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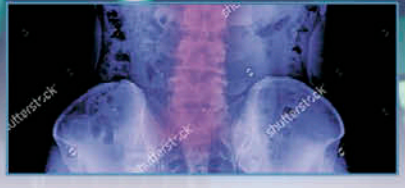

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Telemedicine - a miracle cure for everything?

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Keywords:

e-health, Telemedicine, telepsychiatry

Abstract

Background: Telemedicine is an interesting area of modern treatment. It enables contact between patients and doctors at long distance. In this paper, we present the latest studies, conducted among Polish doctors about the utility of the telemedicine as a therapeutic tool.

Methods: One of the methods was an anonymous questionnaire presented to psychiatrists from Poland (105 physicians). The second study was based on a questionnaire filled by participants (scale: 1-inappropriate to 5-very useful). It was part of the Polish Telemedical Project (grant no.POIG.01.04.00-04-219/12) conducted to assess medical Platform 'Moneo' in the therapy of the areas other than psychiatry.

Results: All healthcare institutions noticed advantages of Medical Platform. The Platform's functionalities, rated as the best by healthcare directors were: educational materials, appointment and therapy planning. Managers indicated parts which could be improved in e-prescribing system, the process of collecting information about hospitalizations, operations. Functionalities regarded by doctors as desirable in improving the platform include: e-prescribing system, reporting side effects, planning visits, educational materials.

In the psychiatrists' study, they had confirmed the potential of telemedicine in psychiatry. They chose mood and neurotic disorders as the most adequate for that treatment. However, 60% of doctors would not widen the implementation of telepsychiatry in Poland. Probably it is due to their awareness for the need of new software, legal and refunding system.

Conclusion: Telemedicine is a useful method for specialists and directors. It can improve quality of healthcare services. However, lots of improvements in telemedical services are needed to make it a miraculous cure for everything.

Introduction

Telemedicine is a very interesting area of modern treatment, using a comprehensive spectrum of communication technologies. As the prefix 'tele' suggests, it enables the contact between patients and doctors no matter what the distance is, via e-mail, SMS or videoconferencing. Additionally, it consists of web pages with data about diseases and their therapy, video- and audiobooks, which patients can use at home. Contemporarily, videoconferencing has become the mainstream in telemedicine treatment and other forms defined as e-health.

The main objective of telemedicine is to save time, improve access to professional treatment for all patients, remind patients of health goals, make appointment planning as well as therapy homework more efficient[1].

Modern telemedicine has begun with experiments, conducted to provide medical services evenly to everybody, such as those by Willem Einthoven's 1905 long distance transfer of electrocardiograms, through the era of teleradiology and telepsychiatry of the 1950s. The development of telemedicine matured in the 1990s and has reached its final in the adoption to the present technology[2].

Nowadays, telemedicine is a proven way to improve patients' attendance at appointments and it has positive effects on patients with chronic diseases[3,4]. Efforts to make telemedicine part of common treatment in Poland are still in process. Reliable web pages are being developed day by day, however, there are still some problems with communication, concerning fear of abuse, lack of knowledge in practitioners, lack of actual law regulations and financial support from the health system[5]. Due to the lack of researches on acceptance and attitude of Polish professionals towards telemedicine, we decided to conduct two studies on utility of the telemedicine as a therapeutic tool in different medical specialties.

Materials and Methods

The aim of the study was to examine doctors' attitude to telemedicine. The first study was part of the Polish telemedical project, granted from National Center for Research and Development (grant no.POIG.01.04.00-04-219/12) conducted to assess medical Platform Moneo as a therapeutic tool in the therapy of the areas other than psychiatry. It also serves to evaluate the potential ability of introducing this to standard therapy. Method of the study was based on a questionnaire filled with the use of a scale scored from 1 to 5, where 1 means "unsuitable" and 5 "very useful". The survey was directed at the staff of health care management: individual medical practice (25 people), private health care center (25 people), state hospitals (25 people), private hospitals (25 people) - Giving us a total of one hundred people from Poland. The survey was also dedicated to 12 specialist doctors.

The second study was based on authors' anonymous questionnaires distributed amongst psychiatrists from Poland (105 doctors aged 26-74, including 74 women and 31 men).

	Polish Telemedical Project	Study about telepsychiatry in Poland
Study group	1) Cardiologists 2) Urologists 3) Pulmonologists 4) Managers	1) Psychiatrists 2) Psychiatric Patients ****
The number of respondents	4) 100*, 12**	1) 1052) 102
Method	Evaluative research with the use of CATI ***	Anonymous survey

Table 1.

** The survey was directed at the personnel of health care management: Individual medical practice (25 people), Private health care center (25 people), State hospitals (25 people), Private hospitals (25 people) - Giving a total one hundred people from whole Poland.*
*** The survey was also dedicated to 12 specialist doctors.*
**** Computer Assisted Telephone Interview; realized with the use of information tools based on CATI study script from 13.10.2014, without patients' participation.*
***** Patients of the Department of Psychiatry and Psychotherapy of Medical University of Silesia.*

	Individual medical practice	Private health care center	State hospital	Private hospital
>4	educational materials	appointments' planning	therapy planning, educational materials, appointments' planning, side effects reporting	therapy planning, educational materials, appointments' planning, side effects reporting
3 -4	therapy planning , compliancemeasurement, appointment planning, side effects reporting	video conference	video conference	examination with the use of clinical scales
<3	report about clinical factors, examination with the use clinical scales			

Table 2.

Results

Managers

All healthcare institutions noticed advantages of the possibility of using Medical Platform as a therapeutic tool. In the question which estimates currently available Platform functionalities, in an individual medical practice group 'educational materials' received the highest grade (average 4.12). For private health care centers 'planning appointments' was the best option (average 4.36) and in public and private hospitals it was 'therapy planning' - it received the best score (average 4.24). The worst rated was the concept of 'videoconference' (average 3.04) and 'examination using clinical scales', it was rated at the lowest level (2.92).

As regards the question about proposals for improving the Platform, considered as "useful" or "very useful" (average more than 4) the following were approved: 'improvement of e-prescribing system' (4.12), 'collection of information about hospitalizations of the patient' (4.07), 'collection of information about operations' (4.05). Only options 'entering the results of laboratory tests by the patient/guardian', 'monitoring patient's physical activity' and 'monitoring the patient's diet' received on average less than 3 points.

Opinions of the management of health care institutions, concerning the possibility of employment of telemedicine were divided (average score 2.71). The level of interest in the offered solutions fluctuated around 2.45. The situation was similar when assessing charging fees for using the telemedicine. Majority of respondents, i.e. 61%, rated this possibility in the range of 1-2 (average 2.25).

Managers were unanimous in evaluating the amount of first-time visits that could be done through the Platform - 84% of respondents indicated range of 0-20%. In the case of follow-up visits, opinion of respondents were divided, but majority of respondents (89%) do not see the possibility that more than 60% of the visits could be done through the Platform.

As regards the question: "Have you noticed the need of the introduction of telemedicine services in patients aged more than 65 years?", responses were split in proportion to each level of the 5-point scale. The average was 2.93. However, the possibility of implementing the Platform in patients aged more than 65 years was rated more critically (average 2.36).

In the presented analysis, this Platform received the highest rate from the management of private hospitals, while the lowest mark was given by the management of private practices. Evaluation obtained from Non-public Health Care Centre and public hospitals were very similar.

Pulmonologists, cardiologists and urologists

The survey was used as a tool for evaluating the available opportunities to use the Platform: videoconferences, clinical examination scales, cognitive training, treatment planning, compliance measurement, educational materials, visit planning, reports about clinical parameters and side effects reporting (1-5 rating scale). It also allowed us to gather suggestions regarding optimization.

The average rate of all tested possibilities of the Platform was evaluated as more than useful (average score 4.13) in conducting treatment by pulmonologists (4.3), cardiologists (4.11) and urologists (3.97). The most frequently chosen functionality was 'planning visits' (4.67), 'videoconference' then 'treatment planning' (4.58), then 'compliance measurement' (4.33) and then 'educational materials' (4.08). The most uncommonly selected component was 'clinical reports' (3.58).It is worth emphasizing that the average assessment of individual medical specializations did not differ among themselves.

Functionalities regarded by doctors as desirable to increase the utility of the Platform are: 'e-prescribing system', 'reporting the patient side effects', 'visits planning', 'educational materials' dedicated to different groups of patients.

Figure 1. Evaluation of the implementation of the new functionalities

The next step was to gather suggestions regarding the preferences and expectations of doctors about the possible use of telemedicine and information that could be provided through the Platform.

According to cardiologists, the Platform could be supplemented with i.a. reporting of clinical parameters, compliance measurement, videocommunication plus clinical scale examination, nonpharmacological recommendations for patients, the results of laboratory and diagnostic tests and monitoring of the therapy. Cognitive training, the need for specific reports regarding nonpharmacological recommendations, monitoring diet and activity of the patient were evaluated as unnecessary for further development

According to urologists, the Platform should be expanded in the following fields: assessment of symptoms (using e.g. the IPSS scale, which is used to rate the severity of symptoms among patients with urination disorders in the course of benign prostatic hyperplasia). Furthermore, it is recommended that clinical scales appropriate for a specific group of patients be introduced. It is also desirable to develop educational materials dedicated to different groups of patients.

Optimization of the platform at the pulmonological level should include: opportunity of conversation between doctor and patient, self-measurement of PEF, opportunity to make an appointment, transfer of treatment scheme and its changes during observation of the patient, compliance's check, disease control (ACT test - patients with asthma, COPD assessment test - in the context of chronic obstructive pulmonary disease) and patients' education (lectures about diseases, their treatment and prevention (quitting smoking, avoiding allergens etc.)) and wide range of presentations (for example drug inhalation technique).

Psychiatrists

According to the study conducted amongst psychiatrists, only 15% of them claim to have an extensive knowledge on telepsychiatry, 76% has a general knowledge about it, 6% heard about it but do not know what it means, and 3% never heard of it. Merely 16% of doctors used telepsychiatry, 84% never tried it [5]. Vast majority of the respondents perceive telepsychiatry as a useful method of treatment in many situations. Almost all of them evaluate this method as a potential complement to conventional therapy.

As seen on the diagram, the most preferable methods of telepsychiatry chosen by psychiatrists were 'educational materials for patients'. In second place came 'contact with a doctor in crisis situations, when immediate help is necessary', and the last on podium was 'conferences for patients' families'. 'Control videoconferencing' was fourth, and 'the first conversation with an anonymous patient' came in as least popular.

According to the physicians, telepsychiatry would be most effective in mood and neurotic disorders (wherein men did not take it into account) and less effective in mental disabilities and mental development disorders. Majority of older doctors, despite their greater willingness to introduce telepsychiatry, could not bring up any disease in which telepsychiatry might be useful. Although doctors noticed positive aspects of this method, 60% of them would ignore its widespread implementation in Poland. Simultaneously, 60% of physicians claim that if they had an opportunity to try telepsychiatry, they would do that. Furthermore, most doctors claim that this method would be particularly useful for people living far away from hospital.

However, these doctors strongly agreed that before common insertion of this method, legal- and refunding system changes should be made. They also noted the need of new software. Simultaneously they were concerned about the disclosure of personal data, the loss of medical secrecy and abuse of this method by patients.

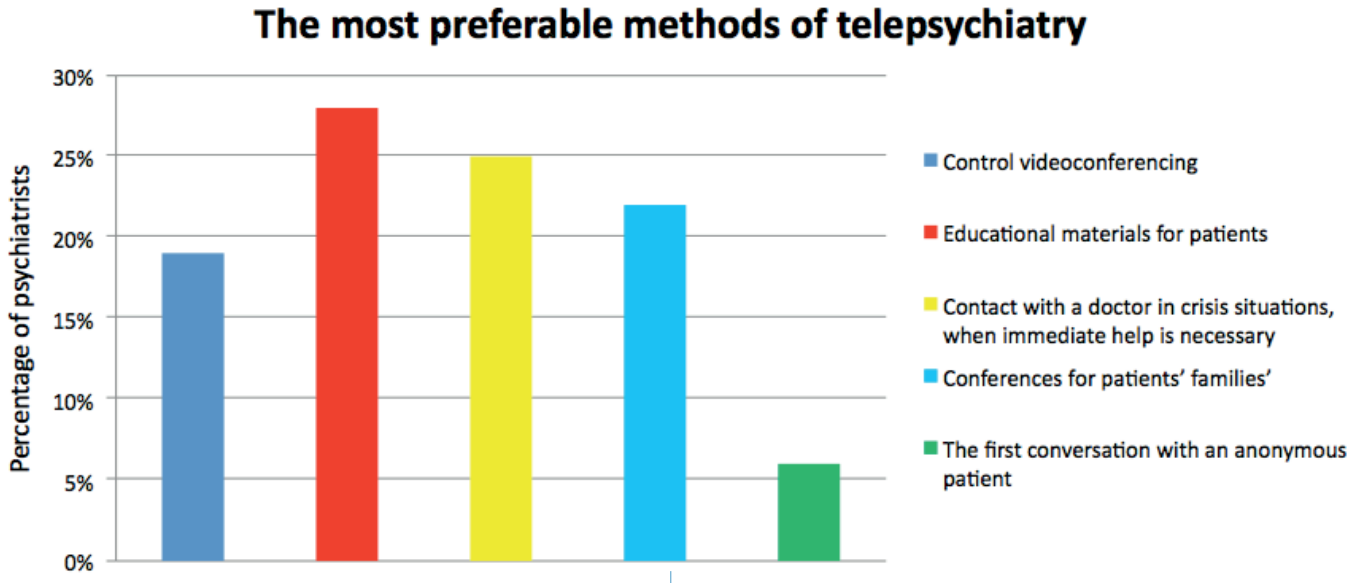

Figure 2. The most preferable methods of telepsychiatry

Discussion

Telemedicine as the cure

The World Health Organization defines telemedicine as beneficial use of information and communication technology in the support of health and healthcare [6]. Accordingly, despite all differences between these two aforementioned studies, both of them suggest that telemedicine is a valuable method worth implementing in Polish medical service. Psychiatrists, together with urologists, pulmonologists, cardiologists and managers unanimously perceive telemedicine as useful in treatment. Administrators and psychiatrists consider 'educational materials' as the most useful functionality. On the other hand, the first group agrees with the specialists that 'planning appointments' is an extremely convenient one too. Psychiatrists also confirmed that telemedicine would be useful in therapy of a wide range of psychiatric ailments, especially mood and neurotic disorders. As proven in many publications, telemedicine is an effective medical tool used to cure a comprehensive spectrum of diseases in almost every medical specialty. In psychiatry: e.g. schizophrenia was treated with great success[7], dermatology[8], radiology, cardiology and even stomatology [9]. Telemedicine is used in treatment of both chronic diseases[10,11] and sudden cases[12,13]. It is also confirmed that this method can be used in adults[14] as well as children and neonates[15].

All arguments mentioned earlier confirm that this technique is not only a cure for patients but also a profitable medium to improve healthcare service and patients' self-awareness, as well as to make prevention more effective.

Telemedicine as the miracle

For some people telemedicine is the only chance to consult a doctor, and as proven by a group of scientists from India [16] it is an effective method of treatment for people living in high mountains. From this perspective, telemedicine could be considered a miracle of application of contemporary technologies to bring help to patients inaccessible by traditional medicine.

Telemedicine is not the cheapest and easiest method to implement in the world, although this treatment method can be cheaper than traditional methods without losing its effectiveness. That fact was proven in the study on two groups of general practitioners, who had similar patients, and the direct cost of the visit to an outpatient clinic in internal medicine turned out seven times greater per patient than those of an electronic consultation[17]. Additionally, this insertion requires legal and refunding system changes, which might become more difficult than introduction of the method itself. Those problems had been noticed by psychiatrists. Doctors and managers have given the opportunity to propose improvements such as compounding the system with the possibility to use clinical scales to asses patients and of reporting patients' side effects. Thus, telemedicine has a potential to be a real miracle, but as all miracles it needs convenient conditions to actually become one.

Conclusions

Considering all data, telemedicine is a useful method for specialists and for directors. It can improve healthcare service and make an access to it possible for some people. However, it might be implepented in Poland too only if some effort will be made to introduce legal and refunding system changes as well as improvements in telemedical services, especially in terms of expanding it by adding more fields of action.

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Protection of sensitive data in telemedicine services

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Keywords:

telemedicine, BYOD, cyber security, protection of sensitive data, SIEM

Abstract

The article presents security risks related to the use of telemedicine services and technical guidelines for protection of the medical records in terms of their confidentiality, integrity and availability. It also mentions regulations related to protection of sensitive data that are required by the Polish government.

Introduction

The common and ubiquitous use of information technology impacts life of humans in all dimensions. One of them is health care, which changes the way both patients and health professionals cooperate. This materializes with the fast development of telemedicine and e-health applications, which have become standard medical practice and are in daily use across dozens of countries.

Telemedicine relates to the practice of health care professionals to evaluate, diagnose and treat patients in remote locations using telecommunications technology. This provides also the possibility for the patients in remote locations to access medical expertise quickly, efficiently and without travel. In developed and developing countries telemedicine offers a reduced cost solution to delivering remote care when and where it is needed without the building and staffing additional facilities. Local practitioners can also consult with their peers and with clinical experts when needed.

The advantages of telemedicine applications in daily medical practice has been valued highly by the medical practitioners. However realization of telemedicine applications relates strictly to the necessity of processing of patients sensitive personal data, usually stored in electronic medical records (EMR's), which now can be accessed from the Internet. Patients personal data, including health and diagnostic reports must be properly protected from unauthorized access. Information technology which is the enabler of telemedicine applications comes with all standard threats known from Internet that apply to the systems, hardware and software. Unfortunately, most healthcare providers treat application security and infrastructure security independently.

The article provides review of security risks related to sensitive data in telemedicine (chapter 2), Polish regulations in the area of medical records protection (chapter 3) and security measures that can be used to protect them (chapter 4). The last chapter provides summary of the guidelines for protection of telemedicine services.

Security risks related to sensitive data in telemedicine

Government regulations, electronic health records, and new Internet health services create numerous security challenges for healthcare compliance and information security teams.

According to Reuters (September 2014)[1] medical information is worth more to hackers than a credit card number on the black market. The data for sale includes names, birth dates, policy numbers, diagnosis codes and billing information. Fraudsters use this data to create fake IDs to buy medical equipment or drugs that can be resold, or they combine a patient number with a false provider number and file made-up claims with insurers, according to experts who have investigated cyber attacks on healthcare organizations.

Medical identity theft is often not immediately identified by a patient or their provider, giving criminals years to use such credentials. That makes medical data more valuable than credit cards, which tend to be quickly canceled by banks once fraud is detected.

According to an Annual Benchmark Study on Privacy & Security of Healthcare Data by the Ponemon Institute think tank from 2014[2], the percentage of healthcare organizations that have reported a criminal cyber attack has risen from 20 percent in 2009 to 40 percent in 2013. This trend continues. The latest annual report from 2016[3] emphasizes that data breaches in healthcare are increasingly costly and frequent, and continue to put patient data at risk. Based on the results of this study, there has been estimated that data breaches could be costing the healthcare industry $6.2 billion in 2016. Nearly 90 percent of healthcare organizations represented in this study had a data breach in 2014-2015, and nearly half, or 45 percent had more than five data breaches in the same time period. The majority of these breaches were small, containing fewer than 500 records. The report emphases that no healthcare organizations, regardless of size, are immune from data breach and are even more vulnerable than other industries. Despite this, about half of all organizations have little or no confidence that they can detect all patient data loss or theft.

For the second year in a row, in 2016 criminal attacks are the leading cause of data breaches in healthcare. In fact, 50 percent of healthcare organizations say the nature of the breach was a criminal attack and 13 percent say it was due to a malicious insider.

Indeed, cyber attacks remain a primary concern for healthcare organizations. In 2016, ransomware, malware, and denial of-service (DOS) attacks are the top cyber threats facing healthcare organizations. They were also significantly concerned about employee negligence, mobile device insecurity, use of public cloud services, and employee-owned mobile devices or BYOD (Bring Your Own Device) - all threats to sensitive and confidential information.

Polish regulations

Patient data confidentiality continues to grow as a leading concern for healthcare organizations. In Poland this has been regulated by the Personal Data Protection Act (from 29th August 1997 with subsequent changes) [4] in which health records fall into broad category of sensitive data the access to which in general is prohibited. One of the special situations when data processing is allowed is during realization of medical services (also telemedicine), however such data must be specially protected from unauthorized access. Processing of data is defined as all operations regarding personal data like gathering, saving, storing, modification, releasing, and deleting.

Regulation of the Minister of Health in terms of Electronic Health Records System (from 6thJune 2013)[5] indicate the necessity of implementation of the security management system that should meet requirements of the Public Entities Computerization Act and specifically – follow ISO/IEC *27002 Information technology – Security techniques – Code of practice for information security management standard*.

ISO/IEC 27002 provides best practice recommendations on information security management for people responsible for initiating, implementing or maintaining information security management systems. It covers 14 security controls describing their objectives and implementation guidance. In the remainder of this paper, 5 of them will be presented in more detail: access control, cryptography, protection from malware, technical vulnerability management and communications security.

Protection of sensitive data in telemedicine services

According to the Personal Data Protection Act, protection of sensitive electronic medical records must be performed during the whole cycle of data processing. Additionally Regulation of the Minister of Health in terms of Electronic Health Records System indicates that the control over this process must rely on the process of information security management, performed according to ISO/IEC 27002 standard. That is why the problem of protecting sensitive data has been described in two dimensions, taking as example 3 data processing steps: release of information, their storage and modification, as well as 5 suggested security controls: access control, cryptography, protection from malware, technical vulnerability management and communications security.

Information release

In general – all telemedicine services rely on information release. Patients' electronic records are made accessible remotely through the network to the patient himself or to his physician for monitoring purposes, additional diagnosis or statistics. Since the whole process involves several devices (i.e. end - user device; server – with telemedicine service running) and networks (usually – Internet, and possibly some internal inter-hospital network), the process of secure information release relates to two sub processes: access control and communications control.

Access Control

First of all, sensitive medical records can be released only to the authorised parties. In general this would be the patient himself and his physician, taking care of the patient. It is necessary therefore to provide identity management in the system that would allow to define user identity together with his role in the system. Based on this information it is possible to design and implement authentication service – for verification of WHO is trying to access particular electronic record. This mechanism can rely on a simple tuple: username and password used to log into the system. The simplicity of this solution is its big advantage (does not require much effort from the user), however this can also be a drawback:

- easy password can be guessed
- people tend to write passwords down where they can be easily accessible
- it is possible to perform brute force attack on the system to find out the password of the user.

That is why in the public domain it is more and more common practice to use qualified X.509 certificates to identify the user, confirmed by a trusted third party (certification authority – in Poland e.g. Certum, PWPW Sigillum).

Additionally, on the basis of the confirmed user identity and his role (e.g. patient, clinicist, researcher, manage-

ment) – authorization service is able to decide whether a user is actually allowed to access particular record. This mechanism must be tailored to the logic of the service taking into account necessity of data anonymization when it is to be used for the purpose of statistics (usually also for researches).

Communications control

Information, while transferred over the network can be subject to e.g. eavesdropping and modification. Information release imposes therefore the necessity to provide:

- Integrity of released information – making sure the information released has not been changed on its way to the requestor, and
- Confidentiality – making sure the information has not been available to any other parties than the authorised during its transfer to the requestor.

Integrity can be realised with the use of digital signature based on the aforementioned qualified X.509 certificates. The digital signature is attached to the requested information. It is calculated with the use of asymmetric cryptography and the keys generated from the X.509 certificate (so called public key – available publicly, and private key – that must be stored securely by the owner – usually on a smart card protected with a secret PIN number). The algorithm allows the sender X to create a hash from the message, and then encrypt it with its private key (known only to the sender). Then if the remote site is able to decrypt the signature, it believes that it is a valid digital signature from sender X. A valid digital signature gives a recipient reason to believe that the message was created by a known sender, that the sender cannot deny having sent the message (authentication and non-repudiation), and that the message was not altered in transit (integrity).

The information, while being sent through the network, can be eavesdropped. This is especially important when the devices are using wireless connections with shared wireless medium (often unprotected Hot Spot WiFi) and when the traffic can be easily captured and read.

Confidentiality of information can be provided with encrypting the information itself or encrypting the communications channel. This also can be done with the use of digital certificates. Public key of the requestor can be used to encrypt the information. After that only the requestor will be able to decrypt the message (with its private key). X.509 certificates can be also used to encrypt the communications channel (using e.g. TLS or SSL connections with one side or mutual authentication).

Another important subject that must be emphasised when discussing information release is non-repudiation. All actions on sensitive information data stores (who accessed which information, with timestamp) must be properly logged for further audit.

Information storage

Sensitive health records are usually stored in databases the protection of which is crucial. It is highly recommended to enforce encryption of data at storage which provides both confidentiality and integrity as well as makes the attempts to read stolen database unsuccessful. Of course sensitive data, after being received from the service, are also stored at user devices. These can be both office computers that are used in hospitals and other medical facilities, but also smartphones, more and more often – private devices used also for official matters. This attitude is usually called "Bring Your Own Device" (BYOD) and is perceived by security specialists as particularly risky due to a very fast growth of threats targeting mobile devices and very careless use of smartphones, which should be treated as personal computers. Each mobile device must have at least antivirus software running. It is also highly recommended to apply for using telemedicine services so called protected profile which allows to encrypt data processed while it is activated.

Information protection

Protecting the confidentiality, integrity, and availability of patient information is a complex task. A foolproof solution must secure both the clinical applications and the underlying IT infrastructure. Dozens of healthcare personnel—registration, accounting, nursing, physicians, technicians, and associates—have access to clinical applications. To safeguard patient privacy, healthcare providers must monitor access to applications and protect against inappropriate data disclosure without impeding legitimate use or obstructing patient care.

The security specialists[6,7] emphasize that implementation of access control, encryption, audit mechanisms are not enough. The overwhelming inflow of security threats, new attack paths and malware types cause that application-layer surveillance alone is not sufficient. Providers must also monitor underlying IT systems (implementing security management system) , employee communications, and endpoints for policy violations. A rogue administrator can avoid an application-centric privacy monitoring solution by accessing raw patient records from databases or network storage devices. However sensitive data can also be leaked via email, chat, removable media, or something as simple as printing patient records in a public area.

	Privacy Monitoring	Security Information and Event Management
Purpose	• Patient privacy	• Network and system security
Focus	• Internal threats	• Internal and external threats
	• Clinical applications	• IT infrastructure
Examples	• Medical record snooping	• Malicious attacks (viruses, worms, Trojan horses)
	• Internal identity theft	• External identity theft
		• Eavesdropping
Audience	• Privacy and compliance personnel	• Information security personnel
	• Business-oriented	• Technology-oriented
Audit Sources	• Clinical applications	• IDS, IPS, firewalls, AAA, switches, routers
Managed Attributes	• Patient, user, and department function codes	• IP addresses, MAC addresses, TCP/UDP ports

Figure 1. SIEM vs Privacy Monitoring by MacAfee[6]

Many healthcare providers treat protection of sensitive data in compliance with government regulations and infrastructure security independently. The functions are performed by separate teams using separate tools. However in order to safeguard the data in the whole cycle of processing these two approaches must be combined. Both privacy officers and security officers need to meet the same regulations and both have a stake in ensuring patient privacy and the integrity of the healthcare systems. Yet what has been lacking is a common set of tools to identify and isolate threats and a way to correlate clinical application events with IT infrastructure events. Such tools are called security information and event management (SIEM) solutions. They identify, collect and analyze important events observed in the network and systems itself and protect against both internal and external threats.

According to MacAfee[7] (see Figure 1.) collective defence based on SIEM is able to identify eavesdropping, external identity thefts and hidden activity of different malicious attacks (caused by viruses, worms or Trojan horses) whereas privacy monitoring alone can only recognize e.g. medical record snooping or internal identity thefts.

Summary

Protection of sensitive data in telemedicine services must follow the best practice of IT security based on standards. Increasing value of patients records on the black market and growing number of threats to computer systems make it necessary to use advanced solutions known from IT systems for cyber defence. It is necessary to implement security management system following ISO/IEC 27002 standard targeting all security dimensions. One of them is also a security culture of the personnel that should be aware of the risks that are related to their behaviour and use of computer devices. There is no single technology solution or best practices guideline that will achieve success without a security culture apparent to all medical practitioners in the organization. It is necessary to carry out periodic trainings presenting both security threats as well as required behaviour of personnel in relation to medical records.

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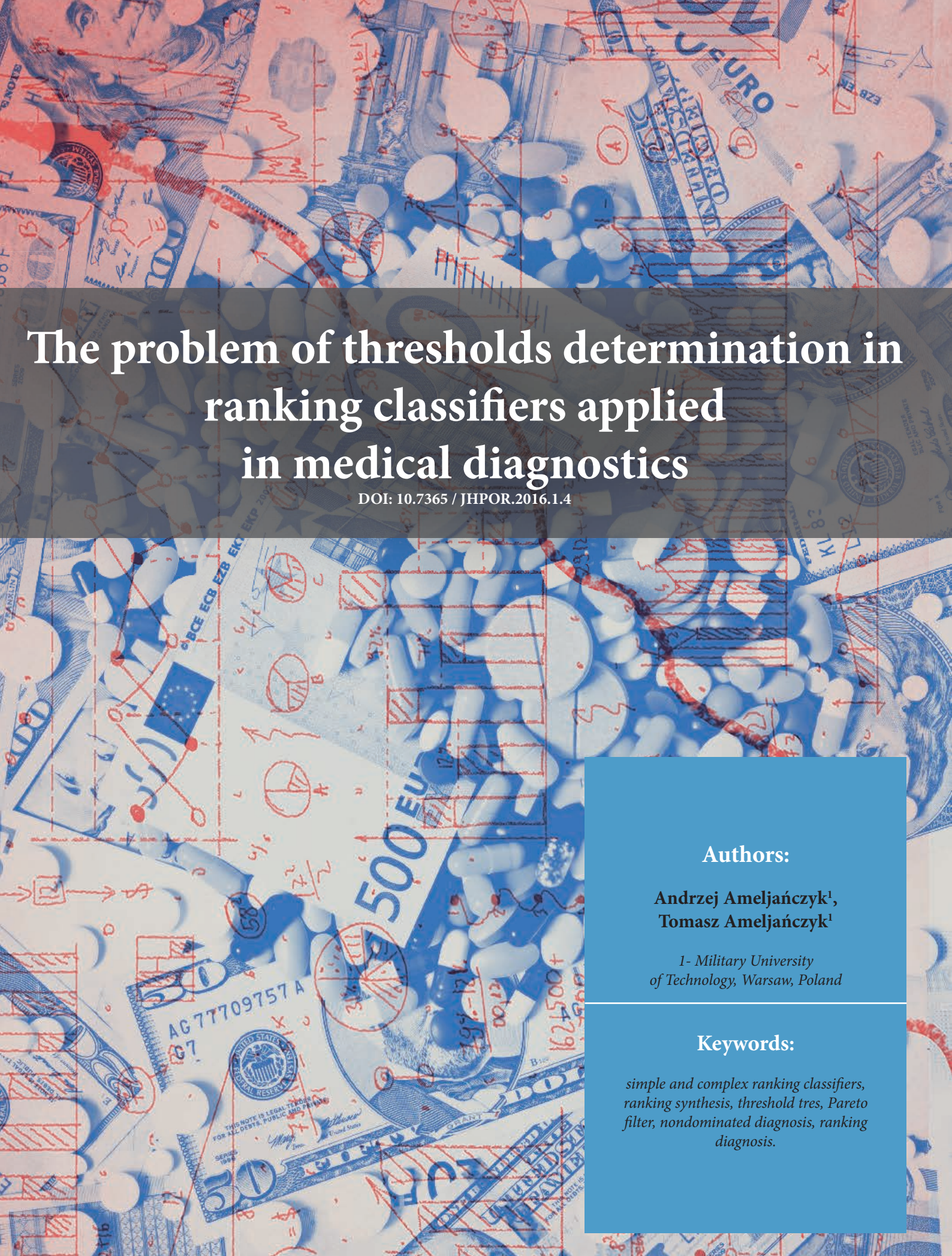

The problem of thresholds determination in ranking classifiers applied in medical diagnostics

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Abstract

The paper presents the opportunity for using multi-objective optimization for the development of ranking meta-classifiers being a synthesis of simple ranking domain functions. The method of threshold determination in the developed ranking classifiers applied in medical diagnostics was presented. Analysis was conducted of properties of medical diagnoses acquired with the application of thresholds for both simple and complex classifiers and for meta-classifiers.

1. Introduction

Diagnostic information on the patient's health contained in medical data in the area of disease symptoms, risk factors and results of specialist laboratory tests are highly diversified and in most cases of a multimedia character[8,9,13,15]. The development of classifiers deriving from such comprehensive, complex and differentiated medical data is a difficult task. The development of simple classifiers e.g. domain and in particular binary is much easier.[6,24,28]. This leads to a problem of fusion of the acquired diagnostics information, reduced in most cases to so-called simple classifier synthesis. The specific nature of medical diagnostics, due to uncertainty and incompleteness of medical data and due to the fact that the patient may suffer not from a single disease but from two or more, gives preferences to the multi-label (multi-class) classifiers[6,7,13,15]. Application of single-label (single-class) classifiers , including in particular ranking ones, requires the determination of a relevant threshold tres. As explained above, the ranking-leading diagnosis does not need to be correct, not to mention the concomitant diseases positioned further in the ranking. The tres should enable extending the diagnosis beyond the ranking-leading diagnosis in a way to ensure that the actual diseases are covered by the threshold set on one hand and that this threshold set is not excessively 'comprehensive' on the other hand. An excessively comprehensive threshold set extends and increases the costs of the diagnostic process. This set forms the basis for further diagnostics activities (iterations) consisting in the selection of a relevant set of specialist laboratory tests or consultations to make the diagnosis more precise. Due to the commonness of ranking classifier application in the medical diagnostics support algorithms, the problem of determining relevant tres value gains on importance. This paper is an attempt to present the method of tres value determination without the need to use the subjective findings of the decision-making body. Content of diagnosis set resulting from a specific tres value of the simple (component) classifier should be higher, the 'poorer' or less reliable the classifier that was applied. The rankings developed on the basis of correctly performed synthesis (fusion) of simple classifiers[2,8,10,13,28] should have relevantly higher thresholds and therefore less numerous sets of resulting diagnoses. The condition that the set of diagnoses resulting from the threshold value of a classifier being a synthesis of simple classifier should contain an intersection (product) of sets of diagnoses resulting from the thresholds of all component classifiers seems to be intuitively obvious. When introducing the term of thresholds in the rankings generating the single-class classifiers, we may convert them into multi-class classifiers. The specific nature of the medical diagnostics processes, due to common uncertainty and incompleteness of data and possibility of the presence of concomitant diseases, practically excludes the support algorithms using the single-label classifiers. On the other hand, the vast majority of medical diagnostics support algorithms are algorithms that apply the ranking functions defined on the basis of various mathematic similarity (fitting) models[24]. Thus the problem of correct determination of thresholds in medical diagnostics ranking development becomes of great importance.

2. Threshold in ranking applications

Let X determine the finite set of medical diagnostic data sets (observations, instances, results), called an observation space.

Let $\mathsf{L} = \{l_1,...,l_m,...,l_M\}$ - set of labels (objects) of disease units, numbered with the $m \in \mathsf{M} = \{1,...,M\}$ index.

A single-label classifier will be the function

$$C : X \to \mathsf{L} \tag{2.1}$$

Each observation (instance) $x \in X$ is 'associated' with the single label $l_m \in \mathsf{L}$

$$C(x) \in \mathsf{L},\ x \in X \tag{2.2}$$

A multi-label classifier will be the function

$$C : X \to 2^{\mathsf{L}} \tag{2.3}$$

Thus

$$C(x) \subset \mathsf{L},\ x \in X \tag{2.4}$$

For each observation $x \in X$ we may define a relation of ranking preferences R_x in a way that $(l_i, l_j) \in R_x$ when and only when for the observation $x \in X$, lablel l_i is more preferred (is 'better', more 'fitted') than label l_j.

The symbol $r(R_x)$ will determine the ranking generated by relation R_x[2,5]. In practice, the models (relations) R_x are frequently defined (determined) using ranking functions:

$$f_x : \mathsf{L} \to R^1 \qquad (2.5)$$

values of which are in general determined on the basis of different similarity ('fitting', 'distance') models, for example: Tversky, Bayes, Jaccard, Hamming, Dice, Sokal, Russel, Lance and others) observation x to disease unit labeled $l \in \mathsf{L}$ [6,7,24,28].

$$R_x = \left\{(l_i, l_j) \in \mathsf{L}^2 \middle| f_x(l_i) \geq f_x(l_j)\right\} \qquad (2,6)$$

Functions $f_x(l)$, $l \in \mathsf{L}$ are sometimes called the utility functions or similarity or fitting ratios. In this paper, we will further assume that the functions $f_x(l)$ are normalized in the range of $[0,1] \subset R^1$[2, 18, 25, 26, 27].

Thus, if for any $l_i, l_j \in \mathsf{L}$it is true that $f_x(l_i) \geq f_x(l_j)$, from the perspective of result (observation) $x \in X$, l_i is placed in the ranking before the label l_j. Definition (2.6) uses purposefully the sign '≥", which results mostly from the fact that the ranking functions are generally not injective functions (this feature results usually from the properties of a model used for definition),[2,20]. Such an assumption results in that the relations of preference R_x. are not antisymmetric[20] which means that these determine only the so-called quasi-order[2]. The rankings acquired in this way are not permutations of set L (are not linear rankings). Adopting the weaker assumptions is implied, however, by the 'practice' of defining the ranking functions, which – as already mentioned – are usually not injective functions. The symbol $r(f_x(l))$ shall determine the sequence (L set ranking) acquired with the use of function $f_x(l)$ [5]. Such ranking functions are frequently used for classifier development. Let $f_x(l)$, $l \in \mathsf{L}$ be a certain ranking function determined on set L.

This function determines the classifier

$$C : X \to 2^{\mathsf{L}}$$

according to the following formula:

$$C(x) = \arg\max_{l \in \mathsf{L}} f_x(l), \; x \in X \qquad (2.7)$$

Relation (2.7) may be presented as follows:

$$C(x) = \arg\max_{l \in \mathsf{L}} f_x(l) = \left\{ \overset{*}{l} \in \mathsf{L} \middle| f_x\left(\overset{*}{l}\right) = \max_{l \in \mathsf{L}} f_x(l) \right\} \qquad (2.8)$$

The relation (2.8) presents the association between the classifier $C(x)$ and the ranking function $f_x(l)$. The classifier of type (2.7) shall mean the simple ranking classifier. The specific nature of medical diagnostics makes the single-label classifiers, including in particular those developed on the basis of ranking functions, insufficient for physicians. As an initial diagnosis, they select a certain number of classes (disease units) placed in the ranking at top positions. This generates a significant problem of determining the values of the so-called threshold – tres, on which the 'content' of initial diagnosis $D_x(tres)$ (threshold diagnosis) depends. It may be written as follows:

$$D_x(tres) = \left\{ l_m \in \mathsf{L} \middle| f_x(l_m) \geq tres \right\} \qquad (2.9)$$

The value of the real number of tres is of significance since it determines a certain diagnostic compromise between striving for increased reliability of initial diagnosis and the number of subsequent diagnostic iterations and, therefore, the total time and cost of the diagnostic procedure. *Tres* in diagnostic classifiers based on the ranking functions are generally the higher, the more precise and reliable are the models being the foundation of the functions.

Synthesis of simple classifiers, as a result of which more precise and reliable classifiers are obtained (with lower classification error) increases the thresholds and, therefore, narrows the set of result diagnoses. The consequence of such an approach is in general a shorter period of the diagnostic process and its lower cost. 'Component' classifier thresholds are obviously lower due to their lower accuracy and reliability.

3. Simple ranking synthesis – meta-rankings

Let further be $\mathsf{L} = \{l_1, \ldots, l_m, \ldots, l_M\}$ - a finite label set and ranking function of the following type:

$$f_x : \mathsf{L} \to R^N$$
$$f_x(l) = \left(f_x^1(l), \ldots, f_x^n(l), \ldots, f_x^N\right) \in R^N, \qquad (3.1)$$

This function generates the following set (committee) of simple (ranking) classifiers):

$$C(x) = \{C_1(x), \ldots, C_n(x), \ldots, C_N(x)\} \qquad (3.2)$$

where

$$C_n(x) = \arg\max_{l \in \mathsf{L}} f_x^n(l) \qquad (3.3)$$

Set Y_x shall be the ranking image of set L for the observation $x \in X$, given by the function f_x (3.1).

$$Y_x = f_x(\mathsf{L}) = \left\{ y = f_x(l) \in R^N \middle| l \in \mathsf{L} \right\} \qquad (3.4)$$

Element $y \in f_x(\mathsf{L})$ is an image of label l in the meaning of its assessment by all ranking functions $f_x^n(l)$, understood as multi-objective level of similarity (fitting) of the observation $x \in X$ to the disease unit labeled $l \in \mathsf{L}$.

Thus $y=(y_1,...,y_n,...,y_N)=\left(f_x^1(l),...,f_x^n(l),...,f_x^N(l)\right)\in \mathsf{R}^N$ (3.5)
where $y_n=f_x^n(l)$ ranking value of label $l\in \mathsf{L}$ in the meaning of n-ranking function associated with observation $x\in X$. For each $x\in X$ it is true that $Y_x\subset Y=[0,1]\times...\times[0,1]$. Set Y shall mean the classifier synthesis area. The synthesis relation (or relation of preferences of classifier committee) shall be the following relation:

$$R\subset f_x(\mathsf{L})\times f_x(\mathsf{L})=Y_x\times Y_x$$

defined as follows:

$$R=\{(y,z)\in Y_x\times Y_x|\text{"committee prefers } y \text{ over } z\text{"}\} \quad (3.6)$$

The synthesis relation R expresses the principle of preferences of committee in the area of deciding whether label l_k is 'better fitted' to observation $x\in X$ compared to label l_m. There are many known preferences applicable to such synthesis. The most typical principle is the Pareto principle (relation, filter). It states that label l_k is more preferred (better fitted to observation x) than label l_m provided that l_k is at least at the same position (or higher) as label l_m in the ranking of each committee member[2,26]. This means that the following must be true:

$$f_x^n(l_k)\geq f_x^n(l_m),\ n\in \mathsf{N} \quad (3.7)$$

The Pareto Filter (PF) is an algorithm enabling determination from any set of elements the set of elements of the highest quality in this set (in the meaning of Pareto relation)[3,4,26]. The effect (result) of applying the Pareto filter on set Y is so-called 'Pareto front' (set of nondominated (minimum)) elements in the meaning of Pareto relation Y_N^R defined as follows:

$$Y_x^{RN}=\{y\in Y_x|n_{\text{does not exists with x that (z,y)}\in R}\}$$

Therefore, the result of the filtration process is decisive for the adopted preferences (filtration) relation R (in more detail – its properties). So, such a relation is frequently called a preference filter or briefly: filter. The general reflection of the Pareto filter is a cone filter (CF), in which the filtration reaction is generated by a cone[2,3]. The CCS task – complex (integrated) classifier synthesis – may be defined as multi-objective optimization[2,3,4] of the form:

$$CCS=(\mathsf{L},f_x,R) \quad (3.8)$$

which may be abbreviated to[2,3,26] :

$$(Y_x,R) \quad (3.9)$$

The synthesis relation R may be used to develop a complex, multi-label classifier (meta-classifier) and meta-ranking (committee ranking), being a 'specific synthesis' of component rankings determined by the ranking functions $f_x^n(l),\ n\in \mathsf{N}$. For meta-ranking and component rankings one may determine the relevant (in the meaning of preference relation R) thresholds, which will enable the acquisition of justified and extended multi-label classifications upon application. The solution of the task (3.8) is thus an anti-image[4,20] of the task solution (3.9), i.e. subset of labels, from which there are no 'better' labels in the set L (better fitted) to the observation $x\in X$.

$$\mathsf{L}_x^{RN}=f_x^{-1}\left(Y_x^{RN}\right) \quad (3.10)$$

where $Y_x^{RN}=\{y\in Y_x|\ \overset{does\ not}{exists\ with}\ z\in Y_x-\{y\},that(z,y)\in R\}$ (3.11)

thus $\mathsf{L}_x^{RN}=f_x^{-1}\left(Y_x^{RN}\right)=\{l\in \mathsf{L}|f_x(l)\in Y_x^{RN}\}$ (3.12)

Set L_x^{RN} is called a nondominated label set or Pareto set (front)[3,4,26,27]. This is a subset of these labels from the set L, from which there are no better 'fitted' labels to the observation $x\in X$. The integrated classifier in the meaning of relation R (meta-classifier) is the complex classifier

$$C_R(x)=f_x^{-1}\left(Y_x^{RN}\right)\subset \mathsf{L} \quad (3.13)$$

This is in general the multi-label classifier, which assigns to each observation (instance) $x\in X$ the 'optimum' subset of nondominated labels L_x^{RN} in the meaning of relation R. In medical diagnostics, this diagnosis is considered the 'best fitted' diagnosis corresponding to observation $x\in X$ This proposal is the most important and the most frequently applied diagnostic reference in the process of computer diagnosing support [6,7]. Having the set of simple classifiers based on the ranking functions, we may develop a meta-classifier (component classifier) based on the ranking function F (ranking meta-function), being a synthesis of the applied ranking functions $f_x^n(l),n\in \mathsf{N}$. It is done by determining the 'resulting' ranking $r(F)$ the most similar' to the component rankings $r\left(f_x^n(l)\right),\ n\in \mathsf{N}$. A simple method for the development of meta-ranking $r(F)$ is using the ranking function defined on the basis of the integrated classifier synthesis task (3.8) considered as a typical task of multi-objective optimization[3,4,26]. The ranking meta-function F may be defined using the Minkowski standard in the following manner (3.14) :

$$F\left(f_x(l)\right)=F\left(f_x^1(l),...,f_x^n(l),...,f_x^N(l)\right)=F(y)=\left\|\overset{*}{y}(x)\right\|_p-\left\|\overset{*}{y}(x)-y\right\|_p,\ y\in Y_x,\ p\geq 1$$

The symbol $\|y\|_p,\ p\geq 1$ shall apply to standard with parameter p [2,3]. Element $\overset{*}{y}(x)=\left(\overset{*}{y}_1(x),...,\overset{*}{y}_n(x),...,\overset{*}{y}_{N1}(x)\right)\in \mathsf{R}^N$ is a greatest lower bound of set Y_x for relation R[3,4], i.e. so-called ideal point (utopian point)[3,4,26]. The element (point) $\overset{*}{y}(x)\in \mathsf{R}^N$ an image of utopian (virtual) label of the highest possible ranking parameters, i.e. such that

$$\overset{*}{y}_n(x)=\max_{y\in Y_x} y_n=\max_{l\in \mathsf{L}} f_x^n(l),\ n\in \mathsf{N} \quad (3.15)$$

Assuming for convenience that all ranking functions are normalized to the range of $[0,1]\subset \mathsf{R}$, we will obtain(3.14) upon normalization:

$$F(y)=1-\frac{1}{\left\|\overset{*}{y}(x)\right\|_p}\left\|\overset{*}{y}(x)-f_x(l)\right\|_p=1-\alpha_x\left\|\overset{*}{y}(x)-f_x(l)\right\|_p$$

i.e. in consequence a normalized ranking meta-function

$$F(f_x(l))=1-\alpha_x\left\|\overset{*}{y}(x)-f(l)\right\|_p,\ l\in\mathsf{L},\ p\geq 1 \qquad (3.16)$$

where α_x - normalization coefficient[7].
The ranking meta-classifier shall adopt the following form according to (2.7):

$$C_F(x)=\arg\max_{l\in\mathsf{L}}F(f_x(l))\subset\mathsf{L} \qquad (3.17)$$

Set $C_F(x)$ may be considered an initial diagnosis. In many cases this is a single-element set[3, 4,26]. The extension of initial diagnosis with regard to the specific nature of medical diagnostics may be a set of diagnoses compliant with ranking $r(F)$ above the determined tres:

$$D_F(tres)=\{l\in\mathsf{L}|F(f(l))\geq tres\} \qquad (3.18)$$

The *tres* symbol shall be the value of threshold in the ranking acquired thanks to ranking meta-function (3.16). The problem of the method for determining an optima (relevant) value of such threshold arises here.

4. Method of ranking function threshold determination

Tres in diagnostic applications should meet a series of conditions referred to in Clause 2 of this paper.

One of the key conditions to be met by tres is a request that the threshold label set (3.18) contains the set of all labels, of which there are no better (more fitted or similar) labels in the label set L in the meaning of the adopted preference relation R, i.e. the set of nondominated labels L_N^R. Set of threshold labels cut off by the determined value of tres is specified by the relation (3.18). To meet this condition, the following must be true:

$$\mathsf{L}_x^{RN}=f_x^{-1}\left(Y_x^{RN}\right)\subset D_x(tres) \qquad (4.1)$$

The correlation between the preference relation R and the ranking function $F(y)$ is specified by the following lemma.

Lemma 1
Let R be the preference relation (3.6) and function F be a ranking meta-function (3.14). For each pair $(y,z)\in R$ it is true that $F(y)\geq F(z)$. This means that y is higher in the ranking than z (i.e. if y is better from z in the meaning of the adopted preference relation R, y must be placed nearer the ideal point than element z) .

Proof:
The condition $F(y)\geq F(z)$ may be written as follows:

$$\left\|\overset{*}{y}(x)\right\|_p-\left\|\overset{*}{y}(x)-y\right\|_p\geq\left\|\overset{*}{y}(x)\right\|_p-\left\|\overset{*}{y}(x)-z\right\|_p,\ p\geq 1$$

Subtracting by sides $\left\|\overset{*}{y}(x)\right\|_p$ we obtain

$$\left\|\overset{*}{y}(x)-y\right\|_p\geq-\left\|\overset{*}{y}(x)-z\right\|_p \text{ and further}$$

$$\left\|\overset{*}{y}(x)-y\right\|_p\leq\left\|\overset{*}{y}(x)-z\right\|_p \qquad (4.2)$$

For Minkowski metric[2,26]:

$$\left\|\overset{*}{y}(x)-y\right\|_p=\left(\sum_{n\in\mathsf{N}}\left(\left|\overset{*}{y}(x)-y_n\right|^p\right)\right)^{1/p},\ p\geq 1 \qquad (4.3)$$

To prove the lemma, we must demonstrate that for any pair $(y,z)\in R$ is is true that (4.2).
if $(y,z)\in R,\ y_n\geq z_n,\ n\in\mathsf{N}$ (4.4)

From the definition of greatest lower bound $\left\{\overset{*}{y}(x)\right\}$ of set Y_x:

$$\overset{*}{y}(x)\geq y \quad \text{for each } y\in Y_x \qquad (4.5)$$

Therefore it is true that:

$$\begin{aligned} &a)\quad \overset{*}{y}_n(x)\geq y_n,\ n\in\mathsf{N}\\ &b)\quad \overset{*}{y}_n(x)\geq z_n,\ n\in\mathsf{N}\end{aligned} \qquad (4.6)$$

With regard to (4.6), the relation (4.3) shall be as follows:

$$\left(\sum_{n\in\mathsf{N}}\left(\overset{*}{y}_n(x)-y_n\right)^p\right)^{1/p}\leq\left(\sum_{n\in\mathsf{N}}\left(\overset{*}{y}_n(x)-z_n\right)^p\right)^{1/p} \qquad (4.7)$$

The relation (4.7) will be met if we demonstrate that:

$$\left(\overset{*}{y}_n(x)-y_n\right)\leq\left(\overset{*}{y}_n(x)-z_n\right) \text{ for each } n\in\mathsf{N}$$

Subtracting from both sides $\overset{*}{y}_n(x)$, we obtain

$$-y_n\leq-z_n \text{ that is } y_n\geq z_n,\ n\in\mathsf{N}$$

This is true since $(y,z)\in R$ and this means that $y_n\geq z_n$ for each $n\in\mathsf{N}$.

Lemma 1 may be also read as follows: if element y precedes element z in the meaning of preference relation R (is better in terms of R the element y is in the meta-ranking $r(F)$ at higher position (at east at the same position) than element z, which further means that if label l_m such that $f_x(l_m)=y$ is preferred (in terms of R more than label l_k such that $f_x(l_k)=z$, then in the ranking $r(F)$ determined by ranking meta-function F, label l_m precedes label l_k . To meet the general condition (4.1), value of *tres* should

be such that even the most distant from the ideal point (in terms of the adopted metric) element $y \in Y_x^{RN}$ should be placed in a set cut-off by tres.

Let's determine with $\overline{tres}$ symbol the number equal to $\max_{y \in Y_x^{RN}} \left\| \overset{*}{y}(x) - y \right\|_p$ (4.8)

Thus the *tres* value meeting the condition (4.1) may be defined as follows:

$$tres = \left\| \overset{*}{y}(x) \right\|_p - \overline{tres} \tag{4.9}$$

The set of 'cut-off elements' by the threshold of function $F(y)$ shall be as follows:

$$Y_x(F) = \{ y \in Y_x | F(y) \geq tres \} \tag{4.10}$$

The anti-image of this set may be considered the value (indication) of the new ranking meta-classifier $C_F^{\overset{*}{y}}(x)$:

$$C_F^{\overset{*}{y}}(x) = f_x^{-1}(Y_x(F)) = D_x(F) \tag{4.11}$$

This set may be considered the extender initial diagnosis.

The key property of this new extension is the fact that the content (indication) of the integrated classifier $C_R(x)$ is a subset of values (indications) of the ranking meta-classifier $C_F^{\overset{*}{y}}(x)$ i.e. $C_R(x) \subset C_F^{\overset{*}{y}}(x)$. This is true since $Y_x^{RN} \subset Y_x(F)$ i.e. for each $y \in Y_x^{RN}$ it must be true that: $F(y) \geq tres$

According to relation (4.8) for each $y \in Y_x^{RN}$ it is true that

$$\left\| \overset{*}{y}(x) - y \right\|_p \leq \max_{y \in Y_x^{RN}} \left\| \overset{*}{y}(x) - y \right\|_p$$

thus $$-\left\| \overset{*}{y}(x) - y \right\|_p \geq -\max_{y \in Y_x^{RN}} \left\| \overset{*}{y}(x) - y \right\|_p$$

addiing to both sides $\left\| \overset{*}{y}(x) \right\|_p$ we obtain

$$\left\| \overset{*}{y}(x) \right\|_p - \left\| \overset{*}{y} - y \right\|_p = F(y) \geq \left\| \overset{*}{y}(x) \right\|_p - \max_{y \in Y_x^{RN}} \left\| \overset{*}{y}(x) - y \right\|_p = tres$$

thus for each $y \in Y_N^R$ we obtain $F(y) \geq tres$

Therefore $$f^{-1}\left(Y_x^{RN}\right) = L_x^{RN} \subset f_x^{-1}(Y_x(F) = D_x(F))$$

thus $$L_x^{RN} \subset D_x(F)$$

A set of labels $D_x(F)$ may contain, apart from labels from set L_x^{RN}, the labels ('diagnosis extensions') which do not belong to this set. These labels are of unique properties, specified (among others) by the two following lemmas.

Lemma 2

If in the set $D_x(F) \setminus L_x^{RN}$ (in the set of the remaining initial diagnosis labels) there is a label better than any other label in set L_x^{RN} in the meaning of ranking meta-function *F*, in set L_x^{RN} there is at least one label better than such label in the meaning of preference relation *R*.

Proof:

Let $l_k \in D_x(F) \setminus L_x^{RN}$ such that
$F(l_k) \geq F(l_m)$ for a certain label $l_m \in L_x^{RN}$

Since $l_k \notin L_x^{RN}$, according to (3.10) and (3.11) in set L_x^{RN} there must be such label l_r, that $(f_x(l_r), f_x(l_k)) \in R$

Lemma 3

For each label $l_k \in D_x(F) \setminus L_x^{RN}$ in set L_x^{RN} there is such label l_m, which is higher from this label (at least at the same position) in the meta-ranking $r(F)$.

Proof:

In set L_x^{RN} there is such label l_m, which is better than label l_k in the meaning of relation R (see (3.10),(3.11)) i.e. such that $(f_x(l_m), f_x(l_k)) \in R$. If so, under lemma 1 the following is true:

$$F(f_x(l_m)) \geq F(f_x(l_k))$$

which means that l_m is positioned higher in the meta-ranking that label l_k. Thus, the tres defined in (4.9) determines the nontrivial 'cut-off diagnoses set' containing all non-dominated diagnoses (3.12) and the additional ones meeting lemmas 2 and 3.

The ranking meta-function $F(y)$ may be considered as the effect of synthesis of ranking functions $f_x^n(l)$ $n \in \mathbb{N}$ and ranking $r(F)$, respectively, as the synthesis of component rankings $r(f_x^n(l))$, $n \in \mathbb{N}$.

For the component ranking functions $f_x^n(l)$ we may determine the value of $tres(n)$, $n \in \mathbb{N}$. These numbers, identically as the *tres* value, must meet the following conditions (among others, be a part of the 'cut-off' label set, labels from which there are no better fitted labels L_x^{RN}). Thus we may determine them as follows (see (3.11),(3.12)):

$$tres(n) = \min_{y \in Y_x^{RN}} y_n, \quad n \in \mathbb{N} \tag{4.12}$$

$$Y_x(tres(n)) = \{ y \in Y_x | (y_n \geq tres(n)) \} \tag{4.13}$$

It is easy to demonstrate that

$$Y_x^{RN} \subset Y_x(tres(n)) \text{ for each } n \in \mathbb{N} \tag{4.14}$$

m	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
f_x^1	0.3	0.4	0.5	0.6	0.6	0.5	0.5	0.3	0.2	0.5	0	0.1	0.2	0.4	0.5	0.4	0.3	0.2	0.3	0.4
f_x^2	0.6	0.7	0.6	0.4	0.3	0.2	0.1	0.1	0.1	0.5	0.4	0.6	0.6	0.5	0.4	0.3	0.2	0.4	0.5	0.6

Table 1.

Set of labels (diagnoses) determined by *tres*(n) is as follows:

$$D_x(tres(n)) = f_x^{-1}(Y_x(tres(n))) \qquad (4.15)$$

For each $n \in \mathsf{N}$ it is obviously true that:

$$\mathsf{L}_x^{RN} \subset D_x(tres(n)) \qquad (4.16)$$

5. Ranking synthesis – diagnostic example

The example concerns determination of initial diagnosis for the patient on the basis of diagnosed symptoms of disease and risk factors with regard to their intensification. The applied diagnostic model, described in the papers[5,6,7] also considers the significance levels for the applicable symptoms and risk factors in diagnosing individual diseases. Data on the patient's health condition (observation $x \in X$) were divided by domains into two areas: data on symptoms presence and data on risk factors and their intensification. These data formed a basis for developing two classifiers.

$f_x^1(l)$ - similarity rate for symptoms[6,7]
$f_x^2(l)$ - similarity rate for risk factors[6,7] (5.1)

Set $\mathsf{L} = \{l_1,...,l_m,..,l_{20}\}$ in the analyzed example is a set of twenty disease units (labels) indexed with $m \in \mathsf{M}$, presented in Table 1. This table also contains (for the adopted observation of medical results $x \in X$) the values of both ranking functions (5.1). As we see, these values are not injective, therefore the rankings $r(f_x^1)$ and $r(f_x^2)$ developed on the basis thereof will be not linear.

On the basis of the a/m functions, the following two classifiers were developed:

$$C_1(x) = \arg\max_{l \in \mathsf{L}} f_x^1(l)$$
$$C_2(x) = \arg\max_{l \in \mathsf{L}} f_x^2(l) \qquad (5.2)$$

Classifications acquired with these classifiers (initial diagnoses) are as follows:

$$D_1(x) = C_1(x) = \{l_4, l_5\},\ D_2(x) = C_2(x) = \{l_2\} \qquad (5.3)$$

Diagnostic concluding on the basis of these results is most probably hindered and doubtful, for example due to the fact of their divergence:

$$C_1(x) \text{Ç} C_2(x) = \text{Ć} \qquad (5.4)$$

Determining the applicable thresholds - *tres* (1) and *tres* (2) – we could 'extend' the sets of indications (5.3), increasing the safety of further diagnostic process. The rankings of set L generated by the ranking functions (6.1) are 'highly diversified' and have the following form:

$$r(f_x^1) = \langle 4,5,3,10,15,6,7,2,20,14,16,1,19,17,8,13,18,9,12,11 \rangle$$
$$r(f_x^2) = \langle 2,3,20,1,13,12,10,14,19,4,15,18,11,5,16,6,17,7,8,9 \rangle$$

Assuming on arbitrary basis that $tres(1) = 0{,}5$ and $tres(2) = 0{,}6$ we obtain:

$$C_1(tres(1) = 0{,}5) = D_x(tres(1)) = \{l_4, l_5, l_3, l_{10}, l_{15}, l_6, l_7\}$$
$$C_2(tres(2) = 0{,}6) = D_x(tres(2)) = \{l_2, l_3, l_{20}, l_1, l_{13}, l_{12}\}$$

Referring to ((5.3) and (5.4)) we obtain the initial indication:

$$D_x^1(0) = D_x(tres(1)) \cap D_x(tres(2)) = \{3\} \qquad (5.6)$$

Adopting the proposal $D_x^1(0)$ as an initial diagnosis is risky – only one element l_3, whereas adopting the proposal $D_x^2(0)$ is safer, however, expensive due to time and costs of further diagnostic iterations making the diagnosis more precise.

Figure 1 presents the area of synthesis Y as well as ranking image Y_x of set for observation $x \in X$ (3.5) and ideal point $\overset{*}{y}(x) = (0{,}6; 0{,}7)$ (see (3.15). This point is a ranking image of virtual label (utopian label) of such a disease unit, which would have the highest similarity rate in terms of symptoms and risk factors under observation $x \in X$ [6,7,24]. As the synthesis relation the Pareto relation was adopted – the most common in such cases[2,3,4,6,26,27]:

m	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
$F(l_m)$	0.06	0.722	0.781	0.622	0.522	0.412	0.314	0.251	0.201	0.699	0.251	0.412	0.510	0.639	0.606	0.475	0.339	0.422	0.562	0.699
$r(F)$	3	2	10	20	14	4	15	1	19	5	13	16	18	6	12	17	7	8	11	9
$r(f_x^1)$	4	5	3	10	15	6	7	2	20	14	16	1	19	17	8	13	18	9	12	11
$r(f_x^2)$	2	3	20	1	13	12	10	14	19	4	15	18	11	5	16	6	17	7	8	9

Table 2.

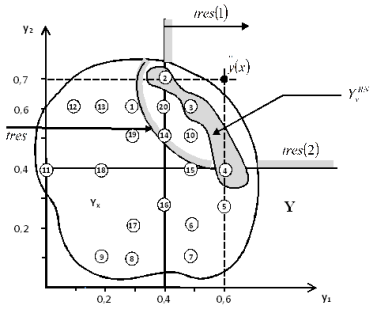

Figure 1. Area of synthesis Y and set Y_x along with ranking reference point $\overset{*}{y}(x)$

According to (3.11) and (3.13), an integrated classifier (generated in result of synthesis) shall be the classifier:

$$C_R(x) = f_x^{-1}\left(Y_x^{RN}\right) \subset \mathsf{L} \qquad (5.8)$$

Set $Y_x^{RN} = \{2,3,4\}$, present in (5.8) was marked in Figure 1

Thus

$$C_R(x) = f_x^{-1}(\{(0,4;0,7),(0,5;0,6),(0,6;0,4)\}) = \left\{l_m \in \mathsf{L} \middle| f_x(l_m) \in Y_x^{RN}\right\} = \{l_2, l_3, l_4\}$$

that is $C_R(x) = \mathsf{L}_x^{RN} = \{l_2, l_3, l_4\} \subset \mathsf{L}$

This is a set of disease units (labels), from which there are no 'more fitted' units in set L with regard to observation $x \in X$ in the area of diagnosed symptoms and risk factors. This is the effect of operation of the integrated classifier (3.13).

Let's notice that

$$C_R(x) \cap D_x(tres(1)) = \{3,4\}$$
$$C_R(x) \cap D_x(tres(2)) = \{2,3\} \qquad (5.10)$$

An obligatory condition (4.1) is therefore not met which means that the arbitrary values *tres*(1) and *tres*(2) were not selected properly.

Further part of this paper presents the results of classification acquired by application of an additional complex classifier developed based on ranking meta-function (3.16). Values of this function and applicable rankings are presented in Table 2.

For simplified form, instead of $\|y\|_p$, we will use $\|y\|$ (assuming that p=2). Threshold *tres*, in line with (4.9) has a value of:

$$tres = \left\|\overset{*}{y}(x)\right\| - \overline{tres}\ , \text{ where } \left\|\overset{*}{y}(x)\right\| = \|(6,7)\| \cong 0{,}922$$

wheras $\overline{tres} = \max_{y \in Y_N^R} \left\|\overset{*}{y}(x) - y\right\| = 0{,}3 \qquad (5.11)$

Thus $tres = 0{,}922 - 0{,}3 \cong 0{,}62$

Figure 1 presents the cut-off area according to threshold tres=0,62 and cut-off set $Y_x(F)$

$$Y_x(F) = \{y \in Y_x | F(y) \geq 0{,}62\} = \{2,3,4,10,14,20\}$$

Thus according to (4.11) we obtain:

$$C_F^{\overset{*}{y}}(x) = D_x(F) = \{l_2, l_3, l_4, l_{10}, l_{14}, l_{20}\} \qquad (5.12)$$

It is true that:

$$C_R(x) \subset C_F^{\overset{*}{y}}(x) \text{ that is } \{l_2, l_3, l_4\} \subset \{l_2, l_3, l_4, l_{10}, l_{14}, l_{20}\}$$

As we see, $C_F^{\overset{*}{y}}(x)$ is the extension of diagnosis of the integrated classifier $C_R(x)$ by certain new labels (disease units):

$$C_F^{\overset{*}{y}}(x) \setminus C_R(x) = \{l_{10}, l_{14}, l_{20}\} = C_R^{\oplus}(x) \qquad (5.13)$$

The labels from this set are better in terms of meta-function *F* from label no. 4 (see Lemma 2). In line with Lemma 2, if there is a label in this set, which is better than any other label from set $C_R(x)$ in terms of meta-function *F*, there is a label in set $C_R(x)$ better than such label in the meaning of *R*. Therefore:

for $l_{10} \in C_R^{\oplus}(x)$ such label is l_3,
for l_{14} such label is l_2 and l_3,
for l_{20} such label is also l_2 and l_3.

The ranking function $F(y)$ generates the ranking meta-classifier (3.17):

$$C_F(x) = \arg\max_{l \in \mathsf{L}} F(f_x(l)) = \{3\} \qquad (5.14)$$

For analytical purposes is is worth to determine the values of *tres*(1) i *tres*(2) for the rankings leading to simple classifiers $C_1(x)$ and $C_2(x)$ (see 4.12). Pursuant to (4.12) we will obtain the following values *tres*(1)=0,4 and *tres*(2)=0,4 and therefore the applicable cut-off sets (4.13):

$$Y_x(tres(1) = 0{,}4) = \{4,5,3,10,15,6,7,2,20,14,16\}$$
$$Y_x(tres(2) = 0{,}4) = \{2,3,20,1,13,12,10,14,19,4,15,18,11\}$$

The obtained results and their properties are presented in the table below.

Table 3 presents the list of indications of the individual classifiers on the basis of observation $x \in X$ with reference to set L.

As we see, a significant discrepancy of the component rankings $r(f_1)$ and $r(f_2)$ resulted in lowering the *tres*(1) and *tres*(2) and thus led to highly 'extensive' (blurred, non-expressive) diagnostic proposals.

The last two columns of the table present information on conformity of the conformity rate of the indication of the given classifier with 'baseline indication' L_x^{RN}, concerning the set of labels, from which there are no other better fitted (see (3.15)). The last column of the table contains the values of Jaccard's conformity (similarity) index[24,28] of indication of a given classifier with a set of diagnosis, from which there are no better fitted (see (3.11) and (3.12)). The next to last column contains information on 'intersection' of the indication of a given classifier with the set of nondominated labels $C_R(x) = L_x^{RN} = \{l_2, l_3, l_4\} \subset L$ and coverage index with regard to intersection (proportion of a number of nondominated labels contained in the classifier indication to the total number of nondominated labels).

7. Summary

The paper presents the method of synthesis of simple classifiers based on the ranking function and using the multi-objective optimization methodology. The synthesis applies the simpliest relation used in the multi-objective optimization (3.7), the so-called Pareto relation. Using the Pareto classifier (3.13) also enables additional determination of the tres values for ranking classifiers (simple) and any complex classifiers. Among others, the paper defines the ranking meta-classifier (3.17) and applicable tres. Also, the specific properties of the additionally obtained diagnoses present in the cut-off set $D_x(F)$ were discussed. In practice, determination of tres (4.9) must not require determination of Pareto set, which may be complicated. Useful estimation of the tres value may be a distance of the lexicographic element of set Y_x the most distant from the ideal point, which is much easier to determine[3,4]. The method of threshold determination may be used for any ranking classifiers, among others, those developed on the basis of weighted totals of component rankings, averaged rankings, voting rankings, etc. Even a brief analysis of the results obtained in the example (including analysis of Figure 1) demonstrates obvious benefits resulting from synthesis of classifiers leading to increased value of many indexes used for the assessment of quality of classifiers, such as: ranking function injectivity index, ambiguity index, expressiveness index and reliability of indications [1,6,7,28].

NO.	Classifier	CLASSIFIER INDICATIONS INITIAL DIAGNOSIS	INTERSECTION WITH SET L_N^R	JACCAR'S CONFORMITY TO SET L_N^R
1	$C_1(x)$	$\{l_4, l_5\}$	$\{l_4\}$, 1/3	1/4
2	$C_2(x)$	$\{l_2\}$	$\{l_2\}$ 1/3	1/3
3	$C_1(tres(1)) = 0{,}5$	$\{l_4, l_5, l_3, l_{10}, l_{15}, l_6, l_7\}$	$\{l_3, l_4\}$ 2/3	1/4
4	$C_2(tres(2)) = 0{,}6$	$\{l_2, l_3, l_{20}, l_{11}, l_{13}, l_{12}\}$	$\{l_2, l_3\}$ 2/3	2/7
5	$C_1(tres(1)) = 0{,}4$	$\{l_4, l_5, l_3, l_{10}, l_{15}, l_{16}, l_6, l_7, l_2, l_{20}, l_{14}, l_{16}\}$	$\{l_2, l_3, l_4\}$ 1	1/11
6	$C_2(tres(1)) = 0{,}4$	$\{l_2, l_3, l_{20}, l_1, l_{13}, l_{12}, l_{10}, l_{14}, l_{19}\}$	$\{l_2, l_3, l_4\}$ 1	3/13
7	$C_F^{\cdot}(x)$	$\{l_2, l_3, l_4, l_{10}, l_{14}, l_{20}\}$	$\{l_2, l_3, l_4\}$ 1	1/2
8	$C_F(x)$	$\{l_3\}$	$\{l_3\}$, 1/3	1/3
9	$C_R(x)$	$\{l_2, l_3, l_4\}$	$\{l_2, l_3, l_4\}$ 1	1

Table 3.

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Budget impact analysis of breast cancer in the Russian Federation

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Breast cancer is one of the leading causes of cancer-related morbidity and mortality in the female population of the Russia and its incidence is rapidly growing. Advanced breast cancer is a disease currently intreatable, but up-to-date management strategies result in significant improvement of symptoms, life expectancy and quality of life. Implementation of new technologies always results in extended healthcare expenditures, therefore requiring pharmacoeconomical justification.
Russian Society for Pharmacoeconomics and Outcomes Research performed health economics evaluation of typical management strategies of patients with advanced hormone-dependent HER2-negative breast cancer, based on survey of experts. The questionnaire developed for this purpose including data relevant to epidemiological and pharmacoeconomic assessment of management of such patients. Calculation of expenses incurred by medications and medical care was performed based on experts' data and according to the medical care standard #612н. Markov model in Microsoft Excel® application, as developed by York Health Economics Consortium, was used for pharmacoeconomic analysis. The model was based on approaches to treating patients with breast cancer for the duration of 5 years. Managing postmenopausal patients diagnosed with advanced hormone-dependent HER2-negative breast cancer with and without administration everolimus were assessed as alternative approaches, and the method of health economic analysis of budget impact was used to compare them. According to the analysis results, implementation of everolimus administration in the treatment strategies for postmenopausal patients with advanced hormone-dependent HER2-negative breast cancer does not incur significant increases of healthcare budget expenses in the Russian Federation.

Introduction

Breast cancer is the most common malignancies in the female population of economically developed nations. According to the global statistics, every year more than 1.2 million women develop breast cancer, and 450 000 succumb to that disease[1]. In Russia breast cancer ranks as first in the overall structure of cancer incidence and cancer-related mortality in the female population.

In certain prognostically favorable populations of patients with early breast cancer 5-year disease-free survival is 98%[2]. Nevertheless, more than half of breast cancer patients develop remote metastatic lesions. The highest rate of tumor dissemination is at 2-3 years after treatment initiation, although the risk of metastatic spread remains relevant even after 5-10 years after the end of treatment.
Advanced breast cancer is an intreatable disease, but up-to-date treatment approaches have resulted in clinically significant advances in improving both symptoms and life expectancy. Median of overall survival in advanced breast cancer is approximately 24 months[3]. However, in postmenopausal patients with hormone-dependent advanced breast cancer median overall survival can reach 4 years, ranging between 5 and 50 months, even despite multiple metastatic lesions[1].

Pharmacological treatment of advanced breast cancer is aimed at achieving maximum therapeutic effect, improving survival and quality of life. Prognosis is favorable in patients with hormone-dependent cancers, accounting for 70% cases, when beneficial effect of hormonal treatments can be expected[2]. However, hormone medications ultimately result in tumor resistance to such therapy, i.e. treatment failure[3].

Improvement of understanding of the molecular background of cancer pathogenesis has resulted identifying significant number of new targets, correlating with developing new methods of antineoplastic therapy. Development of target agents is focused on specifically affecting certain molecules or receptors in cancer cells, involved in the processes such as cell invasion, metastatic spread, apoptosis, controlling cell cycle and tumor-related angiogenesis.

The PI3K/AKT/mTOR signaling pathway plays a major role in key cellular functions – growth, proliferation. Recent studies show that in in patients with malignancies amplifications, mutations and translocations result in the activation of the PI3K/AKT/mTOR signaling pathway. Activating PI3K mutation has been described in approximately 40% of primary breast tumors, suggesting the importance of PI3K in breast cancer pathogenesis. The mTOR signaling pathway is pivotal in the processes of cell growth, proliferation, regulating apoptosis, angiogenesis and metabolism. Abnormal activation of this pathway by signals passed down from estrogen receptors triggers mechanisms decreasing treatment sensitivity and promoting therapy resistance[4].

One of the latest antineoplastic medications recognized to be beneficial in the treatment of advanced breast cancer is everolimus (Afinitor®) – a selective inhibitor of serine-threonine mTOR kinase. Laboratory experiments have shown that everolimus administration in breast cancer may restore sensitivity of cancer cells to endocrine therapy[5].

Results of a phase 3 randomized multicenter clinical trial (BOLERO-2), including 724 postmenopausal patients with hormone-dependent advanced breast cancer who progressed after treatment with non-steroidal aromatase inhibitors have demonstrated that everolimus, in combi-

nation with exemestane, restores sensitivity to endocrine interventions, improving clinical response rate and overall survival [6]. In the group of patients taking everolimus in combination with exemestane, progression-free survival was 6.9 months, as compared to the group primary out-patient facility patients taking exemestane as a single agent (11.0 and 4.1 months, respectively). Objective and clinical response rates in the combination arm were 12.6% and 51.3% whereas in the monotherapy arm they were 1.7% and 26.4%. Safety profile of such combination of two agents proved to be quite acceptable, whereas adverse events were expected and manageable [7].

Therefore, administration of everolimus, a mTOR inhibitor, restores sensitivity of tumor cells to hormonal therapy and increases its antineoplastic activity. Combination of everolimus with exemestane is a novel and effective strategy in postmenopausal patients with hormone-dependent breast cancer resistant to aromatase inhibitors. Everolimus (Afinitor®) provides practical oncologists with new potential options for that will significantly improve treatment outcomes in advanced breast cancer [6,8,9,10]. However, implementation of new technologies always incurs additional healthcare expenses, requiring clinical economical justification.

Therefore, **the aim of this study** was to perform clinical economics analysis of everolimus administration in the treatment of hormone-dependent HER2-negative advanced breast cancer and its use in postmenopausal patients who progressed after treatment with aromatase inhibitors.

Study objectives:

1. To perform analysis and adaptation of the electronic model version provided by the Sponsor for evaluating budget impact of everolimus inclusion in treatment algorithms for hormone-dependent HER2-negative advanced breast cancer in postmenopausal patients.
2. To develop a questionnaire for experts dedicated to epidemiological and pharmacoeconomical assessments of managing postmenopausal patients with hormone-dependent HER2-negative advanced breast cancer.
3. To perform a survey of experts, from different Russian Federation regions, experienced in managing postmenopausal patients with hormone-dependent HER2-negative advanced breast cancer.
4. To adapt the model for evaluating budget implications of everolimus inclusion in treatment algorithms for hormone-dependent HER2-negative advanced breast cancer, with Russian data obtained based on expert survey.
5. To evaluate the disease burden associated with breast cancer, when everolimus is included into treatment strategies, as compared to the current treatment strategies in the Russian Federation.

Materials and methods

Evaluating routine practice

Routine practice of managing postmenopausal patients with hormone-dependent HER2-negative (ER+/HER2-) advanced breast cancer was evaluated with a questionnaire containing the following groups of questions: proportion of patients with different breast cancer forms in a given Russian Federation region; medications a their administration schemes in the respective region for the 1st, 2nd and 3rd lines of treatment for postmenopausal patients with ER+/HER2- advanced breast cancer; annual rate of hospitalizations; laboratory and instrumental assessment data, consultation by specialists to which such subjects are referred to on an out-patient basis; adverse events associated with the administration of medications during the treatment of such subjects and the algorithms of their pharmacological management.

Experts who participated in the survey performed their professional activities in the following Russian Federation regions: Moscow, St. Petersburg, Khakassia republic, Omsk region, Primorsky region, Krasnoyarsk region.

Analysis of costs

The medical care standard #612n, approved by the Order of the Ministry of Health of the Russian Federation on November 07, 2012, was used to calculate direct costs incurred by the treatment of one breast cancer patient. When costs incurred by a hospitalization of breast cancer patient were calculated for the period of 10 days, according to the medical care standard, accommodation-related expenses (for hospital stay) were taken into account, along with expenses related to laboratory and instrumental workup, costs of consultations by specialists and medicinal treatments. When costs incurred by medicinal treatments were analyzed, medications administered in more than 30% cases were taken into account. The dose of a chemotherapeutic agent was calculated based on mean body surface area of 1.72 m2.

Costs incurred by medical care were determined using the method developed by Russian Society for Pharmacoeconomics and Outcomes Research according to the medical care prices established by Moscow regional Compulsory Medical Insurance Fund (2013). The proportion of financial contribution from the Compulsory Medical Insurance Fund is approximately 1/3 of the total medical care expenses, which is why the overall sum of medical care expenses for the areas captured by the Compulsory Medical Insurance Fund price establishments were multiplied by 3 [11].

Costs incurred by medicinal products were determined using the average prices as specified in Medline (www.rlsnet.ru) and Pharmindex (www.pharmindex.ru) databases for March-April 2014.

Data relevant to out-patient management of breast cancer were derived from expert survey and included costs incurred by laboratory and instrumental assessments, as well as specialist consultations.

By definition, indirect costs are costs incurred by patient disability or death due to disease or by working losses experienced by caregivers in families. Indirect costs are measured based on working time lost by the patient or her caregivers. However, calculation of such costs requires the data on the friction period – the latter term referring to the time interval after which the employer will fully restore the impaired efficiency (between the first working day lost and up until complete restoration). This value is applicable both to the patient and to her caregivers. Therefore, friction costs constitute a reduction in losses incurred by the patient's being off work, as other employees take over her responsibilities. Such measurements of the friction period and such, consequently, calculations have never been performed in Russia. Therefore indirect costs were not evaluated in this study.

Markov model was used to calculate costs incurred by managing one postmenopausal patient with ER+/HER2- advanced breast cancer on the 1st, 2nd or 3rd lines of treatment. Subsequently the data was extrapolated to analyze the budget implications for the total female population of patients with such disease in the Russian Federation.

Modeling

The following were included into the model:

- The total number of patients of patients with breast cancer in Russia;
- Mean annual increase in the number of breast cancer patients;
- Proportion of patients with advanced breast cancer among breast cancer patients;
- Proportion of postmenopausal patients with ER+/HER2- advanced breast cancer on the 1st, 2nd or 3rd lines of treatment;
- Proportion of postmenopausal patients with ER+/HER2- advanced breast cancer administered everolimus on the 1st, 2nd or 3rd lines of treatment;
- Efficacy of chemotherapy regimens, exemestane and everolimus administration.

Two models of 5-year breast cancer budget implications were quantified during the study; with 1 year duration of each Markov cycle, 5 cycles in total.

Model 1. Treatment of postmenopausal patients with hormone-dependent HER2-negative advanced breast cancer without everolimus.

Model 2. Treatment of postmenopausal patients with hormone-dependent HER2-negative advanced breast cancer with everolimus, if indicated.

The structure of the analysis investigating budget implications of Models 1 and 2 is presented on Figure 1.

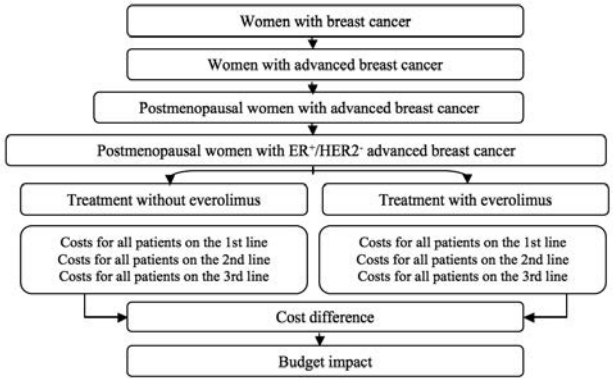

Figure 1. The structure of the model investigating budget implications of everolimus administration in postmenopausal patients with hormone-dependent HER2-negative advanced breast cancer

Study results

Entry of results from two Russian Federation regions has confirmed that the electronic version of the model is valid for investigating budget implications of including everolimus in hormone-dependent HER2-negative breast cancer following progression on aromatase inhibitors in postmenopausal patients. This model is applicable for evaluating budget implications of novel medications in the Russian Federation regions, using data derived from experts in epidemiology and patient management.

The data entered into the model has been derived from the following sources and have the respective values as shown below:

- Data on the total number of breast cancer patients was based on the analysis of malignancy incidence and mortality in the population of the Russian regions as of 2012, taking into account the average annual increase in breast cancer prevalence, resulting in 381.2 cases per 100,000 population[12];
- Data on the mean annual increase in breast cancer prevalence was based on the analysis of malignancy incidence and mortality in the population of the Russian regions as of 2012., resulting in 10,7% [12];
- Data on the proportion of patients with advanced breast cancer was based on the review of oncology care to the Russian Federation population as of 2012, resulting in 9,2[13];

- Data on the proportion of postmenopausal patients with ER+/HER2- advanced breast cancer receiving 1st line treatment, as provided by expert physicians, resulting in the mean value of 55%;
- Data on the proportion of postmenopausal patients with ER+/HER2- advanced breast cancer receiving 2nd line treatment, as provided by expert physicians, resulting in the mean value of 26%;
- Data on the proportion of postmenopausal patients with ER+/HER2- advanced breast cancer receiving 3rd line treatment, as provided by expert physicians, resulting in the mean value of 19%;
- Data on the proportion of postmenopausal patients with ER+/HER2- advanced breast cancer who were administered everolimus as 1st line treatment, as provided by expert physicians, resulting in the mean value of 2,5%;
- Data on the proportion of postmenopausal patients with ER+/HER2- advanced breast cancer who were administered everolimus as 2nd line treatment, as provided by expert physicians, resulting in the mean value of 3,2%;
- Data on the proportion of postmenopausal patients with ER+/HER2- advanced breast cancer who were administered everolimus as 3rd line treatment, as provided by expert physicians, resulting in the mean value of 4,2%;
- Data on chemotherapy efficacy was obtained from Sjostrom et al. study, (1999) [14];
- Data on exemestane and everolimus efficacy was obtained from the BOLERO-2 study (2013) [15].

The number of breast cancer patients in the Russian Federation as of 2013 was 533,433, of them 49,076 patients had advanced breast cancer. The total number of postmenopausal patients with ER+/HER2- advanced breast cancer was 17,491 cases.

Expert physicians have described treatment strategies applied to postmenopausal patients with ER+/HER2- advanced breast cancer. Results of analysis and summary of expert-provided data are in Table 1.

According to the experts, in average 3% of postmenopausal patients with ER+/HER2-advanced breast cancer receiving 1st or 2nd line of treatment, and 4% postmenopausal patients with ER+/HER2- advanced breast cancer receiving 3rd line of treatment were administered everolimus. According to the experts, the following chemotherapy regimens were used: FAC, CMF, AC, paclitaxel in combination with or without capecitabine, docetaxel, vinorelbin. In average, patients undergo in-hospital treatment 5-6 times a year, according to the administered chemotherapy regimens.

After data entry into the Markov model, the total 5-year costs of managing all breast cancer patients in the Russian Federation have been as follows:

- Without everolimus in treatment strategies for postmenopausal patients with hormone-dependent HER2-negative advanced breast cancer – 75 599 822 707 Russian roubles,
- with everolimus administration – 78 612 254 890 Russian roubles.

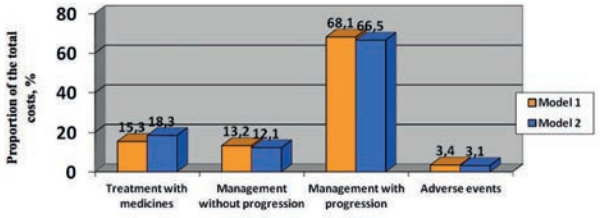

Figure 2. The structure of costs in the analysis of budget implications related to breast cancer over 5 years (Model 1 – treatment without everolimus, Model 2 – treatment with everolimus)

The most significant costs incurred by breast cancer are related to managing patients after disease progression rather than managing complications. Expenses incurred by medicines and treatment till progression are significantly lower than post-progression treatment – both with or without everolimus as part of the treatment strategies for postmenopausal patients with hormone-dependent HER2-negative advanced breast cancer. Only 3% of all patients having indications to everolimus administration were put on treatment regimen containing everolimus, according to the model.

Discussion of results

The main function of the state is to protect citizens' health. Breast cancer constitutes the area of women's health protection that draws particular attention. Analysis of the disease burden is an essential requisite to plan distribution of healthcare resources, make objective decisions regarding the scope of medical initiatives and determine prices to be used between entities involved in

Treatment regimen	1st line (%)	2nd line (%)	3rd line (%)
Letrozol/Anastrozol	25	42,5	8
Chemotherapy	30	42,5	68
Tamoxifen	40	3	0
Fulvestrant	2,5	10	21
Avastin + paclitaxel	2,5	2	3
Total:	100%	100%	100%

Table 1. Mean rate of antineoplastic therapy administration for advanced breast cancer

healthcare and medical insurance.

The disease burden associated with breast cancer, according to the results of modeling based on input of 5-year data provided by experts from different regions is consistent with 3.8% increase of costs incurred by this disease if everolimus is used in the treatment strategies for postmenopausal patients with advanced hormone-dependent HER2-negative breast cancer. The medicinal product itself constitutes the largest part of such costs. However, the costs incurred by managing patients and treating complications are reducted when such drug is administered. I.e. treatment with administration of everolimus requires the same costs as treatment without everolimus, if all costs are taken into account, including those incurred by managing complications and significantly advanced tumor forms.

Experts believe everolimus use in managing patients with advanced breast cancer may expand as new data demonstrates its high efficacy in the treatment of bone metastatic lesions.

Summary

1. Administration of everolimus in postmenopausal patients with advanced hormone-dependent HER2-negative breast cancer does not result in significant increase of costs, as compared to treatment strategies without such medicinal product. Its inclusion into treatment strategies increases costs by 3.8%, demonstrating negligible implications to the healthcare budget of the Russian Federation. The 5-year disease burden associated with breast cancer was as follows: without including everolimus into the treatment strategies for such patients– 75 599 822 707 Russian roubles, with everolimus – 78 612 254 890 Russian roubles.
2. Analysis of the electronic version of the model for evaluating budget implications of everolimus inclusion in treatment strategies for advanced hormone-dependent HER2-breast cancer progressing after treatment with aromatase inhibitors in postmenopausal patients has demonstrated its validity in evaluating budget implications of novel medications.
3. The questionnaire developed for the entry of data complication epidemiological and pharmacoeconomical assessment of managing postmenopausal patients with advanced hormone-dependent HER2-negative breast cancer progressing after treatment with aromatase inhibitors ensures input of regional data to the model for its validation.

Conclusion

Therefore, results of the completed study demonstrate that everolimus administration in postmenopausal patients with advanced hormone-dependent HER2-negative breast cancer progressing on/after treatment with aromatase inhibitors, has only negligible implication for the healthcare budget of the Russian Federation.

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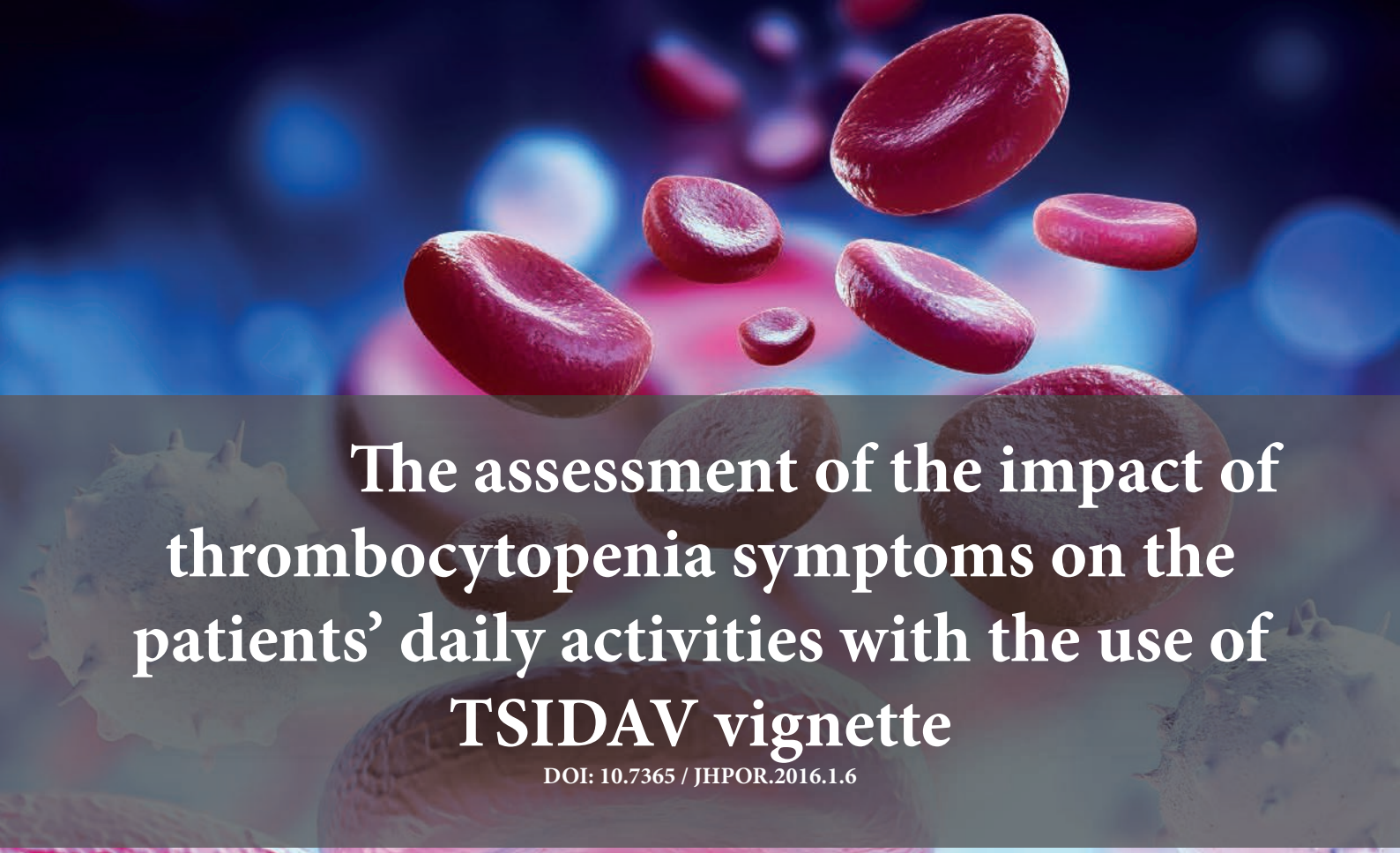

The assessment of the impact of thrombocytopenia symptoms on the patients' daily activities with the use of TSIDAV vignette

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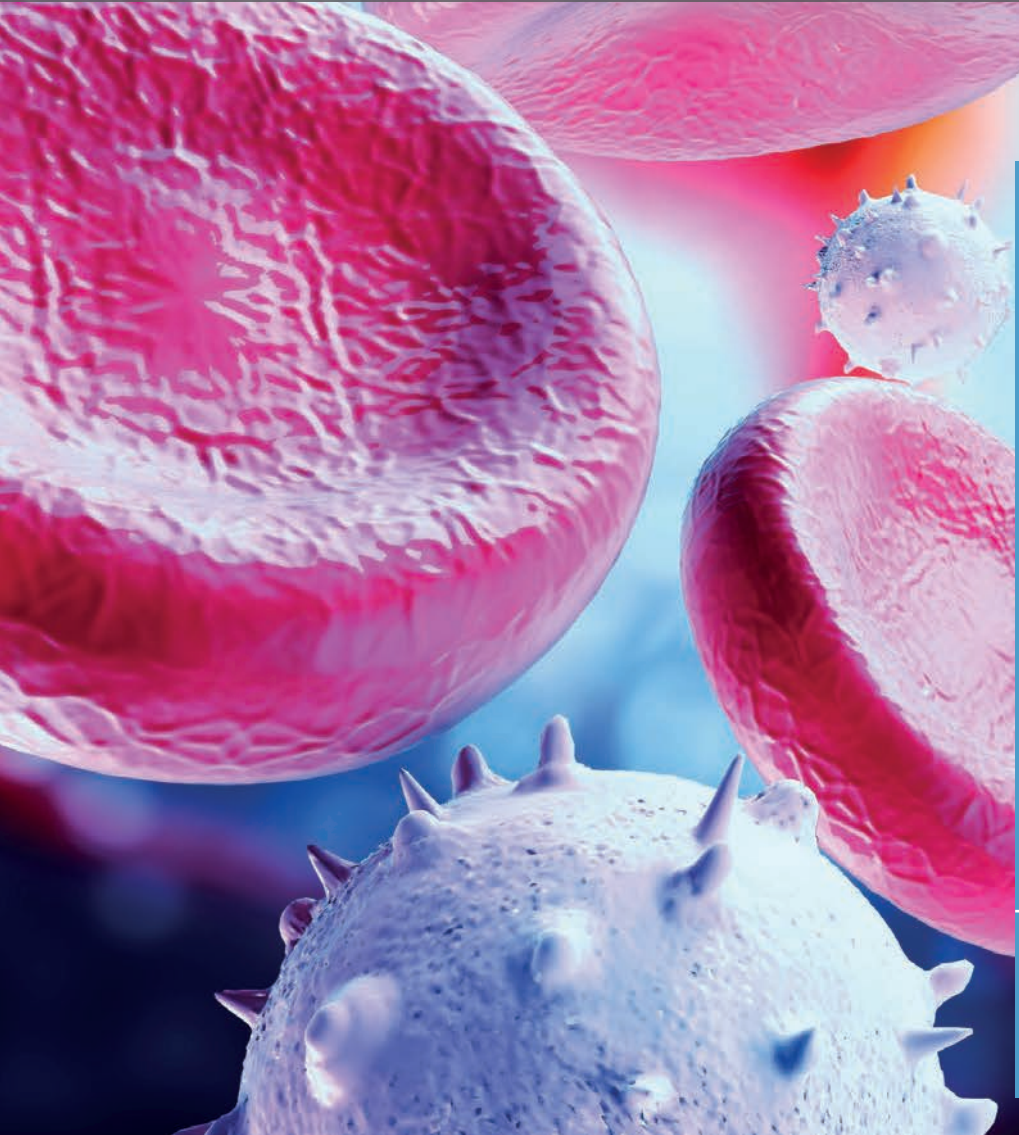

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Keywords:

symptoms, thrombocytopenia, vignettes

Abstract

Objective: Assessment of the impact of thrombocytopenia symptoms on patients' daily activities using vignettes.

Methods: Vignettes were used to collect information from adult patients and children's caregivers in order to assess the impact of thrombocytopenia symptoms on patients' daily activities. Each vignette consisting of two parts aimed at collecting qualitative information about major health problems related to thrombocytopenia symptoms and at measuring the intensity of the symptoms' impact on daily activities in a quantitative way.

Descriptive part collected patients' qualitative information about symptoms influencing their daily functioning or those bothering them the most. Quantitative part using Likert scale assessed the impact of specific symptoms on patients' lives.

Results: We collected 61 questionnaires from 31 women, 17 men, 13 children's caregivers. Among men the biggest impact on activities was observed in relation to petechiae and easy bruising (both symptoms were declared as significant by 29% of respondents). 68% women considered skin and mucosa petechiae, 65% indicated easy bruising and 52% bleeding from gums and nose as having significant impact on daily activities. 62% of parents or caregivers believed that petechiae and mucosa had significant impact on the performance of the children's daily activities, same significance was referenced to easy bruising (54%) and bleeding from gums and nose (42%).

Conclusions: Thrombocytopenia symptoms influence patients' daily activities and the most frequently mentioned symptoms influencing those across all groups were petechiae and easy bruising. According to the calculated vignettes values the highest impact on daily activity of the symptoms was indicated for children.

Introduction

As a continuation to our previous research which assessed the potential usage of vignettes in relation to quality of life, we have designed a vignette to capture information about the impact of thrombocytopenia symptoms on patients' lives[1,2]. The name of our vignette is TSIDAV - Thrombocytopenia Symptoms and their Impact on patients Daily Activities assessment Vignette.

Thrombocytopenia is a rare disease, but its symptoms can make both the patients' and their care givers' daily life difficult. Immune thrombocytopenic purpura (ITP) is an autoagressive disease and is usually diagnosed in children between 1st-7th year. In 80% of the cases it is acute and the remission is observed after 2-4 months. In 20% of the cases it becomes a chronic or recurrent disease [3].

In case of life-threatening consequences such as bleeding into the central nervous system (CNS), in children it occurs rarely, only in 0.2% to 0.9% of ITP, but it worsens the quality of life of the patients and is of great concern to the parents and the physicians mainly due to the need of repeated immunosuppressive treatment.

Among adults in Poland ITP incidence is estimated as 3.5: 100 000 The annual incidence of ITP in the adult population is 2/100 000. The disease can occur at any age and both in male and female population. In adults spontaneous remission of the disease is less likely. Most of the cases are diagnosed at 20-50 years of age

The most characteristic symptoms of thrombocytopenia are petechiae, purpura as well as skin and mucosa bleedings. The most frequent bleedings are from the nose, gums, urinary tract and from the genital tract in women. Intracranial bleeding also happens and is treated as life threatening complication[4]. Those symptoms can impact the patients' quality of life and with the specially designed vignettes we aimed to collect data which will allow us to qualify symptoms and have better understanding of such influence.

Methods

The data were collected at Lublin hospital among hematology clinic adult patients as well as children's caregivers in the period: from 1st March to 30th April 2016.

The inclusion criterion for the study was diagnosed thrombocytopenia.

The study was a survey using the TSIDAV vignette and it was carried out among patients and caregivers of patients with thrombocytopenia regardless of the cause.
The investigator interviewed the patients or caregivers before or after a visit to the doctor's office. In the course of the conversation he filled out the *researcher survey* which included the TSIDAV vignette.

The Ethics Committee approval was granted and all patients signed informed consent forms. The collected data were anonymous. The vignettes were used to collect information from both adult female and male patients and children's parents or caregivers in order to assess the impact of thrombocytopenia symptoms on the quality of life of the patients.

Each vignette consisting of two parts aimed at collecting qualitative information about the major health problems related to the thrombocytopenia symptoms in each studied group and to measure the intensity of the symptoms' impact the quality of life in a quantitative way.

In the descriptive part of the vignette, the patients were asked to provide qualitative information about the symptoms which either affect most their daily activities or bothering them the most. The second part was quantitative and was using the Likert scale to assess the impact of specific symptoms on patients' lives. The options to be chosen by respondents were as follows: significant impact, medium impact, indifferent, small impact, no impact.

Results

In total we have collected 61 questionnaires, 31 were from women, 17 from men and 13 from children's caregivers. The study involved 61 people (48 adults and 13 children's caregivers).

The group of adults consisted of 31 women and 17 men. 13 children's caregivers filled the survey with the vignette (of 8 girls and 5 boys).

The average age of adults was 50.8 years (median = 53 years; min = 23 years; max = 86 years). In women, the average age was 47.74 years (median = 51 years; min. = 23 years; max = 85 years), while in men the average age was 56.47 years (median 59 years; min. = 23 years; max = 86 years). In the children group the mean age was 7.1 years (median = 7 years, min = 3 years, max. 16 years). The girls' age ranged from 3 to 16 years (mean = 8.4 years; median 7.5 years) and boys' age was 3 to 8 years (mean = 4.5 years; median = 3.5 years).

The place of residence for 28 patients was a village, and a city for 33. Among female patients 14 were living in the countryside and 17 in the city. In case of male patients, 11 were living in the city and 6 in the countryside. Among children, 8 lived in the countryside, and 5 in the city.

Among men 29% have declared a significant impact of skin and mucosal petechiae on their daily activities and in the opinion of 12 % of men there was no impact at all (table 1).

Score	Number of responses	%
2	2	12%
1	3	18%
0	6	35%
-1	1	6%
-2	5	29%

Table 1. Impact of skin and mucosal petechiae on daily activities among men

Score	Number of responses	%
2	3	18%
1	3	18%
0	4	24%
-1	2	12%
-2	5	29%

Table 2. Impact of easy bruising on daily activities among men

29% men considered easy bruising as significant impact on their daily activities, while 18% did not perceive it as having any impact. (table 2)

Score	Number of responses	%
2	7	41%
1	3	18%
0	2	12%
-1	1	6%
-2	4	24%

Table 3. Impact of bleeding from gums and nose on daily activities among men

In case of 41% of men there was no impact of gums and nose bleeding on their daily activities, while in the opinion of 24% it was significant (table 3).

When asked to provide detailed information on what symptoms are those which most affected their daily activities, 41% of men reported weakness, fatigue and lack of strength.

47% of men expressed no concerns related to thrombocytopenia symptoms.

Within female group the analyzed results have shown that 68% of women considered petechiae on their skin and mucosa as having significant impact on their daily activities and 65% declared as significant impact also easy bruising (table 4, table 5).

Score	Number of responses	%
2	2	6%
1	1	3%
0	4	13%
-1	3	10%
-2	21	68%

Table 4. Impact of skin and mucosal petechiae on daily activities among women

Score	Number of responses	%
2	1	3%
1	2	6%
0	2	6%
-1	6	19%
-2	20	65%

Table 5. Impact of easy bruising on daily activities among women

In relations to bleeding from gums and nose, according to 52% of women, the impact on daily activities was significant. However 23% of them declared that there was no impact at all. (table 6).

Score	Number of responses	%
2	7	23%
1	0	0%
0	1	3%
-1	7	23%
-2	16	52%

Table 6. Impact of bleeding from gums and nose on daily activities among women

We also asked women about prolonged menstrual bleeding. 45% stated no impact on their daily activities, while 35% declared a significant impact (table 7).

Score	Number of responses	%
2	14	45%
1	1	3%
0	3	10%
-1	2	6%
-2	11	35%

Table 7. Impact of prolonged menstrual bleeding on daily activities among women

In the second part of the vignette when we asked about what symptoms are those which affected the daily activities most, 35% of women reported weakness.

Women expressed biggest concern about weakness and bleedings (both abundant menstruation and the risk of bleeding). In total 39% of women were concerned with it. As far as children are concerned, we have asked their parents or the caregivers to provide answers to our vignettes. 62% of parents believed that the petechiae on the child skin and mucosa had a significant impact on the performance of daily activities by their children (table 8).

Score	Number of responses	%
2	0	0%
4	0	0%
0	2	15%
-1	3	23%
-2	8	62%

Table 8. Impact of skin and mucosal petechiae on children daily activities according to caregivers

54% of parents believed that the easy bruising had a significant impact on the activities performed daily by a child. According to 23% it was indifferent (table 9).

Score	Number of responses	%
2	0	0%
1	0	0%
0	3	23%
-1	3	23%
-2	7	54%

Table 9. Impact of easy bruising on children daily activities according to caregivers

2% of parents believed that bleeding from the gums or nose had significant impact on the daily activities of the child (table 10).

Score	Number of responses	%
2	1	8%
1	1	8%
0	3	25%
-1	2	17%
-2	5	42%

Table 10. Impact of bleeding from gums and nose on children daily activities according to caregivers

Having analyzed the second part of the vignette, regarding the symptoms that most affect the daily activities of a child we found that in parents' and/or caregivers' opinion the most frequently mentioned ones were bruising and weaknesses as those which make daily activities difficult to their children. And the main concern was related to bleedings.

Discussion

Our study aimed to analyze the impact of thrombocytopenia symptoms on daily activities of both adult patients and children. In our research, to the question: "Please describe which of the symptoms associated with the disease hinder activities of daily living, by limiting the activity?" we obtained information that among women there was a wide variation in terms of reported symptoms that influence their daily activities. 35% of them most commonly reported weakness. It was also significant for men since as many as 41% reported weakness, fatigue and lack of strength as mostly affecting their daily routines. Caregivers answered that their children frequently found bruising and weakness hinder their daily activities and only one respondent replied that nothing interrupted the child's activity.

As far as the question related to the symptoms that cause concern women mainly mentioned weakness and bleeding, abundant menstruation and the risk of bleeding.

A total of 39% of women were concerned about it. 47% of men did not have any particular concerns with symptoms of thrombocytopenia. Among children's caregivers the symptoms of particular concern were the current bleedings or those which can occur in the future and they mentioned different types of bleeding.

The second part of the vignettes was based on the Likert scale. Respondents indicated the degree of difficulty in performing daily activities due to the symptoms of the disease. Likert scale included the following answers: *a significant impact, medium impact, indifferent, slight impact and no impact*.

Having analyzed the obtained results it was observed that for 68% of women petechiae had a significant impact on daily activities, while in the men group 35% of them considered it neutral, 29% significant influence, and only 12% indicated no impact. 62% of caregivers / parents thought that petechiae had a significant impact on the performance of daily activities of their children. None of the caregivers indicated that there was no impact or that it was only slight.

For 65% of women easy bruising had a significant impact on activities of daily living, 29% of men believed that there was a significant impact of easy bruising to their daily routines, and 18% of men believed that easy bruising had no impact on their daily activities. 54% of parents believed that the easy bruising had a significant impact on the daily activities performed by their children. According to 23% of caregivers it was indifferent, but no one thought that the effect was only slight or that there was no impact at all.

52% of women believed that bleeding from the gums or nose had a significant impact on the activities performed by them daily, while 23% believed that they had no influence. 41% of men believed that there was no impact of bleeding from the gums or nose on their daily activities, while 24% believed that the impact was significant. 42% of parents believed that bleeding from the gums or nose had a significant impact on the daily activities of their children.

For 45% of women prolonged menstruation did not impact the performance of daily activities, but 35% declared that is had a significant impact.

According to literature data on Health-Related Quality of Life (HRQoL) of children with chronic ITP remain rare. However researchers in China have assessed QoL in children with chronic immune thrombocytopenia and they confirmed that ITP affects HRQoL of both children and parents. Parents were much more concerned with the disease than their children [5].

In relation to newly diagnosed thrombocytopenia patients in Netherlands researchers analyzed 107 children aged 6 months-16 years using the Pediatric Quality of Life Inventory™ and Kids' ITP Tools questionnaires at diagnosis and during standardized follow-up comparing results with healthy children. In children who recovered significantly higher health-related quality of life scores than in children with persistent immune thrombocytopenia were obtained[6] .

Other research focused on the impact of therapy on the reported HRQoL in children with primary immune thrombocytopenia using the Kids ITP tool. The observation was that treatment of ITP did not improve, and could worsen, the HRQoL of children with ITP[7].

Among adult patients with persistent primary ITP there was a HRQoL study performed using as the primary QOL outcome measure the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36). The questionnaire consisted of 36 items covering following domains:physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. The authors concluded that persistent primary ITP patients were those who were experiencing the most important limitations in both physical and mental HRQOL domains in comparison to the general population[8].

An interesting research was performed in China where authors used the KIT with children diagnosed with ITP and their parents to assess HRQoL among children and also the QoL of the parents. The study included 43 children with newly diagnosed ITP and their parents. The children's version of the KIT consisted of 26 items divided into 5 domains: treatment side effects, intervention-related, disease-related, activity-related, and family-related concerns. The KIT used to assess parents QoL consisted of 26 items divided into 6 domains: diagnosis-related, monitoring-related, child's restricted activity-related, daily life-related, disease outcome, and emotional impact. The authors, similarly to our research , used the Likert scale. It was a 6 points scale, from 1 (not at all) to 6 (a great deal) and the high score represented a high concern level. Parent KIT scores were significantly higher than the child KIT scores, and it suggested that QoL of parents was significantly lower than children's.

Among the children KIT, the highest mean score was noted in the "intervention-related" and "activity related while among the parents the highest score was noted in the "emotional impact "and "disease outcome". The older the children were, they cared for more and were more worried about the disease. Interestingly, the parents' scores were no different in different age groups. That was

interpreted by researchers that whatever the children are old or young, Chinese parents worried about ITP disease in the same degree[9].

In the published literature we have not found a similar vignette to our TSIDAV assessing the QoL of patients with thrombocytopenia in relation to specific symptoms caused by the disease.

Conclusions

Thrombocytopenia symptoms influenced patients' daily activities both in adults and children. The most frequently mentioned symptoms influencing daily activities in all groups was petechiae and easy bruising. According to the calculated vignettes values the highest impact on daily activity of the symptoms were declared for children as declared by parents or caregivers.

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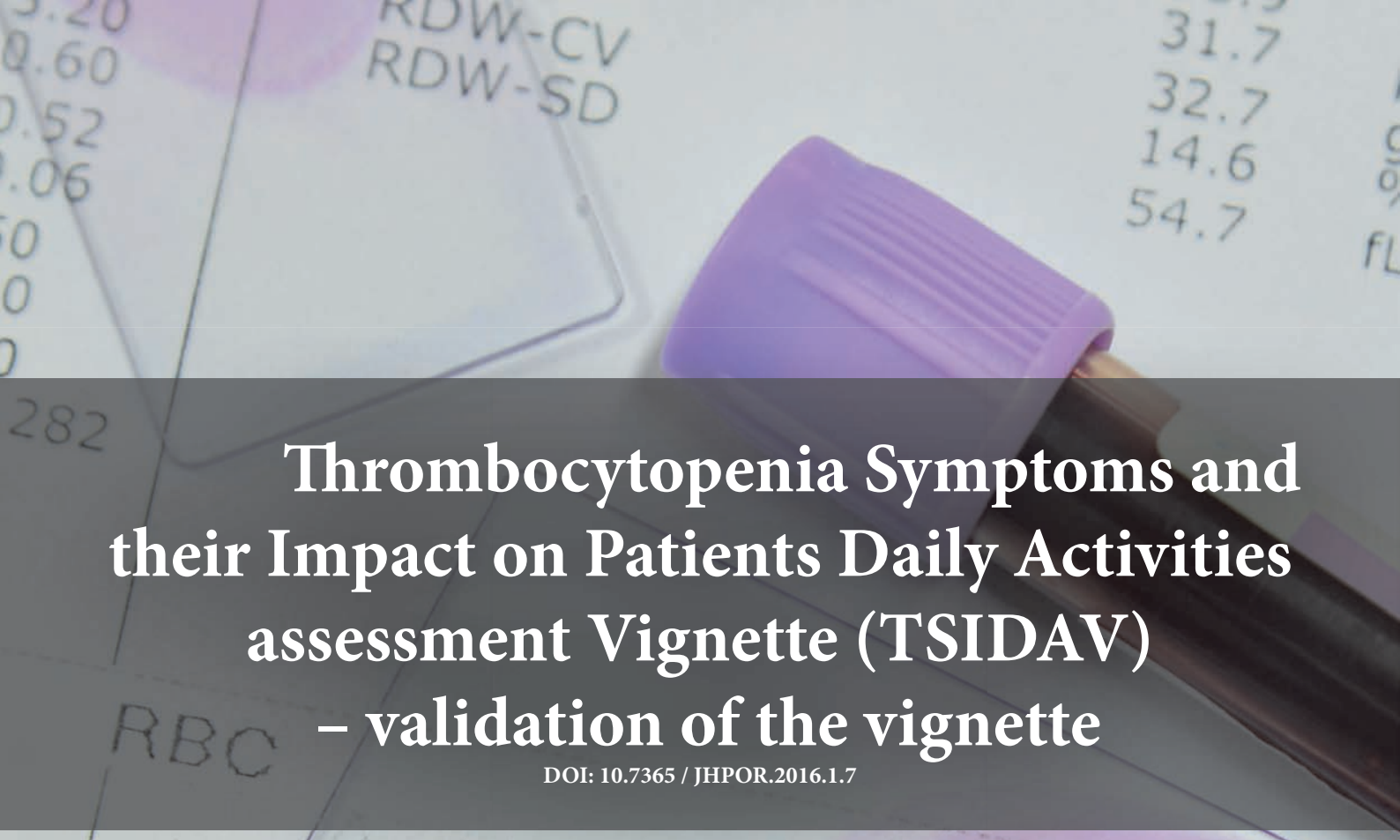

Thrombocytopenia Symptoms and their Impact on Patients Daily Activities assessment Vignette (TSIDAV) – validation of the vignette

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Keywords:

thrombocytopenia; vignette; validation

Abstract

Objective: Our aim was to validate the TSIDAV vignette in thrombocytopenia patients.

Methods: The vignettes validation was performed during a study on adults and children with thrombocytopenia. The data were collected among Lublin hospital patients within the period from1st March to 30th April 2016.

Results: We have validated the vignette based on the 61 questionnaires collected among thrombocytopenia patients and children's caregivers. 31 vignettes were from female patients, 17 from male patients and 13 from children's caregivers. The most frequently mentioned symptom influencing daily activities in all groups was petechiae and easy bruising. Among men 29% declared it as significant, 68% of women also considered petechiae on their skin and mucosa as having significant impact on their daily activities and 65% declared a significant impact of easy bruising. Among parents and caregivers 62% of them also indicated petechiae as having significant impact on their daily lives and 54% also declared significant easy bruising. We have used a developed special scale for the numerical presentation of the obtained results allowing their interpretation.

Conclusions: The properties of the vignette make it appropriate to assess the impact of the thrombocytopenia symptoms on patients daily activities.

TSIDAV and its dual construction lets us collect the catalogue of different symptoms of thrombocytopenia and their impact of daily life, which could be very helpful in working with thrombocytopenia patients from the psychological and medical point of view.

Introduction

There is a variety of tools to study the QoL, but the instrument that allows collection of two types of data is a vignette. We decided to check whether in such cases it will also be an efficient tool allowing reaching of reliable conclusions. From the psychological point of view the perspective is different, and the vignette is a tool which enables to discover the impact of symptoms on QoL which may contribute to the care of the patient and help doctors become more holistic and prioritize their treatment against the symptoms that most impact their patients' daily activities. An in-depth analysis of the vignettes used as tools other countries gave us the confidence that thanks to such type of tools will ensure high quality of the results obtained in the study. However, since no such tools exist in Poland yet our vignette should be validated in order to confirm if it is consistent and if it measures what it is intended to measure.

Methods

The validation process consisted of three parts.

The first part consisted of preparation of a tool which would be used to obtain qualitative data on the impact of the most frequent thrombocytopenia symptoms on patients daily activities and quantitative data indicating the intensity with which a symptom of the disease has an impact on the perception on daily activities of patients.
In the second part of the validation process we rated psychometric properties of the new tool: Thrombocytopenia Symptoms and Their Impact on Daily Activities patients assessment Vignette (TSIDAV).

In the third part for the TSIDAV vignette we have developed a scale to determine the impact of thrombocytopenia symptoms on daily activities of patients with thrombocytopenia or their caregivers.

Validation of the vignettes was performed using the guidelines on how to create a tool like the vignette[1].

Vignette validation process followed the following steps:

1. 1. Preparation of principles for creating the vignette;
2. 2. Preparation of a vignette in three versions: for men, women and caregivers of children with thrombocytopenia;
3. 3. The use of vignettes in a defined population (Thrombocytopenia Symptoms and their Impact on patients Daily Activities assessment Vignette -TSIDAV);
4. 4. Assessment of the psychometric properties of the vignettes;
5. 5. Evaluation of the impact of disease symptoms on daily activities of men, women and caregivers of children with thrombocytopenia.

The aim of the first phase of the validation was to develop the guidelines on how to create a tool such as a vignette. The vignette we created aimed at being a tool for qualitative and quantitative research. The guidelines for the construction of a working model of the tool were developed based on the analysis of the tools used in France and the USA [ref].

The next step was to prepare the three versions of vignettes for different populations: women suffering from thrombocytopenia, men with thrombocytopenia and a version for caregivers of children with thrombocytopenia.

Characteristics of the validation group

The data were collected among Lublin hospital patients within the period of 1st March-30thApril 2016 among 61 thrombocytopenia patients and children's caregivers - 31 vignettes were from women, 17 from men and 13 from children caregivers.

The next step was to verify whether the tool can be used to assess the impact of the disease symptoms on the daily activities of people suffering from thrombocytopenia and those who are caregivers of children suffering from thrombocytopenia. Its use can also apply to the qualification process of the symptoms that are perceived by patients and caregivers as more and less burdensome.
The subsequent step in the process of validation of the tool was to preserve the principle of a facade equivalence of maintaining compatibility in terms of graphical representation, the amount of questions and the formulation of questions and the form of response to the questions included, as well as the instructions for research and for selection of the research group.

The vignette for women consists of a descriptive part followed by two questions with the aim to collect qualitative information. The second part included questions related to specific symptoms adjusted for women and included also questions related to menstrual bleeding. The assessment was done using the Likert scale.

The vignette for men contains the descriptive part and two questions aiming at providing qualitative information about the symptoms. The second part included questions related to specific symptoms and the assessment was done using the Likert scale.

The vignette for caregivers of children with thrombocytopenia contains the descriptive part adjusted to children's activities and two questions aiming at providing qualitative information about the symptoms. The second part included questions related to specific symptoms and the assessment was done using the Likert scale.
The phase 3 of the validation was to develop a special scale used for the numerical presentation of the obtained results and allowing for their interpretation. The vignette includes open-ended questions, to which the patients provide answers without limitations, in an open way. These responses are classified into 5 main domains (Table. 1), which are assigned to values.

Domain	Score
Symptoms associated with thrombocytopenia, related to coagulation	-2
Other thrombocytopenia symptoms	-1
No symptoms	0
Concern, anxiety	1
Other diseases symptoms	2

Table 1. Domain classification of answers to open questions

All the responses to the open questions should be classified for each domain. If the answers are contained in a number of domains, then the obtained scores of each domain should be summed up and divided by the number of completed domains according to the formula:

$$x = \frac{\sum_{i=1}^{n} d}{n}$$

x – value of the question
d – domain value
n – number of completed domains.

According to the above formula it is possible to calculate the value for the questions 1 and 2 of the vignette.
Answers provided in the closed questions, including the Likert scale were assigned to the values.
Next, the score of all the questions must be summed up and divided by the total number of questions included in the vignette, i.e.: vignette for men - 5, for women - 6, for children caregivers - 5. The calculations are made according to the following formulas.
For men:

$$TSIDAV_m = \frac{\sum_{i=1}^{5} p}{5}$$

TSIDAVm – vignette value for men
p – value of the question.
For women:

$$TSIDAV_k = \frac{\sum_{i=1}^{6} p}{6}$$

TSIDAVk – vignette value for women
p – value of the question.
For children – provided by parents or caregivers:

$$TSIDAV_d = \frac{\sum_{i=1}^{5} p}{5}$$

TSIDAVd – vignette value for children – provided by caregivers / parents
p – value of the question
The obtained vignette value may be in a scale between the values of 2 to -2.
The interpretation of the result obtained should be conducted according to the key presented in the Table 2.

Value	Interpretation
1.1 – 2.0	Very low impact on daily activity
>0 – 1.0	Low impact on daily activity
0	No impact on daily activity
<0 – -1.0	High impact on daily activity
-1.1 – -2.0	Very high impact on daily activity

Table 2. TSIDAV scale

Results

We have validated the vignette based on the 61 questionnaires collected among thrombocytopenia patients and children's caregivers. 31 vignettes were from women, 17 from men and 13 from children's caregivers. The most frequently mentioned symptom influencing daily activities in all groups was petechiae and easy bruising. Among men 29% declared it as significant, 68% of women also considered petechiae on their skin and mucosa as having significant impact on their daily activities and 65% declared a significant impact of easy bruising. Among parents and caregivers 62% also poindicated petechiae as having significant impact and 54% also pointed to significant easy bruising. We have used the specially developed scale for the numerical presentation of the obtained results allowing their interpretation.
The reliability of TSIDAV indicates its semantic and structural similarity to the results described in the epidemiology of thrombocytopenia, which helps to have confidence in vignette as a tool to figure out symptoms of a specific disease and to describe its influence on a daily life of patients.

Conclusions

The properties of the vignette make it appropriate to assess the impact of the thrombocytopenia symptoms on patients' daily activities.
TSIDAV and its dual construction allows for collection of a catalogue of different symptoms of thrombocytopenia and their impact of daily life, which could be very helpful in working with thrombocytopenia patients from the psychological and medical point of view.

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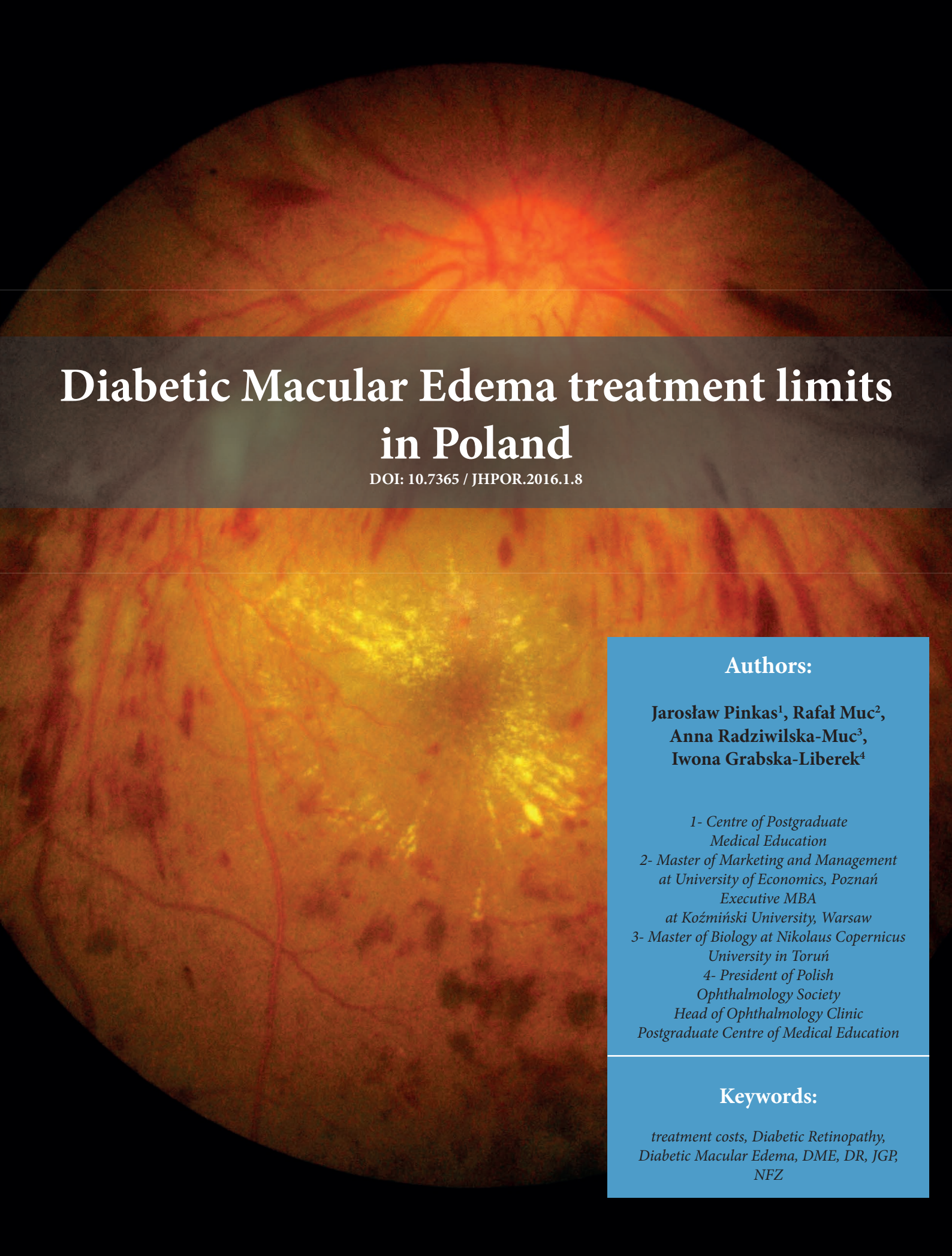

Diabetic Macular Edema treatment limits in Poland

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Keywords:

treatment costs, Diabetic Retinopathy, Diabetic Macular Edema, DME, DR, JGP, NFZ

Abstract

Diabetic Macular Edema (DME) is a severe disease, related to Diabetic Retinopathy (DR). All diabetic patients are at risk of DME development. The disease severity may vary from mild to moderate, with a risk of loss of vision. Diabetic Retinopathy, including Diabetic Macular Edema patients in Poland, are treated within Diagnosis Related Groups (JGP) system, that allows settlement of costs of performed medical procedures, including vitreoretinal procedures, fotocoagulation, and administration of VEGF inhibitors.

In this article authors tried to analyse what are the costs of treatment of DME patients within Diagnosis Related Groups (JGP) in Poland, what are the trends in expenditures of DME treatment, and what are the recommended steps to the decision makers in vision loss prevention amongst mellitus patients in Poland?

The study and analyses in this article are based on Diagnosis Related Groups (JGP) statistical reports available for years 2009-2015, published by the Polish National Health Fund (NFZ).

DME treatment spendings within the JGP groups in Poland, are notably low, vary from 1,2 MM PLN in 2009, achieving its maximum of 1,5MM PLN in 2010, and resulting in <1,1 MM PLN in year 2015. The number of treated patients decreased markedly from more than 800 in year 2009, achieving its minimum of 198 patients in year 2014.

DME treatment in Poland within the public system is remarkably below needs, and it does not meet standards of vision loss prevention amongst mellitus patients. The situation is mainly caused by under-diagnosis at the primary healthcare outpatient clinics, long waiting time for an ophthalmologist consultations and treatment budget limits within JGP groups in hospitals.

Diabetic Macular Edema (DME) is a severe disease, related to the Diabetic Retinopathy (DR). All diabetic patients are at risk of DME development. The disease severity may vary from mild to moderate, with risk of loss of vision. 25% to 30% non ophthalmology treated, and up to 15% ophthalmology treated diabetic patients might be affected by moderate loss of vision due to DME. Based on the Rohit Varma, Neil M. Dressler study published in JAMA Ophthalmology weighted DME prevalence in USA is 3,8% (2.7%-4.9%) of diabetes, however the meta-analysis of 35 studies (22,896 patients from United States, Australia, Europe and Asia) calculates DME prevalence on 7.48% (7.39–7.57) of the overall diabetes population.

Progression to DME affects 3% of mild non-proliferative DR eyes, 38% moderate and severe non-proliferative DR eyes and relates up to 71% eyes of the proliferative Diabetic Retinopathy - the most vision-threatening form of the disease,.

According to the Los Angeles Latino Eye Study and in the Proyecto VER study - 18% of participants with diabetes of more than 15 years' duration had the proliferative DR, with no PDR percentage difference between Type 1 vs Type 2 diabetes.

Polish National Health Fund (NFZ) estimates diabetes patients on 2 millions in Poland. Based on NFZ data and referring to cited above Rohit Warma as well as Joanne Yau studies, authors calculate DME prevalence from 76.000 to 149.000 patients in Poland.

In this article authors tried to assess what are the Diabetic Macular Edema treatment limits in a Polish healthcare system perspective.

To answer this question, the Polish National Health Fund (NFZ), Diagnosis Related Group (JGP) data were used. For any other calculations in this article, authors accounted 7,48% DME prevalence amongst mellitus patients as the most relevant to Poland.

NFZ regularly publishes JGP statistics, and since year 2009, there are specific common treatment baskets relevant to eye diseases (JGP B1 to B98).

As for the ICD-10 classification, Diabetic Retinopathy H 36.0 with ICD-9 procedures (E10-E14) are included in NFZ hospital JGP statistics presented in the table 1.

Procedure JGP	Description of the procedure	Maximum possible JGP points	Minimum possible JGP points
B16	Procedures including vitrectomy with the use of silicone oil or decalin, including multi-procedural	163 / 147*	147 / 132*
B17	Procedures including vitrectomy, including multi-procedural	140 / 126*	126 / 113*
B83	Vitreoretinal - medium procedures	29	26
B84	Vitreoretinal - small procedures	16	13
B98	Eye conservative treatment	42	5

Table 1. Diabetic Retinopathy settlement within the JGP system, Poland (years 2009-2016) *from year 2016

Based on the above information, we can observe that during Diabetic Retinopathy treatment in hospitals in Poland, ophthalmologists utilise B16, B17, B83, B84 and B98 JGP groups in order to settle the costs of a treatment, however the value of groups significantly differ in points. Taking into account that 1 hospital JGP point equals to approximately 52 Polish Zloty, DR treatment in years 2009 - 2015 were being settled on value from minimum 260 PLN, up to 8.476 PLN depending on list of medical ICD-9 procedures within a JGP group and type of a hospitalisation performed ('full' hospitalisation, planned hospitalisation, 1 day hospitalisation).

All the presented JGP statistics in the NFZ JGP platform do not cover specifically Diabetic Macular Edema, fortunately there are available Diabetic Retinopathy hospitalisation data, so for the purposes of this article, authors have included all cited above outcomes of the DR and DME medical studies.

To calculate Diabetic Macular Edema treatment costs, based on the available JGP data, we propose to use a mathematical formula, directly related to DME progression to non-proliferative and proliferative Diabetic Retinopathy (H 36.0). The formula is presented as below:

DME Hospitalisations =
DR Hospitalisations *((82%*38%) + (18%*71%))

Where:

82% - non-proliferative patients ratio amongst Diabetic Retinopathy
18% - proliferative patients ratio amongst Diabetic Retinopathy
38% - non-proliferative moderate and severe DR eyes ratio
71% - proliferative DR eyes ratio

Using the formula it can be estimated a number of DME hospitalisations and DME patients.

Diabetic Retinopathy, calculated Diabetic Macura Edema JGP hospitalisations and number of treated patients are presented in the table 2.

Analysing the number of the DR and DME hospitalisations, as presented in the table 2, we can remark that, the number of DR and DME treated patients within the JGP groups is significantly low. As described above, in Poland there are approximately 2 millions of diabetes patients, and referring to Joanne W.Y. Yau, DME prevalence as of 7.48% of the overall diabetes population, the number of DME patients equals to around 149.000. Considering that about 50% of them have moderate and severe symptoms of DME, it looks like that in order to achieve high level of vision loss prevention amongst DME patients, ophthalmologist in Poland would have to intensively treat at least 2000 patients per year. Currently there is a huge gap, between a number of treated patients within the public healthcare system versus treatment needs that would prevent worsening or even loss of vision amongst mellitus patients.

	Year	Total Diabetic Macular Edema (calculated)	TOTAL Diabetic Retinopathy (H36.0)	JGP B16	JGP B17	JGP B83	JGP B84	JGP B98
Hospilatisation Days	2009	1494	3830	90	123	99	3518	0
	2010	1286	3295	171	191	56	2877	0
	1011	607	1555	123	188	110	1134	0
	2012	535	1370	125	235	145	865	0
	2013	526	1349	125	288	106	426	404
	2014	487	1247	122	194	2	356	573
	2015	331	849	119	215	0	200	315
Number of Patients	2009	862	2210	80	116	49	1965	0
	2010	812	20181	149	180	30	1723	0
	2011	398	1019	106	177	72	663	0
	2012	374	958	106	220	85	547	0
	2013	279	715	104	267	65	278	0
	2014	198	508	103	181	2	221	0
	2015	273	699	100	201	0	131	267

Table 2. Diabetic Retinopathy and Diabetic Macular Edema hospitalisations and patient

Like in other diseases in Poland, there may be some budget limitations, that reduces level of treatment due to potential high cost of treatment to the healthcare system. To answer this doubt, there are calculated DR and DME patients costs of treatment within the JGP groups, presented in the figure 1.

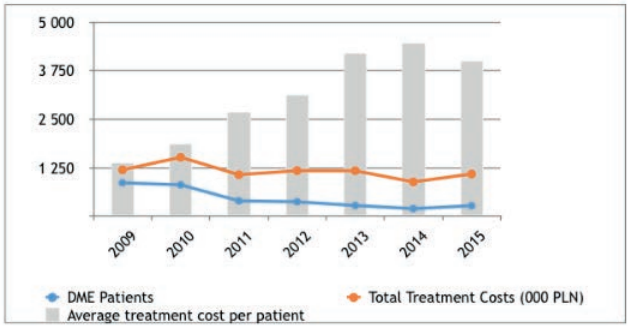

Figure 1. DME patients vs Total Costs of treatment vs Average treatment cost

According to the data presented in the figure 1, authors observe a stable, low annual treatment costs for DME patients treated within the JGP groups. The spendings vary from 1,2 million PLN in 2009, achieving its maximum of 1,5 million PLN in 2010, and resulting in less than 1,1 million PLN in year 2015. Simultaneously the number of treated patients decreased markedly from more than 800 in years 2009 and 2010, to close to 400 in years 2011 and 2012, achieving its minimum of 198 patients in year 2014. Constant costs of treatment with decreasing trend of treated patients resulted boosting average cost treatment per 1 statistical DME patient.

The calculation of the number of treated patients, average cost of treatment and total costs of treatment of DME patients within the JGP system are presented in the table 3.

As per table 3 presented data, authors conclude, that the root cause of significant decrease of DR and DME treated patients with simultaneously kept overall expenditures is mainly caused by giving up treatment within less valued JGP groups as of B83 and B84. Especially in the JGP group B84 there is a drop of treated patients from almost 2000 in year to 2009 to barely 131 patients in year 2015. Within this procedure a laser fotocoagulation is available for the treatment only. On the other hand, within the JGP procedure B98, where there is a possibility to administer VEGF inhibitor, in year 2015 ophthalmologists started to treat 267 DR patients. The most valued JGP groups B16 and B17 have kept the level of treated patients over the discussed period of years 2009 - 2015.

Trend of DR treatment costs within JGP groups is presented in the figure 2.

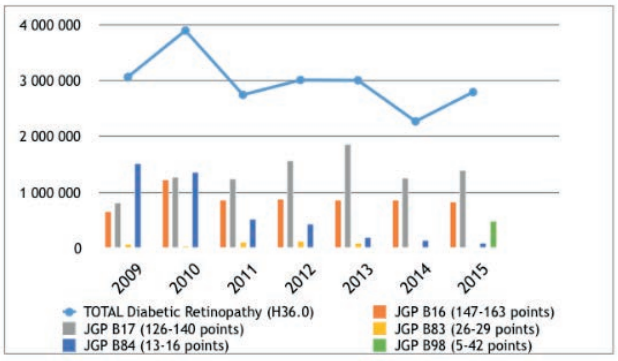

Figure 2. Diabetic Retinopathy treatment costs within JGP groups (PLN)

Discussion

This study aimed to show, what are the DME treatment costs in Poland, based on NFZ JGP statistics. The results show, small and decreasing number of treated DME patients within the JGP groups in Poland which is contrary to the disease prevalence and treatment needs that should focus on vision loss prevention amongst diabetes mellitus patients. However, the current JGP system points within the groups as of B16, B17, B83, B84 and B98 allows DME treatment, but in fact the valuation of a group, consisting form ICD-9 procedures is not directly linked with DME treatment (in opposite to i.a. age-related macular degeneration - AMD). Also, hospitals are not interested in treatment of either DR or DME patients within low valued JGP groups (like B84 - laser fotocoagulation) as it is not economically attractive, so they have retained the treatment within the most highest valued groups like B16 and B17 - vitrectomy - which is mainly used for the highest severe DR and DME patients.

Taking into account current situation in outpatient clinics where there is a very limited patients' access (long queues) to the specialist, that limits DR and DME early stage diagnosis also considering JGP system structure and valuation, all of these circumstances markedly prevents from proper DR and DME treatment and vision loss prevention in the discussed population.

Current direct costs of DME treatment in Poland are low, and there is a space for improvement, as indirect costs of not treating the DME, including social security costs due to the deterioration of vision amongst diabetes patients might significantly exceed the costs of the disease treatment. Also further analyses, especially calculating

	Year	Total Diabetic Macular Edema (calculated)	Average DME cost of treatment	TOTAL Diabetic Retinopathy (H36.0)	JGP B16 (147-163 points)	JGP B17 (126-140 points)	JGP B83 (26-29 points)	JGP B84 (13-16 points)	JGP B98 (5-42 points)
Number of Patients	2009	862		2210	80	116	49	1965	0
	2010	8212		2081	149	180	30	1723	0
	1011	398		1019	106	177	72	663	0
	2012	374		958	106	220	85	547	0
	2013	279		715	104	267	65	278	0
	2014	198		508	103	181	2	221	0
	2015	273		699	100	201	0	131	267
Treatment Costs within JGP groups (PLN)	2009	1 196 815	1 388	3 067 185	657 040	814 218	72 475	1 523 451	0
	2010	1 521 064	1 873	3 898 164	1 224 132	1 273 074	43 599	1 357 358	0
	2011	1 072 014	2 696	2 747 345	868 421	1 244 801	106 540	527 582	0
	2012	1 175 357	3 143	3 012 191	882 880	1 561 364	127 990	439 957	0
	2013	1 173 391	4 208	3 007 152	868 653	1 857 939	89 005	191 555	0
	2014	886 269	4 473	2 271 321	856 856	1 259 901	2 917	151 647	0
	2015	1 090	4 001	2 795 386	827 399	1 396 302	0	90 388	481 296

Table 3. Diabetic Retinopathy and Diabetic Macular Edema patients vs JGP costs of treatment vs average JGP treatment cost

DME costs in a social security system perspective might be helpful in taking any decisions regarding changes in the current treatment possibilities within the JGP groups system.

On top of the pharmacoeconomical divagations, there is a need to start a national program of evaluation of prevalence and incidence of diabetes mellitus related diseases including Diabetic Retinopathy and Diabetic Macular Edema.

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Cost-effectiveness study of diagnosis strategies of acute viral infections in Ukraine

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Keywords:

acute viral infection, analytical model, cost-effectiveness method, diagnosis strategy

Abstract

Background: Efficient and accurate laboratory diagnosis of viral pathogens is of primary importance for clinical care in terms of health care system reforms. The methodological approach of cost-effectiveness analysis of laboratory diagnosis tests for viral infections from payer's perspective was presented. We argue on an expository software-based technique for assessing the costs of newer laboratory tests.

Methods: We applied decision tree modeling techniques to compare expected costs and effectiveness of strategies for the diagnosis of viral infections. We conducted univariate and Monte-Carlo method based multivariate sensitivity analysis.

Results: Operating characteristics of diagnostic methods have been described. The analytical modeling, based on the cost-effectiveness method for the detection of human viruses were conducted. We considered three strategies: the use of only rapid tests for detection of one pathogen – adenoviruses; multiplexed PCR for 12 viruses, including adenoviruses; and combined strategy with confirmation of negative result of rapid test via use of PCR method. Univariative analysis showed that the cost savings achieved by use of PCR were 45% less per unit of effectiveness than the cost per effectiveness unit of rapid tests. Moreover multivariate probabilistic analysis, taking into account uncertainty of all operating characteristics, showed similar results for PCR method.

Conclusions: Acceptability and usability of the applied cost-effectiveness methodology was outlined and provided in computer application for the analysis of diagnosis strategies of acute viral infections.

Feasibility of study results implementation by managers was discussed to improve laboratory services and to support patient management and disease control in Ukraine.

Introduction

Efficient and accurate laboratory diagnosis of viral pathogens is of primary importance for clinical care in the Ukrainian settings in terms of health care system reforms. The significance of economic consequences and costs of laboratory diagnosis and diagnostic tests is needed to be assessed. Current trends towards convergence of medical facilities to the patient, i.e. the presence of ambulatory health-care institutions in geographically most remote areas, the need for medical care, including blood transfusions, urgent intervention in case of critical conditions (trauma, environmental disasters and other emergencies) require the development and use of sensitive and specific methods of laboratory diagnosis of infectious diseases. The priority infectious diseases in Ukraine are: HIV/ AIDS, viral hepatitis B and C, influenza and other acute respiratory and intestinal infections [1-7]. Due to the research results of different authors of viral agents' role in the structure of infectious morbidity and mortality vary considerably not only in case of multinational studies in countries with different political and economic situation, but also within the same country. Typically such variability is closely linked to many factors, such as use of different methods of laboratory diagnosis, diagnostic test kits, inappropriate reagents and apparatus, inappropriate terms and conditions of selection, storage and transport of clinical material to a specialized laboratory [2].

In Ukraine laboratory diagnosis of viral diseases includes classic methods of viral agent isolation in appropriate biological systems for its identification and titration of specific antibodies from patients with the use of different serologic reactions (neutralization, hemagglutination inhibition, complement fixation, immunodiffusion, precipitation etc.). Usually, these methods are prolonged in time lasting from 3-5 days to 2-3 weeks. Meanwhile infectiology requires certainty regarding the etiology of an infectious disease. Rapid diagnosis of infectious diseases allows pathogen or antigen detection directly in clinical material for several hours during working day and are successfully used in laboratory practice today. Among them – the fluorescent antibodies method (IFA), indirect hemagglutination assay, latex agglutination test (LAT), enzyme-linked immunosorbent assay (ELISA), radioimmunoassay analysis (RIA) and others. The use of emerging technologies such as molecular-genetic method (PCR) or rapid methods (simple/rapid tests) at the earlier stage will improve the etiological diagnosis of viral diseases [1-2].

Among the priority issues for laboratories of virological profile in Ukraine are the following: quality and effectiveness of laboratory diagnosis and minimization of costs for laboratory research. Cost-effectiveness method allows to calculate cost-effectiveness ratio and incremental cost-effectiveness ratio of each diagnostic technology. Improvement of the quality of laboratory diagnostics and cost cutting for additional diagnostic procedures deemed appropriate use of cost-effectiveness studies in choice of not only a method of etiologic diagnosis, but also a comprehensive diagnosis strategy for the most relevant pathogens of viral infections due to the dynamics of infection and the nature of the disease process: acute or chronic. Acute viral infections, e.g. influenza, begin suddenly and are characterized by short average duration of illness[1,5,7]. That is why the diagnosis of acute viral

infections requires rapid determination of the pathogen via the use of various diagnostic strategies – combinations of different technologies for pathogen detection, whether serological methods, PCR or rapid tests [2].

Implementation of cost-effectiveness methodology, applied to laboratory medicine requires primarily determination and definition of key characteristics to be used: prevalence and incidence of disease, sensitivity and specificity of the diagnostic test, total cost of diagnosis strategy and its expected effectiveness. This article presents a methodological approach for evaluation of laboratory testing strategies of viral infections and an expository software-based technique for assessing the costs of newer laboratory tests with the use of the above-mentioned parameters. In this article we used basic terminology:

Etiological diagnosis technology (or method) - a set of actions aimed to identify the etiological agent of infectious disease with the use of certain approaches and chemical reagents.

Algorithm of etiological diagnosis - a sequence of physician's or laboratory technician's actions for determination of etiologic agent with the use of certain diagnostic technology.

Diagnostic strategy - a set of activities, aimed to use available human and financial resources efficiently for determination of etiologic agent of infectious disease with the use of certain diagnostic algorithms.

Methods

Operating characteristics of diagnostic tests

Operating characteristics are used to characterize informative diagnostic research methods [8]. The most important operating characteristics of each diagnostic technology are:

- diagnostic spectrum (p),
- sensitivity (Se),
- specificity (Sp).

Auxiliary operating characteristics are:

- accuracy (Ac),
- positive predictive value (PPV),
- negative predictive value (NPV).

A simple tool for determination of the aforecited characteristics is contingency table 2 × 2, including different diagnostic results, positive or negative, according to possible health status of the patient: presence or absence of infectious disease (Tab. 1).

Test result	Infectious disease		Sum
	present	absent	
Positive	a	b	a+b
Negative	c	d	c+d
Sum	a+c	b+d	n= a+d+c+d

Table 1. Contingency table 2 × 2

a - number of positive results
b - number of false positive results
c - number of false negative results
d – number of negative results
a/n - detection rate
(a+b)/n - share of positive diagnostic results
(a+c)/n - diagnostic spectrum (p)
a/(a+c) - diagnostic test sensitivity (Se)
d/(b+d) - diagnostic test specificity (Sp)
a+d/n - diagnostic accuracy (Ac)
a/(a+b) - positive predictive value (PPV)
d/(c+d) - negative predictive value (NPV).

Diagnostic spectrum

Diagnostic spectrum is the frequency or probability of detection of pathogens - targets for certain diagnostic test across the completely etiologic spectrum of viruses detected in tested patients with the same clinical symptoms. Thus, a certain spectrum of diagnostic test or test systems for a particular period may be determined as prevalence of the disease and defined as:

$$\text{Prevalence} = \frac{\textit{Number of cases}}{\textit{Population subject to the risk}} \quad (1)$$

Prevalence is cumulative characteristic that shows the number of disease cases per 1 or 100 thousand people over a certain period of time, for example, month. Incidence is flow characteristic and defined the number of disease cases per 1 or 100 thousand people in every unit of time, for example, day. Ratio of prevalence and incidence determines average duration of illness subject to other variables held constant:

$$\textit{Average duration of an illness} = \frac{\textit{Prevalence}}{\textit{Incidence}} \quad (2)$$

It can be illustrated as the volume of liquid in the tank (prevalence) and the liquid flow rate per unit time (incidence). So the average duration of an illness can be explained as average residence time of molecules of the liquid in the tank (Fig. 1)[9].

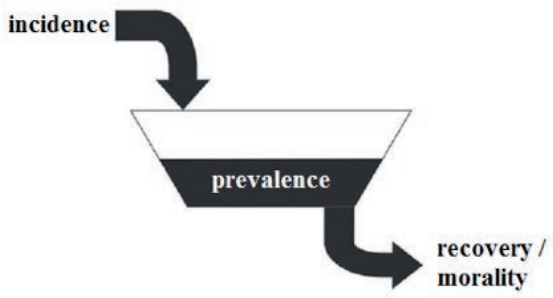

Figure 1. Schematic representation of prevalence and incidence

Acute viral diseases such as influenza have short average duration of illness, so its incidence rate is much higher than the prevalence, defined in the same period.

Prevalence of disease is also a priori probability of the disease, which is determined by historical data, personal experience, and official statistical data or from literature that is more general.

Sometimes authors in the medical literature also use the term risk and it indicates the likelihood of the disease, but it is an unfortunate use of the term as the general use of risk associated with economic uncertainty, which correlates with the likelihood of possible outcomes.

Sensitivity, specificity and accuracy

Sensitivity of diagnostic test is its ability to detect the maximum number of true positive samples, and specificity – its ability to detect only target pathogen, that characterizes minimum number of false positive results. In other words, the sensitivity of the test – is probability of true positive result across all positive results and specificity – probability of true negative result across all negative ones. Thus sensitivity characterizes discriminatory power of test towards detection of infected persons, and specificity –healthy ones. Probability of health state, determined with certain test is called prognostic value of the test. We distinguish between positive and negative forms of predictive values.

Accuracy (Ac) – is the proportion of correct test results (i.e., the sum of true positive and true negative results) of all studied patients.

Thus accuracy shows how many correct results can be obtained with application of this method of research. Sometimes this criterion is also called the index of the diagnostic efficiency, diagnostic efficiency.

The accuracy of diagnostic method depends on:

- method itself,
- used equipment,
- selected criteria of pathology,
- target population.

Previously, "quality" or accuracy of diagnostic tests was evaluated by comparing results of testing of obviously sick patients and healthy volunteers. So naturally results expressed significant differences between groups. For actual practice the results of such studies are often little applicable as a hidden disease cases give occasional "likelihood" presence of disease, and the purpose of diagnostic studies is often recognition of implicit symptoms.

Moreover from a practical point of view probability of matching test results with final diagnosis is of interest to assess the results of research. For these purposes performance predictability can be estimated.

Thus criteria of posteriori probability – predictabilities of positive and negative results are important for a proper understanding effectiveness of diagnostic methods. These criteria indicate probability of disease (or its absence) with known results of the study. It is easy to understand that the posterior indicators are more important than a priori ones.

Predictive value and predictability

Test predictive value - probability of disease presence, subject to known results of diagnostic study, and calculated on the basis of sensitivity and specificity values.
Positive predictive value, PPV - is a probability of disease presence subject to positive result of diagnostic test, proportion of true positive results among all test positive results.

Negative predictive value, NPV – is a probability of disease absence subject to negative (normal) results of diagnostic test, proportion of true negative results among all test negative results.

Prognostic value is a characteristic of not only a method, but it depends on its sensitivity and specificity, prevalence of disease in population to be tested, ie the proportion of people with studied disease in a particular population at a given time period. Prevalence - priori or pretest probability, ie the probability of disease detection before the results of diagnostic study have become known.

The more sensitive test is, the higher the negative predictive value (ie increasing physician confidence in the fact that the negative results of the study rejected the presence of disease) is. Conversely, the more specific test is,

the better predictive value of positive result (ie doctor can more safely assume that the positive results confirm the alleged diagnosis) is. As the prevalence of the disease affects the predictive value of diagnostic method, the latter inevitably depends on the conditions of its implementation. If positive results of even highly specific diagnostic method are obtained in populations with a low probability of disease, its great proportion will be false positive.

Expected utility or effectiveness of diagnostic tests

In laboratory medicine one unit of utility or effectiveness of diagnostic technology is determined as excellent pathogen detection or confirmation of its absence – true positive or negative diagnosis result. The expected result of basic utility function according to the rule of John von Neumann and Oskar Morgenstern by multiplying probabilities of diagnostic outcomes on utilities of these outcomes and then summing these products [10]:

$$EU(x) \equiv E\left[U\left(H_y^x\right)\right] = p_1 U(H_1^x) + p_2 U(H_2^x) + \cdots + p_y U\left(H_y^x\right) = \sum_{y=1}^{Y} p_y U\left(H_y^x\right) \quad (3)$$

Thus, formula (3) is general, citing the work of von Neumann and Oskar Morgenstern, and represents the expected utility EU(y) as the sum of the products of elementary utilities U of ydiagnostic consequences H, multiplied by their respective probabilities[10,11].

Methodology of cost-effectiveness analysis for laboratory diagnostic tests

We propose to use cost-effectiveness (CE) method in combination with the methods of mathematical modeling – an approach based on building probabilistic mathematical model - a decision tree, a tool for the selection of optimal version in the presence of incomplete or insufficiently reliable clinical and laboratory information. The branches of decision tree represent a strategic choice alternative (diagnostic scheme) with a probability of occurrence of events and the final result (the cost of each technology and its diagnostic effectiveness) [12-14].

Our method of analysis is based on existing or developed algorithms of diagnosis of viral infections, which can analyze diagnostic strategies with different approaches [15-16]. In this case it can be considered to use only one diagnostic strategy (strategy (i)). Such analytical model or decision tree represents specific etiological diagnosis strategies and has branches, reflecting the diagnostic status of patients (true positive, false-positive, false-negative and true negative). In case of false-positive or false-negative diagnostic status of the patient diagnostic efficiency strategy is equal to zero. In case of use of pair of diagnostic methods, there are five options for comparing the diagnostic spectrum Pi and Pj when selecting a combined strategy (i + j) (Fig. 2).

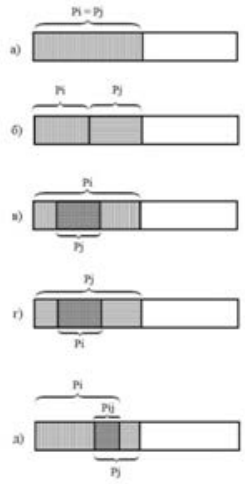

Figure 2. Options for comparison of diagnostic spectrum when combining diagnostic methods (i, j)

Use of combined strategy of (i + j) is necessary in case of verification of negative results with the use of diagnostic technology (j), since a negative result of its use does not preclude a possible infection because of probable insufficient sensitivity of diagnostic technology (i) (Supplemental Figures 2-6).

Appropriate analytical model will allow to make necessary calculations of expected cost and effectiveness as well as CER and ΔCER values. For example, for the strategy (i) (Supplemental Figure 1) such calculation of expected costs and effectiveness is based on a formula (4).

$$\overline{Cost_i} = P_i \times S_i \times Cost_i + (1-P_i)\times(1-Sp_j)\times Cost_i + (1-P_i)\times Sp_j \times Cost_j + P_i \times (1-S_i)\times Cost_i$$
$$\overline{Ef_i} = P_i \times S_i \times Ef_i + (1-P_i)\times(1-Sp_j)\times 0 + (1-P_i)\times Sp_j \times Ef_i + P_i \times (1-S_i)\times 0 = P_i \times S_i \times Ef_i + (1-P_i)\times Sp_j \times Ef_i$$

Calculation of CER and ΔCER is based on a formulas (1-2) with the use of expected cost and effectiveness values (6).

Algorithm of calculation for other decision trees (Supplemental Figures 2-6) is similar.

Characteristics		%	Study group
Age	18-30	78,07	89
	31-60	13,15	15
	>60	8,78	10
Comorbidities	yes	0,87	1
	no	99,13	113
Number of hospitalization days	{7-14}	18,42	21
	{15-21}	68,42	78
	{22-32}	13,16	15
Bacterial agent	Not found	0,88	1
	St. aureus	12,28	14
	St. aureus+Candida albicans	0,88	1
	Str. Viridans	21,05	24
	Str. pneumoniae	31,58	36
	St. Saprophiticus	25,44	29
	St. pyogenes	7,01	8
	St. pyogenes+Candida albicans	0,88	1

Table 2. The study group characteristics

Results

Software

We have developed C++-based software "Pharmacoeconomic analysis of diagnostic strategies of respiratory viral infections" as application, based on proposed CE methodology for evaluation of strategies for diagnosis of community-acquired respiratory viral infections in health care units. Application provides univariate or multivariate sensitivity analysis and indicates a high specificity, requiring attentiveness of physician or head of a specialized laboratory department. Application can be found in Supplemental Materials (Analysis.exe).

Case study of CE methodology use

Usability of developed CE methodology can be showed as application for the analysis of diagnosis strategies of acute viral infections, where probable etiological agents are respiratory viruses. During our laboratory research we have been studying clinical specimens (nasopharyngeal washings and sputum) from 114 patients in the age group of 18-60 years with community acquired pneumonia (CAP). The study group characteristics before viral investigation are presented in Table 2.

Rapid tests and molecular genetic technologies based on PCR method were used for the detection and identification of respiratory viruses. Results are presented in Fig. 3.

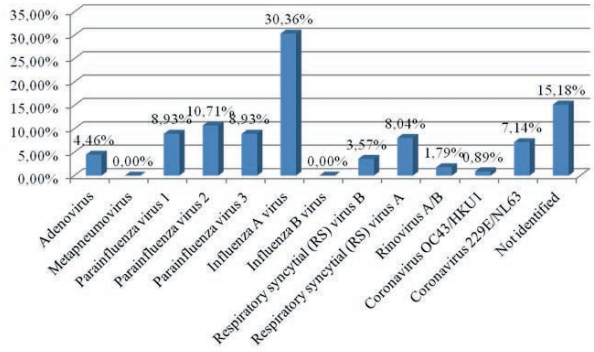

Figure 3. The spectrum of respiratory viruses among patients with CAP in Ukraine

Considering that in Ukraine rapid tests for detection of influenza virus A + B, adenoviruses and respiratory PC viruses are widely used, as example we proposed to investigate laboratory strategies for detection of respiratory adenoviruses. We considered three strategies of choice: the use of only rapid tests for detection of one pathogen – adenoviruses; multiplexed PCR for twelve respiratory viruses, including adenoviruses; and combined strategy with confirmation of negative result of rapid test via use of PCR method. Operating characteristics of both diagnostic strategies, such as sensitivity, specificity and costs have been taken from public sources and instructions to diagnostic tests, diagnostic spectrum – from our laboratory studies (Tab. 3).

Diagnostic strategy with the use of only rapid tests	Diagnostic Strategy with the use of only PCR method
- Sensitivity - 85%- Specificity - 95%- Diagnostic spectrum p_1 - 4.46% (adenoviruses)- Cost per one pathogen detection – 2,35 USD.- Effectiveness - 1 target pathogen (1 unit)	- Sensitivity - 85%- Specificity - 95%- Diagnostic spectrum p_2 - 84.8% (adenoviruses, metapnevmovirus, viruses, parainfluenza 1, parainfluenza virus 2, parainfluenza virus 3, influenza A virus, influenza B virus, respiratory syncytial viruses A, respiratory syncytial virus B, rhinoviruses A / B, coronavirus OC43 / HKU1, coronavirus 229E / NL63)- Cost per twelve pathogens detection- 15,7 USD(Cost per one pathogen detection ~ 1,3 USD)- Effectiveness – 12 target pathogens (12 units)
Diagnostic spectrum p_1 is a part of diagnostic spectrum p_2	

Table 3. Operating characteristics of both diagnostic strategies

Simulation results of univariate analysis towards diagnostic spectrum change showed that in case of high sensitivity and specificity of both tests (80%) diagnostic strategy of only multiplexed PCR method use is rather cost-effective. Its implementation will reduce the cost of one diagnostic effectiveness unit (one identified pathogen) by 45% in average, comparing with only rapid test use. The use of combined strategy will reduce the cost of one diagnostic effectiveness unit by 33% in average, comparing with only rapid test use (Fig. 4).

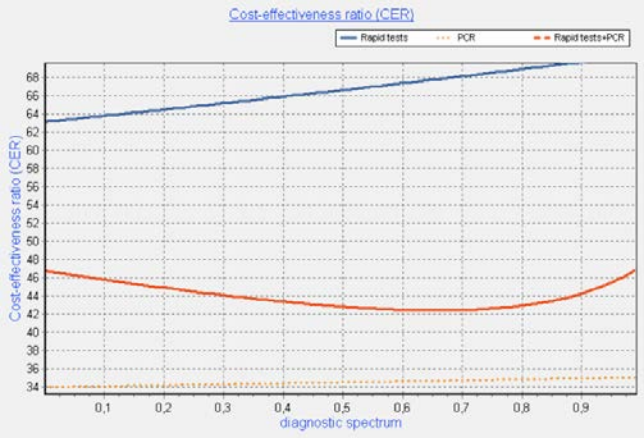

Figure 4. Analysis of dependence of CER diagnostic spectrum of pathogens

Multivariate probabilistic analysis, taking into account uncertainty of all operating characteristics and based on Monte-Carlo method, showed similar results. Implementation of diagnostic strategy of only multiplexed PCR method use will reduce the cost per unit of diagnostic effectiveness by 51.4% versus only rapid test use and the implementation of combined diagnostic strategy – by 38.8% (fig. 5-6).

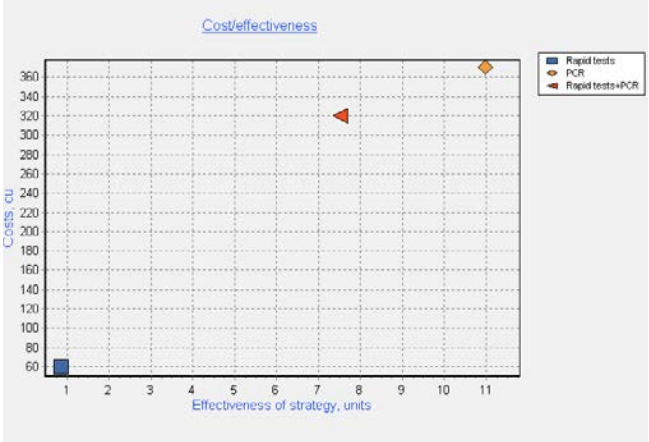

Figure 5. Costs and effectiveness of each diagnostic strategy and its combination (multivariate analysis)

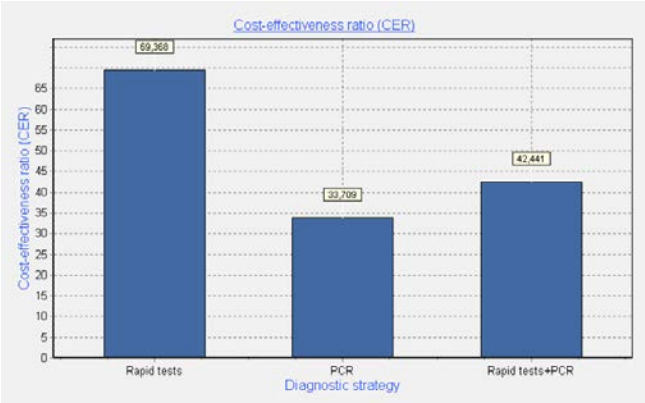

Figure 6. Expected values of CER of each diagnostic strategy (multivariate analysis)

Discussion and Conclusions

A literature review, conducted across Russian-language and English-language articles, dedicated to the similar direction of research, showed that these studies mainly reflect an assessment of diagnostic technologies in terms of subsequent medical interventions. For example, in the Russian-language paper[17], describing cost-effectiveness studies of drugs for the diagnosis of tuberculosis infection cost structure included not only costs of diagnostic but also therapeutic procedures, cost of physician's visit and cost of active pulmonary tuberculosis chemotherapy. The effectiveness of the diagnosis of tuberculosis infection was defined as the proportion of patients with active tuberculosis. Similarly, in another Russian-language paper[18] there was conducted an economic assessment of flow cytometry method used to assess the functional activity of platelets in patients receiving antiplatelet drugs.

Authors assessed the direct and indirect costs for diagnosis and treatment of patients with parallel evaluation of effectiveness of the testing approaches in percentage of patients with disease-free period during the year.

A similar trend is observed in the English-language papers[19]. For example the study of cost-effectiveness of malaria diagnostic methods in sub-Saharan Africa also takes into account both the costs of screening diagnostics and the artemisinin-based combination therapy[20]. The most close to our research is the study of J. B. Mahony et al., in which the authors analyzed the costs of multiplex PCR testing for diagnosing respiratory virus infections[21]. In this study as well as in our proposed approach, cost analysis study was also performed using decision tree modeling. The decision tree model was constructed by using four testing strategies for respiratory virus detection, viz., direct fluorescent-antibody staining (DFA) alone, DFA plus shell vial culture (SVC), the xTAG RVP test alone, or DFA plus the xTAG RVP test. At the same time this study has two significant differences from our one. It compared only the weighted costs of using each diagnostic technology without introducing the concept of effectiveness and applied only to the diagnosis of respiratory viruses.

In our paper we proposed general cost-effectiveness approach for evaluation of diagnosis strategies of any acute viral infections from the point of view of laboratory assistant and physician - head of the diagnostic laboratory. Operating characteristics of diagnostic methods, such as sensitivity, specificity and diagnostic spectrum, costs and effectiveness, have been described. It has been shown their use in analytical modeling, based on the cost-effectiveness method for the better choice of diagnostic strategies for the detection of human viruses. We used decision tree modeling techniques to compare expected costs and effectiveness of studied strategies for the diagnosis of viral infections.

Practical use of developed cost-effectiveness methodology was showed as computer application for the analysis of diagnosis strategies of acute viral infections, which probable etiological agents are respiratory viruses. For such purpose software called "Pharmacoeconomic analysis of diagnostic strategies of respiratory viral infections" has been developed- an application, based on proposed methodology for evaluation of strategies for diagnosis of community-acquired respiratory viral infections in health care units, providing univariate and Monte-Carlo method based multivariate sensitivity analysis.

As an example we used results of our laboratory research studies of 114 patients aged 19 to 25 years with community acquired pneumonia (CAP), using rapid tests and molecular genetic technologies based on PCR method for the detection and identification of respiratory viruses. We considered three strategies of choice: the use of only rapid tests for detection of one pathogen – adenoviruses; multiplexed PCR for twelve respiratory viruses, including adenoviruses; and combined strategy with confirmation of negative result of rapid test via use of PCR method.

Our study, which compared the cost of multiplex PCR testing to the cost of rapid tests, is the first cost analysis study involving multiplex nucleic acid amplification testing for the detection of infectious diseases in Ukraine. As in a different study[21] the fact that multiplex PCR is the least costly diagnostic strategy for the detection of respiratory viruses was surprising and significant for a number of reasons. The introduction of new technology is usually associated with increased costs, as new technology is often more expensive and is deployed as an add-on test which increases costs. In our study, we demonstrated the expected cost per case investigated using these testing strategies and showed that testing by PCR method alone was the least costly approach for the diagnosis of viral respiratory tract infections. It was less costly than the testing algorithm with the use of rapid tests, a strategy which is widely used by many physicians in Ukraine. Univariative analysis showed that the cost savings achieved by use of PCR were 45% less per unit of effectiveness than the cost per effectiveness unit of rapid tests across entire diagnostic spectrum. Moreover multivariate probabilistic analysis, taking into account uncertainty of all operating characteristics, showed similar results for PCR method. Our finding that the PCR method was the least costly strategy at any infection prevalence is particularly important, as this suggests that the savings associated with its use will apply all 12 months of the year, including the months with a lower prevalence of respiratory virus infections in Ukrainian population.

Limitations

The limitations of our study consist, for the most part, in fact that we have developed analytical approach for evaluation of diagnostic strategy individually, using its operating characteristics, i.e., sensitivity and specificity, but not considering them in a common analytical decision support system including quality control, physician's clinical point of view and other key factors of the clinical laboratory management. These issues should be explored further in future studies.

Implications

This kind of analysis can be implemented into the work of managers and healthcare experts, physicians and heads of medical laboratories and will improve the effectiveness of any laboratory department or laboratories of different ownership.

Conclusions

Pharmacoeconomic approaches are increasingly used by managers and experts of healthcare in the assessment of health technologies, also including laboratory techniques. The proposed cost-effectiveness methodology, applied to clinical laboratory management, can be the key instrument in the choice of appropriate cost-effective laboratory technique, saving money and improving quality of laboratory diagnostics especially in Ukraine but also other countries.

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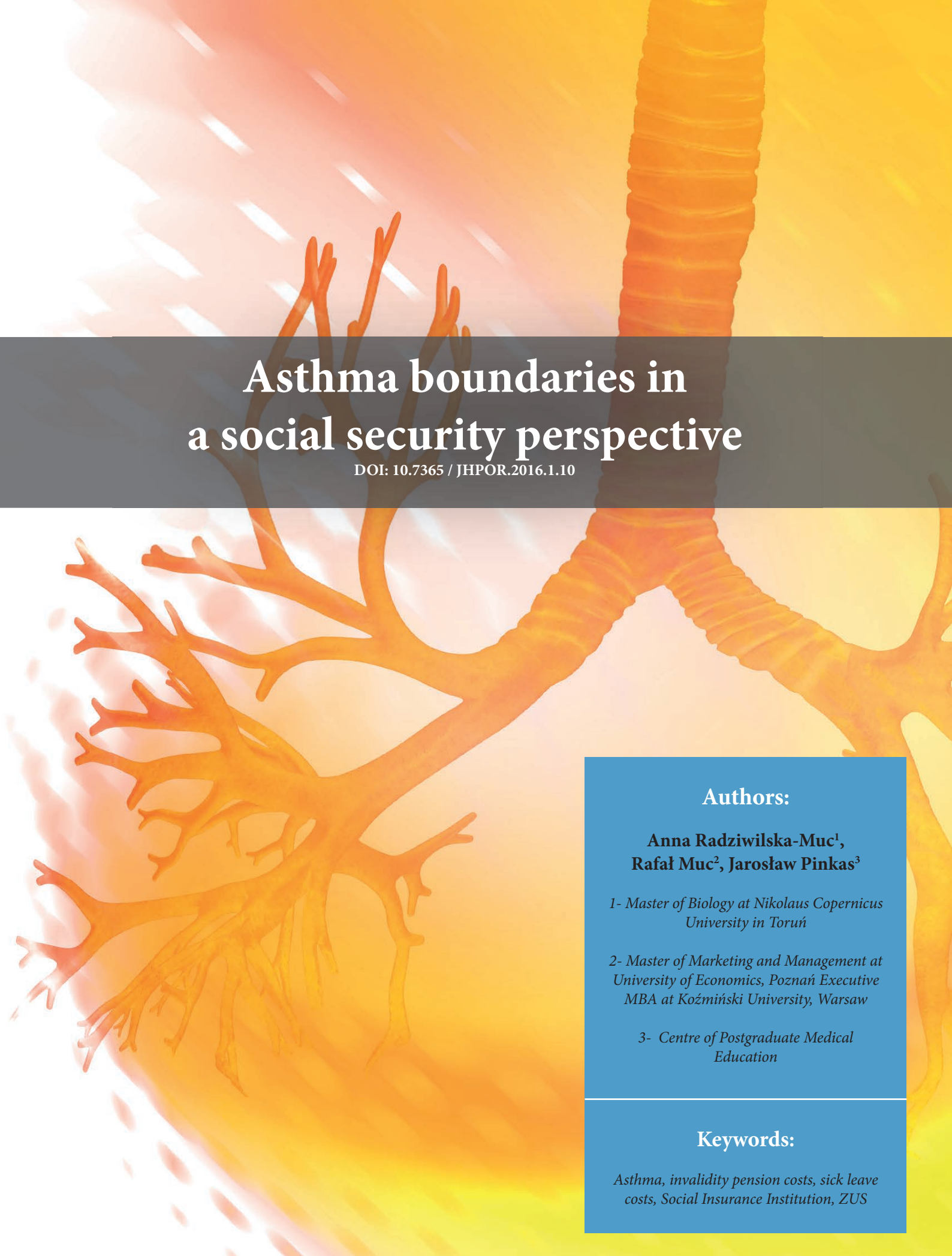

Asthma boundaries in a social security perspective

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Keywords:

Asthma, invalidity pension costs, sick leave costs, Social Insurance Institution, ZUS

Abstract

Introduction: Patients in Poland, including asthmatics are beneficiaries of social security system in case of severe disease exacerbation. Usually sick leave due to uncontrolled asthma is enough to get better and come back to regular life, however some patients with permanent severe symptoms require invalidity pension to secure their social rights and life quality. Nowadays, the social security system is overloaded due to insufficiency of income versus expenditures, and asthma as disease might represent a significant part of this costs due to its prevalence.

Objective of the study: In this article we have analysed trends in asthma management at the social insurance financial perspective, comparing the asthma social security costs to the overall social security system expenses.

Material and methods: The study and analyses are based on the Polish Social Security Institution (ZUS) data publicised in years 2010-2014.

Results: In year 2014 total ZUS and employers spendings on social benefits to ill patients were calculated at 32,5 billion of Polish Zloty. Respectively all respiratory system diseases social security costs accounted 2,2 billion of Polish Zloty, of which estimated asthma (J-45) 64 million of Polish Zloty, and status asthmatics (J-46) 580 thousands of Polish Zloty.

Conclusions: Asthma social security costs represent 0,21% of all diseases social security costs and less than 3% of all respiratory diseases social security costs. Despite variability of the costs over years 2012-2014, there are no significant negative trends of asthma costs into the social security system.

Insured persons in Poland, experiencing sick leave, receive salary compensation, paid by either employer or Social Insurance Institution (ZUS), depending on specific rules. To simplify the understanding of the sick leave insurance system in Poland, generally we can say, that in most cases an employer (>20 employees) is paying sick leave compensation for the first 30 days, after this period ZUS is taking over the financial responsibility for a patient. For smaller companies ZUS is paying sick leave compensation from the first day of the benefit rights acquisition by a patient[1].

In case of longer inability to work, exceeding 182 days, ZUS is stopping payment of the salary compensation, but patients can apply for at first phase temporary, then permanent, invalidity pension. However we need to bear in mind, that sick leave salary compensation usually represents 80% of an employee average salary, but in case of work inability pension - rates are significantly lower. Social Insurance Institute publishes data about insured persons, including employees, self-employed persons as well as retirees remaining in employment. These statements do not include individual farmers, their family members, and uniformed services. The cause of sickness absence is determined in accordance with the International Statistical Classification of Diseases and Related Health Problems Tenth Revision (ICD-10). Patients with disease exacerbations after approaching an outpatient clinic or hospital building, and having professional medical consultation, usually obtaining medical certificates of temporary inability to work, a sick leave certificate. In year 2014 total ZUS and employers spendings on social benefits to ill patients were calculated at 32,5 billion of Polish Zloty (approx 8,1 billion USD), whereas expenditures on sick leaves salary compensations were 13,5 billion of Polish Zloty (approx 3,4 billion USD), while ZUS expenditures on inability to work pensions were amounted 15,6 billion of Polish Zloty (approx. 3,9 billion USD) [2]. These amounts might seem large, but we must bear in mind that average inability pension rate was 1257,3 Polish Zloty per month (approx 314,3 USD), which was in year 2014 - 75% of minimum salary in Poland, and only 18% above of poverty threshold[3].

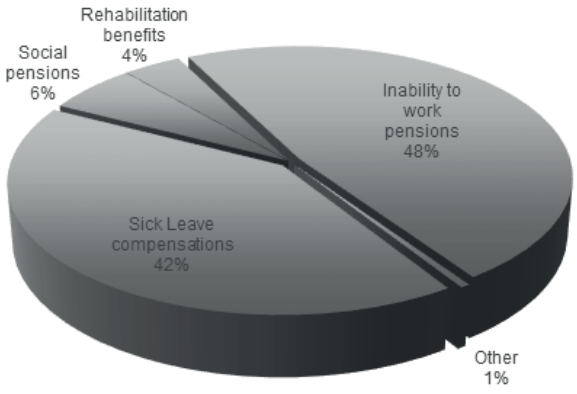

Figure 1. Social Insurance expenditures structure in Poland[4]

Respiratory system diseases are serious social problem due to its inflammatory complexity and prevalence. Especially asthma is one of the biggest management challenges, as despite the number of available modern treatments still seems to be not defeated, just or up, controlled. Based on the two big studies in Poland, asthma prevalence is calculated at 8,6% in children and 5,4% in adults (PMSEAD study) [6] and respectively 4,6% (ECAP study) (approx. 1,7 MM) suffer from asthma symptoms. Also, ac-

	2010	2011	2012	2013	2014
	Invalidity pensions				
ZUS expenditures (in thousands)	14 907 089 zł	15 122 385 zł	15 064 973 zł	15 639 962 zł	15 598 299 zł
Number of beneficiaries (in thousands)	1 227,0	1 169,1	1 111,0	1 074,5	1 033,8
Work inability pension (average per month)	1 012,43 zł	1 077,92 zł	1 129,99 zł	1 212,96 zł	1 257,36 zł
	Sick Leave Salary Compensation (sum of Social Insurance Institution and employers)				
ZUS and employers expenditures (in thousands)	11 142 987 zł	11 713 122 zł	12 280 679 zł	13 315 468 zł	13 522 400 zł
Number of work absence days (in thousands)	187 780	189 504	189 610	197 025	194 237

Table 1. Social Insurance expenditures in Poland 2010 - 2014[5]

cording to the ECAP 66,9% of patients have not had diagnosed asthma despite symptoms, but simultaneously 39% patients have been wrongly diagnosed as asthmatics[7]. In addition, Prof. Przemysław Kardas (Medical University in Łódź) studies shows that up to 90% of patients with asthma, stops regular receiving of prescribed asthma medicaments just after one year after the diagnosis[8].

Taking into account above studies outcomes, we need to raise the question: whether high asthma prevalence in an overall population and at the same time non-compliance of asthma treatment generates significantly higher negative consequences to social security system versus average?

Analysing statistics of sick leave certificates and absence days, the registry [9] of medical certificates data shows that in year 2014 there were registered 16,9 million of medical certificates of temporary inability to work due to illness, that equals to 212,6 million of sickness absence days (ratio 12,5 absence days per 1 certificate). Respectively the respiratory system number of medical certificates amounted 4,1 million and 24,9 million of sickness absence days (ratio 6,07). Asthma (J45) absence medical certificates and absence days weighted 65,5 and 713,9 thousands respectively (ratio 10,9 absence days per 1 certificate). Status asthmatics were counted respectively 0,524 vs 6,5 thousands (ratio 12,34).

Analysing absence days per 1 certificate in years 2012-2014 we can observe, that in contrast to all diseases as well as respiratory system, the ratio of Asthma (J-45) and Status Asthmatics (J-46) significantly decreases, that might bring us into the conclusion, that asthma control is improving over the years.

Based on the sick leave certificates and absence days data presented above we cannot say, that asthma management is more difficult and less controllable than average of all diseases- that would result in an outstanding numbers of sick absences.

But medical certificates and number of absence days might not give us the proper picture of financial consequences to the social security system. Therefore what are the social security costs of asthma, comparing to the total ZUS average expenditures on sick leaves and invalidity pensions?

As mentioned above, in year 2014 total ZUS and employers spendings on social benefits to ill patients were calculated at 32,5 billion of Polish Zloty, but respiratory system diseases social security costs accounted 2,2 billion of Polish Zloty, respectively estimated asthma (J-45) 64 million of Polish Zloty only, and estimated status asthmatics (J-46) 580 thousands of Polish Zloty[11].

Concluding, asthma social security costs represent 0,21% of all diseases social security costs and less than 3% of all respiratory diseases social security costs. Despite variability of the costs over years 2012-2014, there are no significant negative trends of asthma costs into the social security system.

Discussion

This study aimed to show, that asthma due to its prevalence and treatment non-compliance by patients might generate unnecessary cost to the social security system. The results show, that asthma sick leaves and days of absence levels are stable, with no negative trends observed. Security costs represent only 0,21% of all diseases social security costs and less than 3% of all respiratory diseases social security costs. Also based on the above calculations - severe asthma patients experiencing status asthmatics are not generating significant burden to the social security system.

Based on that, we could conclude that in spite of asthma is not defeated as disease, but it is much better controlled than in the past.

Year	Diseases Scope	Scope ICD-10	Number of sickness absence days	Number of medical certificates received	Ratio Absence Days per 1 Certificate
2012	All Diseases	A00-Z99	206 776 323	16 600 095	12,5
2013	All Diseases	A00-Z99	213 392 670	17 333 946	12,3
2014	All Diseases	A00-Z99	212 616 713	16 965 652	12,5
2012	Respiratory System	J00-J99	25 330 312	4 082 612	6,2
2013	Respiratory System	J00-J99	29 543 347	4 778 871	6,2
2014	Respiratory System	J00-J99	24 962 568	4 103 099	6,1
2012	Asthma	J-45	735 410	66 373	11,1
2013	Asthma	J-45	748 474	67 664	11,1
2014	Asthma	J-45	713 979	65 564	10,9
2012	Status Asthmatics	J-46	7 919	587	13,5
2013	Status Asthmatics	J-46	6 444	486	13,3
2014	Status Asthmatics	J-46	6 464	524	12,3

Table 2. Summary of sick leave certificates and absence days[10]

Year	Diseases Scope	Scope ICD-10	% of expenses vs respiratory system	**Social security expenses (000 Polish Zloty)**	**Inability to work pensions (000 Polish Zloty)**	**Sick leave compensations (000 Polish Zloty)**
2012	All Diseases	A00-Z99	-	30 438 586	15 064 974	12 280 679
2013	All Diseases	A00-Z99	-	32 276 116	15 639 962	13 315 468
2014	All Diseases	A00-Z99	-	32 539 825	15 598 289	13 522 400
2012	Respiratory System	J00-J99	100%	2 157 868	846 470	1 285 199
2013	Respiratory System	J00-J99	100%	2 525 276	886 736	1 610 435
2014	Respiratory System	J00-J99	100%	2 239 131	891 632	1 316 728
2012	Asthma	J-45	2,90%	62 649	24 575	37 313
2013	Asthma	J-45	2,53%	63 977	22 465	40 800
2014	Asthma	J-45	2,86%	64 044	25 502	37 661
2012	Status Asthmatics	J-46	0,03%	675	265	402
2013	Status Asthmatics	J-46	0,02%	551	193	351
2014	Status Asthmatics	J-46	0,03%	580	231	341

Table 3. Summary of social security expenses of pulmonary diseases[12]

However, as authors of this article, we must emphasize, that this study does not show the full picture of asthma management costs in Poland. We have not analyzed asthma hospitalization costs, mortality levels, potential male vs female differences in asthma patients. Therefore next studies are required to finally compare available asthma epidemiological data with trends in hospitalization, and only together with social security costs, we could try to hypothesize whether asthma management in Poland is really under maximum possible control or rather it is only smothered, despite of huge physicians' and healthcare system efforts.

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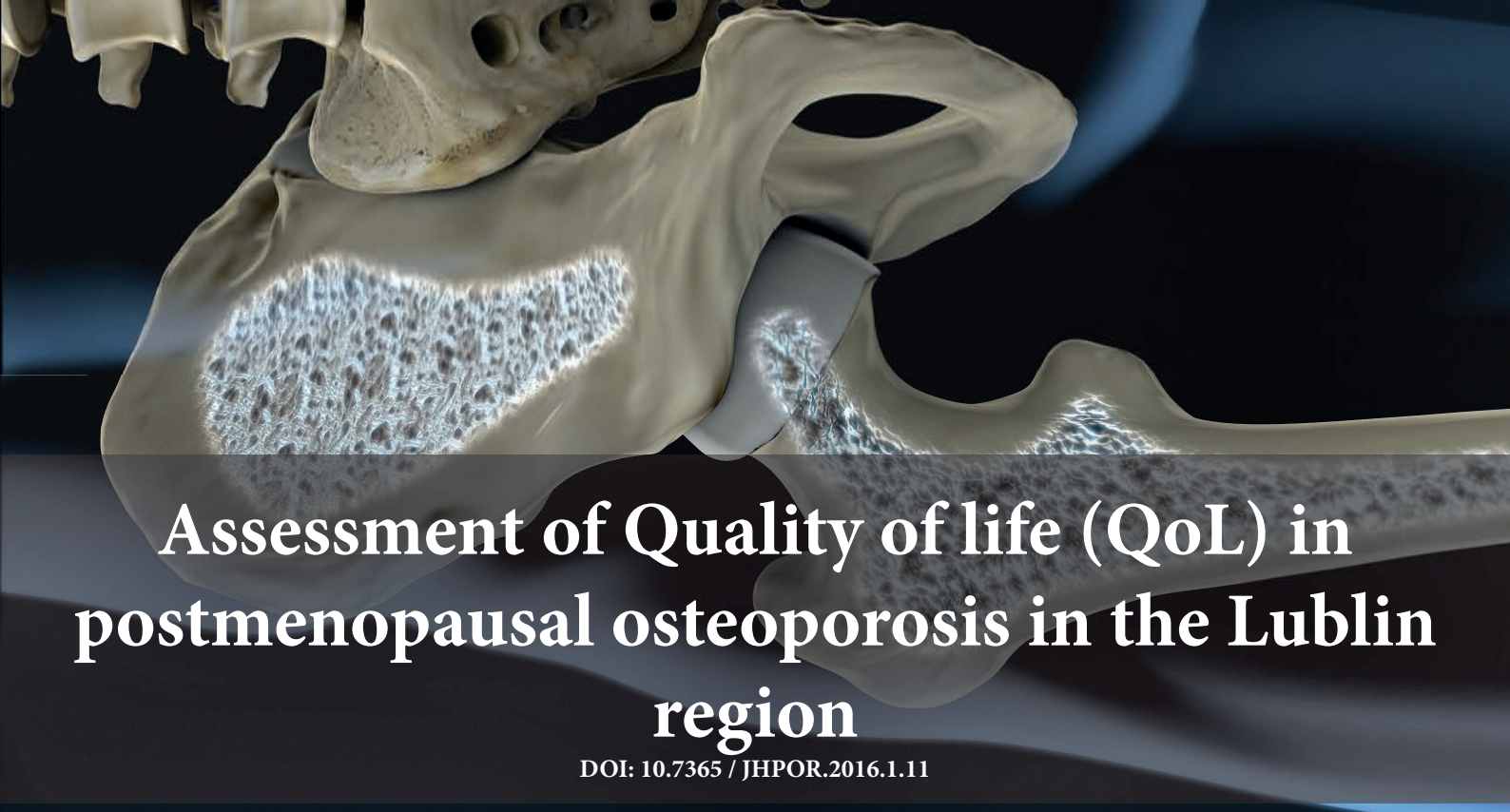

Assessment of Quality of life (QoL) in postmenopausal osteoporosis in the Lublin region

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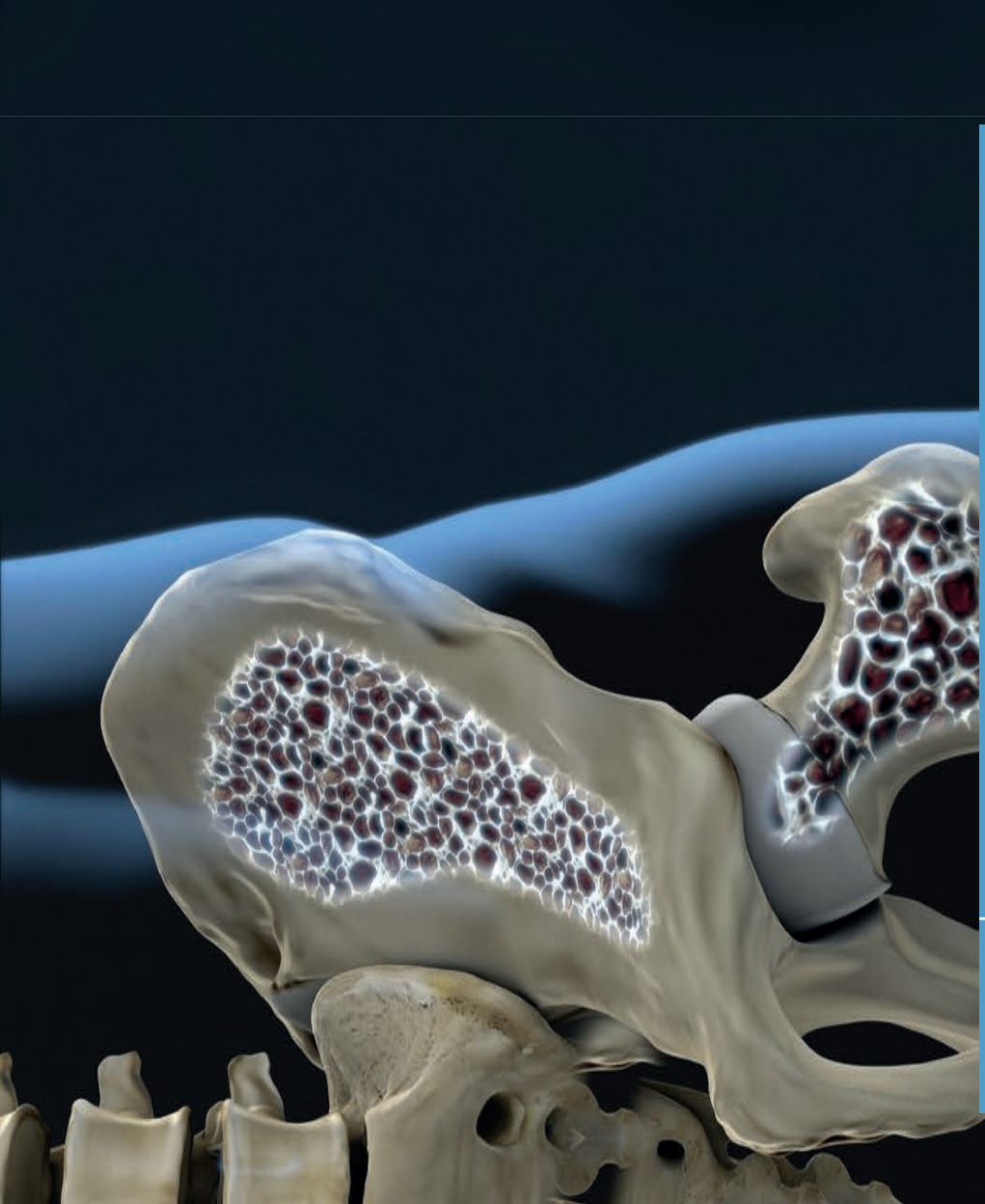

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Keywords:

Postmenopausal osteoporosis, quality of life, questionnaire Qualeffo-41

Abstract

Introduction: Postmenopausal osteoporosis is related to the changes in female body during menopause. The aim was to assess the quality of life of women in the Lublin region suffering from postmenopausal osteoporosis.

Methods: Data was obtained from standardized osteoporosis QoL questionnaire – Qualeffo-41. The survey was conducted in April 2013 in a group of women with postmenopausal osteoporosis treated in ambulatory setting.

Results: In total 55 QoL questionnaires were collected. The mean age was 70 years. The last declared menstruation was between 40 and 56 years. City inhabitants included 41 women, while 14 women inhabited rural areas. There were 28 married women, 25 widows and 2 maidens. The respondents' weight was between 42 - 102 kg. The shortest subject was 147 cm tall and the tallest - 170 cm.

The results of QoL were at 49.38. The results of the individual domains of the questionnaire indicate that the lowest rating was for physical function – mean of 39.41. Mental functions were assessed on average at 53.03. Pain assessment resulted on average at 53.45. The functioning during free time and opportunities for social contact were rated on average at 56.66. The highest result was for overall health with a mean value of 79.55.

Conclusion: The analysis showed that Polish women suffering from postmenopausal osteoporosis have a low quality of life. The results suggest further research to test QoL at the beginning of the therapy and to monitor it during treatment, analyzing the domains that need the most improvement.

Background

Menopause can be defined as a period of transition from a reproductive period to the advanced age. This period is characterized by hormonal changes in the female body which are associated with different diseases and symptoms. Due to their influence the quality of life as well as the interactions with the environment can deteriorate. Many women begin to develop diseases such as obesity, hypertension, diabetes and osteoporosis[1,2].

Osteoporosis as defined by the World Health Organization (WHO, 1994) is "skeletal systemic disease characterized by low bone mass, microarchitectural deterioration and fragility" and "*a bone density 2.5 standard deviations below the mean for young white adult women at lumbar spine, femoral neck or forearm*"[3]. In 2001, the National Osteoporosis Foundation (NOF) and the National Institutes of Health in the USA developed a different definition describing osteoporosis as "a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture"[4]. In 2013 Clinician's Guide to Prevention and Treatment of Osteoporosis was developed. In this Guide NOF in collaboration with experts from different fields of medicine indicate the latest advice on prevention, risk assessment, diagnosis and treatment of osteoporosis in postmenopausal women and men over the age of 50 years. According to the authors of the guide osteoporosis is "a silent disease until it is complicated by fractures—fractures that occur following minimal trauma or, in some cases, with no trauma"[5]. In 2014 Polish guidelines were compared with other international guidelines in terms of diagnostic measures, pharmacotherapy and calcium and vitamin D supplementation [6]. Depending on the cause of osteoporosis development we can differentiate primary and secondary osteoporosis. Most frequent (80%) is the primary disease and can be idiopathic or involutional. The idiopathic form is rather rare and usually affects young people without a known cause. The involutional form can be postmenopausal or senile. The form we predominantly observe is the postmenopausal type (80%)[7,8].

Osteoporosis is considered to be a social disease because of the incidence of the disease and the consequences. It is estimated that, due to complications within six months after the fracture of the femur, 20% of patients die and 50% die within the next year. It is estimated that since the number of hip fractures in 2000 was 1.6 million cases worldwide, then in 2025 it may reach 4 million, and in 2050 even 6 million [7, 9]. These fractures cause patient's immobilization, loss of independence and pain which results in reduction of the quality of life[10]. More than 30% of the vertebral body fractures do not cause clinical symptoms[11]. However all the other patients feel persistent pain and that affects significantly their quality of life[7].

Epidemiological data from 2008, related to Poland indicate that among people over 50 years, 165/100 000 are experiencing osteoporotic fracture. In case of people over 85 years of age, the figure is 666 for men and 1 138 for women per 100 000/year[9]. A study conducted in a Podlasie region showed that the proportion of women with fractures and without them at different ages, among whom a history of osteoporotic fractures occur in the 5th decade of life is reported in 20%, in the 6th - 16.8%, in the 7th - 29.2 % , in the 8th - 33.5%, and in the 9thdecade – 44.4%. On average, in the whole population 27% of the women experienced in the past low-energy fractures[12]. In other study conducted in Poznan it was demonstrated that 40% of respondents after a fracture rated their quality of life as poor. Prior to the trauma, 8% of patients assessed

their QoL as bad, while all the respondents consistently complained about a significant deterioration in relation to pain [13].

The aim of this study was to assess the quality of life in postmenopausal women suffering from osteoporosis. In addition, an attempt was made to verify the correlation between the place of residence, age, BMI, the occurrence of fractures and quality of life of patients.

Material and Methods

In recent years, it has been proven that there are needed questionnaires measuring health status for the research purposes and for clinical practice as well. The questionnaires are based on health status variables, such as mood, physical and social functioning and patient self-management. The general scales to measure health status are used to evaluate patients suffering from various diseases, however these scales are not measuring specific functioning in a given disease. Therefore it was necessary to construct a specific scale for osteoporosis. The questionnaire which is recommended by the International Osteoporosis Foundation (IOF)[14] is the called Quality of Life Questionnaire of the International Osteoporosis Foundation (Qualeffo-41)[15]. The questionnaire consists of 41 questions in the following 5 subscales: pain (5 questions), physical function (17 questions), social function (7 questions), general health perception (3 questions) and mental function (9 questions). When filling out questionnaires only one answer to each question should be selected. For the total score and subscores, "0" indicates a good health status, whereas "100" indicates a poor health status[16].
The studied material consisted of data of the interview conducted by the appropriately trained interviewer. The interviews were conducted among 55 patients undergoing a medical treatment at the clinic for osteoporosis treatment in April 2013. The interview included a questionnaire Qualeffo-41 with the addition of a special copyright questionnaire to characterize the studied group of patients. This additional questionnaire allowed us to collect information about age, weight, height, age of onset of the last menstrual period, the concomitant diseases and history of bone fractures. The interview lasted on average 25-30 minutes. The study was conducted at two clinics treating osteoporosis in Lublin. There was a random selection of the studied group, which included women aged 54 - 86 years, average 70 years (median 72 years). The age distribution of women in the study group is shown in Figure 1. The inclusion criterion was a history of menopause and osteoporosis diagnosed by the patient declared verbally and its written consent to participate in the study. The obtained data were compiled using MS Office Excel 2007, and the results are presented as descriptive statistics and as figures and tables. For the purpose of the statistical analysis the significance index and Pearson correlation and the index α-Cronbach were used. The assumed level of statistical significance was $\alpha = 0.05$. The study received a positive opinion of the Bioethics Committee of the Medical University of Lublin.

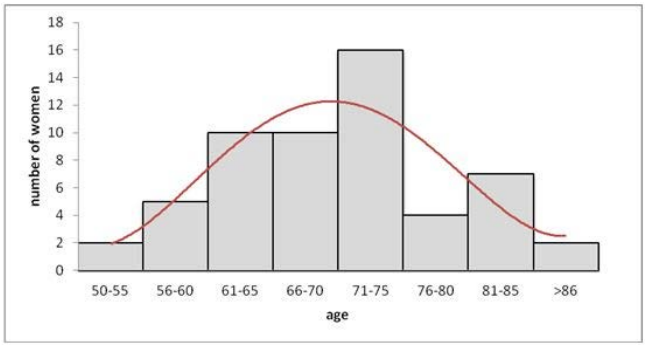

Figure 1. The number of women in the different age groups

Results

Taking into account 55 patients, it should be pointed out that they represented a diverse population of patients with postmenopausal osteoporosis. The assessment of the demographic data of women surveyed is shown in Table 1.

characteristic		Patients N=55
Place of residence	Urban	41 (74.5%)
	Rural	14 (25.5%)
Marital situation	Married	28 (50.9%)
	Widowed	25 (45.5%)
	Single	2 (3.6%)
Weight	Mean	62 kg
	Median	60 kg
Height	Mean	158 cm
	Median	160 cm
Body mass index (BMI)	Mean	24.7
	Median	23.8
	SD	4.2
Age at menopause	Mean	49 years
	Median	50 years
	SD	4.0
Fracture	Yes	21 (38.2%)
	No	34 (61.8%)
coexisting diseases	Yes	42 (76.4%)
	No	13 (23.6%)

Table 1. Socio-demographic characteristics of women with postmenopausal osteoporosis

The fractures declared by women usually concerned the lower limbs (12 persons, 21.8%), including: ankle (3 people, 5.45%), the hip bone (1 person, 1.8%), the toes (3 women, 5.45%). Fractures of upper limbs were reported by12 people, representing 21.8% of the respondents, including: wrist (5 people, 9.1% of respondents), shoulder (2 women, 3.6% of respondents). Broken ribs was reported by 1 person (1.8% of respondents). Vertebral frac-

tures were experienced by 2 people (3.6% of respondents). Broken collarbone was reported by 1 person (1.8% of respondents).

Patients also reported concomitant diseases: hypertension, neurological diseases, thyroid disease, rheumatoid arthritis, gallstones, or kidney stones, glaucoma and cataracts.

In the first step, we analyzed the psychometric properties of the questionnaire Qualeffo-41 in the sample of 55 women. According to the analysis of reliability, four of the five dimensions of Qualeffo-41 questionnaire have good psychometric properties as α-Cronbach ratio significantly exceeds the 0.7, which is considered as the threshold value. The best result concerns the physical functioning domain. The α-Cronbach value below 0.7 was obtained for measuring mental functioning. The properties of this subscale are significantly improved by the elimination of question # 38 (Do you get annoyed by details?).

Domain	No of items	Description	Cronbach α
Pain	5	Back pain; Sleep disturbance	0.792
Physical function	17	Activities of daily living; Jobs around the house; Mobility; Walking outside	0.918
Social activities	7	Sport; Gardening; Hobby; Theatre; Visiting friends; Intimacy	0.812
General health perception	3	General health; overall quality of life; Change in quality of life	0.867
Mental function	9	Fatigue; Depression; Loneliness; Energy; Hopefulness; Fear of becoming dependent	0.628

Table 2. Description and reliability of Qualeffo-41

The evaluation of the quality of life of women with postmenopausal osteoporosis was based on a standardized questionnaire Qualeffo-41. The results are summarized in Tables 3 and 4.

It should be noted that the overall average quality of life of women surveyed is 49.38 (SEM 15.46). However, in various domains of the questionnaire it was found that women assessed the overall health as the worst with an average of 79.55 (SEM 1.80). There was even recorded a maximum value in case of 17 people, i.e. "A very bad condition". The next step was to assess the functioning during free time and opportunities for social contact, rated on average at 56.66 (SEM 2,35) at the lowest value of 0.0 in 2 patients, which can be explained as a lack of disruption in social activities and the highest of 90 in case of 4 women for whom the assessment has shown great difficulty in social activities. "Feeling pain", was another domain with an average score of 53.45 (SEM 2.40). In this case, the lowest value - 0.00 was observed in 5 women, which indicates the lack of pain, as well as the highest value recorded here was 90.00 in 3 women, which is a significant perception of pain. The surveyed women found mental functions on average at 53.03 (SEM 1.36), with the best value 19.44 (1 woman) and the worst 80.56 (3 women). However, despite significant pain, women gave the best rating in physical function - the average value is 39.41 (SEM 1.69), which means that surveyed women had not significant difficulties in the physical functioning in relation to movement.

Correlation between the assessment of the quality of life with the place of residence, age, marital status, BMI and a history of fractures indicated that there was no statistically significant difference in case of analysis in relation to place of residence, marital status, BMI and a history of fractures. Statistically significant differences were demonstrated in the analysis in relation to age and for marital status in the social activities domain. It was found that with age the quality of life should deteriorate, which results in a longer life with the disease. This study confirms that hypothesis. For the pain domain depending on the marital status, the value of calculated p is at borderline of statistical significance.

We also decided to analyze the correlation between the five domains of the questionnaire. The results are summarized in Table 5. Correlation coefficients range from 0.325 to 0.655, assuming that the highest value of correlation is for physical function and social activities. Also it is worth to pay attention to the high correlation (r = 0.610) between the two domains, which are more than any other domain for osteoporosis (pain and limitations in functioning).

Statistics	Total	Qualeffo-41 domains				
		Pain	Physical function	Social activities	General health perception	Mental function
Mean	49.38	53.45	39.41	56.66	79.55	53.03
Median	51.16	55.00	38.24	61.43	83.33	52.78
Minimum	12.80	0.00	7.35	0.00	33.33	19.44
Maximum	80.00	90.00	80.88	90.00	100.00	80.56
SEM	1.46	2.40	1.69	2.35	1.80	1.36
95% CI	2.86	4.70	3.31	4.61	3.52	2.66

Table 3. Results of quality of life measured with Qualeffo-41

		Total	Qualeffo-41 domains				
			Pain	Physical function	Social activities	General health perception	Mental function
Place of residence							
Urban	Mean	49.49	55.98	39.96	56.44	78.86	51.76
	SD	14.09	21.89	17.38	23.64	18.36	13.90
Rural	Mean	48.60	46.07	37.82	57.30	81.55	56.75
	SD	18.98	32.83	19.18	29.79	20.72	15.13
p		0.929	0.327	0.808	0.933	0.832	0.632
Marital status *							
married	Mean	42.35	45.18	32.88	44.76	74.70	49.90
	SD	15.56	28.72	17.12	26.98	18.21	13.62
widow	Mean	57.19	63.20	47.12	70.24	85.67	56.22
	SD	11.49	17.37	16.16	15.15	18.71	14.73
p		0.137	0.083	0.111	0.018	0.386	0.540
Age (years)							
50-60	Mean	23.91	20.71	14.50	15.95	60.71	38.49
	SD	9.22	29.64	5.46	19.07	15.75	11.83
61-70	Mean	47.08	51.84	37.69	51.86	77.63	50.88
	SD	11.59	26.36	16.33	20.43	16.45	12.32
71 and older	Mean	56.82	62.41	46.55	69.63	85.34	57.95
	SD	11.11	15.27	14.71	16.14	18.18	13.52
p		0.001	0.000	0.000	0.000	0.119	0.139
Body weight **							
BMI 18.5 – 24.99	Mean	48.89	53.86	38.40	55.14	80.48	53.81
	SD	16.53	27.20	18.83	25.93	19.49	14.68
BMI 25.0 – 29.99	Mean	50.03	53.57	42.02	59.32	75.60	52.18
	SD	11.73	21.34	15.14	20.33	18.91	13.13
BMI 30>	Mean	45.39	51.00	35.29	53.15	80.00	44.44
	SD	15.79	27.70	17.98	32.85	15.14	7.61
p		0.886	0.954	0.745	0.837	0.912	0.607
History of fractures							
yes	Mean	56.13	59.29	46.08	66.73	84.52	59.39
	SD	12.41	26.33	16.15	16.64	16.31	12.95
no	Mean	45.03	49.85	35.29	50.44	76.47	49.10
	SD	15.52	24.10	17.57	27.48	19.83	13.74
p		0.270	0.366	0.232	0.132	0.526	0.323

Table 4. The average indexes of quality of life assessed by questionnaire Qualeffo-41 and selected characteristics of patients with osteoporosis

** Due to small number single women were not included into calculations*
*** Due to small number of patients with BMI <18.5 not included into calculations*

	Pain	Physical function	Social activities	General health perception	Mental function
Pain	1	0.610	0.522	0.421	0.325
Physical function	0.000	1	0.655	0.591	0.558
Social activities	0.000	0.000	1	0.472	0.357
General health perception	0.001	0.000	0.000	1	0.608
Mental function	0.016	0.000	0.008	0.008	1

Table 5. The correlation matrix between the five dimensions of the questionnaire Qualeffo -41

**In the top of the table is the Pearson correlation coefficient, in the lower its significance*

Discussion

Quality of life as defined by the World Health Organization, is an individual perception of their position in life, taking into account cultural conditions and a system of values in relation to individual objectives, standards, expectations and problems. QoL studies, in particular for diseases that cause an increase in pain suggest that such diseases significantly affect the deterioration of the mental and physical dimensions of quality of life[17].

A survey of one hundred postmenopausal women, aged 66 ± 8.7 years (age range 50-85), affected by osteoporosis with / or without fractures, done by the surgery clinic of the Instituto Italiano Auxologico for a period of about 4 months has shown that pain was present in 50% of cases and in 26% for more than 10 hours per day[18]. In the studies carried out in this work pain was present in 89%. The pain lasted 1-2 hours per day at 32.7%, 3-5 hours in 12.7%, and 6-10 hours at 3.6% of patients. Back pain lasting the whole day occurred in 40% of patients.

In a study conducted at the clinic Instituto Italiano Auxologico, in the area of physical fitness, 46% of women under 65, and also 65% of people over 65 years declared significant changes[18]. For Polish women getting up from the chair causes difficulties in case of 62% of patients, bends - 64%, kneeling – 67%, walking up the stairs – 93%, walking 100 meters – 51%.

In the category of general health perception, according to a study in Italy, 58% of the women had poor well-being. In 21% of the 62 women, a reduction of their health perception was reported. Comparing their current level of health status with that of 10 years before, 58% of women aged below 65 indicate a deterioration, similarly as 83% of people aged 65 or more. Reduced quality of life was confirmed by 41% of women affected by osteoporosis [18]. According to research conducted for this study, most of the patients identified their health as fair - 36.4% or poor - 36.4%. In contrast, 21.8% described it as satisfactory. Most of the patients identified their overall quality of life as satisfactory (40%) and poor (34.5%). None of the patients defined quality of life as excellent. Satisfactory quality of life was reported by 34.5%. Comparing their current level of wellbeing with that of 10 years before, 91% of patients indicated its deterioration. In a study conducted in an Italian clinic, it was estimated that 40% of surveyed women had symptoms of depression[18]. According to our survey 100% of patients were experiencing fatigue. Also, as in the Italian study, we can conclude that approx. 40% of women have symptoms of depression, because they feel depressed, lonely, and only 40% of respondents thought indicated "only sometimes with hope on the future" response.

Papaioannou, A. et al. believe that the experience of osteoporotic fracture has a negative impact on patient quality of life. The factors that play the biggest role is pain and disability, the ability to self-care and mobility[19,20]. Osteoporotic fractures lead to a reduction of efficiency and reduced quality of life and are associated with increased mortality. Because of the pain, impairment of movement and limitation in self-care activities, during the first months of the injury occur and a significant deterioration in QoL regardless of the location of the fracture[20]. The study by Abimanyi-Ochom J. et al. conducted using the EQ-5D questionnaire, found the average decrease in QoL for all fracture locations. Immediately after the injury decrease at an average of 51%, the largest decrease was recorded in the proximal femur fracture 69%, least (36%) of the radius bone. In the case of proximal femur and vertebral fractures, QoL did not return to the level from before the event even after 18 months, with 83- 89% of the initial value [20,21]. In the Swedish study using the same protocol, O. Ström et al. obtained similar results[20,22]. The study in Lublin confirms the results obtained by A. Papaioannou, J. Abimanyi-Ochom and O. Ström et al. Polish women with osteoporotic fractures have reduced QoL.

In the Outpatient Treatment of Osteoporosis and Menopause and Orthopedic Clinic in Poznan, among 100 women aged 50 to 70 years (research carried out for 11 months), a study was conducted to assess the quality of life of women suffering from osteoporosis. The women were divided into 3 groups. The first group consisted of women with osteoporosis, the other with osteopenia, and the third one of healthy women. Worse functioning was demonstrated in women with osteoporosis in the field of performing daily activities, mobility, leisure activities and opportunities for social contact. The first group of women received the best results in the field of mental functioning[23]. This study confirms the results obtained in Poznan. The research of Bianchi et al. showed that 58% of women with osteoporosis assess the overall state of their health as low. The reduced quality of life is reported by 41% of women suffering from osteoporosis. Patients suffering from osteoporosis have a more depressed mood and lower quality of life compared to healthy subjects[18]. The women in this study also found the overall health as the worst amongst the assessed domains.

Research conducted by Professor Horst-Sikorska et al. showed that osteoporosis causes limitations in patients' physical activity, pain and depressed mood, fatigue and insomnia[24]. The study showed that studied women also indicate limited physical and mental activity. According to the study conducted by Vujasinocić et al. in which authors were using the Qualeffo-41 scale, it was demonstrated that women with osteoporosis indicated much worse functioning in every field of the scale[25].

This research confirms that in addition to pain, general health, social and mental activity are assessed as worst by the surveyed women.

In a study conducted in Japan among women with postmenopausal osteoporosis, it was shown that daily activities identified in the domains were equal to 0.2 Standardized Response Mean (SRM), while social activities and the attitude domain reached SRM levels close to 0. In the present study the domain of General Health perception reached the worst value[26]. Wilson S. et al. in order to identify variables that can affect the quality of life (HRQOL) in patients with or without fractures, performed the assessment of bone mineral density (BMD) before the diagnosis of osteoporosis. The mentioned patients with the assessment of BMD before the diagnosis of osteoporosis had reduced physical performance component summary (PCS). In patients without fractures, low BMD indicated a decline in the quality of life[27] . In the present study, it is not possible to refer to the BMD, since such data was not collected, but it can be concluded that the average value of the Qualeffo-41 scale indicates a poorer quality of life for women after fracture than for women who had not experienced fractures. However, statistical analysis revealed no significant differences in this respect. Using the data obtained from 55 women, similar to what was demonstrated in studies by other authors, in this study we confirmed good psychometric properties of the Polish version of Qualeffo-41. In their studies, Lips P. et al.[28] and Bączyk G.[29] also achieved a very high coefficient of reliability of α-Cronbach for measuring physical functioning.

Caputo E. L. and Costa MZ in the review of the literature found that when it comes to the quality of life in the domain of physical aspects such as muscle strength and balance, with the exception of two studies, all reported improved quality of life in the physical domain of the patients after treatment[30]. It is clear from this study that treatment improves quality of life, but especially in case of pharmacological treatment it is important to take your medicines as prescribed by your doctor. Haus D., et al., demonstrated that compliance of women in post-menopausal osteoporosis is weak, but the reduction in dosing frequency of drugs and patient education on the disease and its treatment may improve the compliance[31].

Conclusions

Based on the results obtained in a standardized detailed questionnaire for evaluation of the quality of life in osteoporosis - Qualeffo-41, we can confirm that Polish women with postmenopausal osteoporosis have a fairly low quality of life. Unsatisfactory relations between the domains of Qualeffo-41 in the treated patients indicate a need for improvement in several domains Qualeffo-41, i.e. general health perception, social function, pain and mental function. This result confirms one of the methods to evaluate quality of life, which should be monitored both at the beginning and during therapy, as evidenced by the work Caputo E.L. and Costa M.Z. Quality of life in the course of the treatment would allow for a thorough analysis of the areas that affect most on the deterioration of overall quality of life. The attempt to verify correlation between the place of residence, age, BMI, fractures and quality of life of patients has demonstrated essential statistical dependence of terms of age.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Treatment and prevention of bleeding in adult hemophilia A patients with inhibitor – economic analysis

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Keywords:

hemophilia A, adults, factor VIII, inhibitor, prophylaxis

Abstract

Hemophilia A is caused by an absence or deficiency of coagulation factor VIII. Patients with hemophilia may experience recurrent spontaneous hemarthroses or internal bleeding. Following the treatment with factor VIII concentrates, patients with hemophilia A may develop alloantibodies to factor VIII, evidence of which is critical to diagnose hemophilia with inhibitor. The primary goal of treatment in patients with hemophilia with inhibitor is a durable inhibitor elimination and the interim goal is to stop the bleeding. The aim of this paper is to compare the effectiveness and costs of on-demand therapy and prophylaxis in patients with hemophilia A with or without inhibitor. We conducted a review of studies. The outcomes of the studies included in the review suggested that the difference in annual bleeding rate (ABR) between prophylaxis and on-demand therapy is less pronounced in patients with inhibitor. Furthermore, one study found no statistically significant difference in ABR between prophylaxis and on-demand therapy in patients aged ≥ 40, although the consumption of coagulation factor was significantly higher in the prophylaxis group. Treatment of patients with hemophilia A is associated with high costs of coagulation factor concentrates and frequent, stressful and painful injections. Therefore, while considering the introduction of prophylaxis in adult patients, it appears advisable to select groups of patients depending on the frequency of bleeding episodes and to determine adequate treatment strategy.

Introduction

Hemophilia A is a disorder caused by an absence or deficiency of coagulation factor VIII (FVIII). Depending on the coagulation factor VIII level, hemophilia is defined as severe (<1% of normal factor level, 0.01 IU/ml), moderate (1%-5% of normal factor level, 0.01-0.05 IU/ml) or mild (5%-50% of normal factor level, >0.05-<0.50 IU/ml) [1]. As a consequence of treatment with factor VIII concentrates, patients with hemophilia A may develop alloantibodies to factor VIII, evidence of which is critical to diagnose hemophilia with inhibitor. Approximately 15-30% of patients with severe hemophilia develop factor VIII inhibitor[2].

In accordance with the *Polish National Health Program for Patient with Hemophilia and Bleeding Diatheses (2012-2018) (Narodowy Program Leczenia Chorych na Hemofilię I Pokrewne Skazy Krwotoczne na lata 2012-2018)* 2,263 patients (adults and children) were registered by *Institute of Hematology and Transfusion Medicine in Warsaw*, Poland (*Instytut Hematologii i Transfuzjologii w Warszawie*) by 17th of September 2013, including 1,071, 331 and 713 with severe, moderate and mild hemophilia, respectively[2].

Recurrent spontaneous hemarthrosis is the major symptom of severe hemophilia. Hemarthrosis results in arthropathy leading to significant decrease in physical activity and even early labor market exit. Patients with hemophilia may also develop severe and life-threatening spontaneous bleeding to internal organs and body cavities (e.g. intracerebral hemorrhage or gastrointestinal bleeding) or excessive bleeding after trauma[2].

Management of patients with hemophilia A

The mainstay of treatment for severe hemophilia A is factor VIII replacement therapy, administered as[2]:

a) **on-demand therapy** – factor concentrate injections given for clinically evident bleeding episodes;
b) **prophylaxis:**

- primary prophylaxis – regular injections of factor concentrates initiated before documented arthropathy has occurred and after second, clinically significant episode of large joint bleed in patients before the age of 3 years to prevent arthropathy;
- secondary prophylaxis – regular factor concentrate injections started after 2 or more bleeds into joint/joints and before arthropathy has occurred;
- tertiary prophylaxis – regular factor concentrate injections initiated after arthropathy has occurred;
- short-term prophylaxis – regular factor concentrate injections, for less than 45 weeks per year, in patients with hemophilic arthropathy to stop recurrent bleeding into a particular joint or to prevent bleeding during physiotherapy;
- perioperative prophylaxis – factor concentrate injections started prior to surgery and continued until healing is achieved to prevent bleeding in the perioperative period[1].

The development of inhibitor to FVIII is considered to be severe complication in patient with hemophilia, as coagulation factors administered as replacement therapy become inactive. The primary aim of treatment in hemophilia patients with inhibitor is a durable elimination of the inhibitor and prevention of bleeding. The therapeutic strategy to eliminate inhibitors is to administrate regular injections of factor VIII concentrates (immune tolerance therapy)[2]. Dosing frequency in immune tolerance induction is varied, starting with frequent and regular doses and ending with protocols involving significantly higher doses[3]. In order to control bleeding episodes, bypassing agents, inducing thrombin generation in plasma, are used despite the presence of inhibitor to FVIII. Currently, two bypassing agents are used, i.e.: activated prothrombin complex concentrates (aPCC, Feiba®) and recombinant activated factor VII (rFVIIa, NovoSeven®)[1].

In 2008 a therapeutic program for bleeding prophylaxis in children was implemented in Poland (*Prevention of bleeding in pediatric patients with hemophilia A and B*). The program is reimbursed by Polish National Health Fund. First therapeutic program for adults (*Program for hemophilia and bleeding diatheses treatment with coagulation factors*), reimbursed by the Ministry of Health,was implemented in 2001. The current treatment program for the years 2012-2018 is a continuation of the program for the years 2005-2011[1]. The program provides on-demand therapy and short-term prophylaxis (a few months or weeks) in adult patients with recurrent bleeding into a particular joint or muscle and who are not eligible to primary or secondary prophylaxis[4]. The aim of this article is to review current clinical strategies for treatment of hemophilia in adults.

Results

Prophylaxis vs on-demand therapy in patients aged 40 years or older

In the clinical trials on patients with hemophilia A without inhibitor, compared to on-demand therapy, prophylaxis was associated with a significant reduction in the frequency of bleeding episodes (including joint bleeds), however, the difference between prophylaxis and on-demand therapy is less pronounced in hemophilia patients with inhibitor[5,6]. In addition, in the clinical trials comparing prophylaxis and on-demand therapy, most patients were children and young adults (aged ≤ 40 years old)[1]. Jackson et al. (*Jackson 2015*) conducted one of the few studies in patients aged 40 years or older[7]. In this observational study prophylaxis was compared with on-demand therapy of severe hemophilia A in patient aged 40 years or older and younger patients. The study included 220 adult patients from Canada, with 70% of patients being exposed to prophylaxis and 27% aged 40 years or older. Hemophilia with inhibitor affected about 15.6% and 35% of younger and older patients, respectively. Annualized bleeding rate (ABR) was considered to be the primary endpoint in the study. Jackson et al.(*Jackson 2015*) revealed statistically significant differences between prophylaxis and on-demand therapy in terms of ABR (4 vs. 12 bleeding episodes/year; p<0.0001) in hemophilia A patients with our without inhibitor, who were aged ≤ 40 years old (Figure 1). There were no statistical differences in older subjects, aged ≥ 40 years old (12 vs. 13 bleeding episodes/year; p=0.866), even though the discrepancy between factor utilization for on-demand therapy versus prophylaxis was observed (560 vs. 3447 u/kg/year, p < 0.001). We sent and inquiry to the authors of the study on the difference between prophylaxis and on-demand therapy with regard to ABR in patients with hemophilia A with inhibitor, but no response has been received. In all patient aged 40 years or older hemophilia A with inhibitor affected about 35% of patients. Therefore, it is likely that in this age group no significant differences between prophylaxis and on-demand therapy in ABR are present both, in patients with and without inhibitors.

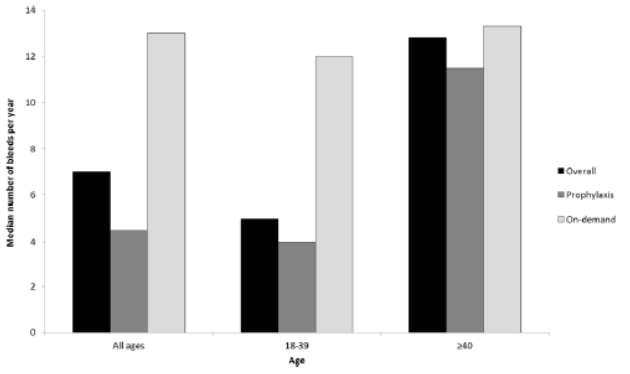

Figure 1. Annualized bleeding rate *Source: Jackson et al.2015*[7]

Comparison of prophylaxis and on-demand therapy for adult patients with hemophilia A with inhibitor

Currently, there are no clear guidelines for the use of prophylaxis in adult patients with hemophilia [4]. These uncertainties are related to the high costs of prophylaxis in patients with arthropathy due to the lack of prophylaxis in childhood and adolescence. The benefits of prophylaxis in this group of patients are limited to reduced bleeding rate, while the influence on inhibition of arthropathy progression is unclear. Scientific evidence shows that secondary prophylaxis in adult patients with hemophilia A aged ≥ 40 years old is ineffective. Hence, the cost of prophylaxis and on-demand therapy in the group of patients aged ≥ 40 years old with hemophilia A with the inhibitor were compared. Data were based on the study *Jackson et al., 2015*[7]. The estimates used median annual number of bleeding episodes in relevant age subgroups.

Two replacement therapies in the prevention of bleeding episodes for patients with hemophilia A with inhibitor are available in Poland: i.e.: NovoSeven® and Feiba®[8,9]. The products are considered to have comparable clinical efficacy[10]. NovoSeven®, according to the product characteristics, is indicated only for the treatment of bleeding and for the prevention of bleeding in patients undergoing surgery or invasive procedures (home therapy available

on request only)[11]. Feiba® is indicated for the treatment and prevention of bleeding (on-demand therapy and prophylaxis)[12]. Considering the comparable efficacy of on-demand therapy and prophylaxis, it is assumed that the only differing cost is associated with the various consumption of coagulation factors.

Prices of coagulation factors were estimated based on Polish National Blood Center data[8] and data from tenders announced by Department of Public Procurement at the Ministry of Health[14]. The Table 1 and Table 2 present estimated prices of one microgram (for NovoSeven®) and a single unit (for Feiba®).

On-demand therapy cost

The treatment costs of a single bleeding episode were estimated taking into account prices depicted in Table 1 and Table 2. The drug doses necessary to control a bleeding episode were adopted on the basis of data reported by *Goszczyńska et al. 2011*[9] *and Lyseng-Williamson and Plosker 2007*[13]. *Lyseng-Williamson and Plosker* summarized data from the following publications: *Dundar et al. 2005*[15], *Hart 2002*[16], *Odeyemi and Guest 2002*[17], *Ozelo et al. 2007*[18], *Plyush et al. 2006*[19], and *Yoo et al. 2007*[20]. The authors of these papers report drug doses used in the general population of hemophilia patients with inhibitor. Estimates of the doses and the costs of Feiba® or NovoSeven® in the treatment of a single bleeding episode are presented in the Table 3. Differences in costs of single bleeding episode treatment with Feiba® and NovoSeven® are about PLN 10 000 in favor of NovoSeven®. Both therapies have similar number of doses required to control a bleeding episode.

Jackson et al. [7] presented results referring to hemophilia patients (with and without inhibitor). Patients aged ≥ 40 years old on prophylaxis had an ABR of 12, while those on-demand use had an ABR of 13. Adult patients aged ≥ 40 years old and on-demand use had an ABR of 12. The estimates of annual costs of on-demand therapy in patients aged ≥ 40 years are depicted in the Table 4.

Cost of prophylaxis

While estimating the annual cost of prophylaxis, doses recommended by the Medical and Scientific Advisory Council (MASAC) [22] were used. Considering the therapeutic indications, it was assumed that in long-term prophylaxis only Feiba® will be used[11,12]. Estimation of the annual cost of prophylaxis made on the basis of MASAC 2013 guidelines is summarized in the Table 5. The recommended dose of Feiba® in the prophylaxis of bleeding is slightly lower in the MASAC 2013 guidelines (three times a week) than in the product characteristics (every other day). However, the dose is still within the range of the recommended dose adjustments and it seems to be in line with everyday clinical practice. Additionally, we performed a non-systematic review of the literature to identify publications reporting prophylactic aPCC consumption in practice. *Negrier et al.* reported significant differences in practical aPCC dosing in prophylaxis[23].

Source	Consumption rFVIIA (µg)	Expenditure (PLN)
Tender ZZP-38/14	13 000 000.00	36 920 000.01
Tender ZZP-159/15	1 800 000.00	5 112 000.00
Tender ZZP-125/15	10 300 000.00	29 252 000.00
Tender ZZP-90/15	11 000 000.00	31 240 000.00
National Blood Center data from year 2013	13 559 000.00	38 507 560.00
Total	49 659 000.00	141 031 560.01
Cost per unit (PLN/µg)	2.84	

Table 1. rFVIIa consumption and expenditure in treatment of hemophilia patients with inhibitor based on data of National Blood Center[14] and Department of Public Procurement at the Ministry of Health[8]

Source	Consumption aPCC (unit)	Expenditure (PLN)
Tender ZZP-130/15	6 000 000.00	22 740 000.00
Tender ZZP-89/15	10 000 000.00	37 900 000.00
Tender ZZP-157/15	5 600 000.00	21 224 000.00
Tender ZZP- 155/14	10 000 000.00	37 900 000.00
Tender ZZP-121/14	1 400 000.00	5 306 000.00
Tender ZZP-36/14	6 000 000.00	22 740 000.00
National Blood Center data from year 2013	8 498 000.00	32 207 420.00
Total	47 498 000.00	180 017 420.00
Cost per unit (PLN/unit)	3.79	

Table 2. aPCC consumption and expenditure in treatment of hemophilia patients with inhibitor based on data of National Blood Center[14] and Department of Public Procurement at the Ministry of Health[8]

		Dundar et al. 2005	Hart 2002	Odeyemi and Guest 2002	Ozelo et al. 2007	Plyush et al. 2006	Yoo et al. 2007	Goszczyńska et al. 2011	Mean
Country		Turkey	Slovakia	Great Britain	Brazil	Russia	South Korea	Poland	na
Mean umber of injections administrated in order to control a bleeding episode	rFVIIa	3.60	2.10	2.30	2.00	1.60	1.70	nd	2.22
	aPCC	4.80	2.00	3.00	3.80	1.70	2.30	nd	2.93
Mean dose required to control a bleeding episode	rFVIIa (ug/kg bw)	204.00	160.00	207.00	190.00	157.00	136.00	219.00	181.86
	aPCC (unit/kg bw)	167,00	105.00	225.00	260.00	135.00	168.00	176.00	176.57
Cost of a single bleeding episode treatment from public payer perspective*	rFVIIa (PLN)	42 009.39	32 948.54	42 627.18	39 126.40	32 330.76	28 006.26	45 098.32	37 449.55
	aPCC (PLN)	45 893.75	28 855.35	61 832.90	71 451.35	37 099.74	46 168.57	48 367.07	48 524.11

Table 3. Costs and drug doses utilized to control single bleeding episode in population of hemophilia patients with inhibitor

bw – body mass, nd – no data, na – not applicable
**taking into account unit price from table 1 and table 2(determined on the basis of National Blood Center data and data from tenders announced by Department of Public Procurement at the Ministry of Health [14]), and assuming a mean body mass of 72.51 kg [21]*

	On-demand therapy using aPCC only	On-demand therapy using rFVIIa only
ABR in subgroup of patients aged ≥ 40years	13.00	13.00
Cost of on-demand therapy (PLN/year)	630 813.38	486 844.16

Table 4. Estimates of annual costs of on-demand therapy for single hemophilia patient with inhibitor

**assuming mean patient body weight of 72.51 kg [21]*

	Dosage based on MASAC 2013	Weekly dosage	Annual cost of drug (PLN)
aPCC	85 unit/kg bw 3 times a week	255.00 unit/kg bw	3 656 532.86

Table 5. Recommended aPCC dosage and costs of long-term prophylaxis per one patient

	Min. weekly dosage	Max. weekly dosage	Annual cost – minimum variant (PLN)	Annual cost – maximum variant (PLN)
aPCC (*Negrier 2016*)	30.61 unit/kg bw	1 075.20 unit/kg bw	438 906.43	15 417 663.24

Table 6. Dosage and cost of prophylaxis per one patient

It is associated with the need for an individual dose adjustment. These values and drug costs are summarized in the Table 6. Given the wide range of doses used in practice, it was assumed that the average annual consumption of Feiba® is equivalent to its consumption determined on the basis of the MASAC 2013 guidelines. It should be noted that in *Jackson 2015* publication, patients aged ≥ 40 years old on prophylaxis were administered higher doses than younger patients. Therefore, it can be assumed that the consumption of coagulation factor (and the cost of prophylaxis) among older patients is higher than the average consumption determined on the basis of MASAC 2013. The Table 7 summarizes the costs of prophylaxis and on-demand therapy, which will be generated by patients aged ≥ 40 years old on prophylaxis. ABR was adopted on the basis of *Jackson 2015* publication. Given the fact that *Jackson 2015* et al. proved no statistically significant differences in the ABR between patients aged ≥ 40 years old on prophylaxis or on-demand therapy, quality of life of these patients may be reduced on prophylaxis due to the frequent dosing (quality of life decrease associated with injections). Prophylactic injections are usually given at least three times a week. *Matza 2013 et al.*[24] presented the influence of injections and infusions on the quality of life in patients suffering from bone metastases. Basing on these results, we assumed that the loss on quality of life due to injections and infusions is comparable in hemophilia patients and in patients with bone metastases. A single injection is associated with a decrease in the patients' quality of life by 0.4%, while the half-hour infusion by 2.3%. Prophylaxis does not guarantee an improvement in general condition in patients aged ≥ 40 years old, and additionally, frequent injections or infusions may be an important factor decreasing the quality of life. The decision whether to administer prophylaxis may be influenced by the difficulties concerning this treatment. This fact may be of particular importance in patients with hemophilia with inhibitor, who tend to receive on-demand therapy[7].

	Value
ABR in the age group aged ≥ 40 years	12.00
Cost of on-demand therapy (PLN per year)	582 289.28
Cost of prophylaxis (PLN per year)	3 656 532.86
Total cost (PLN per year)	4 238 822.13

Table 7. ABR and annual costs of prophylaxis and on-demand therapy of single patient aged above ≥40 years on prophylaxis with Feiba®

Discussion and Conclusions

Patients with hemophilia and related bleeding diatheses represent only a limited part of the general population. However, taking into account the frequent hospitalization need, very high cost of treatment and the difficulties of rehabilitation, it can be stated that hemophilia is a social issue[2]. Hemophilia therapy is associated with high costs of coagulation factor concentrates and frequent, stressful and painful injections[4]. Moreover it often leads to permanent disability which has a huge economic impact on families and the entire society. According to *Forsyth et all* optimal bleeding control therapy decreases pain, prevents further disability and results in better quality of life[25]. We conclude that on-demand treatment is equally effective as prophylaxis in patients aged ≥ 40 years. The Table 8 presents a summary of treatment costs, proving that prophylaxis in hemophilia patients, aged ≥40 years, experiencing an average ABR, compared to on-demand treatment, is associated with several times higher costs. Extrapolation of this age group results from *Jackson 2015* on hemophilia with inhibitor patients allows to conclude that higher costs do not cause a significant improvement of the health state (in patients aged ≥ 40 years, ABR was comparable both on prophylaxis and on-demand therapy). Older subjects with prophylaxis had a higher ABR than younger subjects (12 vs 4). The authors did not provide explanation for ABR age-related differences.

On-demand therapy with NovoSeven® is cheaper than treatment with Feiba®. The difference in the treatment cost for single bleeding episode is about PLN 10 000. It should be noted that prophylaxis, despite its significantly higher cost, does not provide significant improvement for patients aged ≥ 40 years and inconveniences associated with frequent injections (several times a week) may have the opposite effect to that which is intended. Therefore, while considering the introduction of prophylaxis in adult patients, it appears advisable to select groups of patients depending on the frequency of bleeding episodes and to determine adequate treatment strategy (long-term prophylaxis, short-term prophylaxis, indefinite prophylaxis and on-demand therapy)[4].

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	Cost of single patient prophylaxis with aPCC	Cost of single patient on demand treatment with aPCC	Cost of single patient on demand treatment with rFVIIa
ABR in patients aged ≥ 40 years	12.00	13.00	13.00
Cost of acute treatment (PLN per year)	582 289.28	630 813.38	486 844.16
Cost of prophylaxis (PLN per year)	3 656 532.86	-	-
Total cost (PLN per year)	4 238 822.13	630 813.38	486 844.16

Table 8. Summary of costs depending on treatment option in patients aged ≥ 40 years

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Review of the Polish Pharmacoeconomic Society activities' 1/2016

The Polish Pharmacoeconomic Society Sections continue their work on the lexicons:

- The Therapeutic Programs, Pharmaceutical Care and Pharmaceutical Law Section (TPPCPL) has prepared the pricing lexicon and currently it is in the phase of final review.
- Similarly the Quality of Life Section continues working on the QoL lexicon, defining the QoL terms in Polish.

Polish Pharmacoeconomic Society continues cooperation with the Journal of Health Policy and Outcomes Research (JHPOR) and supported the organization of their 3rd Annual Conference. It took place in Warsaw on 18th March 2016 and it was dedicated to Telemedicine in Poland and around the world. There was also a special session on "Medical registries in Poland".

The Conference was divided into three sessions:

1. "Patient Registries in Poland" This session was a continuation of the discussion about registries initiated during the 2nd Annual Conference organized by JHPOR in 2015. The invited guest was prof. Nello Martini from The Italian Medicines Agency. The panel discussion was titled: "Current issues of medical registries in Poland: changed since March 2015" and the panel participants analyzed the current situation and the future need for registries in Poland in comparison to last year status.
2. A plenary session on systemic solutions in telemedicine- with experts from Poland, Germany, USA, Russia and Ukraine. That session, in addition to sharing experience between countries, included discussion about legal regulations in telemedicine, data security and technical aspects of using IT solutions, financing possibilities and also the HTA perspective.
3. A specialist session on practical solutions in telemedicine. During the session multidisciplinary approaches involving specialties such as radiology, pulmonology, psychiatry, cardiology, surgery and dermatology were discussed.

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