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PUBLIC HEALTH CARE

ECONOMIC BURDEN AND HEALTH-RELATED QUALITY OF LIFE OF PATIENTS WITH CYSTIC FIBROSIS IN BULGARIA

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ЭКОНОМИЧЕСКАЯ НАГРУЗКА И КАЧЕСТВО ЖИЗНИ, СВЯЗАННОЕ СО ЗДОРОВЬЕМ У ПАЦИЕНТОВ С ЗАБОЛЕВАНИЕМ МУКОВИСЦИДОЗА В БОЛГАРИИ

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ABSTRACT

Objective: The aim of this study was to determine the economic burden from a societal perspective and health-related quality of life (HRQOL) of patients with cystic fibrosis (CF) in Bulgaria. **Materials and methods:** We conducted a cross-sectional study of 33 patients with CF and 17 caregivers from Bulgaria. Data on socio-demographic characteristics, health resource utilisation, informal care, labor productivity losses and HRQOL were collected from questionnaires completed by patients or their caregivers. HRQOL was evaluated with the EuroQol 5-domain (EQ-5D-3L) questionnaire. **Results:** Median annual costs of CF in Bulgaria were € 24 152 per patient in 2012 as a reference year. Median annual costs for children were found to be significantly higher than those for adults – € 31 945 vs. € 15 714 ($p = 0.012$). This outcome came from statistically significant differences in costs for main informal carer ($p < 0.001$) and costs for other informal carers ($p = 0.022$). As a single cost item, drugs had the biggest monetary impact. Median annual drug costs were € 13 059. Bulgarian CF patients showed low HRQOL results – 50 median VAS score and 0.592 median health utilities. A quarter of patients even rated their health state as worse than death. **Conclusion:** CF patients from Eastern Europe remain a vulnerable population with risk factors for worse health outcomes. Our study provided a state-of-the art analysis that facilitates the elaboration, adoption and application of targeted public health policies to tackle CF-related problems at national and European level.

Key words: *cystic fibrosis, health-related quality of life, costs and cost analysis, economic burden, Bulgaria*

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РЕЗЮМЕ

Цель: Целью данного исследования является определение экономической нагрузки с общественной точки зрения и качества жизни, связанного со здоровьем у пациентов с заболеванием муковисцидоза в Болгарии.

Материалы и методы: Проведено исследование поперечного сечения среди 33 пациентов с заболеванием муковисцидоза и 17 их опекунов из Болгарии. Информация о социально-демографических характеристиках,

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потреблении рессурсов здравоохранения, неформальных заботах, потере производительности труда и качества жизни, связанного со здоровьем собрана при помощи опросников, заполняемых пациентами или их опекунами. Качество жизни, связанное со здоровьем измерено при помощи методологии EQ-5D-3L EuroQol. **Результаты:** Медиана годовых расходов пациента с муковисцидозом в Болгарии составляет € 24 152 за 2012 г. в качестве референтного года. Медиана годовых расходов у детей значительно превышает такую же у взрослых - € 31 945 по сравнению с € 15 714 (p = 0.012). Данный результат является следствием статистически значимой разницы в отношении расходов на основное лицо, занятое неформальным уходом за больным (p = 0.001) и в расходов на другие лица, занятые неформальным уходом за больным (p = 0.022). В качестве самостоятельной статьи расходов наибольшая бюджетная нагрузка падает на лекарства. Медиана годовых расходов на лекарства составляет € 13 059. Болгарские пациенты с заболеванием муковисцидоза показали ухудшение качества жизни, связанного со здоровьем – медиана самооценки качества жизни по VAS шкале EQ-5D-3L составляет 50.00, а медиана полезности для здоровья по той же методологии составляет 0.592. Четверть пациентов даже оценивает своё состояние как „хуже смерти". **Заключение:** Пациенты с муковисцидозом из Восточной Европы продолжают являться уязвимой группой с факторами риска ухудшения здоровья. Наше исследование предоставляет актуальный анализ, который может облегчить разработку, принятие и применение целенаправленных здравоохранительных мероприятий для решения проблем, связанных с муковисцидозом на национальном и европейском уровнях.

Ключевые слова: *муковисцидоз; качество жизни, связанное со здоровьем; расходы и анализ расходов; экономическая нагрузка; Болгария*

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INTRODUCTION

Cystic fibrosis is a monogenic autosomal recessive disease caused by mutations in the CF transmembrane conductance regulator (CFTR) gene. These alterations result in dysfunction of the CFTR protein which takes part in the regulation of transmembrane hydroelectrolytic flux.[1] It is the most common genetic disorder among Caucasians. Estimated prevalence in Europe is between 0.104 – 2.98 per 10 000 individuals, while expected incidence is between 1 in 1 353 and 1 in 25 000.[2]

CF is usually diagnosed in infancy. Symptoms and severity vary significantly in different individuals. Clinical consequences include progressive pulmonary damage leading to respiratory failure, pancreatic dysfunction, liver disease that may progress to cirrhosis, gut motility problems and elevated sweat electrolytes. Virtually all men with CF are infertile due to atresia or complete absence of vas deferens.[1] Prognosis mainly depends on the extent of bronchopulmonary involvement. Aggressive symptomatic treatment and complex multidisciplinary care have led to a dramatic improvement in CF life expectancy – median predicted survival is now approaching 40 years.[1-3]

Despite this important progress at global level, strong health inequalities remain among the different EU member states. Excess premature CF childhood mortality still occurs in less affluent Eastern European countries.[3] Risk factors, such as malnutrition and pulmonary exacerbations, as well as increased hazard for death in women with CF-related diabetes shape CF epidemiology in Eastern Europe. All these problems are particularly persistent in Bulgaria, where CF patients are one of the most vulnerable patient groups. Due to the lack of efficient health policy measures, these people and their families experience substantial economic burden and lowered health-related quality of life (HRQOL). Research and analysis of the burden of CF not only in Bulgaria, but in all Eastern European countries empowers national and European stakeholders to join efforts in tackling these problems and providing better health care to CF patients and their caregivers.

Our study aimed to estimate the social economic costs in a triple dimension of direct health care costs, direct non-health care costs (formal and informal care) and labour productivity losses, as well as to assess the HRQOL of Bulgarian CF patients and their caregivers.

MATERIALS AND METHODS

Research design and subjects

It is a cross-sectional study of people diagnosed with CF who received outpatient care and were living in the community. All patients and caregivers were informed about the study objectives and data confidentiality, and were asked to indicate their agreement to participate. Cases were recruited by the Bulgarian CF patient organisation. Survey was anonymous. The fieldwork was carried out between

December 2011 and March 2012. Questionnaires were administered by e-mail. Information source used in the study was the self-completed questionnaire filled out by patients and their caregivers.

Costing methodology

Prevalence approach was used to estimate costs from a societal perspective. Disease prevalence takes into account all existing cases during a given year and all health care resources used for prevention, treatment and rehabilitation, as well as other resources used (formal and informal care) or lost (labor productivity) within that year as a consequence of the illness considered. Prevalence-based cost-of-illness analysis has the advantage of incorporating measurements of total annual health care expenditure, which is particularly relevant for chronic conditions such as CF, that require long-term treatment. In this context, a bottom-up costing approach was applied to estimate total and average annual costs.[4] Data on resource utilisation were collected for each patient. Unit costs that were obtained from different health care cost databases were then multiplied by the resource quantities to estimate the annual cost per patient with 2012 as the reference year.

Informal care is defined as a group of tasks or care provided by non-professional caregivers (most often relatives), who are not paid for the provided care. Information about informal care was obtained from the questionnaire items concerning the time spent helping the patient with his/her basic activities of daily living. The approach used to quantify the care hours was the proxy good method, which values time as an output. This method estimates the care provided by the informal caregiver considering that if he/she did not provide these services, their presence would have to be substituted by another person who could provide them.[5] Data on loss of labour productivity were obtained from physical units converted into monetary units through a human capital-based approach. Study estimates were based on average earnings (gross wages) of a worker for the year 2012.

Patient and caregiver outcomes

Patient and caregiver outcomes were obtained by means of self-administered questionnaires – EuroQol 5-domain (EQ-5D) and Barthel index questionnaires. EQ-5D is a generic instrument that is commonly used in economic evaluation and technology assessment. There are 5 dimensions covering areas of mobility, self-care, everyday activities, pain/discomfort and anxiety/depression. The values or utilities are indicated on a scale on which 0 is the value of death and 1 is the value of perfect health.[6] Barthel index is a disability assessment tool – it measures the ability to perform 10 basic activities of daily living obtaining a quantitative estimate of the degree of dependence of the subject. A score of 91-99 shows mild dependence, 61-90 shows moderate dependence, 21-60 shows severe dependence, and a score < 20 shows complete dependence.[7]

Statistical analysis

Differences in costs and HRQOL were analysed according to the age of patients - children (under 18 years of age) versus adults. Descriptive statistics and percentage distributions were applied. As data were not normally distributed, Mann-Whitney test was carried out to determine whether variations between children and adults were significantly different at 0.05 level. Analyses were performed using the SPSS software (version 11.5; SPSS, Inc., Chicago, IL).

RESULTS

Socio-demographic profile of CF patients in Bulgaria

33 questionnaires were completed, representing 19% of the Bulgarian CF patients that were treated in outpatient settings in 2012. Respondent sample contained almost equal numbers of children and adults, men and women (Table 1). Sample's mean age, 16 ± 10 years, was pretty high for a condition that is generally treated and followed up by pediatricians. Mean age for pediatric patients was 7 ± 4 years, while mean age for adult patients was 26 ± 5 years. Sample included patients from 14 out of Bulgaria's 28 provinces.

CF patients demonstrated a standard profile of education – all children surveyed attended regular schools, while all adults had completed at least a secondary school (half of CF adults had a university degree). This good educational background, however, did not translate into good employment status. Half of the adults were either unemployed or early retired due to their condition. This lost social economic potential is a direct result of the severity of CF. Half of CF patients reported a need for carer. More than 80% of Bulgarian CF patients have been medically certified for disability and dependence.

Socio-demographic profile of CF carers in Bulgaria

Questionnaire had a caregiver section that was completed by 17 respondents (Table 2). The common profile of a Bulgarian CF caregiver is a woman of working age, most often the mother of the CF

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Table 1. Socio-demographic profile of Bulgarian CF patients

Socio-demographic characteristics	n	%
Number of respondents	33	-
Mean age (years ± SD)	16 ± 10	
Children (under 18 years)	17	51.5
Males	17	51.5
Married (for adults only)	2	12.5
Secondary or higher education (for adults only)	16	100.0
Need of carer	18	54.6
Use of professional carer	0	-
Unemployed or early retired (for adults only)	9	56.3
Disability assessment	27	81.8

Table 2. Socio-demographic profile of Bulgarian CF carers

Socio-demographic characteristics	n	%
Number of respondents	17	-
Mean age (years ± SD)	34 ± 6	
Female	15	88.2
Work limitations	11	64.7

patient. The need for extensive daily care imposes difficulties for the carer to fulfil his/her professional duties – nearly two thirds of respondents indicated that they experience work limitations.

Economic burden of CF in Bulgaria

Median annual costs of CF in Bulgaria were € 24 152 per patient (Table 3). Median annual costs for children were found to be significantly higher than those for adults – € 31 945 vs. € 15 714 ($p = 0.012$). This outcome came from statistically significant differences in costs for main informal carer ($p < 0.001$) and costs for other informal carers ($p = 0.022$). On the other hand, direct health care costs were more or less the same for children and adults. As a single cost item, drugs had the biggest monetary impact. Median annual drug costs were € 13 059. Interquartile range of those costs was minimal, indicating similar medicinal regimens for children and adults. Hospitalisation costs came second. This item amounted for median annual costs of € 1 257 with an interquartile range of € 2 733, possibly due to variations in disease severity. Health care transport costs were found to be almost missing from the direct health care costs.

Despite the high rates of patients indicating a need for carer and having a disability assessment, no respondent reported use of professional (paid) caregiver. All CF patients exclusively relied on informal care by family members and relatives. High interquartile ranges of informal care costs however showed that the impact of those cost items could significantly rise and even exceed the direct health care costs. This economic burden is substantial and is entirely put on patients and their families.

Indirect costs were limited. Although half of the CF adults were unemployed or early retired due to illness, productivity loss and early retirement costs were virtually absent. This is mainly due to the relatively young age of adult patient sample, as there are no such costs in children.

HRQOL of CF in Bulgaria

Twenty-three CF patients completed the EQ-5D-3L description system for HRQOL (Table 4). Respondents reported significant pain (87%) and depression (78%). Patient sample was almost equally split regarding mobility and usual activities problems.

Table 3. Economic burden of CF in Bulgaria

Annual costs (EUR, 2012)	Total respondents (n = 33)	
	Median	Interquartile range
Direct costs	19 008	14 990 – 32 861
Drugs	13 059	13 048 – 13 120
Tests	74	38 – 108
Visits	217	119 – 589
Hospitalisations	1 257	0 – 2 733
Materials	68	19 – 341
Health care transport	0	0 – 0
Social services	0	0 – 228
Professional carer	0	0 – 0
Non-health carer transport	14	3 – 59
Main informal carer	0	0 – 15 524
Other informal carers	0	0 – 4 842
Indirect costs	0	0 – 0
Patient's loss of productivity	0	0 – 0
Patient's early retirement	0	0 – 0
Total costs	24 152	15 554 – 32 861

Table 4. HRQOL in Bulgarian CF patients (EQ-5D-3L descriptive system)

Domain	No problems		Some/severe problems	
	n	%	n	%
Mobility	13	56.5	10	43.5
Self care	17	73.9	6	26.1
Usual activities	12	52.2	11	47.8
Pain/discomfort	3	13.0	20	87.0
Anxiety/depression	5	21.7	18	78.3

Table 5. HRQOL in Bulgarian CF patients and their carers

HRQOL	Median	Interquartile range
Patients (n = 23)		
EQ-5D-3L VAS score	50	10 – 80
EQ-5D-3L utility	0.592	-0.385 – 0.768
Barthel index	85	75 – 100
Carers (n = 17)		
EQ-5D-3L VAS score	70	40 – 83
EQ-5D-3L utility	0.725	0.516 – 0.822

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Bulgarian CF patients showed low HRQOL results – 50 median VAS score and 0.592 median health utilities (Table 5). A quarter of patients even rated their health state as worse than death. On the other hand, Barthel index results showed only mild-to-moderate dependence in CF patients. Having in mind the significant economic burden and decreased HRQOL, it was not surprising that Bulgarian patients reported low satisfaction with the national health system. Mean score of satisfaction was 2 ± 1 on a 10-point satisfaction scale (10 is the maximum level of satisfaction).

DISCUSSION

Driving factors for CF burden and HRQOL

Cross-country analysis of variations in CF burden and HRQOL are difficult due to several limitations. There are apparent differences in rates of care in CF specialised centres, distribution of CF genotypes, antibiotic regimens to treat or prevent infection, as well as variations in nutrition and environmental exposure. National health systems also vary in regard to diagnostic capacity and availability of newborn screening.[8] Nevertheless, cost-of-illness analyses and HRQOL studies are important for a number of reasons. It is becoming increasingly acknowledged that factors including household income, social economic status, body mass index and complications, as well as access to specialised care are predictive of the CF outcome.[9] This type of research provides a state-of-the-art analysis that facilitates the elaboration, adoption and application of targeted public health policies to tackle CF-related problems at national and international level.

CF is a life-threatening and chronically debilitating condition that still causes reduced life expectancy and worsened quality of life. Economic burden of CF in Bulgaria is high. Affected individuals often require a combination of multiple oral and inhaled medications, as well as physiotherapy on a daily basis. There is a clear relationship between disease severity and total health care costs. CF demands more intensive treatments as disorder progresses. Genetic explanations for variations in CF progression are a promising source of information regarding disease biology and pathophysiology, but an understanding of non-genetic factors provides more immediate tools for improving disease outcomes and managing health care costs.[10] Clinical course of CF and subsequent health care costs are greatly influenced by differences in delivery and acceptance of treatments. We found that direct health care costs do not differ significantly between CF pediatric and adult patients, thus representing a fixed cost item. Centres of expertise and reference networks for CF are highly acclaimed to have contributed for the prolonged life expectancy and improved quality of life in CF patients.[11] Our study confirmed another major advantage of CF centralised health care – centres of expertise are also an effective tool to manage direct health care costs. As drugs costs significantly depend on co-morbidities, non-optimal treatment at non-expert centre could lead to a significantly higher burden for the health care system. These considerations suggest that measures to enhance disease self-management skills and to ensure consistently optimal health care practices will improve health outcomes in CF patients and subsequently decrease CF economic burden.

CF indirect costs were found to be of a limited impact. However, previous studies measured this cost item ranging from 6% up to one third of the total costs.[12,13] Indirect costs generally rise with the degree of severity. Chronic ill-health significantly impacts on an individual's ability to work. Adult CF patients with severe disease would have experienced significantly higher indirect costs. Mean age and life expectancy of CF patients have increased and this disease can no longer be regarded as a pediatric condition.[14] Adults with CF are becoming a new ageing population, thus expanding the economic burden of CF. This shift in CF demography is likely to lead to a rising work disability rate and larger indirect costs due to productivity loss and early retirement. A previous study by Targett et al. on the employment status of CF patients in the UK confirmed that 40% of adult patients reported stopping a job due to the disease. Employment of CF patients was found to be strongly associated with educational attainment, locality and HRQOL domains.[15] Appropriate targeted interventions, such as career counseling and working part time, could help to maintain employment despite declining health.[16]

As the life expectancy in CF patients continues to improve, an emphasis on optimising HRQOL has become increasingly important. Worsened HRQOL is a trigger factor for increased CF burden. We found reduced health utility and much bigger informal care costs in CF children in comparison to CF adults. As nowadays these patients are more likely to reach adulthood, there is a strong need to address HRQOL issues from early age. Given the significant economic burden of CF, ascertaining which factors enhance or diminish emotion and social well-being is of paramount importance in order

to inform clinical interventions and ensure better health outcomes. Apart from clinical factors, such as forced expiratory volume, body mass index and pulmonary exacerbations that are known to affect HRQOL in CF[9], recent studies found that greater use of religion, instrumental coping and acceptance are positively associated with social and emotional HRQOL in CF people[17]. These are important tools that could help limiting the overall burden of CF.

Organisation and management of CF care

Despite the great progress made in clinical and public health aspect, significant health inequalities remain at cross-country level in the EU. There is a great age disparity in Eastern European countries, where survivors into adulthood are still a small minority of CF patients. A previous era of unavailability or restricted access to adequate care is often mentioned as a main reason for this situation.[3] Furthermore, our data for mean age of diagnosis suggest that a number of patients continue to be diagnosed beyond infancy as consistent with the fact that CF neonatal screening is not available in Bulgaria. Poorer CF outcomes in Bulgaria and Eastern Europe are generally considered to be a result of the limited public health resources in these countries. However, we believe that better organisation and management of CF care is a key issue for early diagnosis, treatment and hence, improved CF outcomes for a given health care system. Earlier establishment of CF registries and centres of expertise in Western European countries have enhanced clinical and public health capacity to provide better care to patients and their families, thus ensuring increased survival into adulthood and improved HRQOL.[3]

It is also widely recognised that outcomes for CF patients cared for in expert centres are better than for those who are not. Key to the effectiveness of CF centres is the multidisciplinary approach, which should include clinical consultants, clinical nurse specialist, microbiologist, physiotherapist, dietitian, pharmacist, clinical psychologist, social worker and clinical geneticist.[18] CF centres of expertise need to collaborate with other centres at national and international level, especially in the field of registries in order to understand further this disease. With the implementation of newborn screening in many countries, CF centres are now increasingly caring for a cohort of patients who have minimal lung disease at diagnosis and therefore have the potential to enjoy an excellent HRQOL and an even greater life expectancy than was seen previously.[19]

Designation of centres of expertise is a crucial process not only for CF, but for all rare diseases. These entities help aggregating limited resources and scarce expertise, as well as generating new knowledge and understanding of the complex nature of these disorders. To allow high quality care to be delivered throughout Europe, the European Cystic Fibrosis Society (ECFS) published a consensus document setting standards of care for CF patients in 2005. This measure aimed not only to define procedures for routine evaluation, treatment and monitoring of patients with CF in Europe, but also to address organisational and managerial problems, such as infrastructure for a CF center and documentation of results in a standard database.[1] This consensus proved to be of a great added value. It set a uniform framework for treatment and served as a milestone for decreased morbidity and increased survival and HRQOL. Ten years later, ECFS built on this work, elaborating standards for best practice in key aspects of CF care, including screening, diagnosis, pre-emptive treatment of lung disease, nutrition, complications, transplant/end of life care and psychological support.[19]

This centralised paradigm in CF care served as a base for a broader public health approach to rare diseases in the EU. The European Parliament and the Council of the EU adopted a Directive on the application of patients' rights in cross-border health care in 2011. Rare disease-related provisions of this Directive were further strengthened by a series of recommendations of the EU Committee of Experts on Rare Diseases (EUCERD), namely in the field of centres of expertise and European reference networks for rare diseases. These instruments aim to optimise rare disease management and to improve rare diseases patients' care, by ensuring equal access to services and care across Europe.[20] Similar measures were recently transposed in Bulgaria and their practical implementation is expected to begin in the second half of 2015, by the official designation of the first centres of expertise for rare diseases in the country. Having in mind the high burden of CF, Bulgarian health authorities need to make sure the ECFS standards of care are implemented on a regular base at designated centres of expertise, as well as to conduct a feasibility study on introducing CF newborn screening. Ending of health disparities in rare diseases can be achieved only through multidisciplinary efforts to implement all components of high-quality health care (prevention, screening, diagnosis, treatment, follow-up and rehabilitation), and to conduct research that will lead to better prevention and management of

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these disorders. Improved access to adequate and quality treatment would mean reduced economic burden and increased HRQOL in patients with rare diseases and their families.

CONCLUSIONS

Over the past several decades, therapeutic advances have extended the median life span of CF patients. Nevertheless, important health inequalities have remained. Patients from Eastern Europe are a vulnerable population with risk factors for worse health outcomes. Our study aimed to analyse these disparities, by measuring economic burden and HRQOL of Bulgarian CF patients. This type of research provides a state-of-the-art analysis that facilitates the elaboration, adoption and application of targeted public health policies to tackle CF-related problems at national and international level.

In recent years, CF patients have tended to experience longer life expectancy and higher HRQOL despite the lack of etiological therapies. These improved health outcomes are seen as a direct result of the development of health care frameworks, based on the idea of CF centre-cared treatment. CF patients and their families benefit from enhanced health care at a CF expert centre by a multidisciplinary team with emphasis being placed on frequent visits, periodic testing and monitoring adherence to therapy. Better organisation and management of CF care would mean decreased economic burden and enhanced HRQOL. Centres of expertise and reference networks are a key public health policy tool to address health inequalities due to rare diseases in the EU.

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**APPENDIX

BURQOL-RD Research Network

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