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ORIGINAL PAPER

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How Cost-of-Illness (COI) Study Provides Direct and Indirect Costs of Multiple Sclerosis (MS) in Bosnia and Herzegovina ?

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ABSTRACT

Background: This cost-of-illness (COI) study provides deep insight in direct and indirect costs of multiple sclerosis (MS) in Bosnia and Herzegovina (BH). **Aim:** Objective of this study was to analyze the costs and quality of life (QoL) of patients with MS in BH. **Patients and methods:** We applied the same methodology already used in study conducted across nine European countries. Sixty-two patients participated with EDSS score not higher than 6.5. Costs are collected using a questionnaire quality of life was measured by EQ-5D and MSQOL-54 questionnaires. **Results:** Mean age of respondents was 39.8 The mean utility measured by EQ-5D-3L was 0.68 at the beginning and 0.63 at the end of the study. QoL measured by MSQoL-54 showed improvement at the end of the trial. Costs are presented from the societal and payer perspective. Cost of MS in Bosnia and Herzegovina annually amount 124.8 million BAM. Cost driver where indirect and DMDs costs, with significant differences among subgroups. **Conclusions:** This study provides an in-depth analysis of MS costs in BH providing data for health policies development and information for future cost-effectiveness evaluations of new therapeutic options as well as for comparison of MS costs with other countries.

Keywords: multiple sclerosis, costs, indirect costs.

(2). Reasons for this can be partially attributed to increased survival but also improvements in diagnosis and reporting of MS, country disease registries establishment and epidemiologic research. Europe is considered a high prevalence region for MS (prevalence $\geq 30/100,000$ (3)), containing more than half of the global population of people diagnosed with MS but with high differences across regions and countries (4).

Based on published epidemiology research in Bosnia and Herzegovina, since there is no national disease registry, it is estimated that there is around 3,000 patients while incidence and prevalence rates differs across regions (5-7). Majority of patients (80-85%) are diagnosed with relapsing-remitting MS (RRMS) (8).

Even there is no cure for MS pharmacological preventive and symptomatic treatments may help patients in managing the disease especially using new disease-modifying drugs (DMDs) (9). It is also evident that there are variations in MS treatment practice within Europe (10).

The access to innovative treatments across European countries may depend on health policy issues and welfare.

Beside health related problems, MS have negative impact on quality of life, productivity and economy of the individual but the whole society as well.

Cost of illness (COI) studies of MS are commonly performed in order to identify direct and indirect cost impact as a potential tool for healthcare decision makers in setting up and prioritizing healthcare policies and interventions that they are supposed to implement and reimburse (11).

There are a number of COI studies published across the world reporting different types of costs related to MS and identifying cost drivers. As reported by *Ernstsson O et al.* systematic

1. INTRODUCTION

Multiple sclerosis (MS) as neurodegenerative autoimmune disease leads to disability negatively impacting patient quality of life as diseases progresses. It is estimated that 2.3 million person are diagnosed worldwide out of which 80% are young and middle-aged adults 20-40 years old (1).

Atlas of MS 2013 reported increase in disease prevalence comparing to data published in 2008

review the bottom-up method and prevalence approach dominated in studies of COI of MS. Authors also concluded that there are difficulties in comparing absolute costs across studies (12). It is generally reported that main cost driver for less severe MS are costs of drugs while informal care and production losses are related to the most severe MS.

Large observational study included 13,186 in nine European countries patients provided insight for each country the cost of MS at different levels of disease severity (13).

Bosnia and Herzegovina is country in transition with limited resources for novel MS treatments and highly decentralized healthcare system causing inequalities in access to healthcare across the country (14, 15).

2. AIM

The aim of our study was to analyze the costs and quality of life (QoL) of patients with MS using similar methodology as above mentioned study in order to identify costs of MS in Bosnia and Herzegovina.

3. PATIENTS AND METHODS

The study used a prevalence-based bottom-up approach. Data were collected by a cross-sectional survey directly from patients, with the objective of including all costs related to MS. Patients were instructed to exclude consumption not related to MS in order to estimate only costs of MS. Since patients are young age comorbidity is relatively low so reported costs can be fully associated with MS. Questionnaire for cost collection was developed based on previously published studies and adopted to specificities of local healthcare system. Quality of life data have been collected using generic instrument EQ-5D and disease specific instrument MSQOL-54.

The study was conducted at Neurology department at University clinical center Sarajevo from May 2016 to May 2017 among 62 patients with RRMS as the most common form of the disease. All patients were asked to sign an informed consent. The questionnaire and study protocol were approved by the Ethics Committee of the research institution.

Patients have been followed through three visits (initial, after 6-months and after 12-months). Recall period for costs was 3 months in order to capture changes in service and resource consumption (16). Quality of life surveys were admitted at initial and last visit ensuring to capture any changes during one year period. Clinical data related to the level of functional ability, the number of relapses, disease state, type and patient characteristics have been assessed and collected by neurologist.

The sources used for determining the unit costs and any assumptions applied are presented in Table 1. Unit costs were multiplied by amount of resources used and extrapolated for one-year period.

Productivity losses were captured through questions regarding employment status and normal working hours, early retirement (invalidity) and short- and long-term sick leave.

Costs of MS are presented from the societal perspective at annual level.

SPSS for Windows (version 19.0, SPSS Inc., Chicago, IL-

linois, USA) and Microsoft Excel (version 11.0, Microsoft Corporation, Redmond, WA, USA) were used for statistical analysis of the obtained data applying suitable statistical tests.

4. RESULTS

Patient demographics and background information

All 62 patients enrolled completed the study and persist during full study period. Almost two thirds of patients (61.3%) were women and the mean age was 39.8 (Table 2). In our sample majority of patients had high school education (68.0%), followed by university degree (24.0%) and primary school (5.0%). In regards to employment status 53.0% were employed and 39.3% are early retired due to MS.

Disease information and QoL

Detailed disease information is presented in Table 3. On average, patients were 32.5 years old at first diagnosis with first symptoms occurring approximately 3 years earlier diagnosis. Patients in our sample had relatively low EDSS score not higher than 6.5 which means they had mild or moderate disability. We have also divide sample based on treatment used at the moment of the study, where 53.2% of patients are treated with disease-modifying drugs (DMD), 32.3% with high doses of corticosteroids and 14.5% did not

Type of resource, cost item	Sources used and assumptions applied for unit cost figures
Hospitalization, healthcare provider services, diagnostic tests and procedures	Institute for health insurance of Federation of Bosnia and Herzegovina http://www.fedzzo.com.ba/bs/dokument/tarifnik/68
	Health Insurance Fund of Republic of Srpska, Bosnia and Herzegovina https://www.zdravstvo-srpske.org/cjenovnici-i-sifarnici.html
Prescription drugs prices covered by health insurance funds	Federal ministry of health – reimbursement list (2017) http://www.fmoh.gov.ba/index.php/preporucujemo/liste-lijekova
	Health Insurance Fund of Republic of Srpska, Bosnia and Herzegovina – reimbursement list (2017) https://www.zdravstvo-srpske.org/cjenovnici-i-sifarnici.html
Over-the-counter (OTC) drugs, food supplements and not reimbursed prescription drug prices	Patient statements Agency for medicines and medical devices of Bosnia and Herzegovina (maximal wholesaler prices approved in 2017) http://www.almbih.gov.ba/vijesti/obavjestenje-o-a-uriranim-maksimalnim-veleprodajnim-cijenama-lijekova-za-tr-i-te-bih-437.html
Orthopedic devices	Patients' statements
Average income	Agency for statistics of Bosnia and Herzegovina http://www.bhas.ba/
Sick leave	Applicable legislation in the field of health insurance and labor rights
Informal care	Patient statements Available price lists of private institutions

Table 1. Unit cost figures, sources and assumptions applied

Patient demographics	Proportion or mean (SD)
Total number of respondents	62
Gender	
Male	38.7%
Female	61.3%
Age	39.8 (10,9)
Education	
Primary school	5.0%
High school	68.0%
University degree	24.0%
Employment	
Employed	53.0%
Unemployed	47.0%
Early retired due to MS	39.3%

Table 2. Demographics of the sample

receive any treatment for MS. Almost two third of patients (65.0%) experienced one relapse during the study period, 40.0% had two and 13.0% had three or more relapses. Comparison of number of relapses by treatment is shown in Table 4, where that lowest proportion of relapses is registered in the group treated with DMDs and highest in group treated by corticosteroids.

Quality of life (QoL) was measured by disease specific and generic instrument at the beginning and at the end of the study period (after one year).

Using generic EQ-5D-3L instrument the mean utility in the sample was estimated at 0.68 at the beginning and 0.63 after 12 months with no significant difference as presented in Table 5.

When QoL was measured by disease specific instrument MSQoL-54 we found significant improvement at the end of the trial both for physical and mental composite scores (Table 6).

Costs

We have analyzed direct and indirect costs of MS in our sample by treatment used. Direct costs included costs of diagnostic procedures (tests and imaging) and healthcare services (hospitalization, visits to different specialists - neurologist, ophthalmologist, urologist, etc.) and cost of medicines (for MS and symptomatic treatments including prescription and non-prescription drugs). Indirect costs included support by third party, adaptations, orthopedic aids, absenteeism and productivity loss related costs. All costs are expressed in local currency Bosnian Convertible Mark (BAM) which is fixed to euro and has stabile conversion rate (1.95583 BAM for 1 EUR) per patient per year.

In Table 7 summary of direct costs per treatment group

	Proportion or mean
Mean (SD) age at first diagnosis	32.5 (9.9)
Mean (SD) age at first symptoms	29.8 (9.1)
EDSSa level (disease severity)	
EDSS score 0–3	61.3%
EDSS score 4–6.5	37.1%
EDSS score 7–9.5	0.0%
Treatment	
DMD	53.2%
CT	32.3%
NT	14.5%
Relapses during past 3 months	
1	65.0%
2	40.0%
≥3	13.0%

aEDSS Expanded Disability Status Scale; DMD disease-modifying drugs; CT corticosteroids; NT no treatment

Table 3. Disease information

Treatment	N	Total number of re-lapses	Average number of re-lapses	Proportion of patients with re-lapses	Number of re-lapses		
					1	2	≥3
DMD	33	15	0.47	30%	18%	9%	3%
CT	20	29	1.45	100%	50%	40%	5%
NT	9	6	0.66	56%	40%	10%	0%

DMD disease-modifying drugs; CT corticosteroids; NT no treatment

Table 4. Overview of relapses incidence and treatment used

are presented. As we can see there is no difference in cost of diagnostic tests and imaging and medical services (visits to different medical professionals) between treatment groups. Cost of hospitalization are highest among patients treated with corticosteroids followed by no treatment group and significantly different comparing to patients treated with DMD. Cost of medicines is highest among DMD treatment group and driven by cost of DMD drugs. Total direct costs are highest among DMD treatment group driven by cost of DMD medicines, followed by no-treatment group.

Considering indirect costs related to productivity cost due to early retirement amount of 27,86.1 BAM and cost of sick leave amount 1,233.8 BAM per patient per year. Productivity loss related to gross domestic product (GDP) amount 22,834.74 BAM per patient annually.

Total cost of MS in Bosnia and Herzegovina from the societal and payer (Health Insurance Fund) are presented

EQ-5D-3L	N	Mean	SD	Min	Max	Percentile			Wilcoxon Signed Ranks Test
						25th	50th (Median)	75th	
At the end of the study	62	0.3	0.280	0.034	1.000	0.480	0.639	0.903	0.850
At the beginning of the study	62	0.2	0.269	0.074	1.000	0.480	0.688	0.780	

Table 5. Quality of life measured by EQ-5D-3L at the beginning and end of the study

Composite scores	N	Median (25th-75th)		Wilcoxon Signed Ranks Test
		At the end of the study	At the beginning of the study	p
Composite physical health (PHC) score	62	57.3 (38.2-82.9)	49.4 (36.1-61.4)	0.049*
Composite mental health (MHC) core	62	74.7 (61.1-86.8)	53.5 (34.9-70.2)	0.0001*

*p<0,005; significance level

Table 6. Quality of life measured by MSQoL-54 at the beginning and end of the study

in Table 8. Extrapolating these cost on national level, based on available epidemiology data, cost of MS in Bosnia and Herzegovina annually amount 124.8 million BAM.

Figure 1 presents proportion of each direct and indirect cost, showing that majority of MS costs are driven by indirect costs such as sick leave, especially long-term absence.

5. DISCUSSION

In this study we have used methodology proposed by Kobelt *et al.* used for the analysis of the MS cost in study

conducted across nine European countries with necessary adaptation to local specificities of healthcare system of Bosnia and Herzegovina. Using similar methodology make it available for comparison of costs and practices in Bosnia and Herzegovina and other developed Western Europe countries. It is also important to notice that direct comparison and conclusion should be taken with caution. Due to different heterogeneities, such as perspective, cost component, source of data, calculating methods, the time frame of measurement and the final result, studies have rarely been conducted to explore transferability of COI studies from country to country (17). *Ernstsson et al.* conducted a systematic review of the available COI studies in MS concluding that the results of the overall costs per patient vary significantly between the studies or the countries in which they were made, which is probably the result of the various costs involved in such analyzes (18).

This was the first COI study of MS in Bosnia and Herzegovina using internationally verified methodology adopted for local specificities and collected cost of MS data which could be used for future policy decision. Based on data published in 2011 by the European Multiple Sclerosis Platform (EMSP) Bosnia and Herzegovina ranks among the bottom two countries followed by Belarus in terms of

Type of costs and treatment group	N	Min.	Max.	Percentile			p*
				25th	50th (Median)	75th	
Direct cost of medical tests and imaging per treatment group (total)							
DMD	33	0.0	1,728.4	644.2	849.2	1,071.3	0.497
CT	20	0.0	3,431.2	86.4	591.4	1,087.7	
NT	9	0.0	1,712.3	151.9	858.2	936.6	
Direct cost of medical services (total)							
DMD	33	387.6	2,891.3	497.7	571.1	644.5	0.062
CT	20	497.7	1,069.8	571.1	607.8	754.6	
NT	9	461.0	2,219.5	466.0	497.7	607.8	
Direct cost of hospitalization and medical services (total)							
DMD	33	461.0	6,127.8	580.3	1,147.9	2,029.9	0.001
CT	20	1,517.2	7,146.0	2,210.5	3,275.4	4,560.4	
NT	9	1,163.0	3,763.9	1,413.5	1,761.3	2,907.9	
Direct cost of medicines (total)							
DMD	33	17,401.0	26,725.0	19,198.8	20,442.1	22,659.4	0.001
CT	20	3,564.0	23,616.0	5,529.0	7,884.0	10,224.0	
NT	9	1,800.0	25,080.0	4,500.0	6,540.0	13,920.0	
Direct cost of medicines for MS (total)							
DMD	33	15,925.0	17,424.0	15,925.4	16,662.1	17,398.8	0.001
CT	20	2,484.0	2,484.0	2,484.0	2,484.0	2,484.0	
NT	9	0.0	0.0	0.0	0.0	0.0	
Direct cost (total)							
DMD	33	34,803.0	53,451.0	38,397.6	40,884.2	45,318.7	0.0001
CT	20	7,128.0	47,232.0	11,058.0	15,768.0	20,448.0	
NT	9	3,600.0	50,160.0	9,000.0	13,080.0	27,840.0	
*KruskalWallisTest							
DMD disease-modifying drugs: CT corticosteroids: NT no treatment							

*KruskalWallisTest

DMD disease-modifying drugs; CT corticosteroids; NT no treatment

Table 7. Direct medical costs per treatment group (BAM)

	N	Min.	Max.	Percentiles			*p
				25th	50th (Median)	75th	
Health Insurance Fund perspective							
DMD	33	18,893.4	43,860.6	21,580.0	24,142.4	31,516.5	0.0001
CT	20	6,518.9	48,844.1	12,771.8	17,681.2	27,362.5	
NT	9	4,874.8	32,316.5	7,941.8	11,730.4	20,411.4	
Societal perspective							
DMD	33	18,893.4	43,860.6	21,580.0	24,142.4	31,516.5	0.01
CT	20	6,518.6	48,844.1	12,771.8	17,681.2	27,362.5	
NT	9	4,874.8	32,316.5	7,941.8	11,730.4	20,411.4	
*KruskalWallisTest							
DMD disease-modifying drugs; CT corticosteroids; NT no treatment							

*KruskalWallisTest

DMD disease-modifying drugs; CT corticosteroids; NT no treatment

Table 8. Total anual cost of MS in Bosnia and Herzegovina from different perspectives per patient (BAM)

Figure 1. Proportion of MS cost per patient

access to medication that modifies the course of the disease (19). Considering low access to novel medicines for MS, which are considered as expensive, and lack of resources in Bosnia and Herzegovina healthcare system results of the study could be useful for decision makers when allocating resources and taking reimbursement decisions. COI studies are able to show whether new treatments could be valuable in reducing the burden of a specific disease. It can also provide important information for cost-effectiveness analysis by providing the cost estimation since COI study better capture cost information capturing wider costs than just direct medical costs (20).

In our study we have collected direct costs related to healthcare services such as diagnostic procedures, visits to different specialists and cost of medicines for MS but also symptomatic treatment for different health conditions caused by MS including prescription drugs, over-the-counter (OTC) and food supplements (FS). Indirect costs are related to productivity loss due to sick leave and early retirement, but also cost borne by necessary adaptation of houses and orthopedic aids. We divided patients per treatment used in three groups; those on DMDs, corticosteroids and those not treated with any MS pharmacological treatment. The main reason for this was to capture costs among these subgroups in order to identify resource consumption in each group and identify outcomes in terms of QoL. Our intention was to show if there are differences in QoL and costs among those treated with DMDs and those treated with corticosteroid treatment and no-treatment.

As shown the highest direct costs are found in the group of patients treated with DMDs driven by cost of DMDs medicines (MS drugs), but this patient group has the lowest costs of hospitalization and medical services. Contrary, group treated with corticosteroids, as relatively cheap therapeutic option, had highest cost related to hospitalization and medical services. This can be explained by highest rate of relapses in this group and disease progression.

Similarly, the highest rate of early retirement is noticed in corticosteroid group treatment comparing to other two groups of patients.

In terms of QoL we found that both generic instrument EQ-5D-3L and disease specific MSQOL-54 show improvement in QoL. In subgroup analysis of patients treated with DMDs we found significant improvement of QoL comparing to those treated with corticosteroids.

Analyzing indirect costs we found that these costs are driven with long-term absence (sick leave), followed by investments in house adaptations and informal care. Similar findings regarding indirect cost are reported in other COI studies in MS and other chronic and disabling diseases founding that indirect costs constitute a very considerable proportion, usually more than half, of the estimated total costs (21, 22).

The main disadvantage of our study is small number of participants and participation of only patient diagnosed with RRMS. As majority of patients are diagnosed with RRMS corresponding to epidemiology data (23) it could be representative and indicative for conclusion or provide guidance for further research since majority of cost can be allocated and born by this population.

All patients in our study had mild or moderate disease measured by EDSS. Based on previous findings on average 50% of patients are in the early stage of the disease (EDSS ≤ 3.5), 25% are in the intermediate stage (EDSS 4-7) and 5% of patients suffer from very advanced MM (EDSS ≥ 7.5) (24). Considering that all patients had EDSS lower than 6.5 we can suppose that population is relevant and covering majority of patient profiles.

It is expected that costs would be higher if patients with higher EDSS are included (25).

6. CONCLUSION

This study provides an in-depth analysis of the total

societal and payer perspective costs in Bosnia and Herzegovina for MS illustrating the burden of disease. Provided data are important for the development of health policies. Although COI studies cannot be used to assess the cost-effectiveness of specific treatment, the results of this study provide significant information for future cost-effectiveness evaluations of new therapeutic options in MS during reimbursement process in Bosnia and Herzegovina. It is also good basis for comparison of MS costs in Bosnia and Herzegovina and other more developed countries due to similar methodology to already published studies.

- **Author's Contribution:** T.C. and E.S. gave substantial contribution to the conception or design of the work and in the acquisition, analysis and interpretation of data for the work. T.C., J.C. and R.G. had role in drafting the work and revising it critically for important intellectual content. Each author gave final approval of the version to be published and they are agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
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