http:// ijp.mums.ac.ir
Review Article (Pages: 4033-4041)

Treatment Costs for Pediatrics Acute Lymphoblastic Leukemia; Comparing Clinical Expenditures in Developed and Developing Countries: a Review Article

Hadi Hayati[1], Abbas Kebriaeezadeh[1], *Mohammad ali Ehsani[2], Shekoufeh Nikfar[1], Ali Akbari Sari[3], Mehdi Troski[1], Bereket Molla Tigabu[4]

[1]Department of Pharmacoeconomics and Pharmaceutical Administration, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, IR Iran. [2]Department of Pediatric Hematology and Oncology, Bahrami Hospital, Tehran University of Medical Sciences, Tehran, IR Iran. [3]Department of Health Management and Economics, Tehran University of Medical Sciences, Tehran, IR Iran. [4]International Campus, Department of Pharmacoeconomics and Pharmaceutical Management Haramaya University School Of Pharmacy.

Abstract

Background

Pediatric acute lymphoblastic leukemia (ALL) is the most common, yet curable childhood malignancy within the pediatric cancers; but in most developed and developing countries cost of cancer treatment in children with ALL is high. So, we specified the range of expenses for the treatment of pediatric cancer and compared the results in developed and developing countries**.**

Materials and Methods

To evaluate treatment costs in childhood ALL, a review was taken place through published papers during the years 2000 to 2015. We searched multiple well known databases such as Medline, Scopus, ISI Web of Science and Google Scholar on January 2015 with "cost effectiveness", "cost utility", "cost minimization", "cost analysis", "economic evaluation", "childhood", "acute lymphoblastic leukemia", and "ALL" as our keywords.

Results

Regarding the reviewed evidence the essential result was that the total costs for treatment of pediatrics ALL in developing countries such as Asian countries were considerably lower than the costs reported from high income countries in Europe and North America. So different protocols were performed to treat ALL and this matter was significant due to the different durations of hospitalization.

Conclusion

According to the results, the total costs for treatment of pediatrics ALL in developing countries were considerably lower than the costs reported from high income countries.

Key Words: Acute Lymphocytic Leukemia, Children, Costs, Developed Countries, Developing Countries.

*Please cite this article as: Hayati H, Kebriaeezadeh A, Ehsani MA, Nikfar Sh, Akbari Sari A, Troski M, et al. Systematic Review of Treatment Costs for Pediatrics Acute Lymphoblastic Leukemia (Comparing Clinical Expenditures in Developed and Developing Countries). Int J Pediatr 2016; 4(12): 4033-41. DOI: **10.22038/ijp.2016.7791**

Corresponding Author:

Mohammad ali Ehsani: Department of Pediatric Hematology and Oncology, Bahrami Hospital, Tehran University of Medical Sciences, Tehran, IR Iran. Tel.: 0098-21-73013406.

Email: maehsani@gmail.com

Received date Sep.23, 2016; Accepted date: Oct. 22, 2016

1- INTRODUCTION

Most pediatric cancers live in low and middle-income countries that lack healthcare resources. In these situations, the Allocation of resources for treating pediatric cancer is not acknowledged (1). Today the increased medical expenses are due to both the health care costs and the loss of productivity caused by a low health status (2, 3). Also, modern technologies in the health sector effect on both survival and costs (4). Pediatric acute lymphoblastic leukemia (ALL), is the most common, yet curable childhood malignancy within the pediatric cancers (5, 6). But in most developed and developing countries cost of cancer treatment in children with ALL is high. Also, in developing countries, high expenses of treatment for many patients with ALL lead to unfinished treatment (7-9). The small ALL patients who received treatment have caused the comprehensive cost analysis to remain understudied (10).

Financial burdens on the ALL patients should be supported by providing sufficient evidences. Policymakers and physicians should always appropriate economic data when they are managing ALL (11). Currently, there are no published comprehensive studies to compare the costs of treatment for children with acute lymphoblastic leukemia in developed and developing countries. This is of importance, because a precise comparison of costs on ALL treatment has an impact on the process of treatment by physicians and governmental and non-governmental organizations devising the allotted budget share based on the cost of the health service, especially in developed and developing countries (12, 15). But, a critical evaluation of the costs required to treat these conditions has not been done and the case for their cost analysis has not been made. We specified the range of expenses for the treatment of pediatric cancer and compared the results in developed and developing countries to guide prioritization efforts for ALL in that countries.

2- MATERIALS AND METHODS

2-1. Data sources and searches

To evaluate treatment costs in childhood ALL, a systematic review was taken place through published papers during the years on April 2000 to January 2015. We searched multiple well known databases such as Medline, Scopus, ISI Web of Science and Google Scholar with "cost effectiveness", "cost utility", "cost minimization", "cost analysis", "economic evaluation", "childhood", "acute lymphoblastic leukemia", and "ALL" as our keywords.

2-2. Literature search

Through the database search we identified 408 studies in MEDLINE, 380 studies in Scopus, 119 studies in ISI Web of Science and 881 studies in Google Scholar. After identifying and removing duplicates, the titles and abstracts were intently analyzed. 17 of the studies were identified for full-text analysis. From these, 9 studies were excluded, which ultimately lead to the inclusion of seven studies in this review (**Figure.1**). The features of all the eligible studies show that for the economic component of the review, after reviewing the articles, most were specifically relevant to the cost analysis studies of ALL in children. In addition, other characteristics show that most of the studies have less than one hundred eligible patients with up to 15 years of age. Also, the retrospective method of data collection was used from medical records. Four of the studies were conducted in developing Countries like Iran, China, Bangladesh and Shanghai-China, also other studies were in developed Countries like Netherlands, Finland and Canada. Different protocols

were performed to treat ALL and this matter was significant due to the different durations of hospitalization (**Tables 1, 2**), please see the eand of paper.

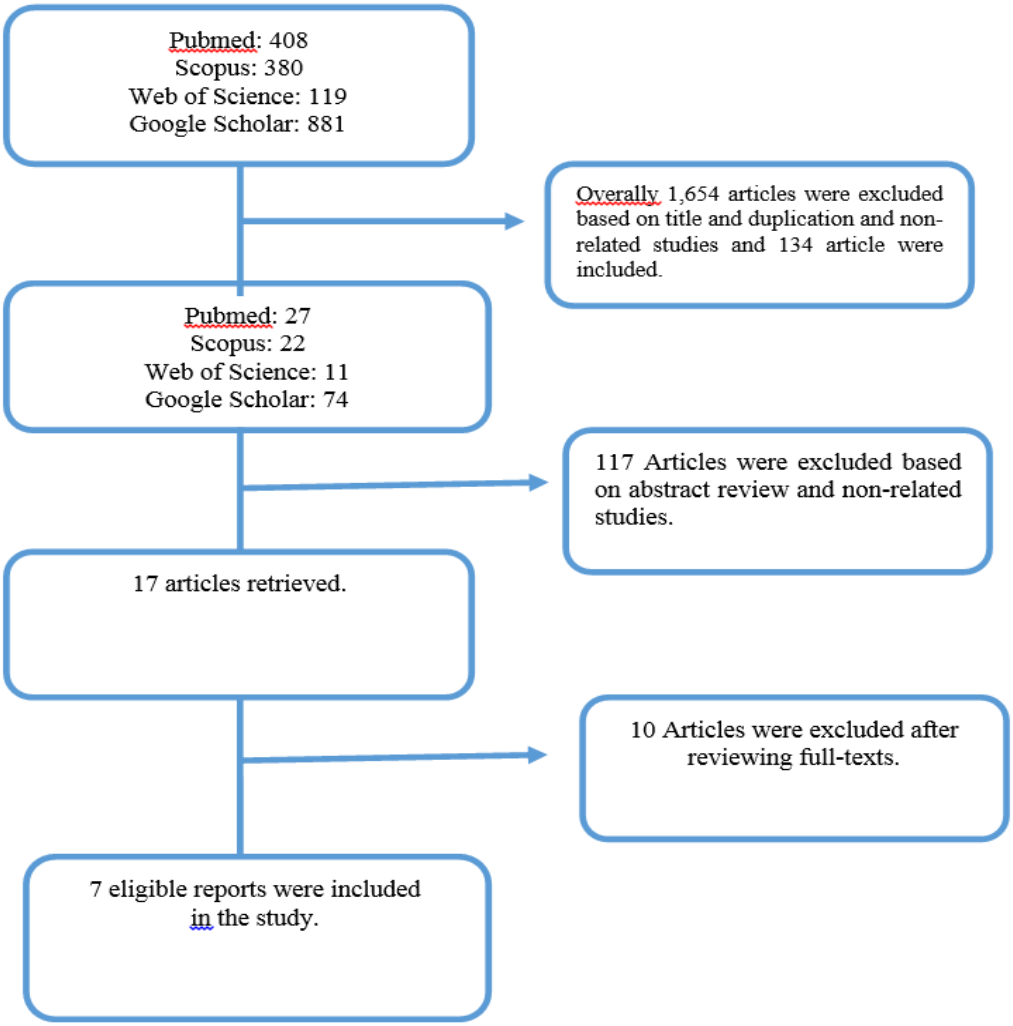

Fig.1: Process of study selection for eligible studies

2-3. Process of study selection

Our inclusion criteria were English language studies on cost of childhood ALL and the exclusion criteria were proceedings, biochemical, pharmacokinetic and non-clinical studies, animal studies and clinical trials.

After eliminating duplicates, the titles and abstracts of the articles were assessed by two of the authors independently in order to rule out irrelevant reports based on the inclusion and exclusion criteria. Through discussion the differences in opinion were resolved and a consensus was reached. After that the full texts of the included articles were double checked and examined by detail to obliterate some other reports regarding the exclusion/inclusion criteria. Also, a data extraction sheet was conducted to standardize the items for extraction.

3- RESULTS

3-1. Results in developed Countries

In most of the studies cost components included general administrative and technical service costs, bed service costs (including food, transport and cleaning), capital costs, also laboratory, radiology and therapy costs (cytostatic drugs, irradiation, operations, procedures, transfusions of red blood cells and platelets, antibiotics, antifungals, antiviral drugs, antiemetics, fluids and total parenteral nutrition).

The mean of the total direct cost per patient ranged from 163,350±38,245 US Dollar (USD) in the Netherlands and 103,250±23,875 USD in Finland (12, 15).
The bulk of the total costs in almost all the studies were associated with hospitalization and drugs it means the factors were main components of entire costs. The least cost in almost all of the studies was associated with blood products, imaging and the operation room. General treatment costs were greatest during the induction phase with a round of 33% to 35% of the total costs in Finland and Netherlands (12, 15).

In Rae' study inpatient stays accounted for the most among all treatment costs for both Berlin-Frankfurt-Munster(BFM) (mean inpatient cost =60,855±11,785 USD) and Dana-Farber Cancer Institute(DFCI) (mean inpatient cost = 59,321±12,896 USD) strategies. Altogether, the mean number of inpatient and outpatient days was 44 and 123, respectively. The analysis of the discounting rates showed difference between strategies in total treatment costs at 0% and 3% (16). In Finland, the majority of the total costs were associated with hospital services. The Finnish study reported a mean number of inpatient and outpatient days of 129 and 39, respectively (12). This matter created in the Fin`s study is probably due to a shift in treatment from inpatient stays to outpatient visits. In the Netherlands study (15), higher costs were related to diagnostic testing (for minimal residual disease), medication [PEG L Asparaginase (pegaspargase)], and more hospital days, that were deflected by longer event-free survival.

3-2. Results in developing countries

The mean of the total direct cost per patient ranged from 6,139±458 USD in Iran to 4,443±896 USD in Bangladesh (13-14). In China the hospitalization cost was the lowest in the Economic Protocol due to less intense chemotherapy, lower incidence of treatment-related complications and a shorter duration of total hospital days. The hospitalization costs were higher on China-98 protocol than on modified protocol, since patients on China-98 protocol had several courses of intensification chemotherapy in hospital during maintenance. This report showedthat hospitalization costs for childhood ALL exceeded 10,000 USD (17). Based on the article's explanation however, in China the fee of blood product transfusion was the highest on modified ALLIC, in which the induction and reinduction chemotherapy were the most intense protocols and resulted with more severe bone marrow suppression, and thus more transfusions of pack red cells and platelets were needed (17).

In the study taken place in Shanghai, the average overall expense of childhood ALL per person was approximately 11,000 USD. In this article all local children in Shanghai can receive support from birth through the government welfare system. In this study, the highest cost was 49,848 USD and the lowest cost was only 5,597 USD. But the medical costs increased sharply once a patient had severe complications. The results show that medicine costs were the main

expenditure for the treatment of childhood ALL. Although, the overall costs decreased because the cost was lower in the clinics rather than the hospital (10). In the study taken place in Iran the average of the direct medical costs per patient were around 3,885 USD for the main protocols in treatment and 2,228 USD for the complementary therapies based on the public medical tariffs. The medication costs were the major cost components of the treatment (365 USD); and the total direct medical costs of ALL based on public medal tariffs were equal to 6,139 USD. Although, considering the hidden subsidy in the public sector, it seems that the figure 17,428 USD is more realistic for costs of managing ALL patients in Iran (14). In Bangladesh the drug costs were the major cost components of the treatment (1,571 USD), and the total cost was 4,443 USD. There are no current provisions of a comprehensive national health insurance scheme for patients in Bangladesh. So their families have to purchase the medicine directly from a pharmacy. According to the information from the health system in Bangladesh every patient studied was admitted to "free beds" (food and bed free of cost). Also, the medical consultations are cost free. Parents did buy all of the needed drugs from outside pharmacies, but blood products were collected from the hospital transfusion medicine department and there is a hospital cost subsidy on these products for all patients (13).

4- DISCUSSION

According to the discussions in the main text of these articles, the incidence of childhood cancer is rising in developing countries (13, 14, 18, 19), along with deaths and high treatment costs and a low income of families. Thus a large number of children living in such low and middle income countries are prohibited from obtaining appropriate and complete treatment. Although the treatment of childhood ALL has improved with a consistent therapy using specified protocols, but after achieving complete recovery, patients require phases of intensive therapy and then an outpatient treatment. Therefore non-compliance with treatment protocols, especially due to the "financial abandonment", is a serious problem (20-22); so, with the consideration of the high costs of treatment in the developed countries, the authors believe that the potentially curative treatment of childhood ALL with a result of a long and relatively good quality of life (23) is not expensive.

The treatment of childhood ALL costs around 100,000 USD per patient based on the results of the studies. Since almost 80% of the childhood ALL are long-term survivors with a good quality of life, the expenses in the terms of gained quality adjusted years are reasonably low, unlike the developing countries. Hisashige showed that the expenses for prevention and treatment of complications were high during the process of treating leukemia, so the overall medical cost of childhood ALL could be reduced to less than 11,000 USD in developing countries such as China. Every pediatric cancer center in developing countries should have data management programs that facilitate careful documentations of medical costs and outcomes; this kind of program would allow doctors to pay more attention to revising treatment costs effectively as well as potentially curing the most possible number of children with cancer chemotherapy at their homes (24, 25).

4-1. Limitation of study

We could not find studies that just about costing in pediatrics ALL, so we considered any economic evaluation in this field to include in this study.

5- CONCLUSIONS

In conclusion the essential result was that the total costs for treatment of pediatrics ALL in developing countries like countries in Asia were considerably lower than the costs reported from high income countries in Europe and North America. Furthermore the most important extra costs in patients with ALL were increased inpatient days and cytostatic drug costs, and also induction therapy accounted for around one third of all costs, so a wide variation can be found in the average cost per patient on each protocol.

The main reason for this is due to the use of different treatments and hospitalization in the health systems of different countries. It seems that the only way to decrease the treatment costs would be to reduce inpatient days by treating patients in the outpatient clinic as much as possible or attempt to reduce hospital costs by administering selected chemotherapy at home. It should be noted that, the cost of ALL treatment is unpredictable because of the individual differences. We could not compare those results together completely because the indications for admission and in-hospital days differ in health systems all over the world.

6- CONFLICT OF INTEREST: None.

7- ACKNOWLEDGMENT

This paper resulted from a Ph.D. thesis of the first author and was supported financially by Faculty of Pharmacy, Tehran University of Medical Sciences. The authors would like to appreciate all who helped conducting this study.

8- REFERENCES

1. Bhakta N, Martiniuk AL, Gupta S, Howard SC. The cost effectiveness of treating paediatric cancer in low-income and middle-income countries: a case-study approach using acute lymphocytic leukaemia in Brazil and Burkitt lymphoma in Malawi. Arch Dis Child 2013; 98(2): 155-60.

2. Kavusi Z, Hatam N, Hayati Abbarik H, Nemati J, Bayati M. Factors Affecting Discharge against Medical Advice in a Teaching Hospital in Shiraz, Iran. Health Information Management 2012; 9(4): 448-456.

3. Kalantari H, Davari M, Akbari M, Hejazi SM, Kalantari M, Zakerin S, et al. The estimation of direct medical costs of treating patients with chronic hepatitis B and C in Iran. Int J Prev Med 2012; 3(3):191–6.

4. Van de Velde AL, Beutels P, Smits EL, Van Tendeloo VF, Nijs G, Anguille S, et al. Medical costs of treatment and survival of patients with acute myeloid leukemia in Belgium. Leukemia Research 2016; 46: 26-9.

5. Schrappe M, Hunger SP, Pui CH, Saha V, Gaynon PS, Baruchel A, et al. Outcomes after induction failure in childhood acutelymphoblastic leukemia. N Engl J Med 2012; 366(15):1371-81.

6. Pui CH, Evans WE. Treatment of acute lymphoblastic leukemia, N. Engl. J. Med 2006; 354: 166–78.

7. Hayati H, Kebriaeezadeh A, Ehsani MA, Nikfar Sh, Mehrvar A. Cost-analysis of Treatment of Pediatrics Acute Lymphoblastic Leukemia based on ALL-BFM Protocol. Int J Pediatr 2016; 4(9): 3381-89. DOI: 10.22038/ijp.2016.7370.

8. Veerman AJ, Kamps WA, van den Berg H, van den Berg E, Bökkerink JP, Bruin MC, et al. Dexamethasone-basedtherapy for childhood acute lymphoblastic leukaemia: Results of the prospectiveDutch Childhood Oncology Group (DCOG) protocol ALL-9(1997–2004). Lancet Oncol 2009; 10:957–66.

9. Tang Y, Xu X, Song H. Long-term outcome of childhood acute lymphoblastic leukemia treated in China. Pediatr Blood Cancer 2008; 513:380–86.

10. Liu Y, Chen J, Tang J, Ni S, Xue H, Pan C. Cost of childhood acute lymphoblastic leukemia care in Shanghai, China. Pediatric Blood and Cancer 2009; 53: 557–62.

11. Pritchard-Jones K, Sullivan R. Children with cancer: driving the globalagenda, Lancet Oncol 2013; 14: 189–91.

12. Rahiala J, Riikonen P, Kekalainen L, Perkio M. Cost analysis of the treatment of acute childhood lymphocytic leukaemia according to Nordic protocols. Acta Paediatrica 2000; 89: 482–87.

13. Islama A, Akhterb T, Eden C. Cost of treatment for children with acute lymphoblastic leukemia in Bangladesh. Journal of Cancer Policy 2015; 6: 37–43.

14. Davari M, Moafi A, Yarmohammadian MH, Khayyam Haghighi E. The Direct Medical Costs of Acute Lymphocytic Leukemia (ALL) In Children in Isfahan Province. Health Inf Manage 2015; 11(7):1046.

15. Raphae¨le RL, van L, Carin A, Uyl-de G, Hein R, Gertjan JLK, et al. Cost-effectiveness of treatment of childhood acute lymphoblastic leukemia with chemotherapy only: the influence of new medication and diagnostic technology. Pediatric Blood and Cancer 2011; 57: 1005–10.

16. Rae C, Furlong W, Jankovic M, Moghrabi A, Naqvi A, Sala A, et al. Economic evaluation of treatment for acute lymphoblastic leukaemia in childhood. European Journal of Cancer Care 2014; 23: 779–85.

17. Luo XQ, Ke ZY, Guan XQ, Zhang YC, Huang LB, Zhu J. The Comparison of Outcome and Cost of Three Protocols for Childhood Non-High Risk Acute Lymphoblastic Leukemia in China. Pediatr Blood Cancer 2008; 51: 204–9.

18. Jemal A, Bray F, Melissa M, Ferlay J, Ward E, Forman D. Global cancer statistics. A Cancer Journal for Clinician 2011; 61(2):269–90

19. You D, New JR, Wardlaw T. Levels and trends in child mortality. Report 2012. Estimates developed by the UN Inter-agency Group for Child Mortality Estimation. New York, NY, United Nations Children's Fund [UNICEF]: 2012; 32.

20. Mostert S, Sitaresmi MN, Gundy CM, Sutaryo S, Veerman AJP. Influence ofsocio-economic status on childhood acute lymphobastic leukemia treatmentin Indonesia, Pediatrics 2006; e1600–e1606. Availasble at: http://dx.doi.org/10.1542/peds.2005-3015.

21. Mostert S, Arora RS, Arreola M, Bagai P, Friedrich P, Gupta S, et al. Abandonment of treatment for childhood cancer: a position statement of a SIOP PODC Working Group, Lancet Oncol 2011; 12(8):719-20.

22. Arora RS, Eden T, Pizer B. The problem of treatment abandonment inchildren from developing countries, Pediatr. Blood Cancer2007; 49: 941–46.

23. Apajasalo M, Sintonen H, Siimes MA, Hovi L, Holmberg C, Boyd H, et al. Health-related quality of life of adults surviving malignancies in childhood. Eur J Cancer 1996; 8: 1354–58.

24. Close P, Burkey E, Kazak A, Danz P, Lange B. A prospective, controlled evaluation of home chemotherapy for children with cancer. Pediatrics 1995; 95: 896–900.

25. Hisashige A. Cost-effectiveness of cancer therapy. Gan-To- Kagaku-Ryoho 2000; 279:1347.

Table-1: General characters of all included eligible studies

Row	Study	Type	Country	Number of patients	Method of cost data collection	Duration of study	Mean duration of hospitalization	Age	Protocol
1	J.Rahiala (2000)	Cost analysis	Finland	11	Questionnaire and retrospective chart reviews	1991 -1994	146 39 d	8.6	(NOPHO)
2	Y. Liu (2009)	Cost analysis	Shanghai	45	Retrospective	2005-2006	75.8_37.9	The median= 5 years (15 months to 14 years)	ALL-2005 protocol
3	C.RAE (2014)	Economic evaluation	Ontario	66 BFM and 28 DFCI	Retrospective from the medical record	1996 -2010	Mean inpatient=44 and outpatient=123	More than 5 years of age	(BFM) and (DFCI)
4	XQ.Luo (2006)	Costing	China	46 = China-98 73 = modified ALLICBFM2002 50 = Economic protocol	Retrospective from the medical record	1999 -2006	------	Children age 1–14 years	*China-98 modified ALLIC BFM2002 Economic protocol
5	Raphaele R.L(2011)	Cost effectiveness	Dutch	26 ALL9 24 ALL10	------	2002 and 2006	ALL10> ALL9 (85 ±36 and 57 ±23,	Up to 18 years of age)	Dutch ALL9 , ALL10
6	M.Davari (2014)	Costing	Iran	106	Retrospective medical records	2007 -2012	------	1-15	UKALL
7	A.Islama (2015)	Costing	Bangladesh	50	Cross-sectional	2010 - 2011	------	Aged 20 months–14 years	Modified UK XI protocol

*Nordic Society of Pediatric Hematology and Oncology; Berlin-Frankfurt-Munster; Dana-Farber Cancer Institute; USD: United States dollar.

Table-2: The investigated factors of all included eligible studies

Row	Study	The most cost components	The least cost components	Total cost per patient US $	Induction cost	Discount rate	Perspective
1	J.Rahiala(2000)	54 974	Cytostatic drugs for 13%, 18 075	103 250	36254 35%	------	Health system
2	Y. Liu (2009)	478.41 Hospital bed/daycare	Blood products 788.7	11,000	2,752	------	Hospital
3	C.RAE (2014)	Hospital services	------	BFM (88 480) DFCI(93 026)	------	5%	Hospital budget . system,
4	XQ.Luo (2006)	Drugs cost China-98 protocol,(46200) modified BFM 2002(23600), Economic Protocol (10300).	Blood products China-98,(5300) modified ALLIC BFM 2002(10000), Economic (10300).	China-98,(93500) modified BFM (74400), Economic (31800).	------	----	Health system
5	Raphaele R.L(2011)	Hospital admissions ALL 9(43.2 %) 50,097 and ALL 10:6,276 - 40.6% overall costs	Imaging ALL 9:1,378(1.2%) ALL 10:1,740(1.1%)	115,858 USD (ALL 9) and 163,350 USD (ALL 10)	For both accounted 33% of total costs	4%	Hospital perspective
6	M.Davari (2014)	Medication (365USD)	OR (5 USD)	6139 USD	------	Inflation rate 41%	Public medical tariffs
7	A.Islama (2015)	(Drugs =1571) 48.6%)	Food and bed free. Blood products 0.6% of all costs.	4443 USD	285 USD to 398 USD		Hospital perspective

OR: Odds ratio; USD: United States dollar.