the first stage, however, there seem to be more costs and complications (mortality & morbidity) on this method (19).

In our study, the total direct medical cost was 6,359,380.88\$ and the direct medical cost per case was 3,460.04\$. The average direct medical

cost in one study was shown to be 819,247 SEK (145,187.43\$) and the total cost was SEK 225,293 million (39,112,350.98\$) in which the portion of costs of induction therapy and consolidation chemotherapy were predominant. About 45% of patients with induction treatment had an average cost was 379,470 SEK (67,249.89\$) per patient and the total cost of induction treatment for them was 104,354 SEK million (18,116,542.79 \$) (20).

The average cost of treatment for these patients was \$73,451(96,363.22\$) (20), while another study reported the cost of treatment between 1997 and 2007 at \$108,138 (124,024.55\$) (21). Besides, the cost of treating such patients in 2007 was \$5,817(7,213.61\$) in Egypt (22) and \$104,386(129,448.08\$) in the Netherlands (23). Based on the reported results of a study (over a decade), the direct medical costs of medication, chemotherapy, and outpatient care, in general, have gradually increased (24). This increase is attributed to ascending trend of medications' costs, wide use of diagnostic technologies and expensive equipment, and improvement of patients' survival (25).

The total direct medical cost of 237 patients with AML who received chemotherapy and transplant was 24,512\$(25,468.88\$). The portion of the direct medical cost of the economic burden is 19% and the portion of indirect cost is 65% which the part of the cost of productivity lost due to mortality was more than indirect costs (26).

In the United States, the indirect costs accounted for 81% and the direct costs for 19% of the total economic burden (27). In another study conducted in Sweden, the indirect costs of the disease were SEK163(65,048,375.06\$) and the direct costs were SEK 86 million(34,320,001.57\$) (28), and in another study, the total economic burden of AML was SEK460,799 million (79,997,746.14 \$), which means productivity lost due to disability in each case was SEK 2,063,834 million(4,51,348.25\$) and the total was SEK22,330 million (3,876,635.30\$) and the average cost of productivity lost due to mortality was SEK 2,920,219 (506,977.40\$) and the total lost produc-

tivity was SEK 213,176 million (40,885,395.16\$) (19).

Few studies have considered indirect costs, but in these studies, indirect costs were a quarter to a half of the economic burden, and the main economic burden of this disease is due to indirect costs and most of it is due to indirect costs (18). The cost of lost productivity was consistent with the present study.

In a Swedish study, an approximate homogeneity distribution was achieved among direct and indirect costs (27), while in another study, direct costs were three times the indirect costs (29). The progression of the disease and the need for more care increase the costs and intensive care, all increment the cost of hospitalization in these patients.

Due to the differences in health systems, the calculation and comparison of results between countries are not almost easy, and the local conditions of each country and the method of calculation (retrospective and prospective) are very important. Obviously, the development of current treatments and newer technologies and access to more efficient drugs with fewer side effects over time significantly increases the survival rate, life expectancy, and can also reduce the economic burden of the disease.

Limitation

The present study includes some limitations. First of all, medical tariffs in Iran may not reflect the actual cost imposed on the health care system, so our result may demonstrate an underestimation; however, the tariff will be increased to cover the actual cost soon. Second, the human capital method has been used to estimate indirect costs; although this method is still widely used, one of its weaknesses is that it underestimates the value of life in some groups, such as children, women, and retirees.

Another limitation of our study came from the lack of access to appropriate data, and some costs could not be actually estimated; these costs included follow-up costs and costs imposed on patients and their families, such as informal treatment and intangible costs (pain and depression).

Conclusion

The economic burden of AML on the health system is very high and most of it is related to indirect costs. Due to the implementation of health programs and hidden subsidies in the Iranian health sector, most of the direct medical costs in these patients are provided through insurance and the health system. And it creates significant costs for the health system to allocate more resources to these patients. Awareness of these costs, therefore, helps policymakers and programmers to allocate resources much more rationally.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflicts of interest

The authors declare no conflict of interest.

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