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The Direct Medical Care Costs Associated with Gastric Cancer in a Third-level Hospital in Iran

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ABSTRACT

Background: Approximately 20 million individuals are afflicted with cancer worldwide. Gastric cancer is the fourth leading cause of death in the world today. The aim of this study was to evaluate the direct medical care costs of gastric cancer patients in a tertiary teaching hospital in Iran.

Methods: The present study is descriptive-analytical, carried out in two main stages. In the first stage we designed a form based on valid international guidelines. The second step identified the costs of diagnosis and treatment of gastric cancer. To analyze the cost data, descriptive statistics such as mean and standard deviation were utilized. We used nonparametric statistical tests such as Mann-Whitney, Wilcoxon in SPSS 16 software for data analysis.

Results: In this study, the records of 449 gastric cancer patients who had referred to Omid tertiary teaching hospital of Mashhad between the years 2005 and 2015 were studied. According to the results, the highest average costs were related to patient hospitalization costs. Based on the significance level of the Mann Whitney test, no remarkable difference could be seen in the total costs of metastatic and non-metastatic patients (P-value: P> 0.05).

Conclusion: Organizations such as: insurance agencies, charities and financial institutions need to adopt new policies to reduce patients' expenditures, remove financial barriers and prevent patients from facing catastrophic costs.

Keywords: Direct Costs, Gastric Cancer, Hospital

INTRODUCTION:

Approximately 20 million individuals are afflicted with cancer worldwide, with this number expected to reach 30 million in 2020. Cancer will be the major cause for mortality and global burden of disease in future decades. In the year 2012, nearly 1 million new cases of cancer and 723000 deaths occurred among men and women across the globe.

Gastric cancer (GC) is the fifth most common cancer (after lung, breast, colorectal and prostate cancers) and the fourth leading cause of death (after lung, breast and liver cancers) in the world[1]. The incidence rate of this cancer varies in different geographic regions. More than 70% of all gastric cancers occur in the developing regions of the world (677,000 new cases and 548,000 deaths), and less than 30% of them are in the developed regions (275,000 new cases and 175,000 deaths). The incidence rate of gastric cancer has the highest outbreak proportion in East Asia and South America, while it has the lowest index in North America, West Africa and Central Asia[1]. Japan, Korea, the regions of China and the Caspian shores are areas with a high incidence rate of gastric cancer[2].

Global variations in the incidence rate of GC and mortality reflect differences in distribution of factors associated with GC in different regions[3]. In addition, the incidence rate of GC in each population is higher among individuals who are poorer and of a lower socioeconomic status[1]. Due to its invasive nature and lack of clinical signs, this disease is usually diagnosed in the advanced stages; therefore, life expectancy is lower for these individuals[2]. The treatment of cancer is not a process that can be ignored, and treatment services for patients are usually invasive, severe and costly. A combination of expensive treatment, decline in quality of life and poor prognosis results in this diagnosis having a remarkably negative effect on the patient. This shortening of life expectancy denies patients of significant years of their life. Moreover, cancer causes loss of income in many communities. This expense is defined as the cost of care of cancer patients and cost related to impact of disease on employment and income generation[4]. Cancer is the third leading cause of death in Iran after cardiovascular diseases, trauma and accidents2. The highest mortality rate due to gastric cancer in Southwest and Central Asia is seen in Iran, which is 19.9 cases per 100,000 cases of death[5]. Unlike in Western countries and Japan, the incidence rate of GC has been increasing in Iran during the past two decades[6].

The treatment of gastric cancer may take place over a short or long period, and its costs may be limited or significant. Owing to individual differences in the stage of diagnosis, various therapeutic methods, demographic characteristics, etc., no two cases are identical; however, similarities exist in average costs[7]. Accurate and reliable information about these costs is important in order to create effective health approaches in an era in which healthcare costs are constantly on the rise, and significant resources are allocated to this sector. In this regard, studies which assess the costs of diseases and produce relevant data for use in decision making are an invaluable resource. As a result, examining the costs of an illness is an important economic tool for policy and decision makers in order to measure economic burden and to identify ways for controlling and reducing these costs. Studies of disease costs require the full support and attention of managers and policy makers due to the extensive amounts of data gathering and analysis that are required, and their high cost of implementation. These studies provide important evidence which is required for evidence-based decision making in the field of resource allocation. Therefore, managers and policy makers of health systems should not just consider these studies as pure descriptive research, but rather as basic economic studies in the field of healthcare[8,9].

The aim of this study was to evaluate the costs of direct medical care which are related to gastric cancer for patients hospitalized in a tertiary teaching hospital in Iran (diagnostic, remedial, caring, rehabilitation and palliative care costs). Direct costs are defined as costs that create an opportunity for the exploitation of resources, and are utilized for the treatment of a specific illness; furthermore, they are the most obvious costs which are created by a disease in a health system.

METHODS:

In this cross-sectional and retrospective study, evaluation of direct cost was done using a prevalence-based epidemiological and bottom-up methodology. The direct costs of 449 patients, who had gastric cancer and referred to a referral tertiary hospital in one of the metropolises in the north-east of Iran, were evaluated. The direct medical costs in this study were defined as diagnostic costs and treatment costs. Intangible and indirect costs were not assessed.

In order to collect data, an interview was conducted with 5 oncologists and radiotherapists who had at least 5 years of experience in the treatment of cancer patients. Based on the results of this interview, important and common clinical guidelines in the field of oncology which are utilized in Iran were identified[10]. Afterwards, services required for the diagnosis and treatment of gastric cancer were extracted using these guidelines under the supervision of an oncologist-radiotherapist. After that, the terminology of these services was assimilated with the service code in the Relative Value of Services book and healthcare of the Islamic Republic of Iran. Following that, the literature of the mentioned services in the clinical guidelines was assimilated with existing modifications in the Tariff Book of Iran.

Finally, a form was prepared containing all the services used for the diagnosis and treatment of gastric cancer. To collect more accurate data, identified services were divided into 10 subgroups. The service subgroups were endoscopy, biopsy, surgery, radiography, CT-Scan, radiotherapy, laboratory tests, chemotherapy, medication and hospitalization. Hospitalization included all expenses related to inpatient visit, specialized counseling, inpatient bed-days and nursing services. The validity of the form, which was provided by a focus group[11], was confirmed by five oncologists, and underwent necessary modifications. The reliability of the form was also evaluated via the parallel method[12] and by utilizing the same forms. To this aim, two oncologists-radiotherapists completed the prepared service form separately. Forms were completed using data records for 10 similar patients. The correlation between the forms was estimated using the Kappa test[13]. Finally, a meeting was held with two specialists to analyze the Kappa statistics; furthermore, the strengths and weakness of the form were identified. Data was collected by two experts in the field of Health Information Technology, who had been trained on how to complete the form by an oncologist-radiotherapist.

All services provided for each gastric cancer patient were entered in the data extraction form (from first admission to the most recent). This data included all the services that the patient had been prescribed or received. Some medications were provided or prepared for the patient outside of the hospital. These services were also entered in the data collection form.

Sample size was calculated using the formula:

$$N = \frac{z^2 P(1-P)}{d^2}$$

(P being the number of services received by each patient (equaling 0.5 in this formula), Z equal 1.96 and d equal 0.05). Sample size was approximately 384. This study was carried out in 2015, but the number of patient records that year were not sufficient for cost estimation. Therefore we began to analyze records from years prior to 2015. The study was completed with patient records from the last ten years (2005-2015). Discounting rate was not utilized for inflation adjustment since econom-

ic fluctuations in Iran are high. Therefore all costs were calculated based on the tariff of one year. To calculate the costs of services a tariff and a common price were utilized. These items were based on the established tariffs of the Supreme Council of Insurance of the Islamic Republic of Iran in 2015. The frequency of services received by each patient was multiplied by its relative value and combined with the basic value of anesthesia (in the case of anesthetic infusion), and then it was multiplied by the tariff of the year 2015 (88,000 Rials or 2.7$). Medication costs were calculated for the year 2015 after extraction of medicinal cost information from the Food and Drug Organization of the Islamic Republic of Iran. In this study, due to limited access to information, the costs of medical commodities were not calculated. Moreover, the costs of hospitalization, including the cost of bed for a normal day, the costs of ICU, and the costs of nursing care services, were calculated using the tariffs for 2015.

In order to identify and interpret cost information more accurately, patients were classified into four groups (1, 2, 3 and 4) based on severity of disease, using the cancer classification system (TNM).

Statistical method:

Descriptive statistics (frequency, percentage, mean, median, standard deviation and 90th percentile) and non-parametric tests including Mann–Whitney or Kruskal–Wallis test were used for data analysis. All statistical analyses were 2-sided and performed using PASW Statistics version 16.0 (SPSS Inc., Chicago IL) at $p<0.05$ significant level.

RESULTS:

In this research, 449 gastric cancer patients who referred to Omid tertiary teaching Hospital in Mashhad between 2005 and 2015 were studied. The results

Table 1. Demographic characteristics of the study population

Variable		Frequency (%)
Sex	Male	342(76.2)
	Female	107(23.8)
Age	26-35	11(2.4)
	36-45	29(6.5)
	46-55	78(17.4)
	56-65	114(25.4)
	66-75	132(29.4)
	76-85	73(16.3)
	86-95	8(1.8)
Background disease	No	376(83.7)
	Yes	73(16.3)
Stage of disease	Stage I	14(3.1)
	Stage II	109(24.3)
	Stage III	80(17.8)
	Stage IV	117(26.1)
	Uncertain	129(28)
Type of disease	Metastatic	117(26)
	Non-metastatic	332(74)

Table 2. Average costs for diagnosis and treatment of the gastric cancer

Type of cost	Percent per total cost (%)	Cost	
		Mean	SD
Endoscopy	3.66%	1754512/249	1409020/162
Biopsy	0.06%	28810/690	317421/225
Surgery	7.38%	3541167/038	4598996/175
Radiography	3.28%	1572769/710	1973025/302
CT-scan	1.10%	528970/156	1642553/314
Radiotherapy	2.47%	1186334/076	1288054/501
Laboratory	13.58%	6510279/198	3725889/089
Chemotherapy	1.69%	812755/457	1584013/579
Medication	23.26%	11155486/414	19648734/589
Hospitalization	43.51%	20865960/802	18213205/474
Total	100%	47957045/791	36628581/402

showed that more than three quarters of patients were male (76.2%) and between 66-75 (29.4%) years old. Most of them had no underlying disease (83.7%), and they had referred to the hospital at an uncertain stage of their illness (28%). Patients were divided into two groups: those with metastases (117 individuals) and without metastases (332 individuals) based on medical records. **Table 1** (see page 48) shows the demographic characteristics of the study population based on stage of disease.

Table 2 shows that hospitalization, medication, laboratory and surgery costs (including surgeon fees, anesthesia fees and operating room costs) incurred the greatest average cost for the patient. In addition, the maximum value of standard deviation (SD) was related to medication, hospitalization, surgery and laboratory costs, respectively. Also **chart 1** shows Percentage of costs of various services for metastatic and non-meta-

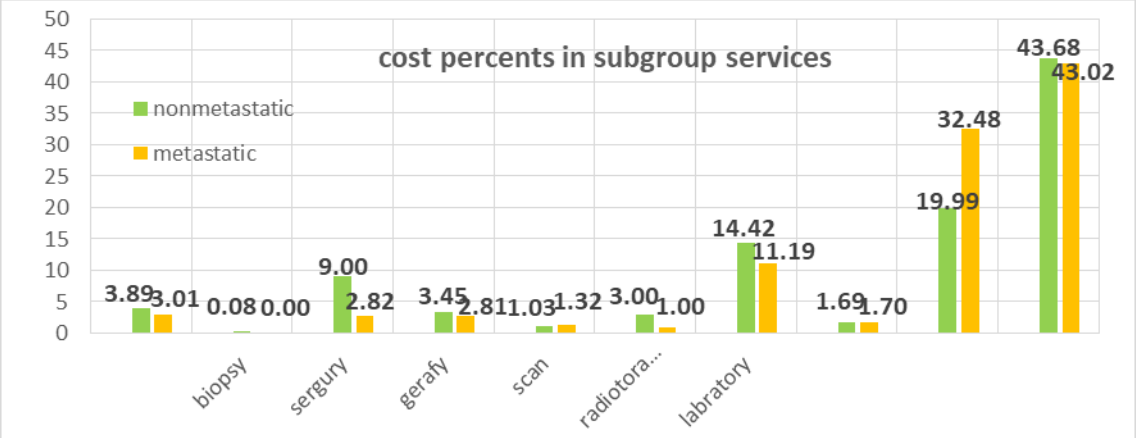

Chart 1. Percentage of costs of various services for inpatients

static inpatients.

The Q_Q chart was designed to determine the normality of patient total cost distribution. As shown in **Chart 2**, the observations deviate significantly from the straight line, indicating that the observations do not have a normal distribution. (p-value<0.05)

The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to confirm the observed results of the chart. According to **Table 3**, which shows the result of the Kolmogorov-Smirnov and Shapiro-Wilk tests, and considering a signification level of 0.05, the assumption that the observations are normal is not confirmed.

Since it appears that the total costs of patients do not follow a normal distribution, the Mann Whitney test was utilized to evaluate a possible difference in total costs among metastatic and non-metastatic patients. As shown in **Table 4**, the costs of endoscopy, surgery, radiotherapy and diagnostic tests are significantly different for metastatic and non-metastatic patients (p<0.05). However, in other cost groups, which include biopsy, grafting, scanning, chemotherapy, and medication, there is no significant difference between metastatic and non-metastatic patients. Based on the significance level of the test, no remarkable difference can be seen

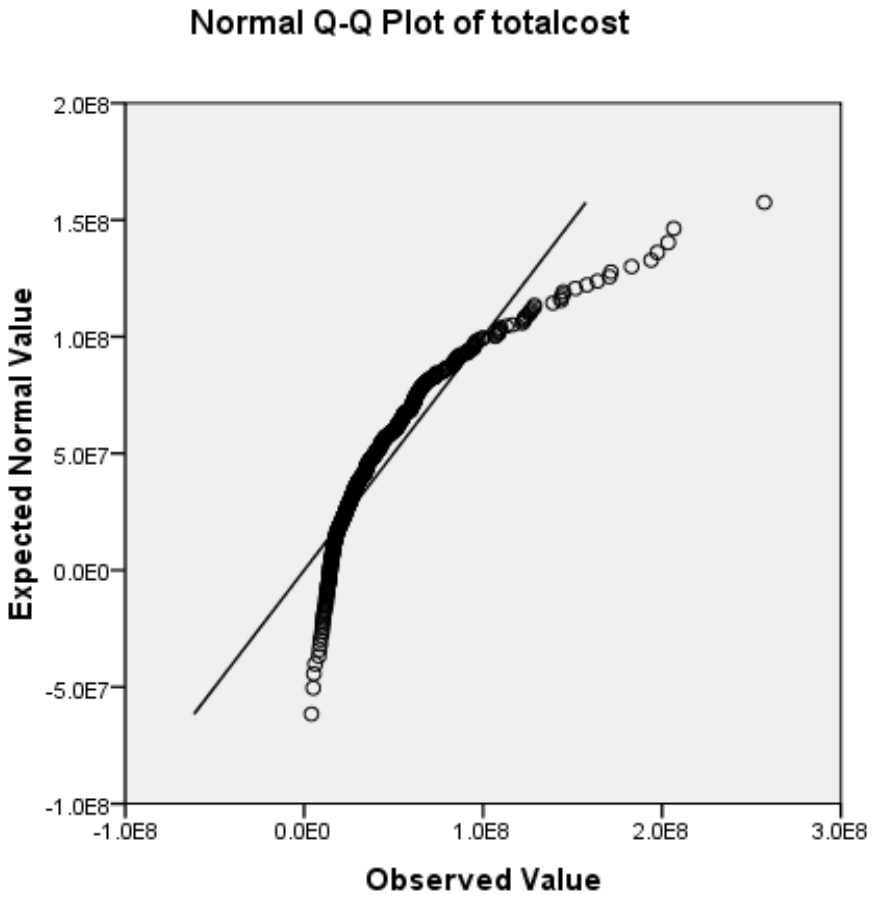

Chart 2. Normality of total costs

Table 3. The results of Kolmogorov-Smirnov and Shapiro-Wilk tests

	Kolmogorov-Smirnova			Shapiro-Wilk		
	Statistic	Df	Sig.	Statistic	Df	Sig.
Total Cost	.130	449	.000	.827	449	.000

in the total costs of metastatic and non-metastatic patients. ($p<0.05$)

Regarding the normalization test and the observation that total costs were not distributed normally, the Spearman correlation test was harnessed to measure the correlation between total costs and treatment period (meaning the period of time between the patient's first and last doctor's visit in the hospital), total costs and hospitalization period, and total costs and patient age. As shown in **Table 5** (see page 52), a significant positive correlation exists between total costs and treatment period. Nevertheless, there is a significant negative correlation between patient age and total costs. In addition, there is a significant negative relationship between treatment period and patient age.

DISCUSSION:

This study aimed to identify and determine the direct medical costs related to gastric cancer, in one of the biggest referral tertiary hospitals in the North-East of Iran. The results of the current study show that most patients with gastric cancer who referred to this hospital were men. Moreover, the average age of patients was 63. Based on the results, the highest average cost was related to hospitalization, medication, and diagnostic tests, respectively. The high value of diagnostic test costs can be explained by the nature of the disease and the necessity of timely diagnosis of disease in order to designate the stage of treatment required by the patient. Furthermore, higher average costs of hospitalization among patients can be attributed to dif-

Table 4. Total cost difference between metastatic and non-metastatic patients by using Mann Whitney test

Cost of service group	Mann-Whitney U	Wilcoxon W	Z	Asymp. Sig. (2-tailed)
Endoscopy	16047	22950	-3/14	0/002
Biopsy	19129/5	26032/5	-1/333	0/182
Surgery	13004	19907	-6/238	0
Radiography	18417/5	25320/5	-0/855	0/392
CT-Scan	19035/5	74313/5	-0/402	0/688
Radiotherapy	11051	17954	-7/414	0
Laboratory	13371	20274	-5/013	0
Chemotherapy	18582/5	73860/5	-0/697	0/486
Medication	16318/5	71596/5	-2/58	0/01
hospitalization	18335	25238	-0/901	0/367
Total	17500	24410	-1/589	0/112

Table 5. Correlation between costs with duration of treatment and duration of hospitalization

			Total cost	Duration of treatment	Age
Spearman's rho	Total cost	Correlation Coefficient	1.000	.659**	-.215**
		Sig. (2-tailed)	.	.000	.000
		N	449	449	445
	Duration of treatment	Correlation Coefficient	.659**	1.000	-.174**
		Sig. (2-tailed)	.000	.	.000
		N	449	449	445
	Age	Correlation Coefficient	-.215**	-.174**	1.000
		Sig. (2-tailed)	.000	.000	.
		N	445	445	445

ficulties in diagnosis of gastric cancer in the early stages, referral of patients in the later stages of the illness and requirement for more hospitalization services. The cost of medication, hospitalization and surgery had the highest standard deviation, respectively, which indicates the different expenses among patients. In fact, this diffusion shows a large difference in the rate of services that patients had received.

According to the results, total costs do not have a normal distribution, and these costs did not differ significantly between metastatic and non-metastatic patients (p-value<0.05). However, a significant difference existed in the costs of endoscopic, surgical, radiotherapy and laboratory services (p-value<0.05). In addition, there was a significant positive correlation between total costs and treatment period and hospitalization cost. We can conclude that trying to expedite services or reduce their unnecessary use is a valuable step in decreasing hospitalization and total costs.

As previously mentioned, based on the results of this study, 76% of gastric cancer patients are men, and 24% of them are women. In a study conducted by Norouzineya et al., 74% of patients were men, and 26% of them were women; these results show that gastric cancer is more prevalent among men than women[14]. Notwithstanding, based on a study by Vahedi et al., 41% of patients were male, and 59% of them were female[15]. This variation can be attributed to the differences between the study populations, since the current study assessed gastric cancer patients, while Vahedi studied gastrointestinal diseases.

According to a study in Japan, the cost of medication was the highest cost that Parkinson's patients had paid during their treatment period. This cost accounted for 90% of their direct costs; in addition, according to the results of another study, carried out in patients with tuberculosis, the costs of surgery and hospitalization were the maximum costs that were imposed on these patients[16,17]. The maximum cost of diabetic patients was related to doctors' visits; moreover, due to the increase in the number of doctors' visits, the costs of medication and diagnostic tests constitute a large part of diabetic patients' costs[18]. Another study assessing the direct costs of colon cancer patients showed that diagnostic costs make up the greater part of direct costs in these patients. Based on the findings of this

study, diagnostic costs include the cost of general surgery, the cost of the emergency department or the cost of any diagnostic services that the patient may have received[19]. The results of other studies were consistent with the current study; furthermore, in this study, hospitalization period had a direct relation with patient costs. These results show that decreasing the number of visits, hospitalization and shortening the duration of hospitalization can further reduce total costs[8,18].

Study results, which have evaluated the costs of breast cancer patients, show that the total cost of medical care for a four-year period after diagnosis depends strongly on disease stage at diagnosis. The costs of patients who had referred to the hospital at stage III to stage V are higher compared with the costs of patients who had referred at stage 0 to stage II of their disease. Findings show that the cost of disease decreases in all stages after the first and second years[20,21]. These findings prove the results of the current study. According to the results of the present study, the sooner patients refer for treatment in the initial stages of their disease, the less costs will be imposed on them and the health system.

Failure to accurately record patient information, impossibility of complete follow-up of diagnostic stages and of treatment of patients due to multiple referrals to various therapeutic centers, and different terminology of registration and publication of clinical information of patients are among the restrictions of the current study.

CONCLUSION:

Hospitalization accounted for the greatest share in direct patient cost. In addition, the highest standard deviation was related to medication costs. This issue shows that standard treatment protocols are not used, and doctors prescribe medicines based on their own discretion. It also indicates a high dispersion of cost among patients. Since the costs of hospitalization are the highest imposed costs, and there is a significant relationship between total imposed costs and duration of hospitalization, we recommend adopting new strategies, such as hospitalization at home. In addition, new policies to reduce the heavy costs of these patients, with the aid of insurance agencies, financial support from financial institutions and charities, the distribution of specialized cancer centers or providing housing for patients who come from rural areas, and the reduction of cancer patients co-payments can not only help realize justice indicators in health but also reduce financial barriers for cancer patients and prevent them from facing catastrophic costs.

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CONFLICTS OF INTEREST:

The authors have no conflict of interests to declare.

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REFERENCES:

1. Sierra MS, Cueva P, Bravo LE, Forman D. Stomach cancer burden in Central and South America. Cancer epidemiology. 2016;44 Suppl 1:S62-s73.
2. Amani F, Sadrkabir M, Saeid Sadeghieh Ahari, Barzghari S, Yazdanbod A, Sabzevari A, et al. Epidemiology of Gastric Cancer in Northwest Iran: 2003-2011. Middle East Journal of Cancer. 2015;6(3):189-93.
3. Stewart B, Wild C. World Cancer Report 2014, International Agency for Research on Cancer, Lyon, France, 2014.
4. Berraho M, Najdi A, Mathoulin-Pelissier S, Salamon R, Nejjari C. Direct Costs of Cervical Cancer Management in Morocco. Asian Pacific Journal of Cancer Prevention. 2012;13:3159-63.

5. Rahman R, Asombang AW, Ibdah JA. Characteristics of gastric cancer in Asia. World journal of gastroenterology. 2014;20(16):4483-90.
6. Renee A. pharmacoeconomics from theory to practice edited by: health economics and managment solutions; 2010.
7. Akbarzadeh A, Esmaeily M, Kimia-Far K. Medical Information Management and estimate direct medical costs of lung cancer. Medical Information Management. 2008;5(2):151-8.
8. Haga K, Matsumoto K, Kitazawa T, Seto K, Fujita S, Hasegawa T. Cost of illness of the stomach cancer in Japan-a time trend and future projections. BMC health services research. 2013;13(1):1.
9. Chodick G, Porath A, Alapi H, Sella T, Flash S, Wood F, et al. The direct medical cost of cardiovascular diseases, hypertension, diabetes, cancer, pregnancy and female infertility in a large HMO in Israel. Health Policy. 2010;95(2-3):271-6.
10. Varvasovszky Z, Brugha R. A stakeholder analysis. Health policy and planning. 2000;15(3):338-45.
11. Burton A, Osborn D, Atkins L, Michie S, Gray B, Stevenson F, et al. Lowering Cardiovascular Disease Risk for People with Severe Mental Illnesses in Primary Care: A Focus Group Study. PLoS One. 2015;10(8):e0136603.
12. Sharma P, Dunn RL, Wei JT, Montie JE, Gilbert SM. Evaluation of point-of-care PRO assessment in clinic settings: integration, parallel-forms reliability, and patient acceptability of electronic QOL measures during clinic visits. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2016;25(3):575-83.
13. Winwood PW, Pritchard HJ. Tapering Practices of Strongman Athletes: Test-Retest Reliability Study. 2017;6(10):e211.
14. Nourozinia F, Rasmi Y, Otarod M, Golizadeh M, Khadem-Ansari M-H. Epidemiology And Histopathology Of Gastric Cancer In Urmia. URMIA MEDICAL JOURNAL. 2013;24(3):170-5.
15. Vahedi m, Moghimi-Dehkordi B, Safaee A, Pourhoseingholi A. Cost analysis of upper gastrointestinal diseases in Tehran Province: a population-based study, 85-1384. Kermanshah University of Medical Sciences. 1391;16(6):457-65.
16. Yoritaka A, Fukae J, Hatano T, Oda E, Hattori N. The Direct Cost of Parkinson Disease at Juntendo Medical University Hospital, Japan. Internal Medicine. 2016;55(2):113-9.
17. Hasoumi M, Nasehi M, Khakian M, Mohseni M, Ziaiifar H, Keykale MS. Cost of Illness of Tuberculosis in Tehran in the Year 2011. Materia socio-medica. 2014;26(5):339.
18. Ng CS, Toh MPHS, Ko Y, Lee JY-C. Direct medical cost of type 2 diabetes in Singapore. PloS one. 2015;10(3):e0122795.
19. Bending MW, Trueman P, Lowson KV, Pilgrim H, Tappenden P, Chilcott J, et al. Estimating the direct costs of bowel cancer services provided by the National Health Service in England. International journal of technology assessment in health care. 2010;26(4):362-9.
20. Zarogoulidou V, Panagopoulou E, Papakosta D, Petridis D, Porpodis K, Zarogoulidis K, et al. Estimating the direct and indirect costs of lung cancer: a prospective analysis in a Greek University Pulmonary Department. Journal of thoracic disease. 2015;7(Suppl 1):S12.
21. Legorreta AP, Brooks RJ, Leibowitz AN, Solin LJ. Cost of breast cancer treatment. A 4-year longitudinal study. Arch Intern Med. 1996;156(19):2197-201.