LOGICAL, STATISTICAL AND COMPUTER METHODS IN MEDICINE

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STUDIES IN LOGIC, GRAMMAR AND RHETORIC 25 (38) 2011

Application of Hardy-Weinberg Law in biomedical research

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Abstract. The aim of this paper is to discuss the Hardy-Weinberg Law which is fundamental for population genetics. It discusses the intuitive expectations connected with the distribution of allele frequencies in a gene pool by using mathematical equations and defines the genetic equilibrium. The conclusions which are consistent with the Hardy-Weinberg Law and relate to biomedical applications seem necessary for the evaluation of data quality. Moreover, ways in which evolutionary forces break genetic equilibrium will be extensively discussed and will be presented using mathematical models of the dynamics of gene pool.

Introduction

Studies in biomedical research often require reference to the genetic characteristics of examined individuals. The genome of each organism provides the basic knowledge of its morphological, physiological, biochemical traits. Instructions contained on the carrier of genetic information like DNA and saved using the genetic code not only allow to specify the characteristics of organisms such as eye color, body build, blood group. They also determine the inheritance properties or allow the detection of susceptibility to certain diseases. Understanding the genetic structure plays a pivotal role in the prevention and treatment of genetic diseases. The current level of knowledge of genetics allows to accurately identify the causes of many diseases of genetic origin. What is more, there are already developed ways to treat genetic disorders by the so-called gene therapy. Genetic screening is also conducted to identify persons, who are carriers of genetic diseases. This research allows to determine the risk of inheritance of disease by offspring or to predict how a disease, which develops in old age, will proceed – and thus, take appropriate remedial steps. Moreover, it is interesting to analyze the genetic structure of some species of organisms owing to the ongoing changes in time. Determining which factors have an influence on the genetic composition of

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populations, it seems necessary to understand the course of evolution. It is worth to look at phenomena of dynamics shaping the genetic characteristics such as natural selection, mutation, migration or genetic drift.

Introductory concepts

A population is a set of organisms that belong to the same species, live simultaneously in a particular environment, influence each other and mate giving fertile offspring. These individuals have a certain set of alleles, which are forms of occurring genes. It is called the gene pool. The characteristics of the population are mainly determined by its genetic composition, and thus the genotypes or alleles frequencies.

If the population consists of N individuals, and there occur n different alleles of a particular gene, then the total number of possible genotypes will be:

$$G = \frac{n!}{2(n-2)} + n = \frac{n(n+1)}{2} \tag{1}$$

To simplify the consideration, let us suppose that there is a population in which there are only two different alleles of a gene – dominant A and recessive a. In accordance with the formula (1) it is possible to obtain 3 genotypes: AA, Aa and aa. Their cardinality in the population is denoted respectively N_{AA}, N_{Aa}, N_{aa}. Then the frequency of each of them will be calculated as a share of a given genotype in N-person population and will be marked as:

$$P_{AA} = \frac{N_{AA}}{N} \quad P_{Aa} = \frac{N_{Aa}}{N} \quad P_{aa} = \frac{N_{aa}}{N} \tag{2}$$

In addition, there is of course:

$$P_{AA} + P_{Aa} + P_{aa} = 1 \tag{3}$$

It is possible to calculate the particular allele frequencies in the gene pool too. However, it should be kept in mind that the population of N individuals, due to its diploidy, brings $2N$ alleles while each homozygote provides twice more alleles considered type than heterozygote. So, if we denote by p frequency of allele A and by q frequency of allele a we obtain the following relationships:

$$\begin{aligned} p &= \frac{2N_{AA} + N_{Aa}}{2N} = P_{AA} + \tfrac{1}{2}P_{Aa} \\ q &= \frac{2N_{aa} + N_{Aa}}{2N} = P_{aa} + \tfrac{1}{2}P_{Aa} \end{aligned} \tag{4}$$

and

$$p + q = 1 \tag{5}$$

Analogous calculations can lead to a greater number of alleles in the population. The field of genetics, which deals with the quantitative study of individual allele and whole genotypes frequencies in population is named population genetics. It analyzes the factors affecting the maintenance of these rates and any changes in time that lead to the evolution of organisms. So it describes the essence of the evolutionary mechanisms. Moreover, it attempts to explain such phenomena as the existence of genotypes associated with genetic diseases, their spread and any changes in these diseases.

Hardy-Weinberg Law (HWL)

A fundamental law, which is considered as the basis of population genetics, is the theorem formulated independently by the eminent mathematician, professor at the University of Cambridge, Godfrey Harold Hardy and German doctor Wilhelm Weinberg in 1908 [1]. It provides a theoretical support for the description of evolutionary phenomena. This law will be presented for a population of N individuals, where there are only two different alleles of a gene, A and a. Their proportions will be denoted as above, respectively p, q. Let us suppose that:

a) population is infinitely large,
b) organisms are diploid,
c) organisms reproduce sexually,
d) in population mating is random (so the population is panmictic) – individuals do not have preference during mating; each male has equal chances of crossing with each female and vice versa,
e) generations do not overlap – therefore, when the offspring matures into reproduction, the parental generation no longer has the ability to reproduce, and thus there is no intergenerational pairs,
f) organisms do not migrate – population is isolated, there is no exchange of individuals between populations of the same species, so there is no flow of genes from one population to another,
g) in the population is no mutation – a swap genetic material is not observed, which can cause the transformation of existing alleles into a completely new form; in addition, there is no transformation of allele A to a and conversely,

h) selection does not affect the tested locus – none of the combination of alleles has more than any other chance of surviving until give offspring, so there is no difference in the adaptation between genotypes.

Then the frequencies of individual alleles and genotypes in subsequent generations do not change [2–3]. In addition, proportions of particular genotypes will be respectively:

$$P_{AA} = p^2 \quad P_{Aa} = 2pq \quad P_{aa} = q^2$$

and they correspond to the distribution of binomial square:

$$(p+q)^2 = p^2 + 2pq + q^2 = 1 \tag{6}$$

Thus, the Hardy-Weinberg law by mathematical modeling describes, how the proportions of alleles and genotypes in the population should be arranged. It defines what we now call the genetic equilibrium [4]. It shows that the processes of reproduction do not cause changes in the frequencies of alleles in the population. If a) – h) assumptions are met, the proportions of alleles in subsequent generations remain constant and the population is not evolving. What is more, any deviations from the Hardy-Weinberg model are removed within one generation. A single random mating, in which there is no migration, mutation and selection pressure, is enough for the population to come back to equilibrium [5].

To prove the thesis posed in Hardy-Weinberg Law is worth recalling the inheritance properties of two different alleles of one locus formulated by Mendel. They will be illustrated on the so-called Punnett square [Tab. 1], which presents the possible combinations of gametes during procreation. This diagram is a method of predicting the frequency of individual genotypes in the offspring generation [6].

Tab. 1. Punnett square

		Male Genotype	
		A	a
Female Genotype	A	AA 1/4	Aa 1/4
	a	Aa 1/4	aa 1/4

All possible situations during reproduction in N-individuals population with two alleles of tested gene present [Tab. 2]. It shows how often members of a certain genotype will be crossed and gives the probability of formation of a particular genotype in the offspring.

Tab. 2. Frequencies and probabilities of offspring genotypes in bi-allelic population

Genotype		Frequency	The probability of genotypes in offspring		
Female	Male		AA	Aa	aa
AA	AA	P_{AA}^2	1	0	0
AA	Aa	$P_{AA}P_{Aa}$	1/2	1/2	0
AA	aa	$P_{AA}P_{aa}$	0	1	0
Aa	AA	$P_{Aa}P_{AA}$	1/2	1/2	0
Aa	Aa	P_{Aa}^2	1/4	1/2	1/4
Aa	aa	$P_{Aa}P_{aa}$	0	1/2	1/2
aa	AA	$P_{aa}P_{AA}$	0	1	0
aa	Aa	$P_{aa}P_{Aa}$	0	1/2	1/2
aa	aa	P_{aa}^2	0	0	1

The proportions of genotypes, which may occur in the offspring, are calculated as follows [7–8]:

$$P'_{AA} = 1 \cdot P_{AA}^2 + \tfrac{1}{2} \cdot P_{AA}P_{Aa} + \tfrac{1}{2} \cdot P_{Aa}P_{AA} + \tfrac{1}{4} \cdot P_{Aa}^2 = \left(P_{AA} + \tfrac{1}{2}P_{Aa}\right)^2 = p^2$$

$$P'_{Aa} = \tfrac{1}{2} \cdot P_{AA}P_{Aa} + 1 \cdot P_{AA}P_{aa} + \tfrac{1}{2} \cdot P_{Aa}P_{AA} + \tfrac{1}{2} \cdot P_{Aa}^2 + \tfrac{1}{2} \cdot P_{Aa}P_{aa} + \\ + 1 \cdot P_{aa}P_{AA} + \tfrac{1}{2} \cdot P_{aa}P_{Aa} = 2\left(P_{aa} + \tfrac{1}{2}P_{Aa}\right)\left(P_{AA} + \tfrac{1}{2}P_{Aa}\right) = 2pq$$

$$P'_{aa} = \tfrac{1}{4} \cdot P_{Aa}^2 + \tfrac{1}{2} \cdot P_{Aa}P_{aa} + \tfrac{1}{2} \cdot P_{aa}P_{Aa} + 1 \cdot P_{aa}^2 = \left(P_{aa} + \tfrac{1}{2}P_{Aa}\right)^2 = q^2$$

The frequencies of particular genotypes in the offspring generation can also be calculated directly from the available proportion of alleles in the parental population [7]. Due to the assumption of random mating, frequency with which male gametes containing allele A (with frequency p in a considered population) fuse in the process of reproduction with female gametes containing allele A, and create offspring with genotype AA is $P'_{AA} = p \times p = p^2$. Similarly, according to the probability theory, the frequency of homozygote aa can be determined as $P'_{aa} = q \times q = q^2$. Whereas setting a proportion of heterozygote Aa in the offspring requires taking into account the fact that they arise from the merger of gametes carrying different alleles, as it is presented in [Fig. 1]. The frequency of offspring with genotype Aa is $P'_{Aa} = 2pq$.

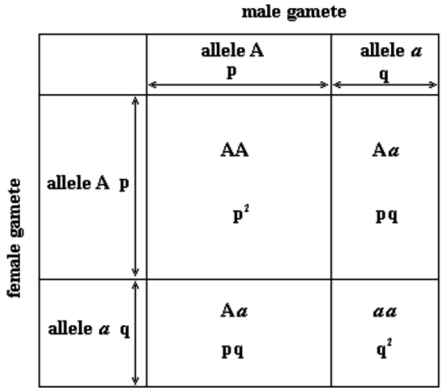

Fig. 1. Scheme of gametes fuse during the crossing of individuals in a population with two alleles of the tested gene

Additionally, it is worth noting that frequencies of genotypes correspond to area of rectangles, and the length of the sides of the figure correspond to frequencies different alleles.

It should be noted that under the assumptions of the Hardy-Weinberg Law, allele frequencies in the population remain constant from generation to generation. If the p', q' denote the frequencies of allele A and a in the offspring, they can be calculated using formulas (3), (4), (5) as follows:

$$p' = P'_{AA} + \tfrac{1}{2}P'_{Aa} = p^2 + \tfrac{1}{2} \cdot 2pq = p^2 + p(1-p) = p$$

$$q' = P'_{aa} + \tfrac{1}{2}P'_{Aa} = q^2 + \tfrac{1}{2} \cdot 2pq = q^2 + q(1-q) = q$$

This allows to conclude that the frequency of genotypes also remain unchanged over time. They depend only on frequencies of alleles in the parental population which, as has been shown, are the same in subsequent generations.

Testing whether the population is in equilibrium

The relationships between frequencies of genotypes in a population, where a locus with two alleles is tested, can be represented graphically. An excellent representation is the De Finetti diagram [7].

Any point inside the triangle illustrates a combination of the proportions of genotypes occurring in the population. For example, a point shown in [Fig. 2] represents a population, in which genotype frequencies are as

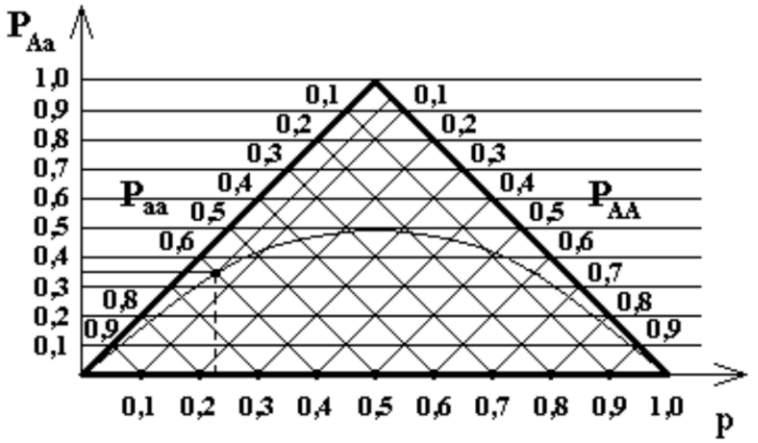

Fig. 2. De Finetti diagram with an exemplary point represents a population, which is characterized by the following distribution of the three genotype frequencies: $P_{AA} = 0.05$, $P_{aa} = 0.6$, $P_{Aa} = 0.35$

follows: $P_{AA} = 0.05$, $P_{aa} = 0.6$, $P_{Aa} = 0.35$. These values can be read by moving along the grid lines inside the triangle, which are routed perpendicular to the appropriate axis. The horizontal axis allows to determine the frequency of alleles occurring in the population. In the above example, you can read $p = 0.225$, which agrees with expectation for the population in the Hardy-Weinberg equilibrium:

$$p = P_{AA} + \tfrac{1}{2}P_{Aa} = 0.05 + 0.175 = 0.225$$

For each point inside the triangle, proportions of genotypes in the population, which it depicts, sum up to 1. Moreover the curve located in [Fig. 2] is the set of all those points that represent the populations in the genetic equilibrium state. Therefore, the De Finetti diagram makes it possible to determine whether the population meets Hardy-Weinberg equation and allows to declare, how much should the proportions of genotypes be, at specified frequencies of a particular alleles, for the population to be in a genetic equilibrium.

The first step during conducting clinical trials is usually to verify the distribution of allele and genotype frequencies in the population in accordance with those suggested by the Hardy-Weinberg Law. For this purpose the χ^2 test may be used. The value of χ^2_α statistics can be computed from the formula:

$$\chi^2_\alpha = \sum_i \left[\frac{(O_i - E_i)^2}{E_i} \right]$$

where:

O – observed frequency of the i-th genotype,

E – frequency of the i-th genotype resulting from Hardy-Weinberg model.

The number of degrees of freedom is equal to the number of possible genotypes of the tested locus minus the number of parameters estimated on the basis of data plus one. This test is sometimes unreliable, especially when the checked gene has a numerous alleles or if the alleles are rare. Then it is proposed to perform an exact test, for example, exact test analogous to Fisher's exact test or the Monte Carlo method [9].

The Hardy-Weinberg Law formulates conditions to assume that allele frequencies in the population remain constant in time. Therefore, it can be used to predict the proportions of genotypes based on allele frequencies observed in the studied population. Conversely, HWL can also assess the frequency of a particular allele if the proportion of one of the genotypes is known. This ability may prove to be helpful, for example, in a conscious animal husbandry [13] to oversee the genetic composition of the herd or during making estimates associated with genetic diseases. If the proportion of organisms suffering from particular disease (homozygous recessive) is known then it is possible to approximate the frequency of allele responsible for the defect and to determine the amount of asymptomatic carriers in the population. For example, it has been stated that haemophilia A and B types, which is the bleeding disorder, affects more or less 1/12000 of the population. It allows to assess the number of people who carry the mutated allele but are free from symptoms of disease at 0.0181. Stating that in the gene pool are violations of alleles and genotypes frequencies expected by the Hardy-Weinberg model suggest the need for formulate a hypothesis on the causes of lack of genetic equilibrium. What is more, it demonstrates the validity of further studies, which seek to identify processes causing any deviations.

Models of the dynamics of gene pool

Hardy-Weinberg Law is limited by several assumptions. In fact, very rarely is the situation that in the study population all the criteria are met [3]. Moreover, the evolution of the tested organisms is constantly observed. It would not be possible, if the frequency of genotypes in populations remain static from generation to generation. So, it is worth to consider the impact

of deviations from some assumptions of Hardy-Weinberg law on the gene pool. It is very interesting as evolutionary mechanisms, such as non-random mating, migration, natural selection, mutation and genetic drift, break genetic equilibrium.

Non-random mating

If individuals have a certain preference during choosing partners for reproduction, we have to deal with non-random mating. There are many causes of selective crossing. For example, an individual may favor those similar to himself/herself, and thus of the same genotype. The number of homozygote will increase in the offspring [10]. This is due, among others, to the fact that individuals with AA genotype crossing with genotypically identical homozygote AA procreate only homozygote AA. Considering this situation, let us suppose that:

$$\begin{aligned} P'_{AA} &= p^2 + M_1 \\ P'_{aa} &= q^2 + M_2 \end{aligned} \tag{7}$$

where M_1 and M_2 correspond to the values of deviations from genotype frequencies expected from the Hardy-Weinberg equilibrium.

Bearing in mind that the frequency of genotypes in the population sum up to one, it is:

$$P'_{Aa} = 1 - P'_{AA} - P'_{aa} = 2pq - M_1 - M_2 \tag{8}$$

It will affect the frequencies of alleles in a descendant generation, as follows:

$$\begin{aligned} p' &= P'_{AA} + \tfrac{1}{2}P'_{Aa} = p + \tfrac{1}{2}M_1 - \tfrac{1}{2}M_2 \\ q' &= P'_{aa} + \tfrac{1}{2}P'_{Aa} = q - \tfrac{1}{2}M_1 + \tfrac{1}{2}M_2 \end{aligned} \tag{9}$$

Therefore, these frequencies will depend on M_1 and M_2 parameters. If $M_1 > M_2$, so individuals with genotype AA often mate with genotypically similar to one another than it is among individuals with genotype aa, then allele A proportion will continue to increase ($p' > p$) and allele a proportion will decrease ($q' < q$) over generation. Otherwise, when $M_1 < M_2$, the situation is reversed, i.e. $p' < p$ and $q' > q$. What's more, if $M_1 = M_2$, then $p' = p$ and $q' = q$. This case is extremely interesting. It shows that, despite the change in the proportions of individual genotypes in the genetic composition of the population, allele frequencies remain constant.

Analogous reasoning can be applied for the population, in which there are clear preferences for individuals of the opposite genotype. Then the number of heterozygotes will increase. This is caused by the fact that individuals with genotype AA crossing with those of genotype aa can only beget heterozygote Aa.

It is possible to find examples of non-random mating both in the world of humans and animals. An important factor influencing the choice of partner is the appearance, for instance, tall individuals generally choose tall partners. Whereas, in the case of livestock husbandry, inbreeding is often practiced. It is the reproduction from the mating of two genetically related parents which consolidates the desired trait to cumulate particularly valuable genes. In nature, this phenomenon is not preferred. It often contributes to the disclose of unfavorable recessive alleles due to increased homozygosity in the population. For example, inbreeding takes place in the population of cheetahs. It is the result of isolation of areas where these predators live due to human activities. It results in this species' danger of genetic disease.

Migrations

In the wild populations are rarely isolated. So there is often movement of individuals from one population to another. Consequently, gene flow occurs between the genetic pools. Migration is responsible for genetic material transfer, and thus results in marked changes in the frequency of genotypes and alleles.

Mathematical analysis of the genetic structure of a population, in which migration occurs, can provide interesting conclusions. For this purpose let us suppose that in the examined sample the frequencies of alleles A and a were respectively p_1 and q_1. To this population were attached individuals from another population, in which tested locus have also allele A and a with proportions p_0, q_0. Let immigrants be the n-th part of the population formulated in this way. The frequencies of alleles after a single mating will be developed as follows:

$$\begin{aligned} p' &= (1-n)p_1 + np_0 = p_1 - n(p_1 - p_0) \\ q' &= (1-n)q_1 + nq_0 = q_1 - n(q_1 - q_0) \end{aligned} \tag{10}$$

Migration causes a change of alleles proportions in the studied population due to the fact that it is very unlikely that allele frequencies are the same in indigenous populations and in outer. However, if that migration is a single phenomenon then one mating with assumptions of the Hardy-Weinberg Law

is enough to return to a state of genetic equilibrium. But when the migration takes place continuously in t generations and in the ratio of n, the frequency of allele A can be calculated by a mathematical induction in the following way:

$$\begin{aligned} p' - p_0 &= (1-n)(p_1 - p_0) \\ p'' - p_0 &= (1-n)^2(p_1 - p_0) \\ p^{(t)} &= (1-n)^t(p_1 - p_0) + p_0 \end{aligned} \tag{11}$$

This formula allows, among others, to determine how quick is the movement of genes to the target population. For example, Afro-American citizens of the United States are descendants of the population coming from Africa as slave labor from XVII century and migrants flowing from a Caucasian population. R_0 allele frequency of the Rh gene in this population is $p^{(t)} = 0.446$. The proportion of this allele in African ancestors population was $p_1 = 0.630$ while its share in the Caucasian population is $p_0 = 0.028$. The migration started about 350 years ago which means about 14 generations. The transformation of the formula (11) allows to get:

$$n = 1 - \sqrt{\frac{p^{(t)} - p_0}{p_1 - p_0}}$$

It makes the possibility to calculate that gene flow occurs at a rate of $n = 2.6\%$ per generation.

Natural selection

An extremely important factor among the mechanisms responsible for evolution is natural selection. It takes place when some organisms have a greater ability to survive and reproduce, depending on their genetic traits. This leads to a gradual increase proportions of such individuals in the population, due to better adaptation to the environmental conditions where they live. The analysis of the selection process allows us to study the directions of its activity and the strength of the phenomenon.

The measure of the adaptation to life conditions of organisms characterized by certain combination of alleles in the tested locus is the fitness coefficient W. It is estimated by the extent of considered allele transfer from generation to generation as compared to other alleles [10]. The absolute fitness is defined as the product of the probability of survival of a particular genotype to reproductive age (F) and the number of offspring released per one parent (L). In the analysis of the phenomenon of selection it is more convenient to use the relative coefficient, the so called relative

fitness, referring to the index calculated for the best suited genotype in the population:

$$W = \frac{W^*}{W^*_{max}} \tag{12}$$

To express the strength of natural selection the selection coefficient is also used, which is the complement of fitness: $s = 1 - W$.

The preference of the environmental conditions of certain genotypes will inevitably affect alleles frequency in the population. To better understand the mechanism of selection, it is worth considering the general model of allele frequencies changes which do not depend on which of the genotypes is favored. Let us denote W_{AA}, W_{Aa}, W_{aa} fitness coefficients corresponding to individual genotypes. Then the frequencies of genotypes will change as follows:

$$\begin{aligned} P'_{AA} &= p^2 W_{AA} \\ P'_{Aa} &= 2pqW_{Aa} \\ P'_{aa} &= q^2 W_{aa} \end{aligned} \tag{13}$$

Moreover, average fitness of the whole offspring population is given by the formula:

$$\overline{W} = p^2 W_{AA} + 2pqW_{Aa} + q^2 W_{aa} \tag{14}$$

Now the total number of alleles in the population will be equal to $2N$. Therefore using the formula (3) it is possible to calculate the frequency of each allele in the gene pool:

$$\begin{aligned} p' &= \frac{p(pW_{AA} + qW_{Aa})}{\overline{W}} \\ q' &= \frac{q(pW_{AA} + qW_{Aa})}{\overline{W}} \end{aligned} \tag{15}$$

However, it seems interesting to determine the allele frequency growth rate that occurred between tested and offspring generation:

$$\begin{aligned} \Delta p = p' - p &= pq\frac{p(W_{AA} - W_{Aa}) + q(W_{Aa} - W_{aa})}{\overline{W}} \\ \Delta q = q' - q &= pq\frac{q(W_{aa} - W_{Aa}) + p(W_{Aa} - W_{AA})}{\overline{W}} \end{aligned} \tag{16}$$

Models presented above show that all changes depend on differences in fitness between individual genotypes. They are also proportional to the variance of allele frequencies, determined by the binomial distribution

$\sigma^2 = pq/2N$. Generally, one can say that the selection is stronger, the greater is the genetic variation in the studied population. Without such variation, selection is impossible [2].

Even more interesting conclusions may be provided by the analysis of the selection against particular genotypes occurring in the population. For example, it is interesting to determine, what effect will cause the weakest fitness of the recessive allele, whose presence is revealed only in the homozygote recessive. This situation is called *selection against homozygote recessive*. This phenomenon commonly occurs in nature. Many diseases or genetic defects are conditioned by the recessive allele. This allele results from a mutation and it causes lack of encoding of a functional protein. The deficiency is compensated by the second occurring allele, which thus becomes dominant. Mutated allele is removed from the population, as a less fitted to the prevailing conditions.

In the case of selection against homozygote recessive, fitness coefficients take values $W_{AA} = 1$, $W_{Aa} = 1$, $W_{aa} = 1 - s_{aa}$. According to the formula (16) the frequency of a recessive allele growth rate will be of negative value amounting to:

$$\Delta q = -\frac{pq^2 s_{aa}}{1 - s_{aa}q^2} \tag{17}$$

Then the proportion of recessive allele in the gene pool will systematically decrease and the strength of removing it from the population will depend, among others, on the initial frequency.

A classic example of selection against homozygote recessive was observed in England at the turn of centuries XIX and XX in reference to the population of the peppered moth (Biston Betularia). This variety of moth initially had mainly light colouration, determined by the recessive allele. It allowed them to effectively camouflage against predators in lichens growing on trees which were inhabited by these organisms. However, with time, as a result of widespread environmental pollution lichens were significantly reduced. Then, more suitable became a variety of dark-coloured because of their ability to hide on the darkened trees. So these individuals began to occur more often. This phenomenon is called the "industrial melanism" [2].

It is also worth analyzing in more detail a case of *selection causing complete elimination of a recessive allele* from gene pool, in a the situation when one of the alleles is lethal. Values of fitness coefficients will be $W_{AA} = 1$, $W_{Aa} = 1$, $W_{aa} = 0$. Therefore, in accordance with formula (15), recessive allele frequency in descendant generation is equal to:

$$q' = \frac{q}{1 + q} \tag{18}$$

Using the principle of mathematical induction it can be proved that, after n generations, the recessive allele frequency will take the form:

$$q^{(n)} = \frac{q}{1+nq} \tag{19}$$

An example illustrates how the changes of recessive allele frequency over generations in the situation when it works selection causing complete elimination of homozygote recessive may look, is given on [Fig. 3].

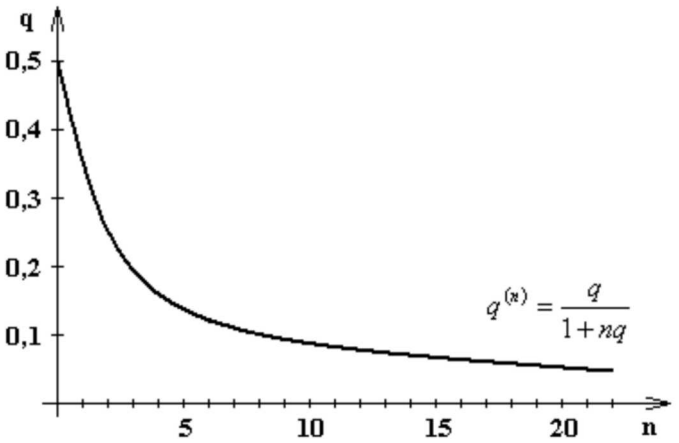

Fig. 3. The function depicting the decrease of the recessive allele frequency (in a population with initial frequency of $q = 0.5$), which presents the effect of actions the natural selection causing elimination of homozygote recessive

For example, if value of recessive allele frequency is equal to 0.5 in the tested population, [Fig. 3] shows how this frequency will change over successive generations. It allows to make the conclusion that the smaller frequency of the allele, the slower it is decreased [2].

These observations lead to the negation of the theses formulated by the theory of eugenics. Its idea was based on the necessity of improving the population by encouraging the reproduction of individuals with desirable heredity traits and discouraging the reproduction of organisms less genetically valuable. It disseminated the fear that the mating of individuals with certain genetic defects may lead to the degeneration of the population by the spread of these defects [10]. As a solution of this problem, eugenics proposed sterilization of people with genetic disorders. Model depicted in [Fig. 3] shows that the postulates of this theory are unfounded. Prohibition of reproduction of organisms with heritable disorders will not remove defective alleles from the population. It can only reduce their frequency. In addition, this decrease will

be small, because of the low initial frequency of the allele responsible for the disease. For example, cystic fibrosis affects about one in 2500 Caucasian individuals (i.e. $q^2 = 0.0004$). Hence, in this population the frequency of the recessive allele causing the disease is $q = 0.02$. According to formula (19), to double reduce the proportion of patients in that population, 21 generations are needed. Tenfold decrease would require 109 generations.

Quite interesting phenomenon occurring in nature is when the best adapted to life are heterozygous organisms. The situation of heterozygote advantage is known as overdominance. So *a selection against both homozygotes* takes place. It means that fitness coefficients are equal to: $W_{AA} = 1 - s_{AA}$, $W_{Aa} = 1$, $W_{aa} = 1 - s_{aa}$. Substituting these values into formula (16) it is possible to obtain:

$$\Delta q = \frac{pq(ps_{AA} - qs_{aa})}{\overline{W}} \tag{20}$$

This allows us to conclude, that the growth rate Δq will be positive, so the frequency of the recessive allele will increase from generation to generation, when $ps_{AA} - qs_{aa} > 0$. After simple transformations this formula gives the relationship:

$$q < \frac{s_{AA}}{s_{AA} + s_{aa}} \tag{21}$$

Otherwise, the proportion of recessive allele in population will decrease with time. However, when the recessive allele frequency will be:

$$q_r = \frac{s_{AA}}{s_{AA} + s_{aa}} \tag{22}$$

then the population reaches a genetic equilibrium. So proportions of alleles in population will remain constant in subsequent generations. It is worth emphasizing that this equilibrium does not depend on the initial allele frequencies, but only on their fitness [2]. Graphical representation of function of recessive allele growth rate depending on the proportion of this allele in the studied population is shown in [Fig. 4].

The pressure of selection against both homozygotes does not remove any of alleles from the population. Each deviation from genetic equilibrium q_r makes that population strives to return to a state of stability.

The only example of overdominance which was previously explored and explained in a widely recognized way is the phenomenon of persistence of the allele causing sickle-cell anaemia in the African population exposed to malaria [11]. Homozygotes recessive suffer from anemia and in 80% of cases die not surviving to the reproductive period (so their fitness is $W_{aa} = 0.20$).

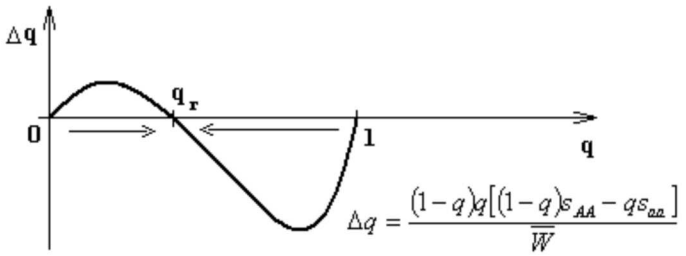

Fig. 4. The function of recessive allele growth rate depending on the frequency of this allele, which is a result of acting a selection against both homozygotes [2]

Although homozygotes dominant are devoid of the defective allele and they do not have immunity to malaria, which is high mortality disease. Therefore, heterozygotes are the best adapted to African life conditions. Admittedly, such individuals are sickle-cell anaemia allele carriers, but do not suffer from malaria.

Important conclusions may be supplied by a case study, when heterozygous individuals are the least adapted to the specific environment. Then *a selection against heterozygote* takes place. For example, such situation may occurs when two populations homozygous to different alleles of the tested gene merge. As a result of mating individuals from such created population will be heterozygous organisms. But their fitness is the lowest in the population [11]. For selection coefficients equal to s_{AA}, s_{Aa}, s_{aa}, where $s_{Aa} \geq \max\{s_{AA}, s_{aa}\}$, it is possible to perform a similar reasoning as above, to get recessive allele growth rate in subsequent generations as:

$$\Delta q = pq\frac{q(s_{Aa} - s_{aa}) + p(s_{AA} - s_{Aa})}{\overline{W}} \tag{23}$$

Genetic equilibrium will be obtained in the population when:

$$q_r = \frac{s_{Aa} - s_{AA}}{2s_{Aa} - s_{AA} - s_{aa}} \tag{24}$$

What is worth emphasising – this is not a stable equilibrium point. Each value of recessive allele a frequency below the value that gives the equilibrium, and hence $q < 0$, will lead to the elimination of this allele from the population due to the selection pressure. On the other hand, such proportions above the value in the equilibrium cause further move away from this state until the fixation of the allele in the population (due to $\Delta q > 0$), and thus result in the removal the alternate allele A from the population. Thus, if on alleles act only the selection against heterozygote, it results in the elimination of one of them.

Mutations

The main cause of any genetic variation is mutations. They can be defined as sudden changes in DNA sequence arising as a result of errors during the replication process or under the influence of physical and chemical factors [10]. Point mutations, such as silent or missense, that change only a single nucleobase, are often neutral. They do not cause dysfunctions of the genome and do not affect the phenotype. On the frequency of allele, which have resulted from mutations, does not interact the pressure of selection. But the majority of mutations, including nonsense mutations, deletions, insertions and reading frame shift can produce dangerous effects. It can result in the rise of alleles with slightly modified functions or entirely harmful and even lethal in homozygous individuals. These alleles are recessive when this error is compensated by the alternative allele, and in homozygous organisms they cause many genetic disorders. An example of this phenomenon is the Tay-Sachs disease occurring mainly among the Ashkenazi Jews population. It is usually the result of insertion of four nucleobase pairs in 11 exon HEXA gene (606869.0001). It makes the reduction of the activity or lack of synthesis of the beta-hexosaminidase A enzyme, what leads to the accumulation of fatty acid-gangliosides GM2 in brain nerve cells. This disease is lethal in homozygous recessive organisms and it causes the death of a 3–4 years old child.

In conclusion it should be emphasized that all types of mutations affect the allele frequencies of particular gene in the studied population. They contribute to creating new alleles, and thus changing the composition of the gene pool. However, for these considerations a situation may be important when in the bi-allelic population occurs a transformation from one allele to another and vice versa. Let allele A be converted by mutation in allele a with probability u, and let the reverse transformation take place with probability v. Then, if there is no pressure of natural selection then a recessive allele growth rate over successive generations is given by formula:

$$\Delta q = up - vq \tag{25}$$

The population will reach genetic equilibrium, which is constantly trying to achieve, when the proportion of allele a will be:

$$q_r = \frac{u}{u+v} \tag{26}$$

Mutant alleles, which have lost their functionality, are recessive. They are revealed in the homozygote recessive [10]. So, selection against homozygote recessive interacts on them. Taking into account both the pressure of muta-

tion and natural selection, changes of recessive allele frequency over generations are as follows:

$$\Delta q = u(1-q) - vq - \frac{(1-q)q^2 s_{aa}}{1-q^2 s_{aa}} \tag{27}$$

Due to the fact that the frequency of the recessive allele in the population is small, the component vq can be neglected. It has only a little impact on the growth rate. Assuming $\Delta q = 0$ and making simple transformations in formula (27) it can be seen that the tested forces will be in equilibrium at the frequency of allele a equal to:

$$q_r = \sqrt{\frac{u}{(1+u)s_{aa}}} \tag{28}$$

In conclusion, it should be noted that the mutation is a slowly progressing factor in evolution. It occurs between once per 10 thousand and once per 100 thousand on allele at generation. Only the mathematical analysis of mechanism of mutations model reveals that they play a really important role. Indeed, the rarer recessive allele a in the population, the higher is its growth rate over successive generations, which is perfectly shown in the formula (27). Then, there are more frequent transformations from allele A to a. Moreover, the influence of selection pressure is less important [11].

Genetic drift

Gene transfer from parents to offspring is random. Any changes in time of allele frequencies in the gene pool, which are not the result of the above described phenomena but are caused by the accidental fuse of gametes in the reproduction, are referred as genetic drift. In a finite population, where frequency of allele a is p and there is no pressure causing evolution, tested allele frequency will not be exactly replicated after a single mating, but will be equal approximately to p. In the next generation such situation will be repeated, but this time studied proportion of allele will endeavor to the new value. Such fluctuation of allele frequencies is unpredictable – the direction or the strength of these changes can not be determined. Sometimes it leads to the elimination or fixation of one of the alleles in the population regardless of its fitness. Thus it contributes to the homogeneity or loss of variability in the population. The speed of this phenomenon depends on the size of the population. This fact is exactly presented on [Fig. 5], where fluctuations were observed in small population of five individuals [Fig. 5a] and large, 100-members populations [Fig. 5b]. In each population, the initial proportion of the tested allele is 0.4.

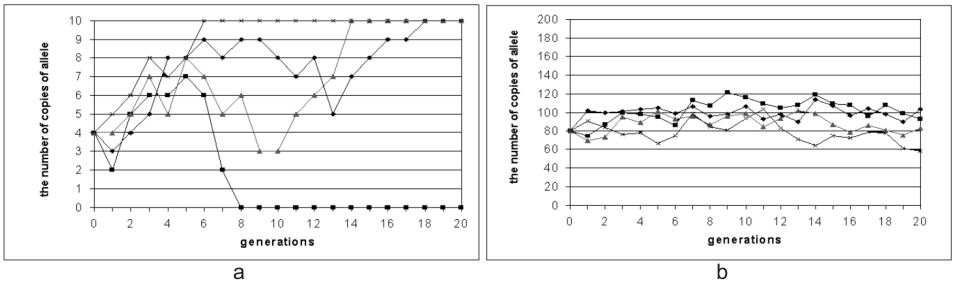

Fig. 5. Computer simulations of changes in the frequency of allele in four bi-allelic populations as a result of genetic drift.

Genetic drift is one of the main mechanisms of evolution, as important as mutations. It plays a pivotal role especially in promoting favorable and rare mutations, before they have stabilized [10]. The effect of drift is clearly visible in a small, isolated population. Such populations may arise, for example, as a result of a bottleneck effect. It takes place when the population drastically reduced their abundance, because of some disaster (drought, flood, earthquake, disease, etc.). The new gene pool is different from the former one because it consists of accidentally selected individuals who do not have all alleles, which were in the initial population, or have them with completely new proportions. Another way to create a population is when several individuals leave the parent population and then inhabit an entirely new area, so form a new population by mating. This phenomenon is called the founder effect. As an example it may be consider a situation of 15 British colonists, who in 1814 established a settlement on the islands of Tristan da Cucha in the Atlantic Ocean. After 150 years, it became clear that in the offspring population disproportionately frequent is recessive allele *retinitis pigmentosa* responsible for a progressive form of blindness. The reason for this phenomenon is the fact that one of the colonists was the carrier of the mutated allele. The difference between the bottleneck effect and the founder effect is that in the case of the first phenomenon one population is transformed into a completely new, and the second one causes the formation of two populations, which occur side by side.

Conclusions

The Hardy-Weinberg Law is still interesting to researchers. For many scientists, who study this principle, it provides new and important conclusions. For example, C. C. Li showed [12] that non-random mating is only

a sufficient condition, not a necessary one, to static frequencies of genotypes in a population across generations.

Knowledge of the Hardy-Weinberg Law and its conclusions is very important in medical science. It is the basis of population genetic research. Moreover, it is used during clinical trials to establish the quality of data by comparing the observed frequency of each genotype with those, which are expected under the Hardy-Weinberg model. When there is no genetic equilibrium, conventional statistical analysis can not be carried out and the data should be usually excluded from further analysis [13]. But, in practice, testing the compliance of genotypes frequencies distributions in the population is often neglected. Any deviations from genetic equilibrium are rarely admitted in the published reports, although they may be crucial for the course of the study [14–15]. They may indicate problems, errors or oddities in the analyzed data. Consequently, any conclusions drawn for the population, in which there is no Hardy-Weinberg equilibrium, can be challenged.

The findings, during trials that the frequencies of alleles and genotypes in the study population are incompatible with the Hardy-Weinberg model demand the necessity to look for reasons [16]. Factors, discussed in the paper, affecting allele frequencies, the conditions under which they may take place, their strength and direction of interaction allow to formulate the assumptions about the phenomenon which cause the disorder. Knowledge related to them is the basis for further research which may lead to the verification of many hypotheses.

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Oligonucleotide microarrays in biomedical sciences – the use and data analysis

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Abstract. The methods used in biomedical research are becoming inadequate to meet current challenges. Frequently occurring problem is the need to find the differentiation tests according to phenotypic features or the particular phenomenon. Previously used morphological evaluation or other laboratory tests many times do not allow for adequate determination of differentiating attributes. In recent years there has been considerable scientific and technological progress in the fields such as genomics, transcriptomics, proteomics and metabolomics, which allow to move the search area into the molecular level. It allows the use of advanced molecular techniques such as PCR or oligonucleotide microarrays and thus allows to compare the gene expression profiles of different types of cells and tissues. The microarray experiment data allow to determine the correlation between the expression of selected genes or even entire genotypes of the phenotypic features, characterizing the studied group. The collected data can not be analyzed using traditional statistical methods, since the number of cases is much higher than the number of considered attributes. For this reason, new statistical methods and procedures are used for microarray data analysis which may focus on theoretical or practical aspects. Theoretical aspect is related to the selection of specific genes expression, finding the ontology or metabolic pathways that are associated with the analyzed phenomenon. The practical aspect can be the creation of a predictive model that can allow to predict the specific phenonon occurrence in the future during the studies of new patients. Microarray experiments and analysis of the obtained results begin new chapters of particular phenomena investigation, which is another big boost in the biomedical sciences development.

Introduction

It is a common practice in the biomedical sciences making the differentiation of the tested material (cells, tissues) in order to find specific phenotypic features or the particular phenomenon (e.g. illness). These studies have been carried out using morphological assessment or other laboratory tests, which do not always allow for adequate determination of specific characteristic.

In recent years there has been a significant progress in such areas as genomics, transcriptomics, proteomics and metabolomics, which allow to

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move the searching area into the molecular level. Genomics is the analysis of the tested organisms genome, in order to determine the genetic material sequence, genome mapping and estimate the relationships and interactions within it.

Transcriptomics is the study of genome activity (individual genes expression) by determining the transcriptome changes dependent on place and time. The transcriptome is a set of mRNA molecules, resulting in a particular cell during particular time as a result of expression of specific genes. The study using transcriptomes methods enable to detect and identify a large number of different RNA molecules. Among these methods, particular attention should be paid to the microarray analyses and their possibilities to study of the entire genomes activity.

Proteomics, in turn, is the study of protein synthesis and structure, relationships between them, as well as their function examination. This area refers to research carried out on a large scale, concerning the entire proteomes. The complexity of the proteins structure as well as their number and variability mean that proteomics is a much more complicated science than genomics and transcriptomics. The protein microarrays, whose principles are similar to DNA microarrays are widely used in the determination of proteomic profiles or an interaction between protein.

The fourth discipline, recently developed is metabolomics. It concerns the study of all metabolites set of the whole body, particular tissue or cell (metabolome). Despite the great progress that has been made in recent years, metabolomics is not understood and developed as well as the previously described "omics" sciences. Partially due to its character and complexity.

Among a variety of techniques including the aforementioned four areas of molecular biology the microarray analysis is one of the most versatile techniques in biomedical sciences. It allows to specify and compare the gene expression profile of different types of cells or tissues. The collected data allow to determine the correlation between the expression of selected genes (or even entire genomes) and the phenotypic, characteristic of the studied groups. This allows for conducting experiments in virtually every field of medicine, including areas where using traditional methods has already been considered exhausted.

Microarrays

The first DNA microarrays were produced in the early 90s of the twentieth century to serve as a tool for DNA sequencing, mutations recovering

and mapping of genomes [11–12]. They became very popular when it was discovered that they can be used to study gene expression profiles [23].

DNA Microarray is a collection of molecular probes which adhere to the base (usually glass or silicon) in a particular order. Due to the construction of probes we can distinguish two types of microarrays: cDNA – long probe, even full-sequences corresponding to the mRNA, and oligonucleotide microarrays – short probes, typically 25–70 nucleotides. The latter can produce a much denser packing of probes on the base, mainly because they are synthesized in situ and not imprinted. Synthesis in situ adds nucleotides one by one until the end of the growing oligonucleotide [8]. To get required complex oligonucleotide sequences photolithography is used. Certain areas of the base are exposed to light, causing their activation and then the selected type of nucleotide is applied on the plate. Nucleotides bind only to chains that had previously been subjected to activating light, and thus each of oligonucleotides is elongated by one (specific) nucleotide. Nucleotide chains of required length and the sequences in the certain positions are obtained by repeating of this process.

Currently oligonucleotide microarrays can contain up to 300 000 probes per square centimeter which gives more than one million probes on a single plate. Gene expression analysis usually do not require such amounts of probes. Therefore more microarrays are placed on one plate what allows to reduce the cost of the experiment. These parameters are determined depending on the nature of the experiment and the type of tested material. Currently there are plates which allow to analyze the expression of the entire human genome for eight samples on a singular plate. To fully reflect the complexity of the microarray structure it is also worth noting that a singular probe on the plate is composed of about one billion copies of the same oligonucleotide chains [8].

The structure and microarray technologies differ, depending on the companies involved in preparation of these products. Nowadays the most commonly used microarrays in Poland are prepared by Agilent and Affymetrix companies [Fig. 1].

Each microarray experiment consists of several basic steps [20]. These include, among others:

- RNA isolation
- labeling
- hybridization
- scanning
- image analysis
- statistical data analysis

Fig. 1. Microarray chips made by Affymetrix company

Depending on the type of experiment one or more groups are analyzed. Often, as in classical biomedical experiments, the test and control groups are analyzed. For example, the experiments in oncology are performed using tumor tissue from treated patients as a test group, while a control group is healthy tissue preparations.

Depending on the character of the experiment as well as the plate type one- or two-colored labeling can be used. Using one color labeling each of the identical samples stained with the same dye and hybridize to different microarrays [23]. Two-color labeling is a labeling of two different samples with two different fluorescent dyes (e.g. Cy3 and Cy5) and then combining of these two preparations and hybridization with one microarray. Two colors labeling can be used for direct comparison of the test and the control group or for simultaneous comparison each of the preparations with specially prepared background, which often allows for better results.

A key step of the experiment is the hybridization plate. It is possible due to the complementarity of nucleic acids and occurs when oligonucleotide chains on the plate have complementary sequences to the nucleic acid coming from the tested preparation. It takes place under particular conditions in the hybridization chamber and to ensure the ability to connect almost all the complementary sequences usually lasts overnight.

Then the plate after hybridization is scanned using confocal laser, resulting in the image where the colored points correspond to the intensity of the

signal and thereby the level of expression of a genes in the tested samples [Fig. 2]. Therefore the resulting image is analyzed in order to save the color and intensity for individual spots using numerical values. Obtained in this way data is subjected to quality controls and a complex statistical analysis.

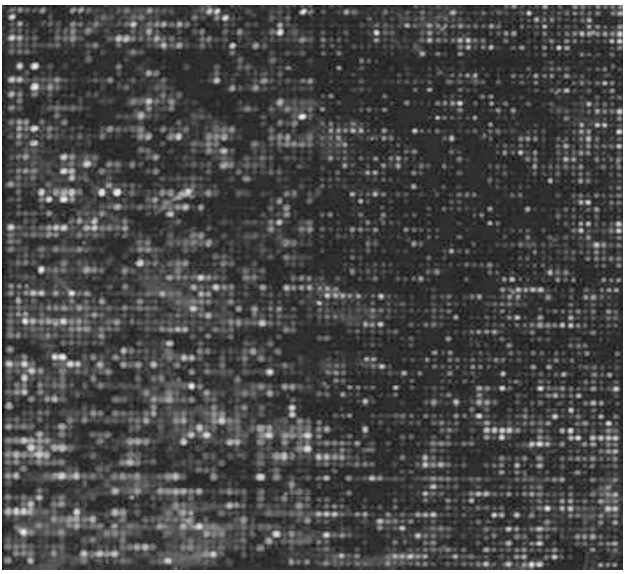

Fig. 2. The image of microarray scanned with confocal laser

Microarrays data

Recorded information in digital form, depending on the technology used may contain various parameters, but the most commonly used in the further analysis are [2]:

- signal intensity for each of the spots with the coordinates of the spot,
- background intensity for each of the spots – this is the average intensity of pixels surrounding the spot, taken as its background,
- pixel intensity distribution – areas of increased and decreased intensity may suggest the occurrence of disturbances during the experiment, in this case obtained data may require appropriate correction,
- spot morphology – the shape and size of individual spots can provide information about the quality of represented data.

The format of ultimately saved for statistical analysis data depends on the type of software. Often on the basis of the collected data sets the intensity of the signal for each spot and for each sample is measured and such infor-

mation is recorded in the form of a matrix where the rows correspond to spots and columns – samples. These arrays typically have a size of several or hundreds of columns and several thousands of rows.

Analysis of microarrays data

The collected data can not be analyzed with traditional statistical methods, since the number of analyzed cases (spots, genes) is much higher (typically thousands) of the number of considered attributes (elements of the population – typically several tens of units). In addition to traditional statistical methods, a number of advanced methods were developed and applied in medicine (eg. neural networks). They are generally called data mining methods [17–18]. However, the nature of the microarrays data necessitated the development of completely new methods and statistical procedures dedicated to these data analysis. They resulted in the development of theories of concomitant test of multiple hypotheses, based on measurening of error such as false discovery proportion (FDP) or proposed by Benjamin and Hochberg – false discovery rate (FDR) [7, 10]. The comprehensive studies, showing how to comprehensively carry out the process of microarray data analysis were formed [2].

Of course there is no possibility to analyze of this type of data without computers and statistical programs. There are numerous different kinds of programs and statistical software on the market, alike more universal and specially dedicated to microarrays, which greatly facilitate the analysis performance. Companies producing equipment and reagents for microarray experiments often develop and distribute specialized software designed to analyze the results (e.g. GeneSpring GX software). These programs are highly automated and do not require particular knowledge of advanced mathematics and statistics. However, on the other hand, they impose certain patterns of conduct, what can be a limitation for advanced biostatisticians and bioinformaticians. Therefore, they choose the software more flexible and more versatile (e.g. Stata, SAS Microarray or R software) [15].

There is no a scheme of microarray data analysis. It depends on the type of experiment as well as the model chosen by the researchers [1]. However, there are a few basic steps that should be included in any analysis: the quality control, various types of data normalization, filtering spots, extract a set of genes for which statistically significant differences were observed in expression between the analyzed groups. [Fig. 3] is a graph of the distribution of the intensity of expression for several samples after normalization with GeneSpring GX software.

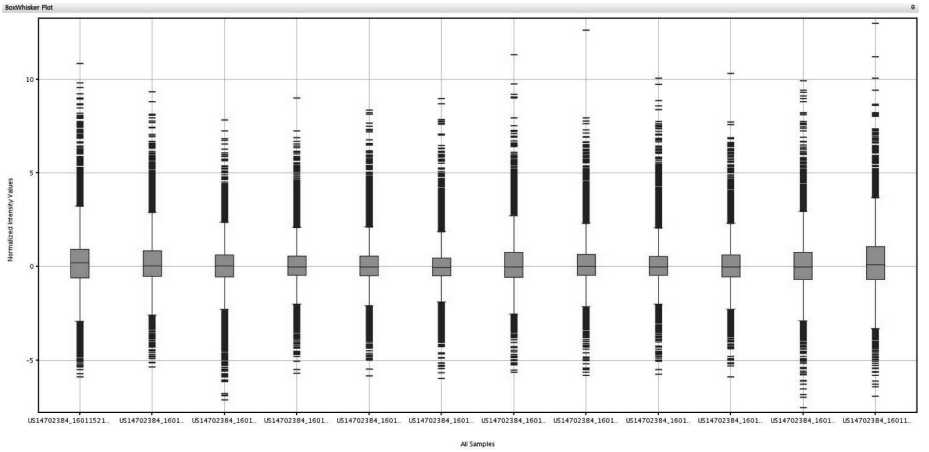

Fig. 3. Graph of the distribution of expression intensity after normalization

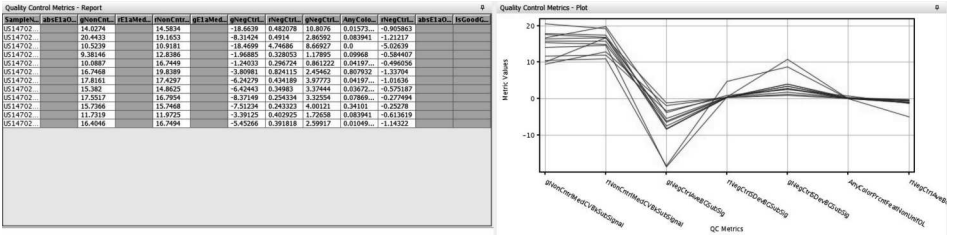

Fig. 4. Quality control metrics (QCM)

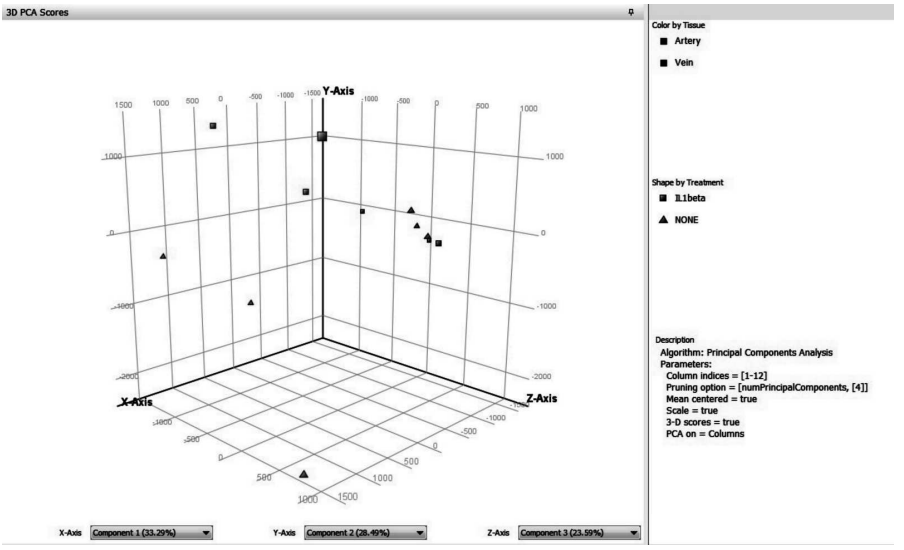

Fig. 5. Results of principal component analysis (PCA)

This application allows at this stage of the analysis to include determination of quality control metrics (QCM) [Fig. 4], to make a principal component analysis (PCA) [Fig. 5] and analyze statistical significance of differences in gene expression – analysis of variance test with multiple comparisons correction Benjamin–Hochberg [7, 10] and a fold-change analysis.

GeneSpring GX software application also provides the opportunity to illustrate subsequent stages of analysis results using various types of tables and graphs (e.g. Venn diagrams, dendrograms).

Determination of a set of genes which expression differentiates the occurrence of the examined phenomenon is a characteristic point opening following stages of statistical analysis and interpretation of molecular research. In the classical approach (without prediction) the ontology of genes, associated with a previously selected set of genes, as well as metabolic pathways in which these genes are involved are looking at the later stage. Ontologies describing the properties of genes and their gene products, consist of three types corresponding to the basic biological research areas:

- molecular function of gene products,
- their role in the multistep biological processes,
- their physical structure – as a components of the cell.

Metabolic pathways are series of successive biochemical reactions where one reaction product is a substrate for another. Ontology or the metabolic pathway are based on selected genes are a structure which action has also impact on the analyzed phenomenon and often allows to find hitherto unknown mechanisms involved in the investigated process.

A powerful research tool to facilitate finding such ontology, metabolic pathways or genes clusters functionally correlated is available on the web application Database for Annotation, Visualization and Integrated Discovery (DAVID).

Predictive model

In the clinical sciences predictive model is used more often than the classical model of microarray data analysis. It consists of creating a model, based on the learning data sets, which allow to predict the condition of the analyzed phenomena for subsequent cases. For example, based on survival time the patients undergoing a medical treatment, it is possible to create a model that will predict the estimated time of survival of another patients undergoing the same treatment.

Microarray analysis allows for the creation of such models where the data set refers to the expression of a set of genes that differentiate the occurrence of the studied phenomenon. With this approach, the less important are the mechanisms responsible for differences in gene expression but more important is the ability to predict the phenomenon of new patients and the application of the model in clinical practice. You can even produce a small, dedicated microarray that they examine only a selected small set of genes responsible for the occurrence of the studied phenomenon [13].

The procedure creation of predictive model is similar to the classical model until selection the set of genes whose expression differs between patients in two groups of interest. The information recorded at this stage for further analysis is a combination of the three numbers for each sample and for each gene:

- the logarithm of expression intensity (geometric mean of intensity of both channels)
- the logarithm of the expression factor
- the level of significance for the value of the logarithm of expression.

Such a model was created during the examination of survival of patients with diagnosed breast cancer [21–22]. The study involved women diagnosed with a tumor smaller than 5 cm, class T1 or T2, in which there was no lymph node metastasis (N0) whose age at diagnosis moment did not exceed 55 years and there was no previous history of cancer. Patients were diagnosed between 1983–1996. All patients had a modified radical mastectomy or breast conserving surgery, then they were monitored until death or until the examination in the case of living patients. Two dependent variables were fixed: the occurrence of distant metastases and death due to cancer. Analysis were performed for each of them separately. Women were divided into two groups:

- the group of "promising" patients without distant metastases (or death in the case of the second variable) within 5 years after the diagnosis of cancer,
- the "negative prognosis" where distant metastasis developed (or death occurred) before the end of 5 years period from the cancer diagnosis.

For both groups of patients the microarray expression analysis were carried out using tumor tissue frozen at the time of diagnosis.

For the final analysis 77 patients (44 without metastases and 33 with metastases after 5 years) and 24 483 genes were qualified. Then the first selection of genes using T-test was performed to determine differences in the expression profile between the groups. Seventy genes which strongly differen-

tiate the two examined groups were selected. For those genes a 70-dimensional vector of averaged expression for the group of patients with good prognosis was assigned. Then the correlation between each patient (in both groups) and the average expression vector (for this purpose is well suited cosine correlation based on a scalar product – the cosine of the angle between vectors) was determined. The correlation determined in this way proved to be a good predictor of distant metastases.

The created model has been tested on a group of validation using the leave-one-out crossvalidation. To confirm the differences the Kaplan-Meier analysis was performed. In subsequent stages of the study the test group was extended with patients with metastatic nodes (N1) and the independence of the model on factors that potentially could affect the results was demonstrated. These factors are namely:

- node metastases occurrence,
- the center of data origin,
- storage time of frozen tissue.

A small microarray for clinical applications (MammaPrint microarray) was prepared based on the carried out experiments. Then the identity of results obtained using commercial and prepared microarrays was demonstrated [9, 13]. The main goal of clinical application of small microarray is less severe treatment of patients who end up in promising groups (e.g. no need for radiotherapy and chemotherapy).

A similar experiment was carried out by a team dealing with treatment of non-small cell lung cancer (NSCLC) [19]. A predictive model of distant metastases was created based on selected during the microarray experiment 72 genes.

Moreover, the attempts of creation of predictive model of the reproductive potential of oocytes and effectiveness of infertility treatment based on cumulus cells gene expression were performed by a team of prof. Samir Hamamah [4–6, 14]. There is no possibility to use the oocyte material for molecular research because it would lead to its damage and the inability to get an embryo and eventual pregnancy. However, it has been shown that cumulus cells have the impact on the quality of the oocyte. They are responsible for oocyte nourishment. Therefore, they were used as a source of material for microarray studies. It was established that there are some genes whose expression differentiates the oocyte with positive outcomes of in vitro fertilization and oocyte taken from patients with IVF failure [3, 16]. It allows to design a small microarray which will support the selection of oocyte with the greatest fertility potential.

Conclusions

Microarray analysis of gene expression brings new information and begins a new chapters of analysis different phenomena, especially in the biomedical sciences. Availability of appropriate equipment and technology at the moment is not large, probably due to high costs. However, this technique is successively applied in medicine, bringing new opportunities and throwing new light on the phenomenon, where traditional methods seem to be already exploited.

Microarrays experiments have forced the development of special statistical methods for data analyzing due to the reverse proportion between the number of attributes and cases. The ability of gene expression determination combined with advanced statistical methods for data analysis is a powerful method in biomedical sciences which will be constantly developed in the future and will undoubtedly bring many revolutionary discoveries in medicine.

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Deep sequencing – a new method and new requirements of gene expression analysis

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Abstract. The determination of gene expression is a very common scientific method used in modern laboratory for a variety of applications. One of the most popular is the real time PCR, a quantitative modification of the classic PCR method where the increase of the amplify nucleic acid is examined cycle by cycle after every amplification step. The analysis of the PCR product during the amplification process allows to compare the initial amount of cDNA synthesized from isolated RNA and calculate the number of particular RNA copies present in examined material. In spite of obvious advantages of real time PCR there are also some inconveniences of this method. First of all, there is no possibility of analyzing more than one gene in a single reaction mixture. It is limited by the necessity of design and usage of different pairs of primers for each analyzed gene. Therefore, it is necessary to predict the cell, tissue or organism response for applied treatment, examined condition, etc. The development of microarray methods enables to overcome these problems and parallel analyze all known genes in the single sample at the same time. There is no need to predict which gene expression might be changed under studied conditions because the microarray data is a comprehensive pattern of the expression of all known genes, which probes are implemented on the microchip surface. Although the microarray data is an excellent method for gene expression comparison, the estimation of the extent of change fold is not very precise and usually is confirmed and determined by real time PCR with respect to selected genes. The method which combines the quantitative precision of real time PCR and the possibility to analyze broad spectrum of the genes is a deep sequencing method also called next generation sequencing. It is a new method developed for the analysis of the whole RNA isolated from a sample without the need to design primers and thus any knowledge of expressed genes sequence. The advantages of this method include the possibility of finding unexpected expression of completely unknown DNA fragments, alternative splicing variants of the genes and differences in DNA sequence. The deep sequencing provides an extremely large amount of information, much more than microarray data, and to analyse it new bioinformatics methods and tools especially designed for this purpose are required.

Introduction

Every cell of the same organism has a complete set of genes written in DNA. But morphology, structure and function of cells of the body of

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multicellular organism are very diverse. For instance human body has four main types of tissue and numerous types of cells [1]. This diversity is created during the differentiation process occurring in fetal development from one zygote formed from two gametes. All these changes are controlled by activation and silencing of particular genes expression according to the local requirements. Despite having a complete genetic information the fully differentiated cells use just part of it and transcribe into ribonucleic acids. Moreover, part of genetic information even in mature cells is activated under specific circumstances as a response to external signals of chemical or physical nature [2]. The pattern of active genes is similar in the same type of intact cells under the same condition. However gene expression of tumors is changed in comparison to their origin cells [3]. The process of carcinogenesis is characterized by specific expression profiles during different stages leading to the transformation of the intact cell into a cancer cell [4]. It concerns especially genes responsible for cell cycle regulation. Determination the sequence of transformation process events and its key points is very important in cancer research.

The eukaryotic genome organization and the process of gene expression

There is less than thirty thousands genes in the human genome [5] but the number of known proteins is much higher [6]. It is obvious that the rule "one gene one protein" is false. The eukaryotic genes are divided into coding parts called exons and non-coding parts – introns. Before the protein synthesis introns are removed from mRNA during RNA splicing which is the RNA maturation process. The pattern of mRNA maturation is not the same in every cell and tissue [7]. Often this process has alternative character and in this way one gene can encode different proteins with different structure and properties. The final protein can be modified in the process of posttranscriptional modification what is the source of additional increase in the number of one gene product diversity.

The knowledge of the genome sequences and gene expression of many species, including alternative splicing processes, has increased considerably in the last decade. Therefore the modern microarrays contain probes allowing for analysis of different variants of the mRNA [8]. However it is always possible that under specific circumstances in the case of particular organism or tissue the expression profiles of the gene (even well known) can be changed and a new type of the protein can appear due to unknown splicing manner.

Part of the expressed genetic information is not translated into pro-

teins but is important as a regulatory factors responsible for the genetic information expression. There are many types of miRNAs or siRNAs which can effect target transcripts of messenger RNA and activate or inhibit their translation. Some investigators suggest that miRNA represents 1% of human genome and regulates about 10% of translated proteins [9]. Probably we still do not know the entire active (transcribed into RNA) genetic information written in DNA even if the whole sequence is already known like in the case of human species.

Moreover, it is necessary to be aware that the concept of one species genome is just a theoretical entity and it does not exist in the reality, even though the internet databases contains thousands sequences of genes, both as a genomic DNA or cDNA library for many species. Every specimen of the species (excluding twins or clones) has a specific set of its own genes responsible for its individual distinctiveness. Children are not exactly the same like parents, grandparents or any relatives. It means that the genome of each individual is unique. Of course the similarity of the genome is really high. For example, human DNA sequence in the whole population is the same in 99.9% but the remaining 0.1% of diversity is enough to create all observed differences between people. There are a lot of single nucleotides polymorphisms (SNPs) and mutations in every population of the organisms belonging to the same species which makes that transcriptome of each specimen different. These individual properties of the expressed genetic material can be sometimes responsible for the subtle differences in physiology and lead to an individual response to the same treatment [10]. In the last few years the idea of the personally dedicated drugs according to patient's genetic specificity have become more and more popular. It indicates that in spite of significant similarity within the same species the occurring genome diversity can not be ignored. Moreover, eukaryotic DNA contains a lot of highly repeated fragments which are not translated into proteins. Previously it was thought that this part of genetic information does not play any role. It was even called "junk DNA". But some results suggest that at least part of the "junk DNA" is expressed into RNA and plays regulatory function of the processes transcription and translation [11]. It means that the transcriptome is far more complex than previously thought.

The limitation of the microarray and real time PCR method

The methods of gene expression analysis used so far in the laboratory required at least the basic knowledge of the analyzed material structure. The order of nucleotides at the beginning and the end of the amplified

sequence is necessary to design primers for real-time PCR. There is no possibility of synthesizing oligoprobes for microarray analysis of completely unknown genes without their prior sequencing. These problems are overcome by the use in gene expression studies new method developed recently – the next generation sequencing. Innovative approach to the sequencing allows to establish the sequence of all transcripts in the sample in a single run: determine SNPs, find new transcript isoforms, identify regular RNAs, characterize intron-exon junction and determine quantitative relation between the transcripts [12].

Classical sequencing versus next generation sequencing

In classical Sanger sequencing the method developed in the middle of 70's the determination is made using 2'-3'-dideoxynucleotides triphosphates (ddNTPs), molecules that differ from deoxynucleotides by the having a hydrogen atom attached to the 3' carbon rather than an OH group. Incorporation of such kind of molecule into newly synthesized complementary strand of DNA leads to termination of this process because without the OH group there is no possibility of forming a phosphodiester bound with the next nucleotide. The presence of a low concentration of four types of dideoxynucleotides in the reaction mixture altogether with higher concentration of deoxynucleotides results in the synthesis of the mix of randomly terminated double stranded DNA which differs in the length of one nucleotide. This mix is separated by gel or capillary electrophoresis according to the length. While four separated reaction mixtures contain one type of ddNTP (separation by gel electrophoresis) or all of them are differentially fluorescently labeled (capillary electrophoresis with fluorescent detector) it is possible to identify the terminated nucleotide and thereby the sequence of analyzed fragment. For successful sequencing with the Sanger method it is necessary to separate analysed fragments of nucleic acids because even with differentially fluorescent labeling of ddNTPs it is possible to determine only one sequence of limited length in one reaction mixture [13].

The situation is different for the next generation sequencing. Despite of the existence few commercially available platforms for the next generation sequencing of total transcriptome which are differ in details there are some similarities between them. In short, the total RNA is purified and randomly fragmented into pieces of required length and special short fragments called adapters are ligated on both ends of every analyzed RNA fragment. The presence of adapters with a known sequence allows for the synthesis

of cDNA and quantitative amplification of all of the fragments of RNA isolated during the sample preparation. Finally, the amplified products are immobilized on the surface of a special chip as an aggregation of identical clones. Contrary to the classical Sanger method the immobilized fragments are sequenced during elongation of second complementary strand of DNA. Moreover, the analyzer can determine the number of copies of the same fragments what is the approximate equivalent of the quantitative analysis of the real time PCR method. The final result of this analysis is a complete sequence of the whole expressed genetic material combined with the information concerning quantitative relation between the number of the copies of particular transcripts [14].

The new requirements of molecular research

The next generation sequencing is a very powerful tool in molecular biology and it has a great potential. But its successful use required development new techniques of data processing and analysis [15]. First of all the deep sequencing generates a massive amount of data, much more than any other laboratory method used so far. The microarray analysis has already forced the development of new statistical method because of the non-typical structure of the data, small number of considered attributes and hundreds (or even thousands) of analyzed cases: genes and spots. The amount of data derived using next generation sequencing is bigger by several orders of magnitude in comparison to microarray analysis. Besides the quantitative comparison of the analyzed genes (similar to microarray analysis) it is necessary to compare the determined sequences in order to identify the expressed material: the type of the gene, presence of mutations, polymorphisms and alternative splicing. It needs a fast progress in creation of complex sequence databases of as much as possible species. Without that any analysis is impossible. It is a crucial thing to know the typical (the most common) sequences of the genes if we want to find any abnormalities.

On the other hand, new data analysis techniques are needed to select among thousands of genes in the genome which are important in physiological responses to particular treatment or specific condition. Several programs dedicated to the analysis of biochemical pathways and ontologies already exist and are used for microarray analysis [16]. But the use of such programs and databases is becoming more and more complicated. In modern molecular biology experiments very often the most complicated work starts after the end of laboratory work and requires knowledge of advanced stati-

stical methods. Many laboratory scientists are facing serious problems with the use of increasingly complex mathematical models and statistical tools. Therefore, they increasingly require the assistance of bioinformatic specialists. Some specialized centers, usually associated with equipment suppliers, were established recently and they offer support in professional analysis of molecular data. The increase in demand for specialists fully conversant with both molecular biology and advanced mathematics will be observed in the near future as a response to the needs of modern science.

Conclusions

The progress in molecular biology research required not only the development of new laboratory methods but also the development of new bioinformatics tools and statistical methods for handling of the growing number collected data. Very often, the end of laboratory work and data gathering is just the beginning of a time consuming process of their selection and statistical analysis. This would not be possible without computer programs which are able to process massive number of data. The existence of internet databases gives an opportunity of access to the constantly growing number of data sets. All these databases will probably grow rapidly in the near future as a response to the increasing number of carried out next generation sequencing experiments. But this constant progress is not be possible without the growth of computing power and the development of new scientific computer programs.

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Nearest neighbor concept in the study of IVF ICSI/ET treatment effectiveness

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Abstract. The effectiveness of IVF ICSI/ET infertility treatment depends on many factors. Their identification and classification of individual cases remains a difficult task. This paper presents application of feature selection algorithm MSIMBAF2 and associated kNN classifier to analyze the data set containing results of the infertility treatment process.

Introduction

Infertility is a social problem whose scale is constantly growing. This is probably associated with the upward trend of age of women giving birth to their first child and delaying motherhood to later years of life. But with the age of women the effectiveness of infertility treatment decrease [7]. Increasingly, the only chance to have children become the methods of in vitro fertilization [9–10]. However, their effectiveness also decreases with age of treated women. In women over 40 it fluctuates within 10–15%, that is even 4-fold lower than in younger women [7]. Hence the need for advanced biostatistical methods, which on the one hand would allow to forecast the results of treatment in specific patients, and on the other hand to form the basis for making certain decisions during treatment, leading to increase the probability of success, that is the birth of a healthy child.

There are many statistical methods, referred to the general term "data mining methods", which can be used to predict the effectiveness of infertility treatment. The most important factor, from the data analysis point of view will be the selection of appropriate algorithms for classification and feature selection. Feature selection is quite often used as a preliminary step in data

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analysis. It involves reducing the original dimensionality of the data set, by rejecting less important features. In the next step, such prepared data set is subjected to classification in order to generate decision rules. Generated rules allows to predict the target observation class for the new data as well. Since medical data are analyzed, those rules should have high efficiency and resistance to accidental errors and over-fitting. Generated decision rules should be simple to understand for the future user, probably a doctor, who will use them. Like the classifier, feature selection algorithm should take into account various types of features and missing data.

IVF ICSI/ET procedure and database for storing information

The process of IVF ICSI/ET infertility treatment take place according to the established procedure, and consists of several main stages. At each stage, information necessary to continue the treatment, and to subsequent statistical analysis is gathered. First, the personal data of patients is collected. Then, medical information on the treatment history and various tests is collected. This information include, but are not limited to man and woman medical interview, laboratory tests, and a USG image with its description. After passing this stage, if the pair is qualified for further treatment, stimulation protocol is selected and the period of treatment begins. Information about the medicaments used in the subsequent days of the treatment and ovulation stimulation is recorded. At later stage of the treatment many other parameters are recorded: the level of estradiol, endometrial thickness and the amount and size of the developing follicles in both ovaries. The next step concerns the embryology, gathering information about the aspiration of ovarian follicles, the preparation of semen and the ART procedure. In the next stage, information on the developing embryos is collected, until the transfer moment and its implementation. The last part is the final treatment which results in collecting data on the pregnancy, childbirth and also basic information about the newborn.

Infertility treatment specificity requires the collection, storage and continuous analysis of collected information, as well as the ability of rapid access to that information. The Department of Reproduction and Gynecological Endocrinology in the Medical University of Bialystok is using a specially designed application for this purpose which is based on an extensive database [4]. The application provides a statistical module that allows to compare the parameters of patients with average values, and carry out basic statistical analysis in the course of gathering information [8]. It is also

shipped with implementation of previously trained neural network, which allows the prediction of treatment efficiency based on the collected data [5].

However, the standard statistical analysis, as well as used neural network technology is still not enough to efficiently and reliably predict the treatment outcome. Hence, the need for exploration and improvement of existing advanced statistical methods which may be effectively used to predict the results of IVF ICSI/ET infertility treatment methods.

Nearest neighbor based feature selection method and classifier

Over the course of many years of research on the feature selection issue, a number of measures and heuristics that can be applied during determining the significance of features process were found. One of the most interesting heuristics notions is the margin. The margin is understood here as the separation extent between observations of different classes. Intuitively, a larger margin induces easier process of classification, and interpretation of the conclusions drawn from it. In [1] the SIMBA, an algorithm was presented which determines the feature importance as a value dependent to a margin generated by it. Used here, the MSIMBAF2 algorithm is a modification and generalization of the following algorithms: MSIMBAF [6], SIMBA [1], Relief [2] and ReliefF [3]. MSIMBAF and MSIMBAF2 algorithms are very similar, therefore most of the equations described latter are the same as the first. The most important difference between them is the modified distance measure (1), and subsequent changes caused by it.

$$\Delta_p(\boldsymbol{x}_1, \boldsymbol{x}_2) = \left\{ \sum_o \left[\alpha(t_o) \phi_{type(o)}(x_{1o}, x_{2o}) \right]^p \right\}^{1/p} \tag{1}$$

where: $\boldsymbol{x}_1$, $\boldsymbol{x}_2$ observation; p metric order; $\Delta_p(*,*)$ observation distance measure of order p; $\alpha(*)$ specific function; o index of feature; t_o "hidden" parameters; x_{1*}, x_{2*} value of feature $*$ for given observation; $\phi_{type(o)}(*,*)$ measures of dissimilarity between single values of feature o with given $type(o)$;

$$\phi_{type(o)}(x_{1o}, x_{2o}) = \begin{cases} \phi_{num}(x_{1o}, x_{2o}) & (a) \\ \phi_{ord}(x_{1o}, x_{2o}) & (b) \\ \phi_{cat}(x_{1o}, x_{2o}) & (c) \end{cases} \tag{2}$$

$$\alpha(t_o) = \frac{1}{\pi} \left(\operatorname{arctg}(t_o) + \frac{\pi}{2} \right) = \frac{\operatorname{arctg}(t_o)}{\pi} + \frac{1}{2} \in (0,1); \quad t_0 \in \Re \tag{3}$$

$$\delta_o = \max_{b,d} |x_{bo} - x_{do}|\,; \quad 0 \leq \varepsilon_{o1} \leq \varepsilon_{o2} \leq 1 \tag{4}$$

$$\phi_{num}(x_{1o}, x_{2o}) = \min\left(1, \max\left(0, \frac{|x_{1o} - x_{2o}| - \delta_o \varepsilon_{io}}{\delta_o(\varepsilon_{02} - \varepsilon_{o1})}\right)\right) \tag{5}$$

$$\phi_{ord}(x_{1o}, x_{2o}) = \min\left(1, \max\left(0, \frac{|x_{1o} - x_{2o}| - \delta_o \varepsilon_{o1}}{\delta_o(\varepsilon_{02} - \varepsilon_{o1})}\right)\right) \tag{6}$$

$$\phi_{cat}(x_{1o}, x_{2o}) = \begin{cases} 0 \Leftrightarrow x_{1o} = x_{2o} \\ 1 \Leftrightarrow x_{1o} \neq x_{2o} \end{cases} \tag{7}$$

where: $\phi_{num}(*,*)$, $\phi_{cat}(*,*)$, $\phi_{ord}(*,*)$ measures of dissimilarity between numeric (a), categorical (b) or order (c) feature values; t_o "hidden" o-th feature weight parameter; δ_o value range of o-th feature; ε_{o1} and ε_{o2} cut-off parameters for o-th feature (there are only 2 such parameters for each feature);

Measure (1) resembles Minkowski metric of order of p. It is the main distance function used by algorithm. Index o iterates through all the features of the train data set. $\alpha(t_o)$ is scale factor as well as feature weight. It is a sigmoidal function (3) of internal parameter t_o. Depending on the feature type, algorithm choose suitable dissimilarity measure between values (2). For numerical features measure (2a) is chosen, for ordinal – (2b), for categorical – (2c). These are described in equations (5), (6), (7).

$$m = \sum_{x \in X} \left[\Delta_p(\boldsymbol{x}, miss\,(\boldsymbol{x}, u)) - \Delta_p(\boldsymbol{x}, hit\,(\boldsymbol{x}, u))\right] - \varepsilon \sum_o \alpha(t_o) \tag{8}$$

$$dt_o = \frac{\partial \Delta_p(\boldsymbol{x}, miss\,(\boldsymbol{x}, u))}{\partial t_o} - \frac{\partial \Delta_p(\boldsymbol{x}, hit\,(\boldsymbol{x}, u))}{\partial t_o} - \varepsilon \frac{\partial \alpha(t_o)}{\partial t_o} \tag{9}$$

$$t_o = t_o + dt_o \tag{10}$$

$$\frac{\partial \Delta_p(\boldsymbol{x}_1, \boldsymbol{x}_2)}{\partial t_o} = \phi_{type(o)}(x_{1o}, x_{2o}) \left[\frac{\alpha(t_o) \cdot \phi_{type(o)}(x_{1o}, x_{2o})}{\Delta_p(\boldsymbol{x}_1, \boldsymbol{x}_2)}\right]^{p-1} \frac{\partial \alpha(t_o)}{\partial t_o} \tag{11}$$

$$\frac{\partial \alpha(t_o)}{\partial t_o} = \frac{1}{\pi(1 + t_o^2)} \tag{12}$$

where: m margin; $\boldsymbol{x}$ observation; $hit(\boldsymbol{x}, u)$ u-th nearest observation of class same as $\boldsymbol{x}$; $miss(\boldsymbol{x}, u)$ u-th nearest observation of class different from $\boldsymbol{x}$; ε penalty factor; dt_o adjustment for o-th feature

MSIMBAF2, like MSIMBAF utilizes gradient optimization (9), (10) of margin (8) relative to the internal t_o parameter of features weight $\alpha(t_o)$.

ε parameter act as extra weight regulation. It is a kind of punishment level, that makes preferable to the algorithm to search for weights with the lowest possible sum. This factor also causes the gradual diminishing of weights for features that have the same values (or many missing values). Due to different distance measure (1), its (partial) derivative with respect to the o-th feature weight form (11) is changed. Categorical and ordinal feature weights are calculated now in the same way as the numerical ones. The MSIMBAF algorithm updated non-numeric feature weights similar to the ReliefF algorithm [3]. This could lead to the selection of a sub-optimal features subset (Relief has no mechanism against feature redundancy.). With the introduced modification, MSIMBAF2 algorithm can detect redundant ordinal and categorical features as well as numerical ones.

KNN (K Nearest Neighbor) is one of the simplest supervised classification methods to apply. It is based on a simple assumption of similarity of the same class objects. To determine the class of an observation, kNN classifier searches for the specified number of other observations of a known class, most similar to the given one (called neighbors). The dominant class among found neighbors becomes the new observation target class. This determines the division of the feature space into distinct decision areas of (strongly) nonlinear boundary which are dominated by points that have known common class. There are a number of measures that approximate the level of (non-)similarity. For the purpose of IVF data classification the following measure of dissimilarity (distance) was used:

$$d_{p'}(\boldsymbol{x}_1, \boldsymbol{x}_2) = \left[\sum_i \left(\frac{|x_{1i} - x_{2i}|}{\delta_i}\right)^{p'}\right]^{1/p'} + \sum_j \phi_{cat}(x_{1j}, x_{2j}) + \\ + \sum_k \frac{|x_{1k} - x_{2k}|}{\delta_k} \tag{13}$$

where: $\boldsymbol{x}_1$, $\boldsymbol{x}_2$ observation; p' metric order; $d_{p'}(*,*)$ observation distance measure of order p'; x_{1*}, x_{2*} value of feature $*$ for given observation.

In case of missing data the following rules were used:

- When for first and second observation for given feature both values are missing, distance between them is set to 0.
- When numerical value is missing, it is replaced by mean value among this feature values.
- When categorical value is missing, distance is probability that category is different than in compared observation.
- When ordinal value is missing, it is replaced by median value among this feature values.

These rules and the measure (13) are the same as for the MSIMBAF algorithm [6]. The main difference is that now they are used not only in the feature selection algorithm MSIMBAF2 (to find $hit(\boldsymbol{x}, u)$ and $miss(\boldsymbol{x}, u)$ in (8) and (9)), but also in the target kNN classifier.

Analysis method and results

Data set generated using the database [4] was analyzed. Diagram of this set is presented in [Tab. 1]. Each of the 1445 observation corresponds to one cycle of infertility treatment and is described by 150 features. The treatment outcome is dependent feature (pregnancy or no).

Tab. 1. IVF ICSI/ET treatment data scheme

		150 features			
		111 numerical	1 ordinal	37 categorical	1 categorical dependent
1445 observations	486 positive outcome	.....	.....	.....	.....
	959 negative outcome	.....	.....	.....	.....

To analyze the data set, MSIMBAF2 feature selection algorithm and kNN classifier were used. The parameters of these algorithms are as follows:

- MSIMBAF2 feature selection
  - metric order $p = 2.5$
  - lower cut-off level $\varepsilon_{o1} = 0.1$
  - upper cut–ff level $\varepsilon_{o2} = 0.9$
  - penalty weight factor $\varepsilon = 0.001$
- kNN classifier
  - metric order $p' = 1$

To reduce final result bias, following cross validation procedure was used (in bracket number of observations is given):

1. choose two random subsets of original data set (1445 obs.): validation (481 obs.) and learning (964 obs.)
2. 250 times make:
   2.1. choose two random subsets of learning data set: train (482 obs.) and test (482 obs.)

2.2. train MSIMBAF2 algorithm on train set
2.3. from feature number $i = 15$ to $i = 149$
  2.3.1. choose i features from train and test set to obtain two "truncated" data sets
  2.3.2. on "truncated" data set learn kNN classification algorithm
  2.3.3. assess the effectiveness of algorithm-learned decision rules on "truncated" data sets: train and test
3. for each feature number from $\langle 15;149 \rangle$ interval search for decision rules with the best accuracy of the 250 runs [Fig. 1].

For further analysis subset of 43 attributes and 482 observations (this was "truncated" train data set, on which kNN algorithm presents maximum efficiency [Fig. 1]) was selected, and kNN classification algorithm was train on it. Validation set was also truncated to those 43 features. [Tab. 2] shows trained classifier accuracy on truncated validation set. Because validation set was not used in learning phase, that accuracy [Tab. 2] is expected to be unbiased.

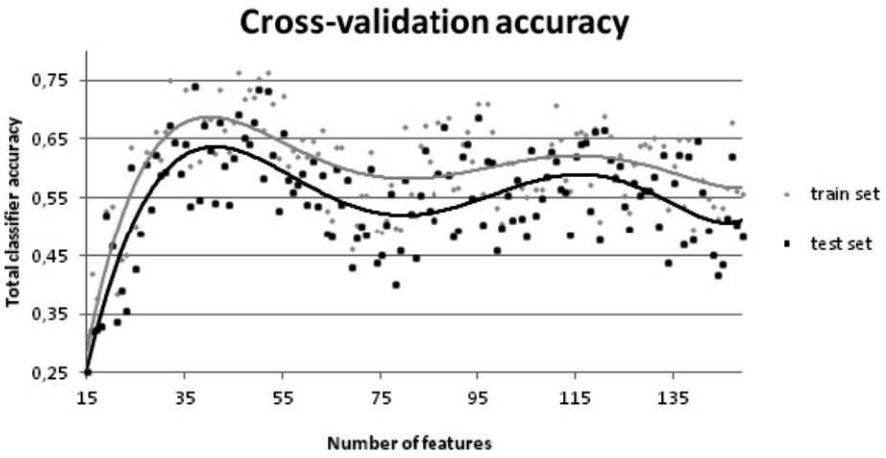

Fig. 1. Train and test set top total classification accuracies from 250 iterations, with approximation lines

[Fig. 2] shows 19 features with the largest weight of the 43 selected. Many of them (endometriosis, male factor, the protocol type of treatment) have been suspected for a long time as having a significant impact on the treatment effectiveness. Most interestingly, some features, previously considered as insignificant, also entered into the prediction model. Their presence probably boosts the predictive power of the model in presence of other selected features and causes higher accuracy achievement.

Tab. 2. Cross-classification accuracy on validate set depending on observed outcome

Total accuracy: 65%		Observed outcome		Total observations
		negative	positive	
Predicted	negative	70% (271 o.)	30% (121 o.)	100% (392 o.)
outcome	positive	54% (48 o.)	46% (41 o.)	100% (89 o.)
Total observations		(319 o.)	(162 o.)	481 o.

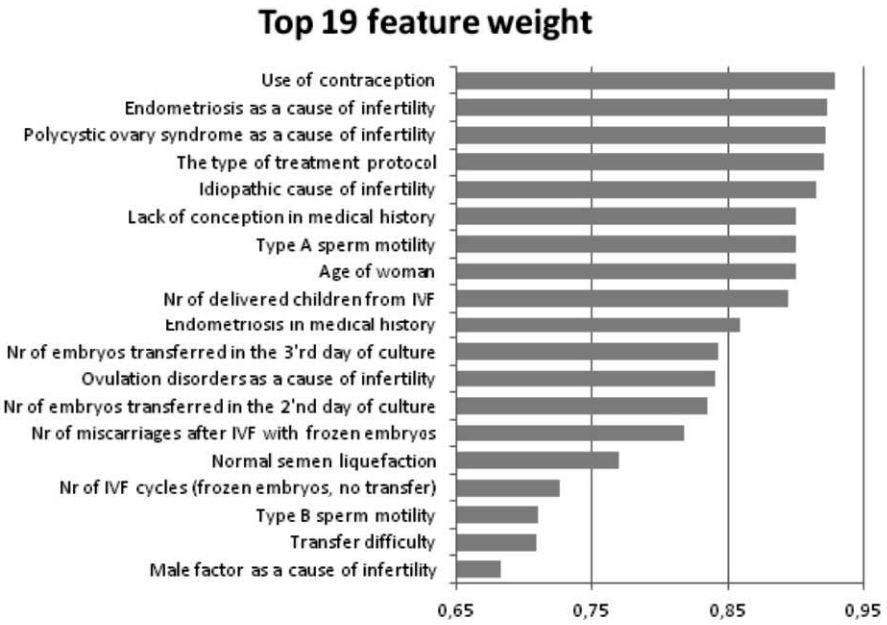

Fig. 2. Top 19 features from 43 according to their presented weights

Conclusions

Cross-validation test results are very promising. It turns out that the reduction in the number of features to 30% (43 of 149) can be performed without the loss of kNN classifier accuracy. For a smaller number of features of the overall accuracy of the classification quickly erodes. The classification error on the validation set has the same magnitude as on the test set, which confirms the resistance of the generated decision rules to bias. Unfortunately, the cross-classification results do not allow to fully predict pregnancy or lack

of it. The algorithm properly predicts the absence of pregnancy in 70% of the cases and its presence in only 46%. The above analysis is somewhat consistent with [5], where used the neural network predicted negative cases with much greater accuracy than positive.

Further research should focus on the use of the weighted average prediction accuracy for both positive and negative results, as opposed to the overall accuracy for the cross-validation procedure. Feature selection algorithm also requires further work. With the change of metrics, the margin function is strongly nonlinear due to the weight, so special methods of optimization should be used. It is suspected that the modifications described above can improve the parameters of the developed model to a satisfactory level, enabling it to be used in clinical practice to predict new cases of treatment effectiveness.

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An analysis of characteristics of children and adolescents physical growth in the context of social and economical situation of families inhabiting the city of Bytom

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Abstract. Underweight, overweight and obesity among children and adolescents is an important epidemiological problem, mostly because of consequences of health perturbations. This paper is intended to present the analysis of characteristics of children and adolescent physical growth in the context of social and economical situation of families inhabiting the city of Bytom. The Box-Cox transformation according to WHO standards for body weight, body height and BMI (Body Mass Index) is applied in the analysis. The transformation is a base for statistical analysis of measurable data using e.g. t-test, or Mann-Whitney test. Frequencies of underweight, overweight and obesity among children and adolescents are determined by centile ranks and growth charts by the Institute of Mother and Child in Warsaw, Poland, and analysed using differences significance test and the post-hoc test by Benferroni for percentages. The influence of social and economical factors are evaluated with χ^2-test and log-linear analysis. The main conclusion of the analysis confirms that the percentage of children and adolescents with overweight or obesity is growing. Moreover, the influence of social and economical factors (e.g. education of parents, or the average income per person) is significant. These are premises for further investigations and research in this field.

Introduction

Social and economical situation, life style and habits, mostly nutrition habits, evolve rapidly in the country of Poland in last years. This implies that scientific, especially statistical, research is still worth running to determine the influence of the environment on children and adolescents physical growth in the age of 7–18 [1]. The research of this age group is essential, mostly because of the fact that different housing and environmental conditions during childhood and adolescence, have strong impact on most of phenotype characteristics. Moreover, incoming problem of overweight and obesity, especially among children and adolescents is a serious premise to investigate and control this phenomenon. Overweight or obesity of children

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and adolescents may cause consequences, mostly non-infectious chronic diseases and increased death rate among people over 50 [2–3].

Reports on anthropometric data and their statistical analysis in highly developed countries show that most people of low socioeconomic class(es) are exposed to overweight and obesity [4]. The research conducted in Poland is most frequently based on population of people inhabiting agglomerations with unemployment rate smaller than the average for the whole country. It is worth noticing that data and analysis of situations in agglomerations where the unemployment rates are large [5], one may expect both malnutrition and obesity problems. An example of such an agglomeration is the city of Bytom, where the unemployment rate exceeded 26% in 2004, while the average rate for the whole country was equal to 18.7% [6].

Thus, the main scope of this paper is to present and analyze the characteristics of children and adolescents physical growth in the context of social and economical situation of families inhabiting the city of Bytom and health conditions of children and adolescents at the age of 7–18.

Methods

The collected data describe results of questionnaire (polled by the Municipality of the City of Bytom, Poland) devoted to the examination of health status of pupils of primary and secondary schools: children and adolescents in 12 age groups, from 7 to 18 years, in the 2003/2004 school year. The dataset contains 13 998 elements, including 6 987 boys and 6 963 girls. The number 13 950 well represents the population, because the total number of pupils in Bytom was 20 426 (2003/2004). In particular, anthropometric data on body height (in cm), body weight (in kg), and age (in years) were collected and taken into account in the presented examples and computations.

In order to detect and identify deviations of children and adolescents physical growth, the following parameters are taken into account: body height (exact to 1 cm) and body weight (exact to 1 kg). Age is evaluated exact to 1 day, but finally, mostly because of specificity of anthropometric data, children and adolescents are divided into the following one-year-age-groups: 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, and 18 years.

The so-called *Body Mass Index*, (BMI, [kg/m^2]) is evaluated from body weight and body height as a descriptive characteristic of each pupil [7]:

$$\mathrm{BMI} = \frac{\mathrm{weight}}{\mathrm{height} \cdot \mathrm{height}} \tag{1}$$

In medical examination and analysis, adults (above the age of 18) are qualified as "underweight" when BMI $\leq$ 20 kg/m^2, as "healthy weight" when $20 \leq$ BMI ≤ 25, as "overweight" when $25 \leq$ BMI ≤ 30, and as "obesity" when BMI ≥ 30. However, for children and adolescents, the so-called *centile ranks* and *growth charts* were worked out by the Institute of Mother and Child in Warsaw, Poland [8]. The suspicion of underweight is found if the BMI is placed below the 5th percentile, overweight – if BMI varies between the 85th and 95th percentile, and obesity if BMI exceeds the 95th percentile [7, 9–10].

The exponential transformation Box-Cox is applied for body height, body weight, and BMI, with attention to age and gender, according to WHO [9] for children between 7 and 18 years. The transformation of z-value for measure X (where $X \in \{$body height, body weight, BMI$\}$) and age t, are computed on the base of the following formula:

$$z_{ind} = \frac{\left(\frac{X}{M(t)}\right)^{L(t)} - 1}{S(t)L(t)} = \frac{X - M(t)}{SD(t)} \qquad \text{for} \qquad L \neq 0 \tag{2}$$

and

$$z_{ind} = \frac{\log\left(\frac{X}{M(t)}\right)}{S(t)} \qquad \text{for} \qquad L = 0 \tag{3}$$

using constant values $M(t)$ – median, $SD(t) = S(t) \cdot M(t)$, $L(t), SD(t)$ – standard deviation [10].

The following determinants of the social and economical environment are taken into account:

- mother's and father's education (primary, vocational, secondary, higher),
- mother's and father's employment (employed, unemployed),
- number of persons in a family (2–3 persons, more than 3 persons),
- a subjectively evaluated economical situation of the family (bad, good),
- monthly income per person in the family (less than 25€ per person, 25-75€, 75-150€, more than 150€ per person).

The data was analyzed with the R language and R software package [11] as well as with Statistica v.8.0 [12]. Statistical significance is determined as $p < 0.05$. Measurable data are described by the mean $\bar{x}$ and standard deviation $\bar{X} \pm S$, and median and interquartile range, IQR, because of skewness of distributions. Percentages are used for nominal samples. The following tests are applied to check whether the distribution of data is normal: the Shapiro-Wilk normality test (for number of records smaller than 5000) and

the Cramer von Mises test. Statistical significance of differences is verified using Student's t-test and the Mann-Whitney test. Percentages are analysed using differences significance test (taking into account the post-hoc test by Benferroni for percentages) and χ^2. Dependencies of two or more nominal samples are described using log-linear analysis.

Results and discussion

The analysed characteristics of children and adolescent physical growth are specific and vary in age groups [Fig. 1]. The analysis of average body weight and body height shows that the largest increase of body height is observed among boys at the age of 13–14, and among girls at the age of 11–13 [Tab. 1]. This is related to the pubertal spurt of boys and girls, respectively. One may also observe the largest increase of body weight among boys at the age of 13–16, and among girls the age of 11–13, also related to the pubertal spurt.

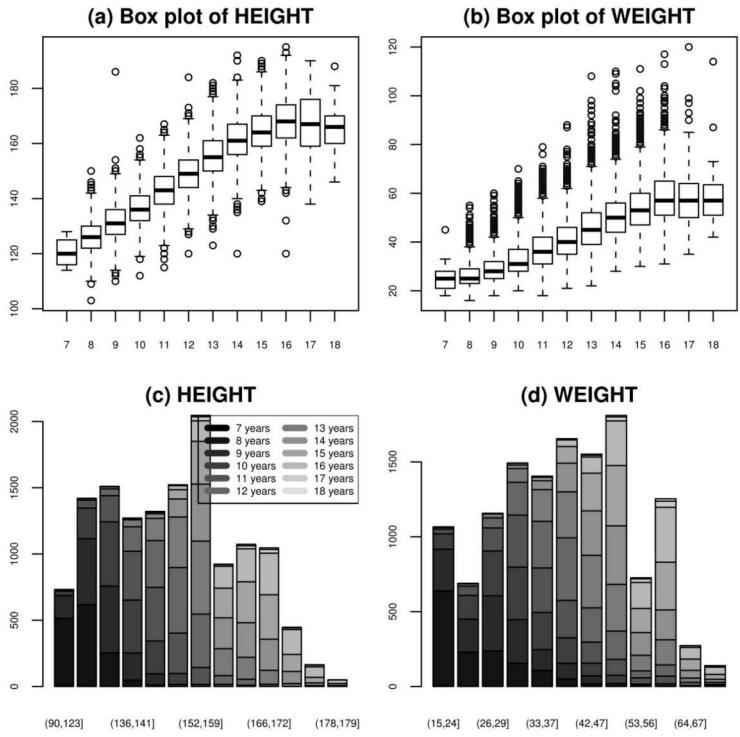

Fig. 1. The structure of body weight and body height in the age groups: 1: boxplots of mean body height and body weight (on the top), and histograms of body height and body weight in age groups (on the bottom)

Tab. 1. Characteristics of body weight and body height of boys and girls in age groups

Age	N	Height			Weight		
		$\bar{x} \pm S$	M	IQR	$\bar{x} \pm S$	M	IQR
Boys	6987	149.8 ±17.1	149.0	28.0	43.2 ±15.1	40.0	22.0
7	1	128.0	128.0	0.0	28.0	28.0	0.0
8	750	126.4 ± 6.0	126.0	8.0	26.9 ± 5.8	25.5	6.0
9	719	132.0 ± 6.6	132.0	8.0	30.2 ± 6.4	29.0	7.0
10	768	137.1 ± 6.7	137.0	9.0	33.5 ± 7.9	32.0	9.0
11	824	143.3 ± 7.5	143.0	10.0	38.1 ± 9.4	36.0	11.0
12	823	148.8 ± 7.3	149.0	9.0	41.3 ± 9.5	40.0	11.0
13	820	155.1 ± 9.1	155.0	12.0	46.6 ±11.5	45.0	15.0
14	760	162.9 ± 9.2	163.0	14.0	52.5 ±12.0	51.0	14.0
15	741	167.8 ± 8.5	168.0	12.0	56.6 ±11.9	55.0	14.0
16	667	173.6 ± 7.5	174.0	9.0	62.7 ±11.8	61.0	14.0
17	85	173.2 ± 8.9	175.0	12.0	62.4 ±13.4	61.0	12.0
18	29	170.3 ± 7.9	170.0	11.0	60.5 ±13.3	59.0	10.5
Girls	6963	147.6 ±14.8	150.0	25.0	41.6 ±13.2	41.0	20.0
7	8	119.9 ± 5.2	118.5	9.0	26.5 ± 8.8	24.5	9.0
8	694	125.3 ± 6.0	125.0	8.0	26.1 ± 5.6	25.0	7.0
9	789	131.0 ± 6.6	131.0	8.0	29.4 ± 6.5	28.0	7.0
10	740	136.1 ± 6.7	136.0	9.0	32.4 ± 7.1	31.0	9.0
11	689	142.8 ± 7.4	143.0	10.0	36.9 ± 8.9	35.0	12.0
12	823	149.4 ± 7.5	149.0	11.0	41.3 ± 9.4	40.0	12.0
13	882	155.4 ± 7.3	156.0	11.0	46.6 ± 9.9	46.0	12.0
14	739	159.9 ± 6.6	160.0	9.0	50.2 ± 9.2	49.0	11.0
15	793	161.6 ± 6.1	162.0	8.5	52.8 ± 9.2	51.0	12.0
16	710	163.4 ± 6.4	163.0	7.0	55.8 ± 9.7	54.0	10.0
17	71	160.2 ± 6.9	160.0	9.0	53.8 ± 8.7	54.0	10.0
18	25	160.8 ± 6.6	161.0	9.0	55.5 ±10.1	52.0	8.5
All Children	13950	148.7 ±16.0	149.0	25.0	42.4 ±14.2	41.0	21.0

Evaluation of influence of social and economical factors at basic measures of physical growth show that boys and girls whose mothers or fathers are employed and declare secondary or higher education, have significantly larger body weight and body height. If average income per person in the family is lower than 150€, body weight and body height of children and adolescent are smaller [Tab. 2, 3], cf. [13].

Tab. 2. Standardized characteristics of body height of boys and girls in the age of 7–10, related to social and economical factors

Social and economical factors	Boys	p-value $\bar{x} \pm S$	Girls	p-value $\bar{x} \pm S$
Mother's education				
Primary/Vocational	-1.01 ± 2.3	$p < 0.0001$*	-0.84 ± 2.4	$p < 0.0001$*
Secondary/Higher	-0.49 ± 2.6		-0.44 ± 2.3	
Father's education				
Primary/Vocational	-0.91 ± 2.9	$p < 0.0001$*	-0.75 ± 2.3	$p < 0.0001$*
Secondary/Higher	-0.52 ± 2.6		-0.48 ± 2.4	
Mother's employment				
Employed	-0.67 ± 2.7	$p < 0.0001$*	-0.59 ± 2.4	$p < 0.0001$*
Unemployed	-1.04 ± 3.1		-0.84 ± 2.1	
Father's employment				
Employed	-0.09 ± 2.8	$p < 0.0001$*	0.56 ± 2.2	$p < 0.0001$*
Unemployed	-1.11 ± 2.8		-1.01 ± 2.4	
Subjectively evaluated economical situation				
good	-0.59 ± 2.5	$p < 0.0001$*	-0.52 ± 2.2	$p < 0.001$*
bad	-1.12 ± 3.2		-0.91 ± 2.6	
Month income per person				
Below 150€	-0.82 ± 2.8	$p < 0.0001$*	-0.71 ± 2.3	$p < 0.001$*
Over 150€	-0.41 ± 2.8		-0.28 ± 2.2	

Standardization according to the WHO Child Growth Standards
* Statistical significance $p < 0.05$, Mann-Whitney test

Tab. 3. Standardized characteristics of body-weight of boys and girls related to social and economical factors

Social and economical factors	Boys	p-value $\bar{x} \pm S$	Girls	p-value $\bar{x} \pm S$
Mother's education				
Primary/Vocational	-0.20 ± 1.2	$p < 0.0001$*	-0.41 ± 1.2	$p < 0.0001$*
Secondary/Higher	0.22 ± 1.2		-0.02 ± 1.2	
Father's education				
Primary/Vocational	-0.11 ± 1.3	$p < 0.0001$*	-0.35 ± 1.2	$p < 0.0001$*
Secondary/Higher	0.19 ± 1.2		-0.01 ± 1.1	
Mother's employment				
Employed	0.10 ± 1.3	$p < 0.0001$*	-0.15 ± 1.2	$p < 0.0001$*
Unemployed	-0.25 ± 1.2		-0.43 ± 1.2	
Father's employment				
Employed	0.09 ± 1.3	$p < 0.0001$*	-0.17 ± 1.2	$p < 0.0001$*
Unemployed	-0.38 ± 1.2		-0.55 ± 1.2	
Subjectively evaluated economical situation				
good	0.13 ± 1.2	$p < 0.0001$*	-0.12 ± 1.2	$p < 0.0001$*
bad	-0.29 ± 1.3		-0.40 ± 1.3	
Month income per person				
Below 150€	-0.05 ± 1.3	$p < 0.0001$*	-0.28 ± 1.2	$p < 0.0001$*
Over 150€	0.37 ± 1.2		0.06 ± 1.1	

Standardization according to the WHO Child Growth Standards
* Statistical significance $p < 0.05$, Mann-Whitney test

According to percentiles about BMI values [7–8], 7.2% children and adolescents are underweighted (6.9% boys and 7.6%, $p = 0.11$). 76% children and adolescents are of healthy weight. About 10% are overweighted and 6.3% are obese, see [Fig. 2]. Percentage of boys with overweight or obesity is 14.4% and is significantly smaller than the percentage of girls that equals 17.0% ($p < 0.0001$). Basing on the analysed data, 95% confidence interval of percentage with underweight of children and adolescents in the age of 7–18 with underweight in Bytom is 6.8–7.7%, and with overweight or obesity – 15.1–16.3%.

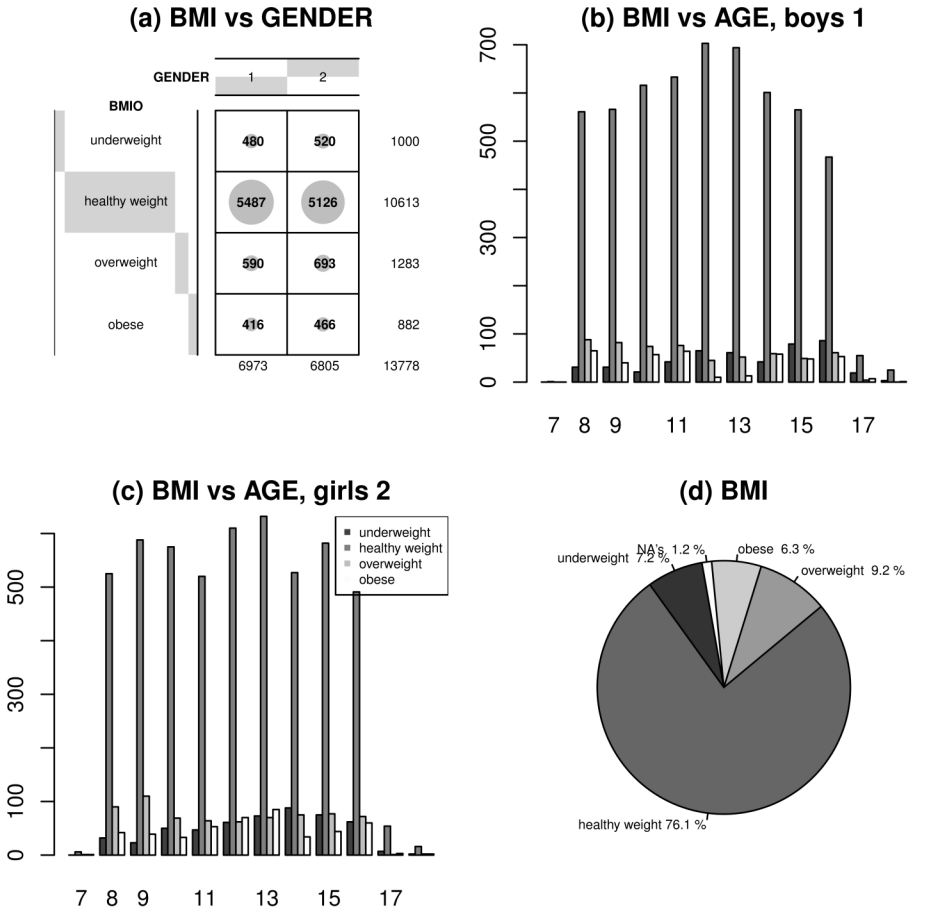

Fig. 2. (a) Summary of BMI according to gender, (b) histogram of BMI according to age (boys), (c) histogram of BMI according to age (girls), (d) Percentage of underweight, healthy weight, overweight, and obesity by BMI

These results are consistent with results from 2005 showing that 16–22% of children and adolscents in the age of 7–17 inhabiting European countries are overweighted or obese, and about 4–6% are obese [14].

Distribution of children and adolescents with overweight or obesity is significantly diversified in age groups ($p < 0.0001$). The significantly largest percentage is observed in the following age groups for both genders: 8, 9, 11, and 16 years old ($p < 0.05$). A similar situation is observed among boys ($p < 0.0001$) – the largest percentage appears for the 8–11 and 16 age groups ($p < 0.05$). The largest percentage of girls with overweight and obesity appears for the age of 8 ($p < 0.05$), see [Tab. 5].

The problem of malnutrition and underweight is significantly different for boys ($p < 0.0001$) and for girls ($p < 0.0001$). Significantly large percentage of boys with underweight is observed among 12–13 and 15–17 age groups. Among girls, significantly large percentage is observed for 14—17, see [Tab. 5]

Comparing the standardized values of BMI for both genders in corresponding age groups, statistically significant differences are observed for 8–14 and 17 age groups, see [Tab. 4].

Tab. 4. Standardized characteristics of BMI due to gender in age groups

Age	Boys $\bar{x} \pm S$	Girls $\bar{x} \pm S$	p-value
7	0.92	0.83 ± 1.7	–
8	0.26 ± 1.3	0.10 ± 1.2	$p < 0.05$*
9	0.27 ± 1.3	0.09 ± 1.1	$p < 0.01$*
10	0.23 ± 1.2	-0.02 ± 1.2	$p < 0.001$*
11	0.22 ± 1.3	-0.13 ± 1.2	$p < 0.0001$*
12	0.01 ± 1.3	-0.25 ± 1.2	$p < 0.001$*
13	-0.05 ± 1.3	-0.24 ± 1.2	$p < 0.05$*
14	-0.18 ± 1.2	-0.31 ± 1.1	$p < 0.05$*
15	-0.30 ± 1.2	-0.26 ± 1.0	$p = 0.52$
16	-0.23 ± 1.1	-0.16 ± 1.0	$p = 0.17$
17	-0.50 ± 1.3	-0.19 ± 0.9	$p < 0.05$*
18	-0.62 ± 1.2	-0.11 ± 1.0	$p = 0.11$

Standardization according to the WHO Child Growth Standards
* Statistical significance $p < 0.05$, t test, Mann-Whitney test

According to the results of research run by National Food and Nutrition Institute in 2000, underweight is observed in 11.8% of boys, and at 14.2% of girls. Overweight or obesity is observed in 12.6% of boys and 12.2% of girls [15]. In comparison to these results, we may observe statistically significant decrease of percentage of underweight children and adolescents

Tab. 5. Frequency of underweight, overweight or obesity in age groups

Age	Underweight N (%)	Healthy Weight N (%)	Overweight N (%)	Obese N (%)	Overweight/Obese N (%)
Boys	480 (6.9%)	5487 (78.7%)	590 (8.5%)	416 (6.0%)	1006 (14.4%)
7	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)
8	31 (4.2%)	561 (75.3%)	88 (11.8%)	65 (8.7%)	153 (20.5%)*
9	31 (4.3%)	566 (78.7%)	82 (11.4%)	40 (5.6%)	122 (17.0%)*
10	21 (2.7%)	616 (80.2%)	74 (9.6%)	57 (7.4%)	131 (17.1%)*
11	42 (5.2%)	633 (77.7%)	76 (9.3%)	64 (7.9%)	140 (17.2%)*
12	65 (7.9%)*	703 (85.4%)	45 (5.5%)	10 (1.2%)	55 (6.7%)
13	61 (7.4%)*	694 (84.6%)	52 (6.3%)	13 (1.6%)	65 (7.9%)
14	42 (5.5%)	601 (79.1%)	59 (7.8%)	58 (7.6%)	117 (15.4%)
15	79 (10.7%)*	565 (76.2%)	49 (6.6%)	48 (6.5%)	97 (13.1%)
16	86 (12.9%)*	467 (70.0%)	61 (9.1%)	53 (7.9%)	114 (17.1%)*
17	19 (22.4%)*	55 (64.7%)	4 (4.7%)	7 (8.2%)	11 (12.9%)
18	3 (10.3%)	25 (86.2%)	0 (0.0%)	1 (3.4%)	1 (3.4%)
Girls	520 (7.6%)	5126 (75.3%)	693 (10.2%)	466 (6.8%)	1159 (17.0%)
7	0 (0.0%)	6 (75.0%)	1 (12.5%)	1 (12.5%)	2 (25%)
8	32 (4.6%)	525 (76.2%)	90 (13.1%)	42 (6.1%)	132 (19.2%)*
9	23 (3.0%)	588 (77.4%)	110 (14.5%)	39 (5.1%)	149 (19.6%)
10	50 (6.9%)	575 (79.1%)	69 (9.5%)	33 (4.5%)	102 (14.0%)
11	47 (6.9%)	520 (76.0%)	64 (9.4%)	53 (7.7%)	117 (17.1%)
12	61 (7.6%)	610 (76.0%)	62 (7.7%)	70 (8.7%)	132 (16.4%)
13	73 (8.5%)	632 (73.5%)	70 (8.1%)	85 (10.0%)	155 (18.0%)
14	88 (12.2%)*	527 (72.8%)	75 (10.4%)	34 (4.7%)	109 (15.1%)
15	75 (9.6%)*	582 (74.8%)	77 (9.9%)	44 (5.7%)	121 (15.6%)
16	62 (9.1%)*	491 (71.7%)	72 (10.5%)	60 (8.8%)	132 (19.3%)
17	7 (10.8%)*	54 (83.1%)	1 (1.6%)	3 (4.6%)	4 (6.2%)
18	2 (9.1%)	16 (72.7%)	2 (9.1%)	2 (9.1%)	4 (18.2%)
All children	1000 (7.2%)	10613 (77.0%)	1283 (9.3%)	882 (6.4%)	2165 (16.1%)

* Statistical significance $p < 0.05$, test of equality of proportions

($p < 0.0001$) inhabiting the city of Bytom, except of boys in the age of 13–15 ($p = 0.17$).

However, the results describing percentages of children and adolescents with overweight and obesity are alarming: they significantly exceed the values from 2000 in all age groups (!) ($p < 0.0001$). The increase of percentages of obese children and adolescents is so rapid, that its reasons should not be searched only among biological factors. Also external (i.e. non-biological) factors, e.g. education or employment of parents must be taken into account [Tab. 6]. Primary or vocational education of fathers, employment of fathers, subjectively good economical situation of the family, and over 3 persons in a family increase statistically significant percentage of children and

adolescent with underweight, overweight or obesity, which is consistent with results described in the literature [13, 16–17]. Underweight, overweight and obesity is related to primary or vocational education of mothers, to unemployment of mothers and to low income per person in a family – 75–150€.

Among reasons of overweight and obesity, the lack of physical activities can be found [1]. Only about 30% of children and adolescents are physically active (except for physical education lessons at school), see [Tab. 6].

Tab. 6. Frequency of underweight, overweight or obesity related to social and economical factors

Social and economical factors	Underweight	Healthy weight	Overweight	Obesity
Mother's education				
Primary/Vocational	652 (66.7%)	5 765 (55.2%)	646 (50.9%)	466 (54.1%)
Secondary/Higher	325 (33.3%)	4 679 (44.8%)	622 (49.1%)	396 (45.9%)
$p < 0.0001$*				
Father's education				
Primary/Vocational	727 (75.3%)	6 794 (66.0%)	789 (63.3%)	568 (66.4%)
Secondary/Higher	238 (24.7%)	3 507 (34.0%)	457 (36.7%)	287 (33.6%)
$p < 0.0001$*				
Mother's employment				
Employed	368 (38.8%)	4 907 (48.1%)	608 (48.6%)	409 (48.2%)
Unemployed	580 (61.2%)	5 304 (51.9%)	644 (51.4%)	440 (51.8%)
$p < 0.0001$*				
Father's employment				
Employed	632 (70.1%)	7 602 (77.0%)	954 (79.8%)	631 (77.6%)
Unemployed	270 (29.9%)	2 265 (23.0%)	241 (20.2%)	182 (22.4%)
$p < 0.0001$*				
Subjectively evaluated economical situation				
good	379 (66.7%)	4 564 (73.5%)	575 (75.8%)	346 (71.6%)
bad	189 (33.3%)	1 648 (26.5%)	184 (24.2%)	137 (28.4%)
$p < 0.01$*				
Month income per person				
Less than 25€	161 (16.9%)	1 177 (11.8%)	118 (9.8%)	99 (11.9%)
25–75€	473 (49.8%)	4 393 (43.9%)	490 (40.5%)	337 (40.6%)
75–150€	263 (27.7%)	3 396 (33.9%)	435 (36.0%)	309 (37.2%)
Over 150€	53 (5.6%)	1 047 (10.5%)	166 (13.7%)	86 (10.3%)
$p < 0.0001$*				
Persons in a family				
2–3	169 (17.2%)	2 501 (23.8%)	369 (28.9%)	236 (27.0%)
More than 3	816 (82.8%)	8 015 (76.2%)	909 (71.1%)	638 (73.0%)
$p < 0.0001$*				
Additional sport activities				
YES	247 (25.1%)	3 197 (30.6%)	360 (28.5%)	225 (25.8%)
NO	739 (74.9%)	7 267 (69.4%)	904 (71.5%)	648 (74.2%)
$p < 0.0001$*				

* Statistical significance $p < 0.05$, χ^2 test

An attempt of determining of log-linear model is the next phase: the model must describe an influence of combination of samples representing chosen social and economical factors at values of BMI. Hence, the following factors:

- mother's and father's education,
- mother's and father's employment,
- subjectively evaluated economical situation of the family

are considered.

The best – because the least complex – model that explains the observed counts as statistically significant ($\chi^2 = 37.19$, $p = 0.96$) contains at most four-factor interactions due to value of BMI. Thus, the following interactions must be taken into account in the model:

- influence of mother's education, father's education and subjectively evaluated economical situation at values of BMI ($p < 0.05$),
- influence of mother's education, mother's employment and subjectively evaluated economical situation at values of BMI ($p < 0.05$),
- influence of mother's employment, father's employment and subjectively evaluated economical situation at values of BMI ($p < 0.05$),
- interaction of all listed social and economical factors ($p = 0.64$).

The log-linear analysis, especially of margin totals of contingency tables in the defined model, allows us to conclude that larger number of children and adolescent with underweight, overweight or obesity is observed among:

- growing up in families with subjectively good economical situation, in which mothers or fathers declare primary or vocational education,
- mothers of which declare primary or vocational education, are employed and in subjectively good economical situation,
- fathers or mothers of which are employed and in subjectively good economical situation of the family.

Conclusions

The presented statistical analysis of influence of social and economical factors on physical growth of children and adolescents inhabiting the city of Bytom allows us to conclude that:

- *Frequency of underweight, overweight or obesity is dependent on age groups*: the largest number of boys with overweight or obesity is observed in the 8–11 and 16 age groups, and of girls – in the age of 8. The largest number of girls with underweight is observed in the 14–17, and of boys – 12–13 and 15–17.

- The percentage of children and adolescents with *overweight or obesity has increased since 2000.* The number of children with *underweight has decreased, except for boys in the age of 13–15.*
- Primary or vocational father's or mother's education, employed father, unemployed mother, subjectively good economical situation, average income 75–150€ per person or over 3 persons in the family *reduce the risk of overweight or obesity.*
- Primary or vocational mother's education and low income per person in a family *causes the possibility* of underweight of children and adolescents.
- Larger *body height and body weight* are observed in the case of children and adolescents of mothers or fathers with secondary or higher education, with subjectively good economical situation and month income larger than 150€.
- We observe dependences between BMI values and:
  - mother's education, father's education and subjectively evaluated economical situation of the family;
  - mother's education, mother's employment and subjectively evaluated economical situation of the family;
  - mother's employment, father's employment and subjectively evaluated economical situation of the family.

Because of upcoming phenomena of overweight and obesity among children and adolescents, preventive treatment and prophylaxis, as far as epidemiological investigations must be considered, to control proper physical growth of children and adolescents.

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Coherence function in biomedical signal processing: a short review of applications in Neurology, Cardiology and Gynecology

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Abstract. The aim of this study is to present a coherence function, which can be used to find common frequencies of two signals and to evaluate the similarity of these signals. Another method is to use wavelet coherence function, which not only can find common frequencies of two signals, but also gives information when these frequencies appear. We would like to demonstrate the usefulness of coherence function in biomedical signal processing – in analysis of EEG, ECG, and uterine contraction activity signals. We have chosen four papers using coherence function in EEG analysis, four in ECG analysis and two in uterine contraction activity signals analysis (where we present some of our original work). Thus, these functions can be useful in analyzing two simultaneously recorded biomedical signals and they can provide some diagnostic value.

Introduction

The study of two signals, recorded simultaneously in one system, is a very interesting task. In case when the system under consideration is a part of human body and we record signals related to the activity of some organ, it can also provide a diagnostic value. For example – we can analyze EEG signals or signals representing uterine contractions and discover some abnormalities in the organ's functions.

To this end we can apply coherence function, which is based on Fourier transform. Word "coherence" is from the Latin word *cohaerentia* – it means natural or logical connection or consistency. The coherence function allows us to find common frequencies and to evaluate the similarity of signals. However, it does not give any information about time. There are two often used methods to calculate the coherence function: Welch method and MVDR (*Minimum Variance Distortionless Response*) method.

A transformation T is said to be linear if applied to linear combination of signals $ax+by$ gives linear combination of results $aT(x)+bT(y)$. Coherence function is based on Fourier transform, which is a linear transformation. However, the coherence function itself is not linear.

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Coherence function

Coherence function is defined as [4]

$$C_{xy}(\omega) := \frac{P_{xy}(\omega)}{\sqrt{P_{xx}(\omega)P_{yy}(\omega)}}, \tag{1}$$

where P_{xx} and P_{yy} are power spectra of signals x and y, P_{xy} is cross-power spectrum for these signals, ω is frequency. In case, when $P_{xx}(\omega) = 0$ or $P_{yy}(\omega) = 0$, then also $P_{xy}(\omega) = 0$ and we assume, that value $C_{xy}(\omega)$ is zero.

The power spectrum (also called periodogram) and cross-power spectrum are defined as [4, 20]

$$P_{xx}(\omega) := |\hat{x}(\omega)|^2 = \hat{x}(\omega)\overline{\hat{x}(\omega)}, \tag{2}$$

$$P_{xy}(\omega) := \hat{x}(\omega)\overline{\hat{y}(\omega)}, \tag{3}$$

where $\overline{x}$ is complex conjugate of x and

$$\hat{x}(\omega) := \int_{-\infty}^{\infty} x(t)e^{-i\omega t}dt \tag{4}$$

is the Fourier transform. It yields the information about frequencies occurring in signals and the dominant frequency for these signals.

Welch Method

A peak in the amplitude of cross-power spectrum means that there is a common frequency present in both signals. However, it is possible that components with that frequency appear in analyzed signals at different time. Thus cross-power spectrum in practical applications may not be subtle enough – we need a method to locate frequencies present in both signals at the same time. To this end we compute the coherence function (or magnitude squared coherence) on averaged estimates of power spectra and cross-power spectrum of segments of the initial signal [4]. It is known as the Welch method and it was proposed by Welch in 1967 [17].

For discrete signals (time-series) we calculate the power spectrum for coherence function in the following way. The signal is divided into K fragments of length M (possibly overlapping)

$$x^l(n) = x(n + lD); \quad 0 \leq l \leq K - 1, \quad 0 \leq n \leq M - 1, \tag{5}$$

where D is chosen lag [20]. Selected signal's fragments are multiplied by a window function $w(n)$ and for all of them we compute the power spectrum

$$P_{xx}^{i}(f) = \frac{1}{E_w} \left| \sum_{n=0}^{M-1} x^i(n) w(n) e^{-2i\pi (f/f_{pr})n} \right|^2, \tag{6}$$

where

$$E_w = \sum_{n=0}^{M-1} w^2(n). \tag{7}$$

Window most commonly used is the Hamming function defined in the following way

$$w(n) = 0.54 - 0.46 \cos\left(\frac{2\pi n}{M-1}\right). \tag{8}$$

Then these modified (obtained for signal multiplied by window) periodograms are averaged in time [7, 20]

$$P_{xx}^{w}(f) = \frac{1}{L} \sum_{i=0}^{L-1} P_{xx}^{i}(f). \tag{9}$$

In order to obtain estimation of cross-power spectrum, we need to average partial cross-power spectra

$$\begin{aligned} &P_{xy}^{i}(f) = \\ &= \frac{1}{E_w} \left(\sum_{n=0}^{M-1} x^i(n) w(n) e^{-2i\pi (f/f_{pr})n} \right) \cdot \left(\sum_{n=0}^{M-1} y^i(n) w(n) e^{2i\pi (f/f_{pr})n} \right). \end{aligned} \tag{10}$$

In practice the overlap of signal fragments is often chosen as 50%, i.e. $D = M/2$ [20], while the number K of intervals is chosen as a compromise between spectral resolution and precision of localization.

MVDR Method

Another method – the MVDR (*Minimum Variance Distortionless Response*) – was proposed by Capon in 1969 [3]. This method in many cases gives more precise results than the Welch method [1–2, 19]. It is based on a specific filter designed to minimalize the power of the output signal [1–3, 18–19]. More information about the MVDR method can be found in the papers by Benesty [1–2] and Capon's paper [3].

Example of the coherence function

In [Fig. 1] we show an example of application of the coherence function. In parts A) and B) of [Fig. 1] we can see chosen signals:

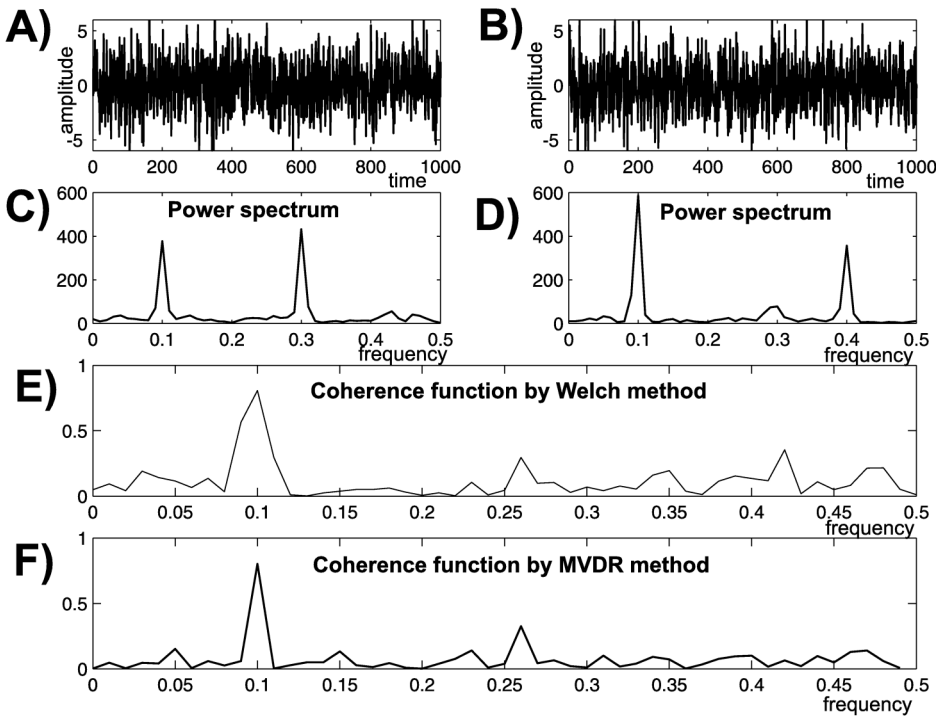

Fig. 1. Example of coherence function: A) signal $x(n)$, B) signal $y(n)$, C) power spectrum of signal $x(n)$, D) power spectrum of signal $y(n)$, E) coherence function by Welch method, F) coherence function by MVDR method (common frequency for two signals 0.1 Hz)

$$x(n) = k_1(n) + \cos(2\pi \cdot 0.1n) + \cos(2\pi \cdot 0.3n), \tag{11}$$

$$y(n) = k_2(n) + \cos(2\pi(0.1n + \psi)) + \cos(2\pi(0.4n + \varphi)), \tag{12}$$

where k_1 and k_2 are white noise, ψ and φ are phase shifts.

Graphs C) and D) show power spectra for these signals. We can observe that in signal $x(n)$ there are two frequencies 0.1 and 0.3 present and in signal $y(n)$ – 0.1 and 0.4. On graphs E) and F) we have plotted the coherence function (using power spectrum obtained by Welch or MVDR method). Here we can see one peak – common frequency for signals $x(n)$ and $y(n)$ is 0.1Hz. All programs were written in MATLAB (ver. 5.2, MathWorks Inc., Natick, USA). We also used the *coherence_MVDR* function written by Benesty (http://www.mathworks.com/matlabcentral/fileexchange/9781-coherence-function/content/coherence_MVDR/coherence_MVDR.m).

Application in biomedical processing

Coherence function in neurology and cardiology studies

In this section we present some applications of the coherence function. We have chosen eight interesting papers on this matter.

Coherence function finds application mainly in neurology (mostly in EEG studies) [8, 10, 15–16] and in heart rate variability investigations [5, 11–12, 14].

Coherence function was applied in EEG signal processing as linear synchronization measure by Quiroga et al. [10]. They studied signals from left and right rat's hemisphere. Authors claim that coherence function can be useful in the investigation of common frequency of EEG signals. They discovered that common frequency for two selected EEG channels is in range 1Hz-10Hz.

Coherence function was analyzed in brain stimulation studies [8]. Miranda de Sá and Infantosi used coherence as a detection parameter of evoked responses to rhythmic stimulation.

Coherence function was also used in studies of synaptic activity using head models and simultaneous recordings of MEG (magnetoencephalography) and EEG [16]. Authors claim that coherence function is useful for finding information about functional interactions across brain regions and neocortical source activity.

In the paper by Sherman et al. [15] we can find that coherence can be a measure between field potentials and EEG channels. They studied a model of linear association between channels during epileptic seizures.

In papers by Ruchkin [13] and Pereda et al. [9] there are interesting reviews of applications of coherence function in neurophysiology and EEG signal studies.

In the paper by Ropella et al. [12] we can find an interesting application of the coherence function in cardiology. Namely coherence was used to quantify the relation between some spectral elements of electrogram, taken from two sites in either the atrium or ventricle during both fibrillatory and nonfibrillatory rhythms. Authors present that nonfibrillatory rhythms exhibited strong coherence throughout the 1–59Hz band and fibrillatory rhythms – weak coherence throughout this band, and moreover harmonics are not present. They claim, that comparison of two electrograms with coherence function can provide discriminate between fibrillatory and nonfibrillatory rhythms. They also investigated the coherence function in various ventricular tachyarrhythmias [11]. In that paper they show, that it is possible to distinguish between monomorphic ventricular tachycardia, polymorphic

ventricular tachycardia, and ventricular fibrillation by means of coherence function. Ropella et al. [11] claim that coherence can be a measure of rhythm "organization".

Also Sarraf et al. [14] claim that coherence function can be used to quantify rhythms organization. They applied this function to the surface ECG studies and found out that it can discriminate between atrial fibrillation and nonfibrillatory atrial rhythms.

Coherence function can be also used in analyzing surface ECG as well as ECG taken directly from the heart [5]. Common frequency was found in 0Hz–60Hz band. They found that propagation of ventricular fibrillation became more organized during the first 10s. It can be an optimal window for defibrillation.

Coherence function in uterine contractility studies

In our studies coherence function was used to evaluate uterine contraction activity. In paper [7] we presented the coherence function obtained by Welch and MVDR methods for four selected pairs of signals from different patients (patient with primary dysmenorrhea, patient with fibromyomas, patient with endometriosis and healthy woman). Signals were obtained during examinations by means of intrauterine pressure method (during menstruation). We recorded two signals – one from fundus and one from cervix.

We found that coherence function can be useful in the analysis of the synchronization of the uterine contractility. The lowest values of coherence function were in case of patient with primary dysmenorrhea, the highest – healthy woman.

In our second paper [6] one can find analysis of the coherence function in groups of patients with primary dysmenorrhea, with fibromyomas, and with endometriosis. Values of common frequencies are in band 0.044Hz–0.056Hz. Values of the coherence function also point to the similarity between signals from fundus and cervix. We also shown that the lowest values are for patients with primary dysmenorrhea.

Wavelet coherence function

In papers [6–7] we also present the wavelet coherence function. In [Fig. 2] we show an example of this function. First we obtain discrete wavelet decomposition (multi-resolution analysis) and find frequency band containing the dominant frequency ($D4$ band and $D7$ band in our example). To this end we reconstructed the approximation signal $A8$ and details D_j $(1 \leq j \leq 8)$. We obtain eight wavelet decompositions representing frequency bands (from $D1$

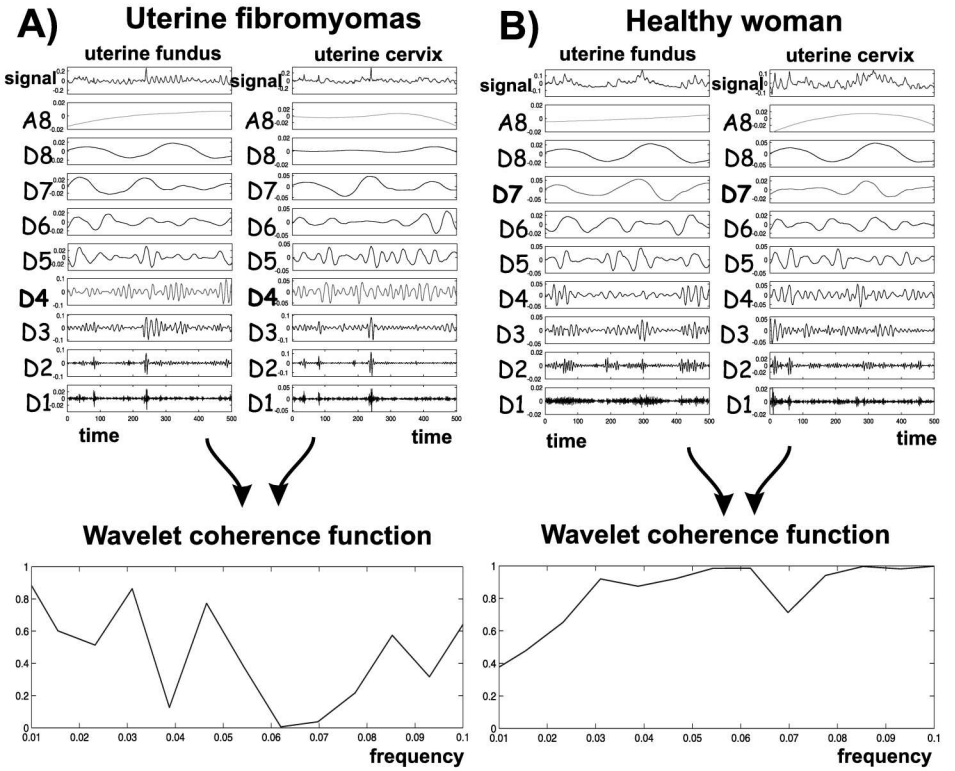

Fig. 2. Example of wavelet coherence function: A) discrete wavelet decomposition ($D4$ is selected frequency band) and wavelet coherence function for signals from patient with uterine fibromyomas, B) discrete wavelet decomposition ($D7$ is selected frequency band) and wavelet coherence function for signals from healthy woman

to $D8$), which are equivalent to period bands: 2–4s, 4–8s, 8–16s, 16–32s, 32–64s, 64–128s, 128–256s, 256–512s. We chose the frequency band which contained dominant frequency calculated by Fourier transform. Then we compute coherence function (in this chosen band, by means of the Welch method) and we receive the wavelet coherence function. By computation of this function we have obtained the information what are the common frequencies and when they appear. We were also able to estimate the similarity of two signals.

Examinations used in this example were conducted in the Department of Perinatology, The State Teaching Hospital of the Medical University of Bialystok.

Conclusions

In this paper we have presented a short review of applications of the coherence function in neurology, cardiology and uterine contractions activity studies. Coherence function is not a new concept, but in biomedical signal processing is rarely used, mainly in EEG signal studies. Since coherence is a frequency domain measure, it allows to find common frequencies in two signals and to evaluate the similarity of signals. Thus it can be useful in analyzing two simultaneously recorded biomedical signals and it can provide some diagnostic value.

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The use of the basket analysis in a research of the process of hospitalization in the gynecological ward

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Abstract. The progress of science and technology allows to create increasingly complex and detailed databases. It leads to the development of modern data analysis methods. Information collected in medical facilities is characterized by great diversity. In this paper we present a description and application of one of the data mining methods, the basket analysis. It will be used on data describing the process of hospitalization on the gynecological ward. A way of searching for association rules the using basket analysis will be presented. This opens great opportunities for the interpretation obtained results.

Introduction

Many companies, government organizations, research centers and medical facilities create extensive databases. Information gathered for many years is a rich source of knowledge. Skilful mining and analyzing allows to improve the operation of facilities, optimize processes and detect irregularities. Basic statistical methods allow to detect some relationships, but may prove that the most interesting and invisible at first glance observations can get away from the researchers note. Meaningful analysis of databases is made possible by data mining techniques, one of them is the basket analysis, also known as the association rules. This method, in contrast to traditional instruments, can detect links between factors, which are rare, for example, relate to an unusual disease entity, which is accompanied by a number of recurring symptoms. A major advantage of this method is the detection of co-existence of many characteristics of an object. Basket analysis indicates even very complex implications. Such observations are undetectable using traditional statistics, especially if the database is large.

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Basket analysis – method

Basket analysis is used to find association rules. The term can be understood as all the implications describing collected categorical data. This technique allows for searching rules of the kind: If X then likely Y. At the same time both body and head may incorporate several factors. Appropriate medical database would allow to build the following sentence, for example: if a patient from ward A smokes cigarettes and suffer from obesity, it is probably that the treatment fails.

In basket analysis fast processing of huge data sets is made possible by using a priori algorithm [1] and its subsequent modifications [2]. Basic concepts, associated with it, relate to sales data:

- $I = \{i_1, i_2, \ldots, i_m\}$ – *items* is a set of binary factors.
- Any subset $X \subset I$ is called *itemset*, in particular subset with k elements: *k-itemset*.
- $D = \{(id_1, T_1), (id_2, T_2), \ldots, (id_n, T_n)\}$ transactions database, where:
  - for any j $id_j \subset TID$ is a unique transaction identifier,
  - for any j $T_j \subset I$ is a set of purchased goods.
- $s(X)$ is the number of transactions containing a set X.
- Association rule is called the implication "if X then Y", where both body and head can mean a single category, but also a list of categories (codes):

$$X \Rightarrow Y,$$

  where $X \subset I$, $Y \subset I$ and $X \cap Y = \emptyset$.
- Let n – number of transactions, $X \subset I$, $Y \subset I$ and $X \cap Y = \emptyset$, then indicators describing the rules:
  - support

$$support(X \Rightarrow Y) = \frac{s(X \cup Y)}{n},$$

  - confidence

$$confidence(X \Rightarrow Y) = \frac{s(X \cup Y)}{s(X)},$$

  - correlation

$$correlation(X \Rightarrow Y) = \frac{s(X \cup Y)}{\sqrt{s(X) \cdot s(Y)}}.$$

- Determined are also two constants: min_sup and min_conf, which mean the minimum support and minimum confidence, which characterize searched association rules. Appropriate deployment of these limits causes find only the relevant implications.

Construction of association rules is done in two steps:

I. Finding all frequent sets $X \subset I$, it means $\frac{s(X)}{n} > min\_sup$.

II. Generating association rules based on frequent sets $X \subset I$, for example by dividing each of these two subsets such that $A \cup B = X$, $A \cap B = \emptyset$ and $support(A \Rightarrow B) > min\_conf$.

Any computer program would not be able to check in real time all the rules. Using the a priori algorithm optimizes the search process and enables the identification of the most important relationships. Using basket analysis the researcher selects thresholds min_sup and min_conf. At this stage, he can decide whether rules apply to typical events, or whether they have a low support and describe anomalies.

Basket Analysis in Medicine

Not without reason, association rules is a tool that was used in trade. This method is ideal for analyzing shopping baskets [3], it indicates preferences and habits of customers of supermarkets, but also online stores. Familiarity with lists of products most often purchased together makes it possible for the seller to arrange them in the store (on the website) to a client looking for them so he will not miss the promotion addressed to him. The results of basket analysis sometimes confirm associations which are visible at first glance and are obvious to the retailers. However the main purpose of this method is to identify the hidden rules. One may wonder what benefit the discussed tool may bring in medicine. Literature indicates the possibility of using basket analysis in medicine mainly as follows:

- Analysis seemingly exploited of data, where the traditional tools were used [4].
- Exploring the relationship between medical concepts, in order to predict future discoveries (new relations between concepts) [5].
- Diagnostic decision support [6].

Medical data that describe the many features are a great facility that can be analyzed using association rules. It works for a large number of multidimensional variables. Description of each patient can have multiple characteristics, they include parameters describing the condition of the patient, laboratory data, as well as genetic. Collected data are extremely diverse: numeric, ordinal, nominal, as well as images. Organizing, building a multi-way tables for such data or describing by basic statistics can be cumbersome

and sometimes practically impossible. Medical data in many cases can be analyzed using this method. Some of them, first of all nominal variables, can be instantly used to build the association rules. Others may be subjected to transformation, to become the clear implication component. There are various methods and suggestions for standardization of the collected data [7]. It is important that finally obtained results were clear.

Analysis of the basket allows the search of the complex relationships between the characteristics included in the database containing the medical data. Meaningful analysis can bring answers to many questions. What are the differences between patients from large and small cities? What factors affect maintenance of normal weight? On which ward often comes to unusual situations and anomalies? It is possible to find answers to specific questions by introducing certain initial conditions, for example, get only the implications for women living in rural areas or people who have some disease. The advantage of basket analysis is that it also indicates the association rules that are not obvious. It is possible that detected regularity will be a far deviate from the generally accepted practices.

Suppose that there is a database containing information about the membership of the group: people who are overweight, underweight, and proper body weight, consumed products and other dietary habits (number of meals, time of last meal, etc.). Building a multi-way table is almost impossible. It would be too large and unreadable, because most cells would be empty. Attempt to create tables for each product and habit, which often is done, is possible, but also has drawbacks. This form makes the information dispersed and allows to see only double associations. Implications describing the relationship between three or more factors will not be detected.

Before proceeding, a database to the analysis should be prepared so that the gathered codes are components of association rules. A minimum level of support and confidence should also be established. Additionally, it can specify what factors we would like to include in the implications, for example, which food products, patient age, gender, disease entities, etc. In order to avoid unnecessary complexity in the rules, the maximum number of codes in body and head can be specified.

Two examples presented below illustrate how to search and generate association rules. The first one will refer to the traditional area, where basket analysis is used. While the second one will illustrate the mechanism of this tool in medical data. Because of the complexity of the method the presented database is very simplified. It aims to illustrate the possibility of basket analysis for the diversity with which we deal in medical data.

Example 1

Let the database contains information about the contents of 6 shopping baskets. Let us introduce codes for each product:

B – bread
M – milk
F – fruits
C – breakfast cereals
H – ham

[Tab. 1] contains 6 transactions.

Tab. 1. Contents of 6 shopping baskets

TID					
1	B				H
2	B	M	F	C	
3	B	M	F	C	H
4	B	M		C	H
5	B	M	F		
6	B	M		C	H

First, the data are browsed in terms of level of support. Calculated are relative frequencies of each code, then each pair, triple, etc. For further analysis selected are frequent sets that means, those which support is higher than the threshold value. Let min_sup = 60%. In the case of this example results are shown in [Tab. 2]:

Tab. 2. Frequent sets, if *min_sup* = 60%

Support	Frequent sets
100%	B
83%	BM, M
67%	C, H, BC, BH, MC, BMC

While the sets O, CO, MO, PW, CMP, CMW, CMPW, which have support level of 50%, are not frequent sets.

In the second step the level of confidence for all pairs of codes selected in the first phase is taken into account. Conditional probability that the observation containing body also contains head is calculated. Let min_conf = 75%. Partial results table will have the following form [Tab. 3]:

Tab. 3. Support and confidence of selected association rules

Rule	Support	Confidence
M ⇒ B	83%	100%
B ⇒ M	83%	83%
C ⇒ BM	67%	100%
BM ⇒ C	67%	67%
BC ⇒ M	67%	80%
CM ⇒ B	67%	100%
...		

The collected results show some regularity. Particularly interesting are those with high confidence. All persons who have chosen milk also bought bread and they accounted for 83% of respondents. It is worth noting that association rules are not commutative. Consider the following two implications: CBM and BMC. The level of support proves that 67% of people had in the basket at least these three products: B, M and C. The first of these rules means that among the people buying breakfast cereals all bought milk and bread. The second says that among the customers who chose the two most popular products 67% bought also flakes.

Example 2

The following table [Tab. 4] contains information about 10 men. They were divided because of the value of BMI, half of them are obese (A), others are characterized by optimal weight (B). Each of them responded to questions about: cycling, cigarette smoking and cardiovascular diseases. In the following table [Tab. 4], "1" means that the person responded affirmatively to the question, while "0" – negative.

Note that writing the data in convention from Example 1 will receive two times more columns. Each cell contains "0" also carries valuable information. In this case the number of characteristics will be doubled. Let us introduce the following additional codes:

C – rides a bike
D – does not ride a bike
E – smokes cigarettes
F – does not smoke cigarettes
G – there are cardiovascular diseases
H – there are no cardiovascular disease

The above [Tab. 4] would have therefore form [Tab. 5]:

Tab. 4. The database characterizing 10 men

TID	Group	Bike	Cigarettes	Diseases
1	A	0	1	1
2	B	0	0	1
3	B	1	0	0
4	A	0	1	1
5	B	1	1	0
6	A	1	1	0
7	A	0	0	1
8	A	0	1	1
9	B	1	0	0
10	B	1	1	1

Tab. 5. Transcoded database

TID								
1	A			D	E		G	
2		B		D		F	G	
3		B	C			F		H
4	A			D	E		G	
5		B	C		E			H
6	A		C		E			H
7	A			D		F	G	
8	A			D	E		G	
9		B	C			F		H
10		B	C		E		G	

Let $min\_sup = 40\%$ and $min\_conf = 80\%$, then:

Tab. 6. Frequent sets, if *min_sup* = 40%

Support	Frequent sets
60%	E, G
50%	A, B, C, D, DG
40%	F, H, AD, AE, AG, BC, CH, DGA, EG, HC

There can be constructed a lot of frequent of association rules. Because of the large number of implications in the below [Tab. 7] there is just a few of them.

Tab. 7. Association rules and indicators characterizing them

Rule	Support	Confidence	Correlation
D ⇒ G	50%	100%	91%
DG ⇒ A	40%	80%	80%
H ⇒ C	40%	100%	89%
C ⇒ H	40%	80%	89%

The obtained results should be understood as follows. The first implication says that among those not riding the bike all suffer from cardiovascular disease. Additionally, we can see that these two characteristics co-occur very often (correlation (D ⇒ G) = 91%). Another association occurs in 40% of cases and indicates that 80% of those suffering from cardiovascular disease and not riding a bicycle are obese. The last two implications illustrate strong relationship between active pastime and good health.

It is worth noting that these examples are far-reaching simplifications. They illustrate how many dependencies can be found even in the case of a small number of objects and attributes. Databases in which we can apply basket analysis are much more complex.

Use of basket analysis to analyze the process of hospitalization in gynecological ward

The process of hospitalization of patients is very diverse. Even if the same diagnoses are observed, there are significant differences in the course of treatment, medication use or length of staying in the hospital. Here may be helpful the above-mentioned statistical analysis based on data mining methods. These tools allow for finding hidden dependencies in databases and present them in the form of association rules. One of these methods are, for example, artificial neural networks, which can be used to predict the outcome of treatment [8].

This paper presents the use of basket analysis on data from hospital cards from the Department of Gynecology. The created database contains information on more than eight thousand processes of hospitalization, described among others with characteristics: primary and secondary diagnosis, date of admission and discharge, patient age and place of residence. The purpose of the performed analysis was to find associations between the parameters describing the hospitalization of patients on the gynecological ward.

Tab. 8. Codes of patient age

Code for age	Age
wiek 1	up to 19 years
wiek 2	from 20 to 29 years
wiek 3	from 30 to 39 years
wiek 4	from 40 to 49 years
wiek 5	from 50 to 59 years
wiek 6	from 60 to 69 years
wiek 7	70 years and more

Tab. 9. Codes of duration of hospitalization

Code for duration of hospitalization	Duration of hospitalization
dł. hosp.1	1 day
dł. hosp.2	2 days
dł. hosp.3	3 days
dł. hosp.4	4 days
dł. hosp.5	5 days
dł. hosp.6	6 days
dł. hosp.7	7 days
dł. hosp. pow.7	from 8 to 14 days
dł. hosp. pow.14	from 15 to 21 days
dł. hosp. pow.21	more than 21 days

Because of the nature of the analysis data has been transcoded. Age is showed in [Tab. 8], while the duration of treatment in [Tab. 9]. Disease entities are coded according to the international statistical classification of diseases and health problems ICD-10 [9]. Place of residence has been referred to the appropriate NFZ code specifying the patient.

The use of basket analysis allowed to obtain the typical patterns of conduct of hospitalization [Tab. 10]. It is a large group of associations with a single-piece body and head, for which the confidence coefficient is very high and exceeds 80–85%. Associations in these cases generally determine the percentages in the various subgroups.

For example, if patients are under 20 years old, in 95% cases they come from the Podlaskie Province (NFZ 10). We interpret it in the following way: "the youngest patients" which are still schoolgirls rarely change residence

Tab. 10. Association rules describing typical patterns of hospitalization

Min. wsparcie = 1,0%, Min. zaufanie = 80,0%, Min. korelacja = 15,0%
Maks. liczność poprzednika = 1, Maks. liczność następnika = 1

	Poprzednik	==>	Następnik	Wsparcie%	Zaufanie(%)	Korelacja(%)
1	**wiek == 1,**	**==>**	**nfz == 10,**	**2,0**	**94,8**	**16,8**
2	wiek == 4,	==>	nfz == 10,	15,7	83,7	44,6
3	wiek == 5,	==>	nfz == 10,	9,9	93,8	37,5
4	wiek == 6,	==>	nfz == 10,	3,9	95,3	23,6
5	**wiek == 7,**	**==>**	**nfz == 10,**	**2,9**	**95,7**	**20,5**
6	**nfz == 1,**	**==>**	**dł. hosp. == 1,**	**1,8**	**95,0**	**17,1**
7	**nfz == 1,**	**==>**	**kod 1 == Z31**	**1,7**	**88,1**	**22,4**
8	nfz == 3,	==>	dł. hosp. == 1,	2,7	90,6	20,6
9	**kod 1 == N92**	**==>**	**nfz == 10,**	**2,3**	**98,0**	**18,7**
10	nfz == 5,	==>	dł. hosp. == 1,	1,7	90,6	16,3
11	**kod 1 == Z31**	**==>**	**dł. hosp. == 1,**	**29,4**	**100,0**	**70,9**
12	nfz == 6,	==>	dł. hosp. == 1,	1,8	89,3	16,6
13	nfz == 6,	==>	kod 1 == Z31	1,6	80,5	21,0
14	nfz == 7,	==>	dł. hosp. == 1,	7,2	81,0	31,5
15	nfz == 9,	==>	dł. hosp. == 1,	1,5	91,5	15,6

(another district NFZ). Similarly, 96% of the oldest age group are women from Podlaskie Province, which is caused by the fact that elderly women often are cured in a hospital close to home because of feeling of safety and closeness of the family.

We can make a preliminary assessment of the causes of migration of patients from other Polish regions to the analyzed hospital. For example, if the patient comes from the Lower Silesia Province (NFZ 1), in 95% of the cases she is hospitalized 1 day and 88% of patients from this province were performed IVF ICSI/ET procedure (diagnosis code Z31). We see that the analyzed ward offers a one-day medical procedure during which patients come from a distant Lower Silesia Province. Furthermore, we find out that performing IVF procedures on the ward is a cause of migration of patients [10].

Associations with a high level of confidence referring to the main cause of hospitalization ("kod 1") indicate as mainly resident Podlaskie Province. Thus, 98% of patients with a diagnosis of "extensive, frequent and irregular menstruation" (N92), hospitalized on the ward lived in Podlaskie Province. Because most of cases is "a sudden situation" in which patients do not choose away hospitals and go to the nearest one [12]. Here we also observe that if the patient has surgery performed ICSI IVF / ET in 100% of the cases the patient is hospitalized 1 day. This observation confirms the fact that the IVF procedure requires a one-day hospitalization.

Association rules network [Fig. 1] shows the most common heads (with the greatest relative support): NFZ 10 (place of residence in Podlaskie Province), 1 day hospitalization, diagnosis IVF ICSI / ET.

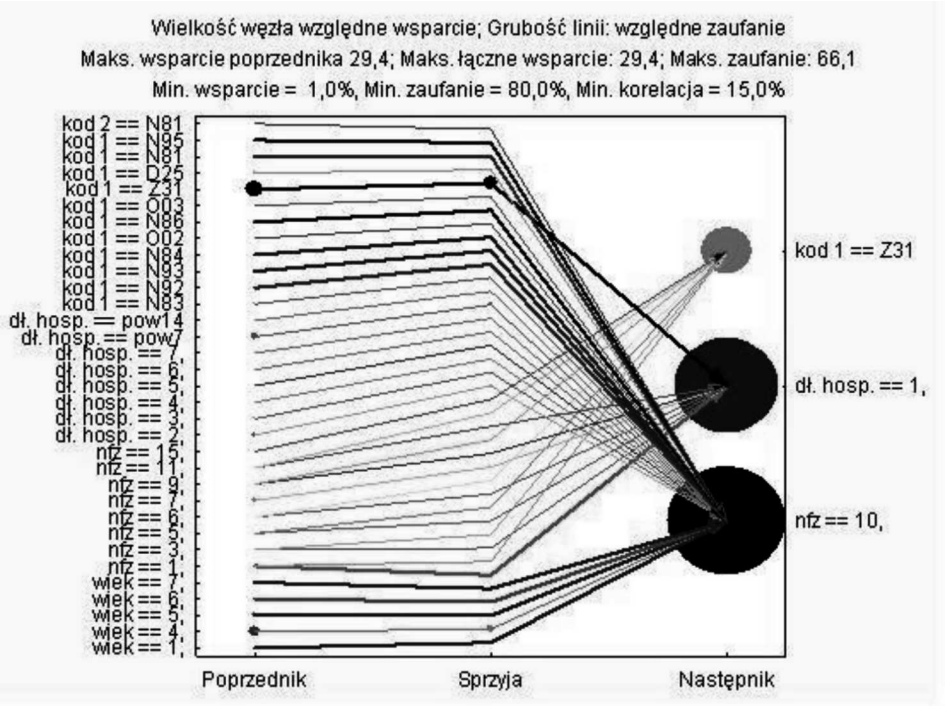

Fig. 1. Association Rules Network, typical patterns of hospitalization

A detailed analysis of the migration patients to this ward can be done apart from the database of those cases, where the resident is assigned to the NFZ 10. 118 association rules were obtained with a confidence above 80%, selected associations are showed in [Tab. 11]. These results support the assessment of migration obtained in [Tab. 10]. We see that the main purpose of hospitalization in the analyzed ward is the treatment of infertility by IVF ICSI/ET. For example, if the patient is assigned to NFZ 3, then in 82% of the cases are performed IVF ICSI/ET procedure, or in 91% of the cases patient is hospitalized for 1 day. Procedure for in vitro fertilization requires hospitalization for one day what we observed with the association rule: if kod 1 = Z31, then in 100% of the cases "dł.hosp = 1". Multicomponent associations also apply to the treatment of infertility. For example, if the patient is 30–39 years old, comes from the NFZ 6 and is hospitalized one day, in 100% of the cases the procedure IVF ICSI/ET (Z31) is performed.

Also popular sets made for patients from outside the Podlaskie Province once again show that the main cause of migration is the treatment of infertility. We see in [Tab. 12] that among patients coming from other provinces 84% were hospitalized 1 day, and 72% had done IVF treatment.

Tab. 11. Association rules for migration of patients from other provinces to the analyzed ward

Min. wsparcie = 1,0%, Min. zaufanie = 80,0%, Min. korelacja = 15,0%
Maks. liczność poprzednika = 10, Maks. liczność następnika = 10
Warunek pomijania: v3=10

	Poprzednik	==>	Następnik	**Wsparcie%**	Zaufanie(%)	Korelacja(%)
1	wiek == 2,	==>	dł. hosp. == 1,	23,7	81,8	48,0
2	wiek == 3,	==>	dł. hosp. == 1,	52,7	89,7	75,0
3	wiek == 3,	==>	kod 1 == Z31	47,4	80,7	72,7
4	wiek == 3,	==>	dł. hosp. == 1,, kod 1 == Z31	47,4	80,7	72,7
5	nfz == 1,	==>	dł. hosp. == 1,	5,3	95,0	24,5
6	nfz == 1,	==>	kod 1 == Z31	4,9	88,1	24,5
7	nfz == 1,	==>	dł. hosp. == 1,, kod 1 == Z31	4,9	88,1	24,5
8	nfz == 2,	==>	dł. hosp. == 1,	2,8	87,9	17,1
9	**nfz == 3,**	**==>**	**dł. hosp. == 1,**	**8,1**	**90,6**	**29,5**
10	**nfz == 3,**	**==>**	**kod 1 == Z31**	**7,4**	**82,4**	**28,9**
11	nfz == 3,	==>	dł. hosp. == 1,, kod 1 == Z31	7,4	82,4	28,9
12	**kod 1 == Z31**	**==>**	**dł. hosp. == 1,**	**72,4**	**100,0**	**92,8**
13	nfz == 5,	==>	kod 1 == Z31	4,6	83,0	23,0
14	nfz == 5,	==>	dł. hosp. == 1,, kod 1 == Z31	4,6	83,0	23,0
15	**wiek == 3,, nfz == 6,, dł. hosp. == 1,**	**==>**	**kod 1 == Z31**	**3,2**	**90,0**	**19,8**

Tab. 12. Popular sets relating to migration of patients

Obliczono częstości zestawów elementów
Min. wsparcie = 1,0%, Min. zaufanie = 80,0%, Min. korelacja = 15,0%
Maks. liczność poprzednika = 10, Maks. liczność następnika = 10
Warunek pomijania: v3=10

	Popularne zestawy	Liczność	Wsparcie%
20	**dł. hosp. == 1,**	2399,000	84,05746
27	**kod 1 == Z31**	2067,000	72,42467
106	**dł. hosp. == 1,, kod 1 == Z31**	2067,000	72,42467
2	**wiek == 3,**	1677,000	58,75964

Association rules network [Fig. 2] shows the main reason for the migration of women as a treatment for infertility. Heads are one-day hospitalization and diagnosis Z31.

We see that the cause of migration is dominated by the treatment of infertility [11]. It is worth asking whether there are other reasons for the choice of this hospital by patients from other provinces. If in the analysis of migrating patients infertility treatment is skipped, we get 17 interesting associations [Tab. 13].

For example, if the patients are 50–59 years and signed up to the treatment of typically gynecological problems – leiomyoma of uterus (D25) in 82% of the cases they come from the Warmia-Masuria Province (NFZ 14). Also in the group of long hospitalizations (15–21 days) 67% of the patients are from the Warmia-Masuria Province. In [Tab. 13] we can observe the coexistence of disease entities. If the second diagnosis is N83 (noninflammatory disorders of ovary), then in 82% of the cases D25 (leiomyoma of uterus) is the main cause of treatment.

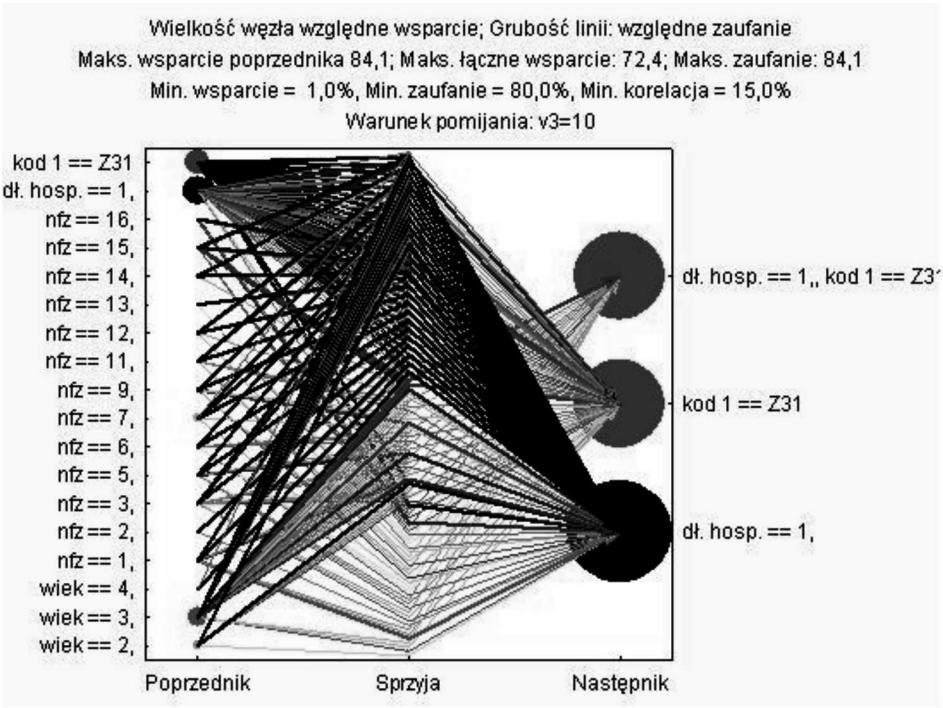

Fig. 2. Association rules network relating to migration of patients

Tab. 13. Association rules for migration of patients from other provinces to the analyzed ward (only gynecological reasons)

Min. wsparcie = 3,0%, Min. zaufanie = 60,0%, Min. korelacja = 15,0%
Maks. liczność poprzednika = 10, Maks. liczność następnika = 10
Uwzględniaj: 889:1004;4994:5162

	Poprzednik	==>	Następnik	Wsparcie%	Zaufanie(%)	Korelacja(%)
1	wiek == 5,	==>	nfz == 14,	14,4	75,9	47,0
2	**dł. hosp. == pow14**	==>	**nfz == 14,**	**3,5**	**66,7**	**21,7**
3	kod 1 == N83	==>	wiek == 2,	7,7	62,9	50,6
4	kod 1 == N93	==>	dł. hosp. == 1,	4,9	70,0	36,6
5	kod 1 == N81	==>	nfz == 14,	3,2	64,3	20,3
6	**kod 2 == N83**	==>	**kod 1 == D25**	**4,9**	**82,4**	**43,1**
7	kod 2 == N81	==>	nfz == 14,	3,5	66,7	21,7
8	wiek == 4,, dł. hosp. == pow7	==>	nfz == 14,	5,3	60,0	25,3
9	wiek == 4,, dł. hosp. == pow7	==>	kod 1 == D25	5,6	64,0	40,6
10	wiek == 5,, dł. hosp. == 1,	==>	nfz == 14,	4,2	70,6	24,5
11	wiek == 5,, dł. hosp. == pow7	==>	nfz == 14,	4,2	70,6	24,5
12	**wiek == 5,, kod 1 == D25**	==>	**nfz == 14,**	**3,2**	**81,8**	**22,9**

In the analysis of gynecological migration we note that there are mainly associations of 14th NFZ. It is the area of the Warmia-Masuria Province, directly adjacent to the Podlaskie Province. The migration of patients is justified by the choice of "better", more prestigious clinical hospital. In

addition, for many years it was the only one in the north-east macroregion III° referral level hospital. More complicated cases that require specialized treatment were directed.

Every hospitalization is associated with specific costs. Shorter treatment is usually more profitable for the hospital. Long hospitalizations are associated with complications and often generate high costs. Therefore it is important to analyze these processes of hospitalization, which last longer than the average duration of treatment in a particular disease entity. In this case all the processes of hospitalization lasting more than 7 days were selected for analysis and a group of more than 1300 items was obtained.

In [Tab. 14] we see that the largest group among the above week hospitalizations are patients with primary diagnosis of D25 (leiomyoma of uterus) – support of 19%. In this group 81% of cases were treated from 8 to 14 days and 19% longer. In the group of long hospitalizations among patients with a diagnosis of N83 (noninflammatory disorders of ovary), 87% stayed on the ward 8–14 days. We obtained association rule: if the first diagnosis is D25 and N83 is the second diagnosis, in 88% of cases duration of treatment is 8–14 days. We have received an interesting information here about co-existing diagnosis: leiomyoma of uterus and noninflammatory disorders of ovaries, which become important, if the patient is treated for a long time.

Tab. 14. Association rules for a long hospitalizations

	Podsumowanie reguł asocjacji Min. wsparcie = 1,0%, Min. zaufanie = 80,0%, Min. korelacja = 15,0% Maks. liczność poprzednika = 10, Maks. liczność następnika = 10 Uwzględniaj: 7112:8428					
	Poprzednik	==>	Następnik	Wsparcie%	Zaufanie(%)	Korelacja(%)
1	wiek == 1,,	==>	dł. hosp. == pow7	1,9	96,2	15,4
2	wiek == 2,,	==>	dł. hosp. == pow7	8,3	82,6	29,8
3	wiek == 5,,	==>	dł. hosp. == pow7	15,3	80,5	40,0
4	**kod 1 == N83**	**==>**	**dł. hosp. == pow7**	**7,4**	**87,5**	**29,1**
5	**kod 1 == D25**	**==>**	**dł. hosp. == pow7**	**18,9**	**81,4**	**44,7**
6	kod 2 == N83	==>	dł. hosp. == pow7	4,7	88,6	23,2
7	wiek == 4,, kod 2 == N83	==>	kod 1 == D25	2,2	93,5	29,8
8	wiek == 4,, kod 2 == N83	==>	dł. hosp. == pow7, kod 1 == D25	2,0	83,9	29,6
9	wiek == 3,, kod 1 == N83	==>	dł. hosp. == pow7	2,2	96,7	16,6
10	wiek == 3,, kod 1 == D25	==>	dł. hosp. == pow7	2,6	85,0	16,9
11	wiek == 4,, kod 1 == D25	==>	dł. hosp. == pow7	11,3	81,9	34,7
12	wiek == 4,, kod 2 == N83	==>	dł. hosp. == pow7	2,1	90,3	15,8
13	wiek == 5,, kod 2 == N83	==>	kod 1 == D25	1,4	82,6	22,6
14	**kod 1 == D25, kod 2 == N83**	**==>**	**dł. hosp. == pow7**	**3,5**	**88,5**	**20,0**
15	wiek == 5,, dł. hosp. == pow7, kod 2 == N83	==>	kod 1 == D25	1,2	80,0	20,5

In [Tab. 15] characteristics for place of residence was also included. We see that 87% of 8–14 days hospitalizations and 89% of hospitalizations lasting 15–21 days concerned Podlaskie Province residents. An analysis of age shows that the older the patient the greater is the percentage of long hospitalizations. Women to up 19 years represent 2% of long hospitalizations,

Tab. 15. The association rules for a long hospitalizations (with the division into NFZ districts)

Podsumowanie reguł asocjacji
Min. wsparcie = 1,0%, Min. zaufanie = 80,0%, Min. korelacja = 15,0%
Maks. liczność poprzednika = 10, Maks. liczność następnika = 10
Uwzględniaj: 7112:8428

	Poprzednik		Następnik	Wsparcie%	Zaufanie(%)	Korelacja(%)
1	wiek == 1,	==>	dl. hosp. == pow7	1,9	96,2	15,4
2	wiek == 2,	==>	dl. hosp. == pow7	8,3	82,6	29,8
3	wiek == 5,	==>	dl. hosp. == pow7	15,3	80,5	40,0
4	dl. hosp. == pow14	==>	nfz == 10,	13,9	87,1	37,0
5	dl. hosp. == pow21	==>	nfz == 10,	6,2	89,0	24,9

women aged 20–29 years – 8%, and patients aged 50–59 years – 15% of all long stays on the ward. Confidence is decreasing, it means that percentage of hospitalizations exceeding 14 days is increasing.

Conclusions

Basket Analysis is a great tool for the medical data mining. This method allows for deeper and more detailed exploration of the collected information than traditional statistics. It may be used for each type of data. Association rules make it possible for a thorough insight into among others case records, diet, habits and customs of patients and medical procedures. It can be applied to monitor the process of hospitalization. It also allows detection of factors that influence the healing process, including those that have not been suspected. Sometimes the basket analysis answers not formulated questions and indicates hidden patterns.

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Verification of the SCORE model for cardiovascular death risk in the Warsaw population

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Abstract. The aim of this paper was to evaluate the 10 year old SCORE model for global risk of death from cardiovascular diseases using the parameters of the algorithm SCORE, establish the predictors and their importance in determining the incidence of death in the Warsaw population in the 34–54 year age group over a 10 year period and verify the SCORE algorithm for global ten year risk of death due to cardiovascular diseases in the Warsaw population. The research was based on individual data from the Warsaw study carried out in 1984, 1988 and 1993 with observation over a 10 year period from 3 screening visits in the Pol-MONICA programme. Death records included the cause of death, with special reference to incidents involving cardiovascular death. The analysis used were the Kaplan Meier life expectancy curves with the log rank test for comparison of the curves (group homogeneity) and the multifactorial Cox proportional hazards model. The measure of fit was defined as the sum of the independent differences in the percentage frequency of death in the risk quartiles of SCORE and the personal quartile index based on the Cox model. As a result of the analysis beneficial changes on the 10 year death risk due to cardiovascular diseases in the years 1984–1993 with a slower death rate observed for the population in further screenings. The level of total cholestrol is not a predictor of death due to vascular disease for the population of the right bank of the city of Warsaw. The SCORE algorythm differs by some 7–15% from the estimated death rate of the male Warsaw population in the age group 35–64 years. For women the difference in fit is less and is between 4–10% of cardiological death rate.

Introduction

The search for factors having an effect on the prevalence, death and death rate due to given disease or group of diseases is one of the main aims of epidemiological studies. As part of the WHO MONICA project – an international multi centre study of the trends and causes of cardiovascular diseases carried out during the eighties and early nineties, the Institute of Cariology carried out three cross sectional studies of the population of the right bank of the city of Warsaw in the age group 34–64 years, named Pol-MONICA Warsaw [1]. The first screening covered 1309 men and 1337 women and was carried out between December 1983 and January 1985. The second screening of 710 men and 723 women was in 1988 and the third of 764 men and 775 women in 1993.

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The results were published in many journals of the Department of Epidemiology, Prevention of Cardiovascular Diseases and Health Promotion and several Polish and internation jounals [2]. The results of the Warsaw screeings were also recently used in synthetic and comparative presentations of the prevalence, awareness, treatment and control of hypertension in 24 centres that took part in MONICA [3].

The second important aim of the MONICA project was to monitor the levels of risk and other factors affecting the health of the population and their changes. From these results and as a result of continuing observations derived towards the prevalence of given cardiological events, models of global risk due to illness and death from cardiovascular diseases were developed and these were used to predict preventative recommendations.

The Department of Epidemiology, Prevention of Cardiovascular Diseases and Health Promotion carried out continual observation of the patients who took part in screenings I, II, III of the Pol-MONICA Warsaw programme during the years 1984–1998. Statistical analysis of the collected data was used to construct a global risk model for cardiovascular diseases, and overall death rate and verify this against the use of other models developed in the NORA, RIFLE, ERICA, MRFIT Framingham and NHANES studies for the Warsaw population [4].

Since 2003 the SCORE algorythm (European Systematic COronary Risk Evaluation) has been used to ascertain the 10 year cardiologic death risk from such factors as, sex, age, level of total cholestrol, systolic blood pressure – SBP and cigarette smoking [5]. The value of the global SCORE was used to form health recommendation on the need to change life style, stop smoking, correct diet and others. Based on the value of the SCORE risk the Polish Cardiological Society also developed recommendations [6].

It is known that the algorythms used in one population may lead to overestimates or underestimates of the risk in other populations [7]. It is therefore necessary to verify the SCORE risk, used to develop recommendations for the Polish population.

Aims

a) Develop a 10 year global risk model for death from cardiovascular diseases using the SCORE algorythm and determine the predictors and their value for death rates in the Warsaw 35–64 year old population over a 10 year period.

b) Verify the SCORE algorythm for the global 10 year risk of death from cardiovascular diseases in the Warsaw population.

Methods

The data collected of individuals randomised in the 1984, 1988 and 1993 studies was based on identical screening visits using a single method in the WHO MONICA studies. The results and methods used in the study are presented in [1]. The methods for data collection during 1984–1998 and the causes of death of the patients studied in screenings I, II, III are presented in [4].

The status of patients examined in screening III in the years 1998–2003 was obtained form the Census Department of the Ministry of Internal Affairs and Administration. The causes of death were obtained from the data base of the Chief Department of Statistics.

Where the cause of death was verified the length of time in observation from the screening date to date to death was calculated (years), where the cause of death was not verifiable observations were stopped exactly after 10 years from the date of the screening.

Using the SCORE algorythm [5] the 10 year risk of incidence of heart disease was calculated for each patient in the Pol-MONICA Warsaw programme, and using the Cox proportional hazards regression model – the individual risk of death.

Statistical methods

Analysis of the life expectancy and power of prediction of the risk factors was made using a multifactorial regression analysis of the Cox proportional hazards test allowing for such factors as age, level of total cholesterol, level of systolic blood pressure, and smoking habit. Using the published SCORE coefficients [5] the risk of cardiovascular death for each patient was determined. THE SCORE algorythm for the Warsaw population was verified by comparison of the frequency of death in the quartiles of the SCORE risk groups with those predicted by the COX test.

The sum of the differences between the frequencies in all quartile groups defines the deviation between the two algorythms.

All analysis for men and women were made separately. The significance level (first degree error) was taken as $\alpha = 0.05$.

Results

The three Pol-MONICA screenings involved 2783 men and 2835 women, 35–64 years of age. [Tab. 1] gives the numbers for each screening and the number of all confirmed deaths and deaths from cardiologic diseases over a 10 year period.

Tab. 1. The numbers of deaths over 10 year period for Warsaw population in the 35–64 year age group

Years of observation	Screening 1.		Screening 2.		Screening 3.		Total	
	All deaths	Deaths due to CVD	All deaths	Deaths due to CVD	All deaths	Deaths due to CVD	All deaths	Deaths due to CVD
To year	9	7	5	2	4	2	18	11
I	24	7	8	2	3	2	35	11
II	26	13	17	8	8	4	51	25
III	21	17	16	6	14	3	51	26
IV	30	14	15	9	13	2	58	25
V	40	19	18	10	17	5	75	34
VI	40	16	19	8	15	2	74	26
VII	48	23	16	7	22	7	86	37
VIII	53	29	13	5	18	5	84	39
IX	36	21	13	3	11	4	60	28
X	37	19	23	11	21	7	81	37
Total	364	185	163	57	146	43	673	285

[Fig. 1] shows the life expectancy curves from total mortality for the ten year period. Statistical significance in the difference between the male life expectancy curves ($p = 0.0007$) was seen. The female life expectancy curves did not show any difference ($p = 0.1974$).

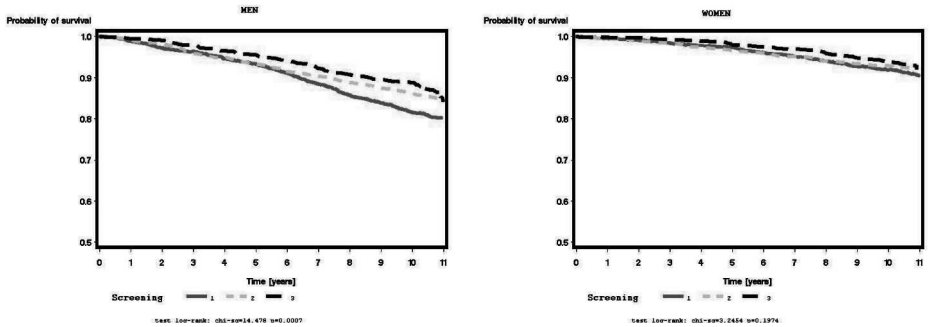

Fig. 1. 10 year life expectancy curves from all causes of death for the Warsaw population in the 35–64 year age group examined in 1984, 1988, 1993

[Fig. 2] shows the life expectancy curves from cardiovascular diseases. Statistical significance in the difference between the male ($p < 0.0001$) and female ($p = 0.0449$) life expectancy curves was seen.

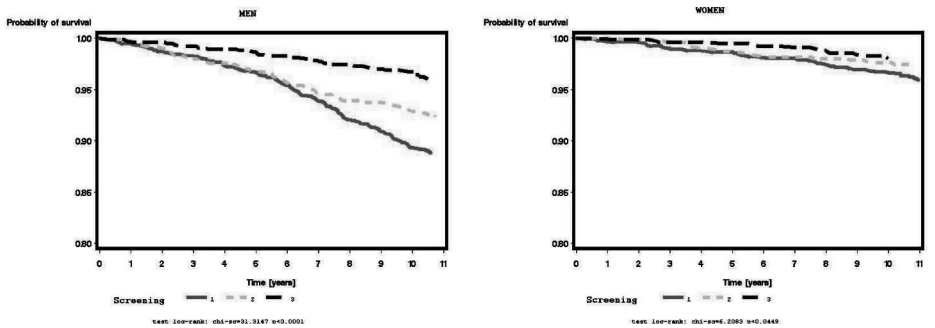

Fig. 2. 10 year life expectancy curves from cardiovascular diseases for the Warsaw population in the 35–64 year age group examined in 1984, 1988, and 1993

In order to determine the 10 year cardiovascular SCORE risk a multi factorial model was used allowing for age, smoking, cholestrol level and SBP. [Tab. 2] shows the Cox analysis results for men and women with the risk factor significance.

Tab. 2. The levels of significance of the SCORE risk factors in the right bank population of Warsaw in the 35–64 year age group

Risk factor	1984	1988	1993
Men:			
AGE	<0.0001	<0.0001	<0.0001
SMOKING	0.0004	0.1053	0.0387
CHOLESTROL	0.0577	0.1836	0.5518
SBP	<0.0001	0.0005	0.0433
Women:			
AGE	<0.0001	0.0065	0.0011
SMOKING	0.0488	0.0150	0.0008
CHOLESTROL	0.7562	0.8107	0.6861
DBP	0.0001	0.1185	0.0107

The total cholesterol level was not found to be a significant predictor of incidence of cardiovascular diseases for the Warsaw population in any analysis.

Tables 3, 4 and 5 present the frequency of death caused by cardiovascular diseases in the SCORE and Cox risk quartiles including the difference between these frequencies.

Tab. 3. The frequency of cardiologic deaths for the quartile groups of evaluated patients in 1984

Algorythm	I quartile	II quartile	III quartile	IV quartile
SCORE	4,8%	7,5%	14,0%	18,1%
Cox	2,8%	6,2%	16,4%	27,6%
Difference	2,0%	1,3%	2,4%	9,5%

a) men $\sum$ Differences = 15,2%

Algorythm	I quartile	II quartile	III quartile	IV quartile
SCORE	1,6%	2,3%	2,7%	9,8%
Cox	0,0%	1,0%	5,5%	13,9%
Difference	1,6%	1,3%	2,8%	4,1%

b) women $\sum$ Differences = 9,8%

Tab. 4. The frequency of cardiologic deaths for the quartile groups of evaluated patients in 1988

Algorythm	I quartile	II quartile	III quartile	IV quartile
SCORE	3,6%	5,3%	5,3%	11,8%
Cox	2,3%	2,8%	3,9%	20,3%
Difference	1,3%	2,5%	1,4%	8,5%

a) men $\sum$ Differences = 13,7%

Algorythm	I quartile	II quartile	III quartile	IV quartile
SCORE	0,6%	1,2%	4,1%	4,1%
Cox	0,0%	2,2%	2,2%	6,2%
Difference	0,6%	1,0%	1,9%	2,1%

b) women $\sum$ Differences = 5,6%

Tab. 5. The frequency of cardiologic deaths for the quartiles groups of evaluated patients in 1993

Algorythm	I quartile	II quartile	III quartile	IV quartile
SCORE	1,1%	2,2%	3,9%	6,2%
Cox	1,7%	1,6%	1,6%	10,0%
Difference	0,6%	0,6%	2,3%	3,8%

a) men $\sum$ Differences = 7,3%

Algorythm	I quartile	II quartile	III quartile	IV quartile
SCORE	0,5%	1,1%	1,1%	4,2%
Cox	0,0%	0,0%	2,1%	5,7%
Difference	0,5%	1,1%	1,0%	1,5%

b) women $\sum$ Differences = 4,1%

Discussion

a) The Polish population shows a decrease in death rate in general and that caused by cardiovascular diseases [8]. The presented data also shows a difference in life expectancy over the 10 year period for the 34–64 age group of the population of the right bank of the city of Warsaw. The life expectancy curves for the male population examined in 1984 (study 1.) significantly decreases more rapidly than the curves of those examined in the 1988 and 1993. The reasons for this should be sought in the changes in the conditions and style of life, medical care and others that have taken place in these years for this cross section of the population. Analysis of the curves for total mortality amongst women has shown that the female population has become more homogeneous with respect to general death rate. A significant difference in cardiovascular death rate in women was seen with a signifcant improvement in the 1993 group.

b) The SCORE algorythm was based on international multicentre prospective studies. These studies did not allow for the Polish population, specifically Warsaw. Hence the SCORE coefficient does not cover the Polish population. Use of the estimated Cox model (since date of death and survival time was determinable) on the same data base was possible to determine the specific values of risk. The degree of fit for the SCORE and Cox models to the observed cardiological death rate was made using the frequency in the risk quartiles. Since the estimate of death risk was made using maxi-

mum factorial probability, the best fit of the observed quartile number of deaths and quartile risk was obtained. The difference of frequency of death in the individual SCORE quartiles and Cox risk describes the over estimation or underestimation of the frequencies in the SCORE with respect to the Cox model. In all cases an over estimation of death rate is seen in the lower SCORE quartiles and an underestimation in the upper quartiles. The independent differences of cardiological death in the sum of all quartiles determines the degree of fit of the algorithm SCORE in the Warsaw population with respect to the estimated Cox risk model. For men this is 7–15% and 4–10% for women.

Conclusions

1. During 1984–1993 changes in the Warsaw population in the 34–64 age groups with respect to 10 year death rate compared to cardiological death rate have been observed. The 1984 population (1^{st} screening) Pol-MONICA Warsaw showed a higher death rate than those screened later.

2. The level of total cholesterol was not a significant 10 year predictor of cardiological death risk in the right bank population of Warsaw.

3. The SCORE algorithm differs from the estimated death risk of the Warsaw male population by some 7–15%. For women the degree of fit is better between 7–10%.

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Computer estimation of skeletal maturation on the basis of cervical vertebrae maturation

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Abstract. The article describes skeletal maturation applied in medicine to estimate biological development of a human being. The method, devised by Baccetti and co-workers (CVM method – Cervical Vertebral Maturation) to determine the moment of pubertal growth basing on a lateral cephalogram, was presented. On the basis of the existing method, a program which determines a CVM stage basing on characteristic points, was written. The list of the results repeatability in traditional assessment as well as with the use of the program is presented in the article.

Introduction

Skeletal maturation, similarly to e.g. the development of secondary sex features, teeth calcification and their eruption, is one of the means of evaluating biological development of a human being. Skeletal maturation is estimated on the basis of the presence of secondary ossification nuclei, changes in their shape and the range of joining diaphysis with its epiphysis. The moment epiphysis is joined to its diaphysis, its growth is completed. Skeletal maturation is not closely correlated to human chronological age. It can be noticed by observing a group of children at the age of e.g. 11, although they are in the same calendar age, their growth can be considerably different, some of them can have permanent dentition while other children can still have primary teeth. Some children in this group may be prior to maximum pubertal growth, others during it, and among some, the pace of growth can be declining. The moment of the beginning of maximum pubertal growth is very varied, it usually occurs between the age of 8 and 11 with girls, whereas with boys between the age of 10 and 14 [1].

Predicting the beginning and ending of maximum pubertal growth, which is correlated to intensive development of upper jaw and mandible [2], is indispensable to estimate proper time of orthodontic therapy and the choice of a treatment method [3].

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Methods

In medicine, two basic methods of evaluating skeletal age are applied:
- based on the analysis of hand and wrist radiographs
- based on the analysis of the change in the shape of cervical vertebrae

Analysis of hand and wrist radiographs

Hand and wrist consist of 30 bones, which composes about 10% of bones of the whole human skeleton. As a result, the advance in the development of hand bones constitutes a reflection of the development of the whole skeletal system.

Atlas method

The evaluation of the stage of skeletal development can be determined by comparing radiographs with atlas photos which display particular stages of wrist bones development. On the basis of similarity, the most similar atlas equivalent is chosen and skeletal age ascribed to the radiogram is read. Greulich and Pyle's atlas [4], which enables evaluating if a child development is delayed or accelerated with reference to their calendar age and sex, is the most frequently applied one. This method is mainly applied in pediatrics or sports medicine.

Skeletal age on the basis of hand bones according to Björk and Helm

On the basis of a series of hand radiographs of growing children, Björk and Helm described dependence of maturation of hand skeleton on the auxetic curve. Observing wrist radiographs, they distinguished bones, maturing of which informs a doctor about a place on auxetic curve where a child is [5–6]. In their estimation, they used evaluation of:
- an extent of joint of epiphysis and diaphysis of proximal phalanx of third finger (A)
- an extent of joint of middle phalanx and diaphysis of third finger (B)
- extents of joint of diaphysis and epiphysis of distal phalanx of third finger (C)
- ossification of ulnar sesamoid of the matacarpopahangelal joint of thumb (D)
- joint of epiphysis and diaphysis of radius (E)

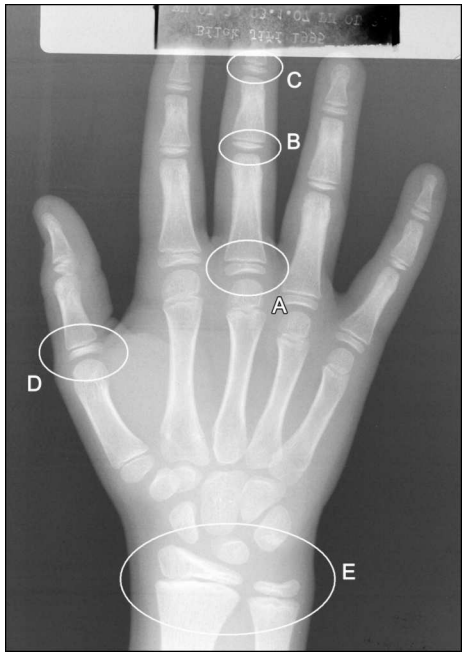

Fig. 1. Hand and wrist radiogram with selected points which undergo evaluation according to Björk and Helm

Analysis of change in the shape of cervical vertebrae CVM

Baccetti, Franchi and McNamara [7–8] have modified the method of evaluating skeletal age on the basis of a change in the shape of cervical vertebrae during growth. In this method (CVM), C2, C3, C4 vertebrae, which are visible on a lateral cephalogram taken as a rule in orthodontic diagnostics, are evaluated. Initial bottom border of all the vertebrae is flat. Gradually, starting from top to bottom, a concavity appears and simultaneously the shape of C3 and C4 vertebrae changes from a trapezium to a rectangle, a square, till a "standing" rectangle [Fig. 2].

Fig. 2. Scheme of a change in the shape of cervical vertebrae according Baccetti

Evaluating skeletal age on lateral cephalograms [Fig. 3] taken routinely before starting orthodontic treatment, it is not necessary to take any additional radiographs.

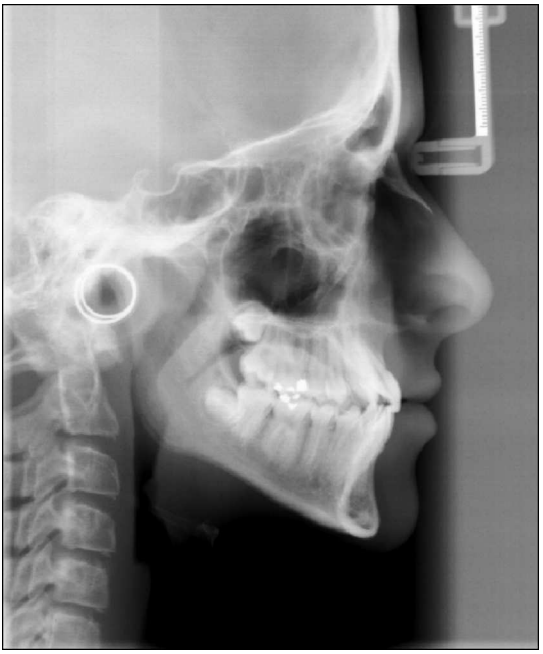

Fig. 3. Lateral cephalogram

In CVM method, 6 stages, from CS1 to CS6, are distinguished. According to Baccetti, maximum pubertal growth begins in CS3 stage, and finishes in CS4 stage.

Stage CS1

Lower border of all the cervical vertebrae is flat. The shape of C3 and C4 vertebrae is similar to a rectangular trapezium, there are minimum 2 or more years left to the beginning tp of maximum pubertal growth.

Stage CS2

A concavity appears on the lower border of C2 (over or equal to 0.8 mm), the lower border in C3 and C4 vertebrae is flat. The shape of C3 and C4 vertebrae is similar to a rectangular trapezium. There is about 1 year left to the beginning of maximum pubertal growth.

Stage CS3

The lower border of C3 vertebra becomes concave (the concavity on C2 is over or equal to 0.8 mm), the shape of C3 and C4 vertebrae stays without considerable changes. It is the beginning of maximum pubertal growth.

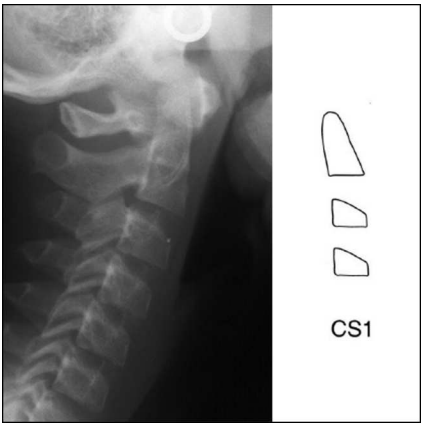

Fig. 4. Stage CS1

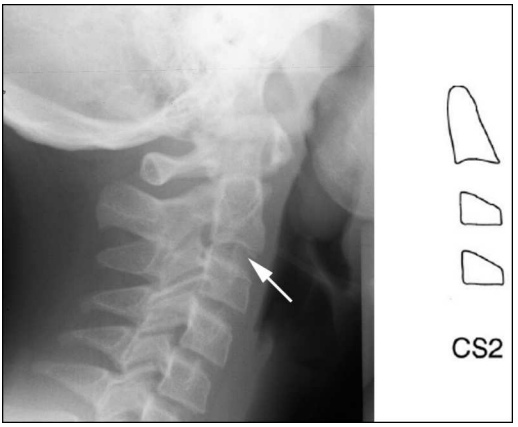

Fig. 5. Stage CS2

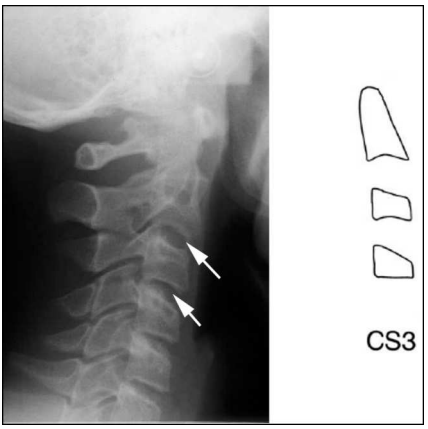

Fig. 06. Stage CS3

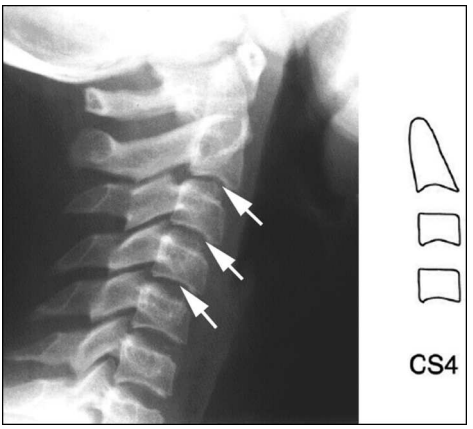

Fig. 07. Stage CS4

Stage CS4

All the vertebrae have a concavity on the lower border, the shapes of the vertebrae turn into a rectangle. It is the end of maximum pubertal growth.

Stage CS5

The concavity on the lower border and the shape of C3 and (or) C4 changes into a square. It has been about a year since maximum pubertal growth.

Stage CS6

There is a concavity on the lower borders and the proportion of the length of the borders of C3 or (and) C4 changes – the vertical borders

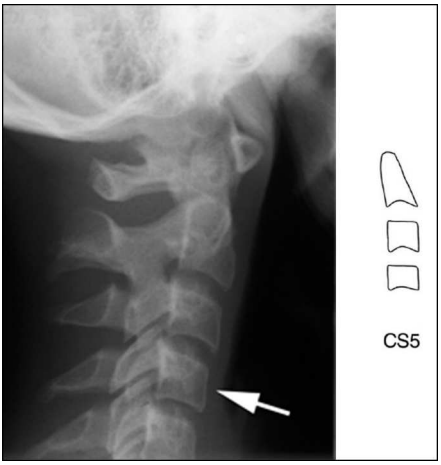

Fig. 8. Stage CS5

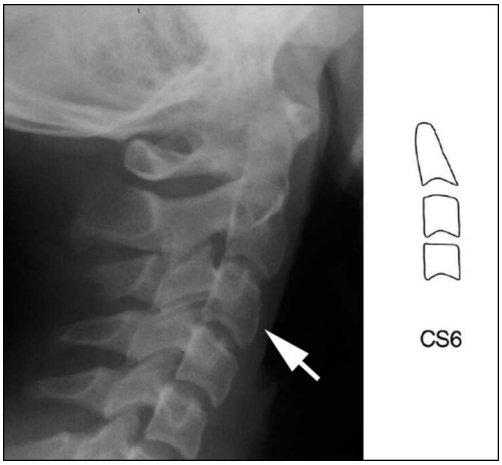

Fig. 9. Stage CS6

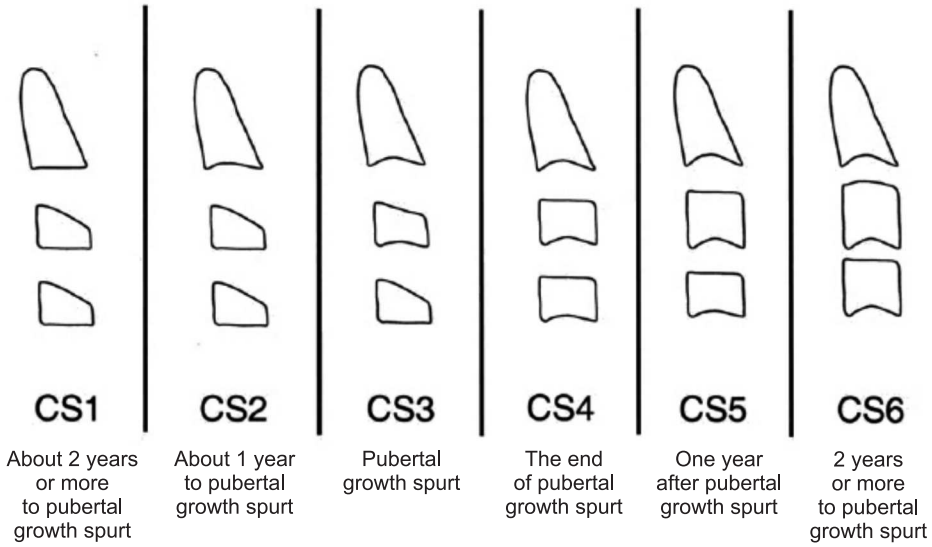

Fig. 10. CVM stages from CS1 to CS6

become longer than the horizontal ones. There have been 2 years or more since maximum pubertal growth.

Computer estimation of skeletal maturation basing on cervical vertebrae

On the basis of the Baccetti method, an algorithm to estimate skeletal maturation was devised. Its function is to determine a CVM stage basing on

the characteristic points indicated by a user. The algorithm is based on the assumptions formulated by Baccetti, i.e. skeletal maturity is estimated on the basis of calculated concavities on the lower border of diaphyses of cervical vertebrae and the lengths of the borders of cervical vertebrae diaphyses. Characteristic points are the utmost points of the vertebrae diaphyses as well as the points which define the largest depth of the concavity. Three points are marked on the second vertebra, on the third and fourth vertebra five points are marked in order given on [Fig. 11].

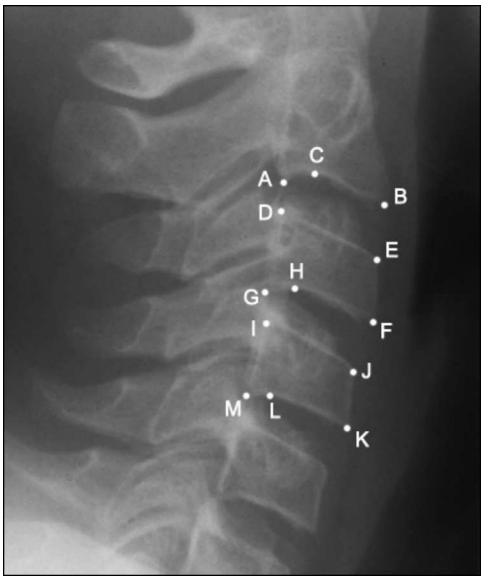

Fig. 11. The order of marking points

Points A, B, C are the characteristic points on the diaphysis of C2 vertebra – top left, bottom right and the point defining the largest concavity respectively.

Points D, E, F, G, H are the characteristic points on the diaphysis of C3 vertebra –top left, top right, bottom right, bottom left and the point defining the largest concavity respectively.

Points I, J, K, L, M are the characteristic points on the diaphysis of C4 vertebra – marked similarly to C3 vertebra.

After the points are marked, the depths on CS2, CS3, CS4 vertebrae are calculated. The depth of the concavity is determined as a distance of the point defined by a user as the deepest point from the straight line that emerged from the combination of two points on the bottom border of the diaphysis [Fig. 12].

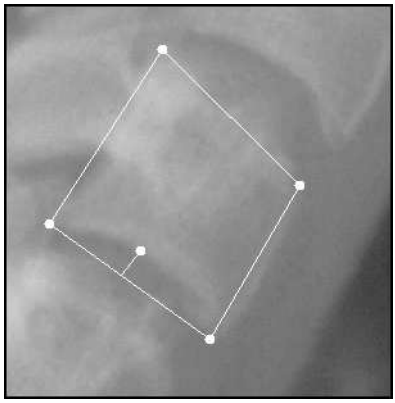

Fig. 12. The depth of the concavity on C3 vertebra

On the basis of obtained values, CVM stage is defined according to the method devised by Baccetti

- the concavity on C2 vertebra is below 0.8 mm – CS1 stage is ascribed to the examined photo
- the concavity on C2 is over or equal to 0.8 mm, and on the others it is below 0.8 mm – CS2 stage
- the concavities on C2 and 3 are over or equal to 0.8 mm and on CS4 below 0.8 mm – CS3 stage
- if all the concavities are over or equal to 0.8 mm, the relation of the sum of vertical borders to the horizontal ones on C3 and C4 vertebrae is examined.
  - if the obtained relation on any vertebra oscillates around value 1 (from 0.9 to 1.1), it is assumed that the shape of the vertebra is similar to a square thus the photo is classified as stage 5.
  - if on any vertebra the relation of the sum of vertical borders to the horizontal ones is over value 1.1, then stage 6 is assumed (the vertical borders are longer than the horizontal ones)
  - if the relation of the sum of vertical borders to the horizontal ones is below value 0.9 on both vertebrae, then the algorithm turns to stage 4.

Comparison of the obtained results

The method proposed by Baccetti and co-workers was tested from the point of view of repeatability of the results evaluating the same photos. For this purpose, cephalograms taken in Orthodontic Department of the

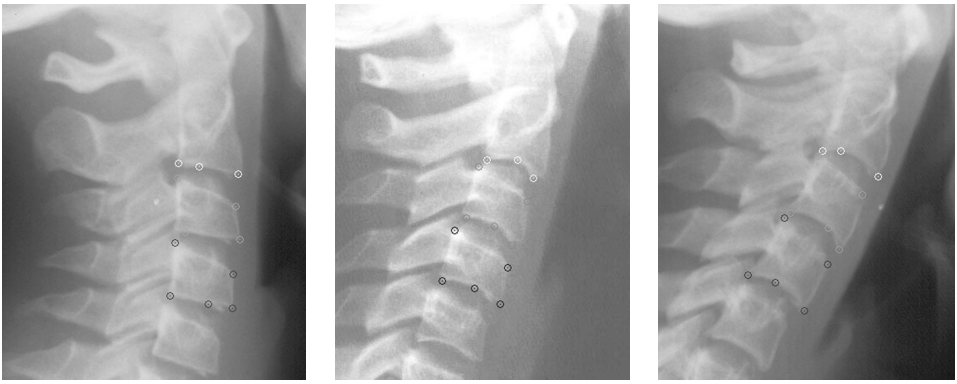

Fig. 13. Examples of algorithm application. A) CS1 Stage, B) CS4 Stage, C) CS5 Stage

Medical Faculty, Palacký University in Olomouc from the period of 1.07.2004 to 11.03.2008 were used. 43 X-ray pictures of good quality were chosen from 132 cephalograms of girls and boys. The examination was done by the second author at 2 month intervals.

The repeatability of the results in a traditional assessment was achieved with 74% of photos. Among 21% of other pictures the difference was at the level of one stage, the rest 4% of photos differed with more than one stage.

After that, the author examined 43 earlier discussed pictures with the use of the devised algorithm. All the pictures were scanned in 150 dpi resolution. Two evaluations of the stages according to CVM were accomplished at a week interval. The repeatability of the results at the level of 78% was achieved. A difference of one stage occurred in 16% of the cases, whereas the difference of more than one stage occurred in 7% of the cases.

The table below [Tab. 1] presents the list of the results obtained in a traditional assessment as well as with the use of the program.

Tab. 1. Comparison of the repeatability of the results

	Nr of picture	**Repeatable result**	**Difference of 1 stage**	**Difference > 1 stage**
Traditional	43	32	9	2
analysis	100%	74%	21%	5%
Analysis with the	43	33	7	3
use of the program	100%	77%	16%	7%

In the computer analysis, the biggest difference in the stages assigned to the same photo was of 2 stages, whereas in a traditional analysis the biggest difference was of 3 stages.

Tab. 2. Spread of the obtained results

	Difference of 1 stage	**Difference of 2 stages**	**Difference of 3 stages**
Traditional analysis	9	1	1
Analysis with the use of the program	7	3	0

Analyzing the obtained results, it is worth paying attention to the fact that in the assessment with the use of the computer algorithm the difference of the stages of 2 applies to the pictures which also in a traditional assessment were not evaluated at the level of the same stage (the difference was of 1).

Among 20 pictures, in the case of which the agreement of the results in a computer assessment was not achieved, 4 pictures were also assessed at the level of different stages in a traditional assessment.

The most frequently occurred differences in a traditional assessment of one picture concerned CS4 and CS5 stages. It can be assumed that the problem is in the assessment of the proportion of the sides, i.e. whether the diaphysis of cervical vertebrae is still similar to a rectangle, or whether its shape resembles a square yet. However, in the assessment with the use of the algorithm, a particularly dominating boundary of the stages, at the level of which the differences most frequently appeared, did not occur. The differences of the assessment spread proportionally to all the stages. Minimal differences in the arrangement of characteristic points, which cause the shift of the assessment from one stage to the other, are the reason for that.

Conclusions

The application of the computer assessment of CVM stages allows to achieve the repeatability of the results similar to the repeatability of the results obtained in a traditional assessment, however, it is worth paying attention to the fact that the program simplifies calculating the depth of the concavity and the proportion of the sides considerably. The assessment

made by a doctor happens not to be much accurate (whether the depth of the concavity achieved the value of 0.8mm or whether the shape of the diaphysis of cervical vertebrae is similar to a square or rectangle), therefore considerable differences in the assessment of one picture occur.

The difference in the CVM stage in a traditional assessment as well as with the use of the program concerned the same cephalograms to a high degree. Therefore, it is probable that the X–ray was taken at the turn of two CVM stages and it is impossible to interchangeably classify it to any of the stages. It is however significant clinical information to a practitioner, whereas one has to decide on one of the stages for the purpose of the statistics. Estimated information about an approximate beginning or ending of a pubertal growth is significant information which allows to take proper measures in treatment.

Applying the algorithm has also some disadvantages: the algorithm is very sensitive to minimal shifts of characteristic points since it makes calculations very accurately. A little shift can cause relocation of an assessment from one stage to the other. However, as it was mentioned earlier, such a difference is of not a significant importance in the process of orthodontic diagnosis.

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Active methods of risk management, systems diagnostics and determinants of the Polish health care system

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Abstract. The article has formulated the concept of a health care system (HCS) with its components, structure, goals, functions and tasks. It also relates to a construction of mission and "good practice" in health care. Then it shows that the notion of evidence based medicine is for axiological reasons significantly opposed to a construction which uses the assumption of "good practice". When constructing theoretical bases and appropriate modelling techniquest widely interpreted logistics may prove useful, e.g. enabling the increase in the number of transplants performed in Poland. The following task was formulated: to lay out, where possible, a direction which rationalises evidence based health care without the need for resolution of moral dilemmas, concerning e.g.: queues, transplants, refusal of services. This can be realised through the use of system diagnostics along with health measurement. The implementation of risk management methods in HCS should also form an important complement to this direction. Active methods of risk management in health care were presented, such as: modification of VaR which enables the assessment of medical, economical and logical effectiveness (MEL effectiveness) and leads to rationalisation of choices on limiting the availability of medical services, a model of modification of risk factors which enables the creation of a post-operative care system on general surgery wards, a method of black spots in hospital care, ETA and FTA methods. The practice of using system diagnostics and health measurement on the basis of ICF platform was then referred to. It was stated, that without axiologically appropriate assessment technologies which are MEL effective may not be selected and as a result a credible basic health benefits basket, nor additional baskets may not be created. At the end the conditions and practice of HCS in Poland were referred to, showing the existing, uncontrollable conflicts. It was established that to conduct rational health care policy and effective MEL risk management in health care the following are necessary: a holistic approach, and e.g. basis of utilitarianism as a theoretical foundation, creation of system assessment tools – aggregates, scales, multidimensional qualitative and quantitative models, data analysis methods (cluster analysis, clustering, data analysis methods).

Introduction

In this paper, a health care system (HCS) will be understood to comprise:

– its components, that is: the set of all service recipients and service providers, "third party" institution – the payer, infrastructure, that is buildings, means of transport, equipment, hardware and existing technologies, knowledge;

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– its structure, that is all relations, whether codified or not: organisational, logistical, social, legal, ethical;

Internal and cooperating institutions and various sub-systems (financial, management, scientific research, education, out-patient and in-patient health care, long term and palliative care and others) are operating around and within the framework of HCS. Also various functions and tasks are being realised, and some of the goals of the system are postulated.

Despite of this complexity one might say, that "every health care system assumes a certain structure and hierarchy of moral values" [1]. This statement may be modified into a following formula: on every stage of development we are able to recognize the basic foundations of relations which constitute relations which prioritise moral values in an existing health care system. That is, we can distnguish one of the elements of a series of models necessary to understand the principles and to provide rational management of health care, or to implement health policy (informational, educational). Such fundamental assumptions which form the basis of the model are not formulated by reform theorists or by politicians and decision-makers, because they only touch the surface of the issue – the real system is in a larger part overly inert and conservative (human factor), and in another part is very dynamic (technology, legislation, economics, antagonistic relations). HCS was not created according to a previously planned and meticulously created design. It is a complex anthropo- and partially socio-technical system, with layers of IT, economical, control and other systems which are not always clearly distinguished. Even if in some reform attempts the system "was designed" from the beginning, its implementation and the action of "human factor" have introduced unforeseen changes. New qualities, functions, goals, technologies and culture of the system have arise, and they are still changing dynamically. HCS has developed in an unstructured manner along with the history of humankind (civilisation, culture, philosophy and scientific and technical progress). Examination of this system for the purposes of management allows constant discovery of its (immanent) laws, goals, functions and tasks. One can also recognize the functioning of antagonistic subsystems or competitive relations, conflicts, and crises – which are certainly not oriented on joint achievement of planned goals of the system.

The notion of the mission of the organisation (system) should determine the basic direction of modelling, imposing a certain ordering hierarchy of compatibility of goals, functions and tasks with the given mission. However, in the real, very complex HCS the mission is not always clear, consciously aware, agreed-upon and unequivocal for persons which are functioning with-

in the system, even to the ones who manage it and carry out the most professional tasks.

In order to differentiate the states of very large organisations and socio-technical systems the notion of "good practice" [2] was created. This is a valuation notion which applies to the category of functional model, and not the structural system. However, it has the values of universal intelligibility and adaptation to the conditions and passage of time. It is also essential that the risk which characterises the state of the system is connected and perceived on all analysed levels, that is, on the level of goals, mission and "good practice" [3]. This applies especially to medicine based on the idea of "good practice". The availability of services related to this idea takes into account a given society with: its culture, its service providers and service recipients, supply and demand, awareness and knowledge and acceptance of risk.

Just as we cannot know profoundly and conclusively the notion of truth nor the notion of justice, we also cannot create a closed model of a health care system which is sufficiently generalised for the requirements of management.

The notion of evidence based medicine [4], which is especially important to this symposium, is for axiological reasons significantly opposed to a construction which uses the assumption of "good practice" in the category of functional description.

A following example is provided for consideration: a touring bus accident has occurred, there are dozens of injured, including children and women. Victims are presenting haemorrhages and cardiac arrests. Aid is provided by one life-saver (a doctor), with a dilemma to whom and in what order help should be given, since without treatment some of the victims will die and some will be permanently impaired. Life-savers are trained in establishing the order in which aid is provided. Let's imagine, that three persons, who might have lived have died. This was due to erroneous decisions, and an ethical dilemma remains – effective medical help was not given to persons in need. This opens the issue of moral and legal responsibility. There is also the issue of selecting an ethical theory, on the basis of which one might relate to the identified dilemma. Assuming an emotivist perspective and, e.g., a biomedical model of health (loss of health) may be supported by the QALY technique and assumed level of "good practice", however this does not ensure the credibility of medicine and individual service provider. There was no holistic approach in the construction of the model. A description could be also implemented wholly on the basis of utilitarianism.

When looking for theoretical bases and appropriate modelling techniques, while assuming remaining on the grounds of evidence based medicine, widely interpreted logistics may prove useful. In this specific case providing as rapid as possible medical support from other life-savers (including personnel present at the place of the crash) and organisation of a system which would enable this. For rare catastrophic events it is easier, but in many other categories of HCS operation the scale of potential costs and organisational involvement is much larger. This applies especially to the issue of rationing of expensive and rare medical services [5]. In the Republic of Poland the issue of queues for the services in question is especially significant when compared to the rest of the EU, and is becoming socially noticeable. However, also here there are partial solutions which might reduce its scope. The increase in the quality of logistic management should significantly increase the number of transplants performed in Poland[1].

The following task will be formulated: to lay out, where possible, a direction which rationalises evidence based health care without the need for individual and constant resolution of dramatic moral dilemmas, concerning e.g.: queues, transplants, refusal of services. This can be realised in particular through the use of system diagnostics along with health measurement. This type of diagnostics enables, among other things, better selection of patients for drug programmes. In case of rheumatoid arthritis one in four patients may be qualified (is susceptible) for the programme of treatment with the most expensive biological drugs[2]; pharmaceutical companies have lobbied for the treatment of all patients, and have even tried to influence the selection of persons deciding on the programme.

The implementation of risk management methods in HCS should also form an important complement to this direction. This applies especially to active methods which are lacking, although there is also a lot to do in the domain of passive methods, such as insurance. This is shown by the subject matter of the symposium. Limited knowledge about the HCS, diffusion of the notion of the mission of the system and different understanding of the part of the ethics in medicine cause the ethical dilemmas to remain. However, they should be better understood and more helpful in management, including risk management in health care.

[1] Wojciech Rowiński – press release.

[2] Witold Tłustochowicz – press release and individual communication.

Active methods of risk management in HCS

Sample methods of active risk management in health care will be presented.

Example 1. VaR method [6]

The use of an equivalent of the VaR method, which is acceptable on the level of community (in axio-medical quantification) even though not necessarily for individuals and pharmaceutical companies, with the use of matrix of transitions between therapies, that is methods that eliminate treatments that are too rare and at the same time too expensive on the level of selected quantile, may lead to a better selected preselection of patients for a drug programme. The VaR method enables the testing of medical, economical and logistical effectiveness (MEL effectiveness), and also taking into account the "human factor", when the MEL effectiveness is treated widely enough, eg. taking into account the measurement of health level on the base of ICF.

0.099	0.044	0	0.033	0	0.011	0	0
0.44	0.264	0.033	0.011	0.011	0.055	0.055	0
0	0	0.022	0.022	0	0	0.011	0
0.033	0.011	0.011	0.011	0	0.011	0.011	0
0	0.011	0	0	0	0	0	0
0.011	0.011	0	0	0	0.066	0.011	0
0	0	0	0.011	0	0.011	0.044	0.011
0	0	0	0	0	0	0	0

Fig. 1. Matrix of transitions between therapies in RA (turning points): $P = \lfloor p_{ij} \rfloor_{i,j \in \overline{1,n}}$

Rows and columns show the classification of the following kinds of therapy:

1 – MTX, MTX +Cyclosporine, MTX + SSA + Arechin
2 – as above + steroids (Encorton, Metypred, Solumedrol, Diprophos)
3 – Arava, Arava + MTX + steroids
4 – Arava, Arava + MTX
5 – Endoxan
6 – Remicade
7 – Enbrel, Humira
8 – Rituximab

Differences in the monthly costs of given therapies are significant, the amounts vary from approx. 30–40 zlotys in case of therapies 1 and 2, and in case of therapy 3 amount to 500–510 zlotys, up to 3000 zlotys in therapy 5 and 5000 zlotys in therapy 7. The matrix of individual costs of therapy may be written down as:

$$C = [c_i]_{i \in \overline{1,n}}$$

And the sum of costs of all therapies in the considered unit will be expressed by the following formula:

$$\sum_{j \in \overline{1,n}} k_j = \sum_{j \in \overline{1,n}} \sum_{i \in \overline{1,n}} p_{ij} c_i$$

The assessment of medical and logistical effectiveness is modelled analogously, although not always on the quantitative level.

A drug programme X in case of RA may be used as an example, when some of the patients are not susceptible to a very expensive and long-lasting therapy, although they have high hopes related to it. *Deciding whether to restrict access to the programme individually* (which is very corruption-generating) or systematically is unethical (one human life, million, or the rest of humanity – Peter Singer [5]). However, the choices may be rationalised on the basis of utilitarianism. The idea is to point out a direction of actions, pursuing to create therapies, medical technologies and diagnostic and therapeutic procedures which are best adapted to the needs of service recipients, in order to achieve a higher MEL effectiveness. And in border case it should avoid rationing of rare goods by their well chosen addressing and allocation.

Example 2. A model of modification of risk factors [7] which leads to the distinguishing of risk groups and creation of a post-operative care system on general surgery wards.

ROC modelling was used (receiver operating characteristic curve in the system of coordinates: sensitivity, specificity) for selected death risk factors and mode of accepting a patient to a general surgery ward. The examined population consisted of 32231 patients enrolled in general surgery wards in 3 clinical hospitals. In the analysed period of 2003–2007 788 persons have died. Control group was formed by patients with other diagnoses.

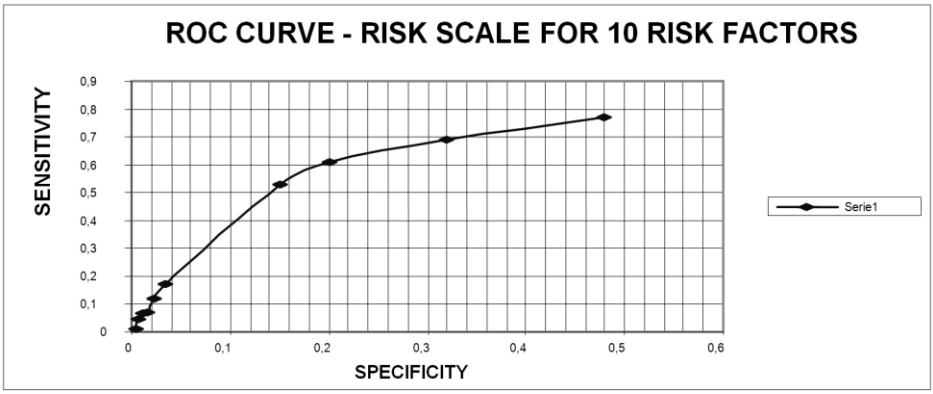

Fig. 2. Risk assessment on the basis of ROC model

Registry of death risk factors contains:

- Malignant tumour
- Non-malignant tumour, or one with an unknown or uncertain character
- Acute peritonitis
- Paralytic ileus
- Acute pancreatitis
- Other inflammatory conditions (eg. abscess, erythema, phlegmon, gangrene), burns and infections
- Gastrointestinal bleeding
- Acute bowel ischemias
- States with obstruction of perforation (puncturing, fistula) of an organ (gastrointestinal tract) or peritonitis
- States with liver failure or its cirrhosis

Also, the mode of accepting the patient to the general surgery ward was accepted as a risk factor.

Taking into account the medical and economical effectiveness there were 5897 patients in a risk group generated using one of the methods (three scales for various models of cutting off the optimum level), out of which 512 persons were rescued. Additional analysis applied to 111 basic diagnoses. On this basis a post-operative care system was created, which takes into account an early identification by an anaesthesiology doctor of sick people with an increased risk of death and post-operative complications.

Mortality on the general surgery ward in a hospital where this model is functioning is approximately three times lower in comparison to studied similar clinical hospitals, characterised by a similar structure of procedures, equipment and medical personnel employment (including professors), operating in the same area.

Example 3. "Black spots" method [8]

A "Black spot" in a health care institution is:
- especially dangerous place, which corresponds to a point event (ward, operational unit, central sterilisation point of the hospital, pharmacy etc.);
- specific medical procedure, during which a large amount of complications was noted;
- a place of significant concentration of adverse events, in which their number is much higher then the average.

The "black spots" method is a set of various methods (including analysis of event trees, fault trees) and partial analyses (expert analyses, epidemiological monitoring etc.). This includes risk identification, ordering of

Tab. 1. Number, types and causes of complications which occur during selected hospitalisations

Type of complication event	Number of complications	Eventual cause of event
repeated hospitalisations in order to correct previous surgeries, that is removing of nose bridge hump, straightening of the nasal septum	8	improper setting of nasal septum, improperly chiseled nose bridge hump, nose shortening required
infection, increase of temperature to 39 degrees, common cold	2	improper conditions on the ward (draughts, low temperature), lowered resistance of the patient or improper behaviour on part of the patient
ungluing of the plaster dressing	1	improper or overly loose dressing, lack of care on the part of the patient
localised changes near the intravenous line	1	improperly placed IV line, insufficient hygiene of the IV line area (disinfection)
bloody vomiting after the procedure	3	reaction of the organism to anesthesia

Ward: Plastic surgery
Number of tested patients: 80
Number of hospitalisations with complications: 14
Average time of stay without complications (days): 5.0
Average time of stay with complications (days): 6.3

Tab. 2. Risk assessment for adverse events during the plastic surgery of nose

Complications	**Risk for the patient during the plastic surgery of nose (on a scale of 1 to 5)**
	Average from three expert opinions
Repair/repeated hospitalisation	3.33
Infection and common cold	1.66
Lesions in the IV line insertion	1
Ungluing of the plaster dressing	1.33
Vomiting	2

Tab. 3. Data for the plastic surgery ward – for the plastic surgery of nose

Complications	**Event frequency (%)**	**Time with complications (days)**	**Approx. extra-ordinary cost (of prolonged stay) (zł) per person-days**
Repeated surgery/ repeated hospitalisation	10.00	7.65	849.51
Infection and common cold	2.50	5	0
Lesions in the IV line insertion	1.25	7	641.14
Ungluing of the plaster dressing	1.25	7	641.14
Vomiting	3.75	5	0

Approx. average cost of person-day: 320.57
Approx. normal cost (zł) (without complications): 1602.9
Approx. average extraordinary cost of complications: 538.56

threats and proposals of remedial actions, such as eg. monitoring or sealing up of procedures. It is cyclical and has a block algorithm structure, that is after removing the most dangerous "black spots" that are removable in another iteration on the subsequent level of hierarchy the risk analysis, selection of "black spots" etc. are performed again. The study was based on 430 disease histories with full medical documentation of patients treated in the hospital 2006–2007. Patients from dialysis stations, ophtalmology, neurosurgery and plastic surgery wards were hospitalised. The study was limited to the following surgical procedures: removal of cataract and glaucoma, removal of brain tumours, plastic correction of nose, and hemodialysis procedure.

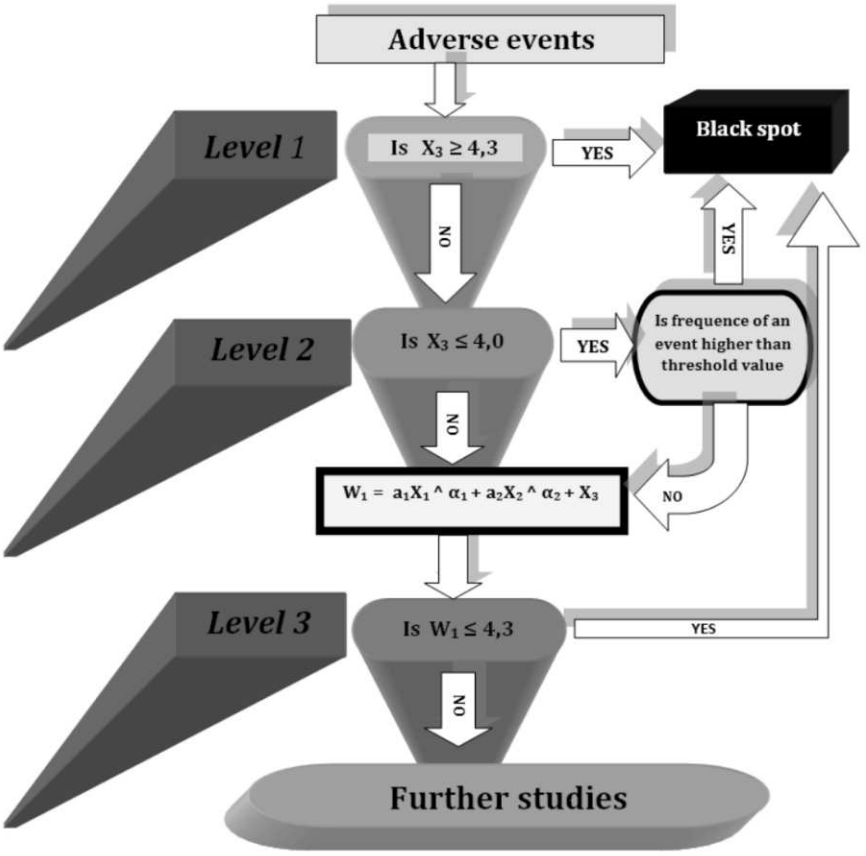

Fig. 3. Model of proceeding when determining black spots

As a result of minimising of the loss function the following values of the parameters of the model which describes the function of risk were obtained:

Tab. 4. Identified values of the parameters of the model

	for all surgeries (with the exception of hemodialysis procedure)	for the hemodialysis procedure
a_1	0.011	0.009
a_2	0.0004	0.0006
α_1	0.50675	0.42675
α_2	1.3155	1.4423

This enabled the creation of a hierarchy of "black spots", taking into account three levels of classification and the ranking of adverse events, in which risk is higher when the rank number decreases.

Tab. 5. Comparison of "black spots" on various levels of hierarchy

Type of procedure/ surgery	Adverse event/complication	Black spot		
		Level I	Level II	Level III (W1)
Plastic surgery of nose	repeated surgery / repeated hospitalisation	NO	YES	YES 5.04
	infection and common cold	NO	NO	2.12
	lesions in the IV line insertion	NO	NO	1.52
	ungluing of the plaster dressing	NO	NO	1.85
	vomiting	NO	NO	2.46

Tab. 6. Ranking of adverse events

Adverse event	Rank	Adverse event	Rank
repeated surgery / repeated hospitalisation	1	haemorrhage to front chamber or vitreous body	1
vomiting	2	inflammation in the front chamber	2
infection and common cold	3	corneal oedema	3
lesions in the IV line insertion	4	flattening of the front chamber	4
ungluing of the plaster dressing	5	Folding of the Descemet's membrane	5
dispersed blood in the vitreous body chamber	1	detachment of the choroid	6
inability to lower the intraocular pressure due to cells blocking the outflow of aqueous humour	2	epithelial oedema	7
tearing of iris adhesion – removal of exuding membrane	3	separation of suture of the basis of the conjunctival flap	8
detachment of lenticular capsule	4	post-operative hypotonia	9
wound leakage	5	death (as a result of ischemic stroke and pulmonary artery embolism, repeated surgery after bleeding into post-operative site, or unrelated to the procedure)	1
corneal oedema	6	epidural haematoma	2
Folding of the Descemet's membrane	7	air near the surgery site and in the chamber system	3

Tab. 7. Ranking of adverse events, contd.

Adverse event	Rank	Adverse event	Rank
post-surgery period complicated by intensification of left-sided hemianopsia	4	reddening in the buttock fissure or of the buttock	14
paraplegia of upper or lower limb	5	significant reduction in RR	1
hospital infections (eg. cerebro-spinal meningitis)	6	chest pain	2
localised changes near the intravenous line	7	vascular rupture during HD	2
vomiting	8	suction from the C1 artery during HD	3
partial damage to the right nerve III	9	clot during HD	4
hydrocephalus – patient required a ventricular-peritoneal valve	10	spine pain during HD	5
postsurgery period complicated by the paralysis of the left oculomotor nerve	11	seeping from the IV insertion	5
hypokaliaemia	12	muscle spasms	5
trauma, eg. sliding from the bed, fall	13	skin itch	6

The study was extended by an analysis of hospital infections for all the hospital wards in the years 2004–2007. 384 cases of infection were identified. It is worth mentioning that a spectrum of techniques were used, not only the analysis of medical documentation (patient medical histories), but also expert interviews and data on the antibiotic therapies from the hospital pharmacy. Detailed techniques for the suppression of "black spots" were recommended, including those connected with the hospital infections.[3]

Example 4. ETA event trees and FTA fault trees

An example of the tree analysis technique in the risk assessment is provided. Frequently both methods (ETA and FTA) are used at the same time during project risk analysis.

[3] Implementation of the black spots method is implemented in the "Latawiec" hospital in Świdnica, see: Topografia czarnych punktów szpitalnictwa, Natalia Adamska-Golińska, Menedżer Zdrowia, March 2011.

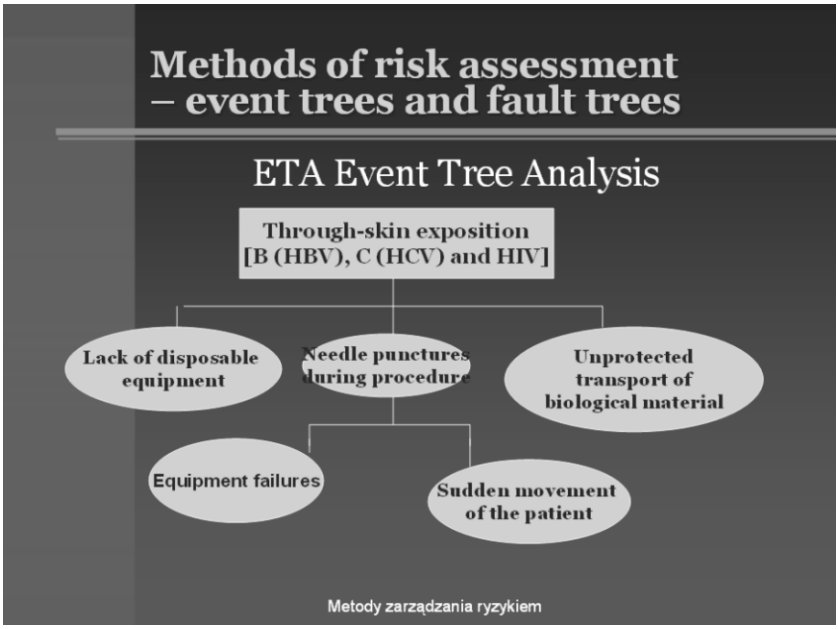

Fig. 4. Modelling of ETA and FTA trees in risk analysis

Example 5. Other risk management techniques, for example the risk drivers method [10] were not yet sufficiently well adapted to the needs of HCS in Poland.

Systems diagnostics

Holistic approach to the HCS modelling, realised on the basis of evidence based medicine, is closely connected with the use of systems diagnostics [11].

Systems diagnostics is a key process, which serves: distinctness, certainty of method, trust, obligation and uniqueness. It enables cooperative action and achieving in quality the optimum results in a diagnostics and therapeutic process. Clinical thinking (or holistic-type approach) covers not only mutual connection of systemic phenomena, but also their influence on the structure as a whole, regardless of [12]:

- *minuteness of detail of the character of studied phenomenon or modifying influence*,
- *organisational level*,
- *connection with the somatic, psychic, social or environmental sphere.*

System diagnostics in collective and cooperative formulation, adapted to the requirements of an IT system in health care and to updated classifications (including the ICF platform) result in:

- unification and objectivisation of diagnostics, certification and decision-making for turning points in the selection of medical procedures and therapies, including: diagnostic, nursing, rehabilitation, care (assessment aggregates, multi-criteria assessments, typological assignment to selected concentrations),
- quality change in the HCS culture, including the customer service formula in this system (therapeutic units, customer relations and internal relations of the system, providing information),
- new techniques for the measurement and assessment of the state of the system and realisation of its goals.

System diagnostics also requires the use of special measurement and information gathering techniques for various description levels [11], which is illustrated by the diagram below.

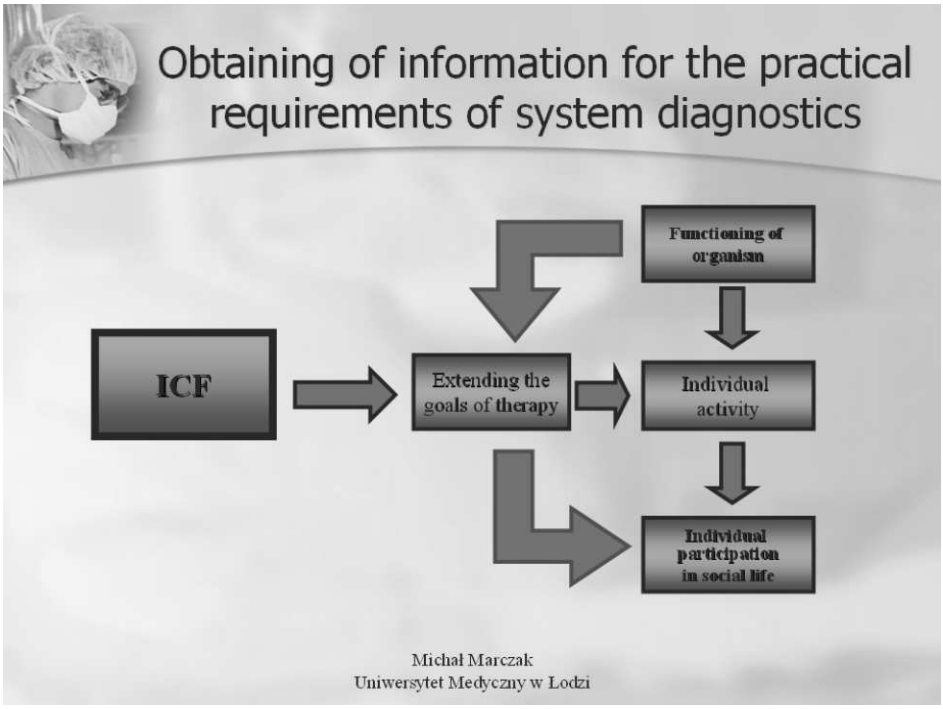

Fig. 5. Gathering information for the purpose of diagnostics of the system and its environment

Measurement of functioning, disability and health (ICF)

Risk management in HCS should be accompanied by appropriate methodology of health measurement (or, more general: of functioning, disability and health, eg. on the basis of the ICF platform). Without assessments that are axiologically appropriate, more effective MEL of medical technologies may not be selected and more *a posteriori* rational decisions may not be reached. As a consequence, it is not possible to create a credible basic health benefit basket, nor additional baskets, nor negative or derivative baskets!

The following ICF characteristic should be emphasized [13]:

- *it describes all aspects of human condition related to health and health-related fields*,
- *is intended for all people, not only for persons with disabilities*,
- *this classification may be used to describe health and health care with all conditions concerning health.*

Below an example realisation of ICF based measurement of functioning and health is presented [14]:

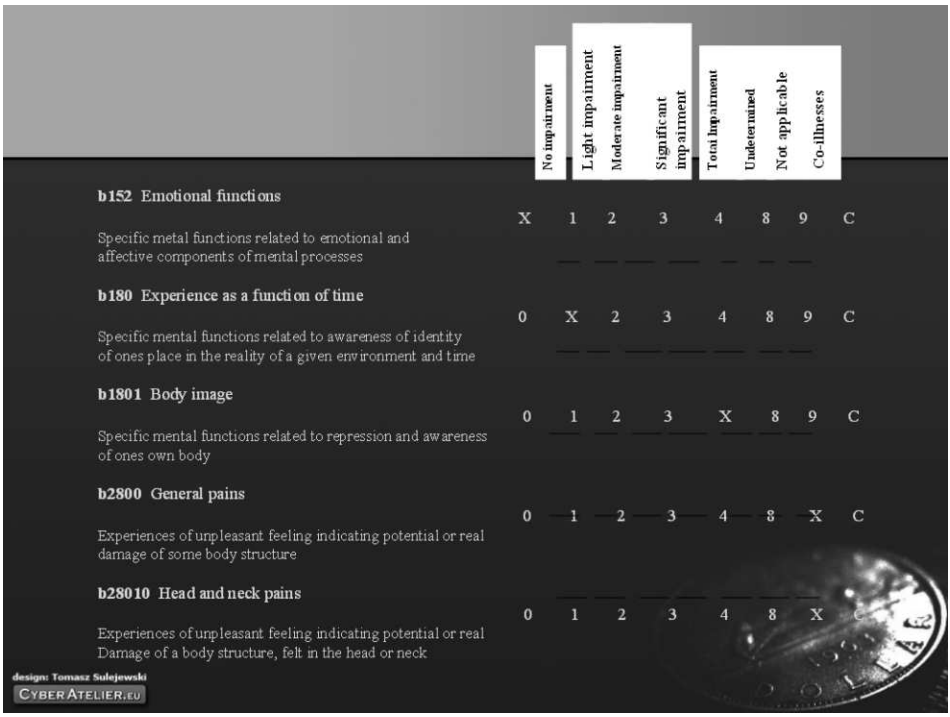

Fig. 6. Assessment of emotional functions, multi-dimensional body image and pain on the basis of selected ICF projection

Diagnostic studies and implementation works from the scope of ICF are performed by CSIOZ under the patronage of WHO. However, after five years, despite some interesting results they seemingly institutionally have returned to the point of origin, that is to education of the initial Polish personnel.

Additional insurance

Free market principles in health protection – well operating in an affluent civil society can not be directly transferred to a poor and less developed society [4]. This also applies considerably to other types of health insurance then obligatory, since it may show the deep social divide and violate the principle of egalitarianism. *The market for private insurance fosters egoistic and demanding attitudes, thus reinforcing negative characteristics related to medicine as an ethical enterprise* [15]. More so that in *Poland there is a constant domination of pensioner and retired households over other socioeconomic groups when comparing the level of household expenses for the purchase of medical services and goods* [16]. System assessment shows that passive methods of risk management, such as insurance, increase the general costs of health care more when medical technologies and services of highly specialised personnel are introduced rapidly. The results of polling of the Polish societal preferences do not show economically significant interest in additional health insurance. This tendency could change, if:

- the society would become more affluent and the socioeconomic consequences of a crisis were minimised;
- a system of obligatory insurance would allow for partial write-offs of insurance for additional services
- a natural change of the social culture in the direction of the development of civic society, an evolution of awareness, change in the level of acceptance of risk would occur; an effective information politics by the Ministry of Health would appear, and the methods of communication by the ministry with the society would change along with appropriate technologies.

Among all the questions and moral decisions [4] concerning additional insurance, especially the following remain topical:

- *What is more important – individual freedom of choice of medical treatments, or solidarity with those, who were harmed by fate?*
- *By whom and how are the rules of justice determined?*

Determinants and management of the HCS in Poland

In order to achieve contrast let's bring an example of sinking of the Lancastria lying off in the Quiberon bay – *when hearing the cry "space for a child" soldiers drew aside, standing with their backs to corridor walls, and they have acted thus every time they saw a women and child, thus they lost precious seconds, which made the difference between life and death*, most of them have died (over 2800 people have died in total). From the point of view of the amount of rescued human lives (half) or even the total amount of their future lives this was an irrational behaviour, soldiers were moving faster and more efficiently than women with children. Also from the point of view of future defence potential of the country. However, the culture of solidarity prevailed, deeply ingrained and state-building need to help the weaker ones.

Moving to another time and another country in Europe: drivers passing near Nowe Miasto next to a site of a bus crash have not stopped, and when asked for help they drove away (all of them). Emergency services were called only by the injured driver of the second vehicle. 18 victims, all together in a very small place required quick extraction and at least an attempt to treat airway obstructions or to reanimate. All have died. Both selected examples are extreme, however they may not be constructed to be a standard and anti-standard.

Polish society is currently characterised by a high level of risk acceptance in health care, and also a low level of activity in voluntary service (social aid, nursing services, counteracting exclusion).

Specifics of HCS in Poland are characterised by conflicts and functioning of antagonistic subsystems with the participation of various professional groups. Tendencies in changes in the structure of employment and scope of realised services in medical professions (education, but also remuneration) is not only not compatible, but frequently opposed to the ones currently observed in more affluent EU countries or in the US[4]. In particular, over 70% of hospital directors do not have education in management. This is a process which results from the conservatism of the medical profession.

The Ministry of Health, in order to meet the needs of CSIOZ based management plans to work out the Information System by summing data achieved for individual patients. However, information on demand for health

[4] Examples here may be: staffing of management positions in hospitals, taking over of providing of some procedures by other medical professions than doctors, that is nurses, EMTs, assistants.

services in a socio-demographic context can not be obtained based on data prepared for an individual patient (history of illness, services, referrals, procedures, prescribed drugs). It is also impossible to conduct rational health care policy and effective MEL risk management in health care. What is needed for such actions is a holistic approach, and eg. basis of utilitarianism as a theoretical foundation, creation of system assessment tools – aggregates, scales, multidimensional qualitative and quantitative models, data analysis methods (cluster analysis, clustering, data analysis methods).

An example of creation of system tools is the construction presented below, modelling the ICF "projection" for the needs of rheumatology.

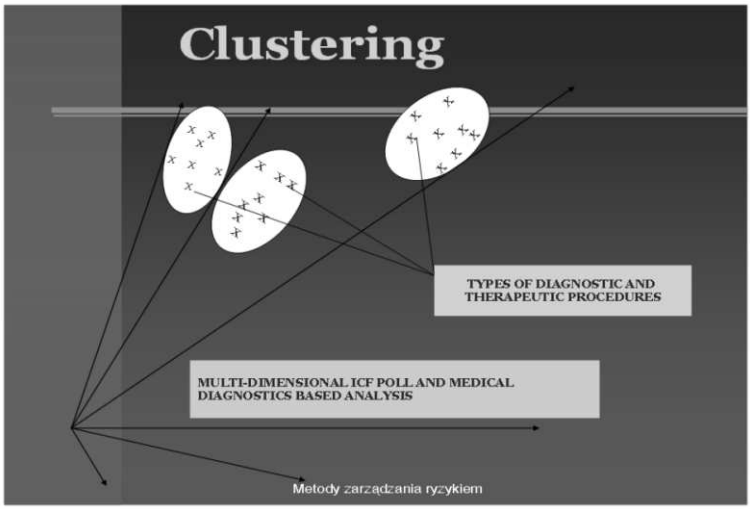

Fig. 7. Cluster modelling when using ICF in rheumatology

The counterexamples attached further illustrate the problems with simple addition or averaging as the basis of methods of data acquisition for the requirements of HCS management.

1. The model of appearance of a Czech soldier (by Franz Joseph I of Austria) can be transferred to a model of health of a Czech soldier,
2. Diversity of therapy for the same disease classification requires the systemic analysis of: reasons for the diversity, dynamics, dependence on socio-demographic qualities. What is needed is a reliable analysis of heterogeneity and assessment of the level of uncertainty of the results,
3. The sum of optimum activities for individuals, eg. the corruption of medical professionals [4] does not have to correspond to the best solutions for the community (health safety),

4. The selection of the most effective drug on the basis of two sample populations[5]; both for women and men the drug A is better, but it is *generally worse* than the drug!

	DRUG A			DRUG B		
	Treated	Improved	Effectiveness	Treated	Improved	Effectiveness
Men	210	50	23.81%	100	20	20.00%
Women	20	15	75.00%	60	40	66.67%
Total	230	65	28.26%	160	60	37.50%

Fig. 8. The influence of population heterogeneity leading to erroneous inference

Epidemiological indicators: expected longevity, newborn mortality, infant mortality, incidence etc. due to their static nature may not be used as a basis for risk management in health care. However, with the information on the value of health insurance premiums and the amount of budget they practically form the basic platform for the communication of Ministry of Health with the society. Other information important for the aware civic society are limited, and thus probably are not politically correct.

The health resort is well oriented in the amount and level of services which it can offer depending on the amount of insurance premiums as a part of the NFZ and health care budget. However, the health care decision makers for many years do not have an information policy[6] and do not maintain a dialogue with the society. They are intuitively, or on the basis of a convictions of the medical profession, strengthened in the opinion that:

– informing the society on the potential of health care services in Poland (a few hundred percent deficit in global perspective, low average quality, high risk level) carries the threat of loss of confidence in the medical profession and further social and political consequences. Usual transfer of responsibility to the historical conditions in the form of low earnings of the doctors became obsolete in the last years;

[5] Created on the basis of: Michał Szurek, Opowieści matematyczne, Warszawa 1987.

[6] With the exception of a test attempted by prof. Zbigniew Religa.

- the political and economical effectiveness of the medical and pharmaceutical companies lobbying is know and tested. The consequence is a small effectiveness of system reforms in the period of last dozen or so years;
- adverse events in health care, medical errors or hospital infections are practically not recorded in Poland. The databases which exist in accordance with the requirements of the law or certifications systems are rudimentary or unreliable. The Agency for Assessment of Medical Technologies nor the Quality Monitoring Centre have any influence on this;
- we are awaiting a necessary and very hard to accept by the society permanent increase of the NFZ insurance premiums and health care budget. Especially that in the changing demographical situation the introduction of a nursing insurance system cannot be put away much longer.

The decision makers do not have specific data, but they accept this state of affairs. Changes related with the increase of the awareness of citizens, and as a consequence the evolution of civic society could force difficult and costly reforms, it might also cause the reconstruction of the political arena and the forms of communication between HCS decision-makers, service providers, insurers and service recipients.

For holistic HCS risk analysis, risk treated as a condition of system, comprehensive measurements and assessments of: quality and costs of services, availability (type of rationing, waiting time), occurrence of adverse events are important. In practice most of these analyses are not conducted in Poland.

"Health care units" limit themselves, with the Ministry of Health remaining passive, to reporting on the level of accounting, and possibly to external customer satisfaction polls. The results of these last analyses are "surprisingly" good, which contrasts with the assessment obtained from indirect studies, that the Polish society accepts almost four times higher level of risk in health care then more affluent societies of countries which are members of the EU longer [3]. This shows the level of awareness of service recipients, their knowledge on: HCS and their rights, medical technologies, epidemiological threats, and on the inability to compare risks between individual health care units.

Against this background the initiative to create a system and database organised by the WHC foundation – CEESTAHC stands out.

In the category which decides on the limiting of availability, that is: *disproportion between the contents of benefits basket and the amount of financial resources from the basic insurance premium which is allocated to health care in Poland*, it is worth emphasizing that ensuring on a minimum,

rational level which does not significantly limit the numbers of population of patients the financing of treatment programmes for only two selected frequent illnesses (RA and MS) would require additional financing on a level of approx 7–10 billion zlotys per year. Significant losses in the level of health and functioning of patients are occurring (exclusion), whereas the efficiency of treatment is rather high and *highly cost-effective*!

The systemic problem with allocation of resources in health care is not only deficient function (lack of activity), but also excessive function (shown in documentation formal increase of the number of patients suffering from diabetes and circulatory system diseases by general practitioners, caused by attractive corrective indices of the capitation fees). This causes a significant lowering of medical effectiveness and increase of the costs of treatment.

An open question remains, is a better servicing of queues, logistics and organisation system, functional implementation of evidence based medicine with system diagnostics, health measurement and risk management will be enough for a satisfactory increase of health care if the HCS in Poland will still remain strongly internally antagonised?

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The quality of patients' data in medical documentation and statistical forms

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Abstract. The analysis of legal regulations on statistical and medical documentation has been performed and the quality of data was evaluated. The patients' records and statistical forms of 31 patients discharged from a local hospital were studied. 127 initial diagnoses, 148 final diagnoses were stated in medical documentation, but only 73 of them were presented as ICD-10 codes. The identical initial and final diagnoses were noted in 57 cases. The average number of initial diagnoses per patient was 4.09 ± 1.97 and final diagnoses – 4.77 ± 1.81. The average number of diagnoses identical at admission and at discharge was 1.84 ± 1.67. Statistical forms of the same patients contained only 93 diagnoses and 93 ICD-10 codes i.e. 55 diseases were not reported in statistical forms. The accordance in ICD-10 codes in medical and statistical documentation was noted only in 30 cases (out of 148 in clinical and out of 93 in statistical documentation). The diagnoses were identically written down in the medical and statistical forms only in 10 cases. All of that means poor completeness but high consistency of statistical data presented as MZ/Szp-11. In contrast, the medical data are of high completeness, validity and accuracy but of relatively low consistency. The further investigations are needed to reveal the most important reasons of discrepancies between medical and statistical data.

Introduction

The methods of collecting primary data in health care determine the quality and reliability of all indicators derived from the medical and statistical documentation. Many organizations (e.g. WHO, OECD, PAHO) stress the importance of quality of primary data collected in healthcare institutions. The use of data from electronic (and/or paper) medical records for any kind of evaluation requires an extraction process. Many efforts have failed because the extracted data seemed to be unstructured, incomplete and ridden by errors [16]. The quality of data can be described by the following terms: completeness, validity, consistency, timeliness and accuracy. However, there is no satisfactory definition for some of those terms. For example, completeness of medical data (full information about the patient) is not exactly the same as the completeness of data in a statistical survey (coverage of all patients). The medical data refer mainly to the individuals and the statistical data should reflect the health status of the population.

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It is assumed that the both kinds of data should be in accordance as well as that the statistical data on hospitalization are simply extracted from medical documentation. However, looking at the hospital morbidity reports one can notice that the number of procedures reported in the statistical forms differ from the figures in individual patient's documentation. On the other hand, there is no underreporting of procedures in reports send from the hospital to the payer. Record documentation by community family physicians in the USA largely reflects the level of services billed using evaluation and management codes. Undercoding and overcoding occur at a similar frequency (21% and 19%, respectively) and differ by more than 1 code in fewer than 4% of visits [14]. Similar problems may be met in Polish hospitals, so it seems reasonable to compare the data collected in medical records and statistical forms to disclose the discrepancies between both sources of information.

Material and Methods

The essential elements of patient's record and in coding systems used in healthcare were reviewed. The processes of stating the diagnosis and problems emerging from different types of diagnoses in medical documentation were presented and compared with the requirements for statistical forms.

Current legal acts on medical documentation in Poland were analyzed with the special reference to the standards on medical information and structure of patient's record. MZ/Szp-26 (clinical) form was used as a standard. Also the selected elements of MZ/Szp-11 (statistical) form – diagnoses and procedures – were reviewed and the content of information in both types of documentation was compared.

The 31 sets of medical records were obtained from a local hospital in 2011. The consecutive records of patients discharged from non-surgical wards were analyzed. An experienced physician (lecturer at the Medical University) reviewed all the records and forms to establish whether there are important differences in documentation from the professional (clinical) point of view. The different sequence of diseases in one patient's documentation was taken as different diagnoses as the difference between main disease and co-morbidity influences the statistical data in MZ/Szp-11. For example, if the main initial disease was hypertension and co-morbidity – ischemic heart disease, but in the final diagnosis the main disease was ischemic heart disease and hypertension was co-morbidity – those data were recognized as different diagnoses. This is because the "main" disease is the reason of hospitalization with all consequences (statistical, economical and epidemiological ones).

The following parameters were calculated:
- the number of initial diagnoses together with their ICD-10 codes,
- the number of final diagnoses and their ICD-10 codes as a measure of completeness of data,
- the accordance between preliminary and final diagnoses (exact description of the disease) as a measure of validity and consistency of data,
- the accordance between preliminary and final diagnoses (ICD-10 codes) in patients' records as a measure of validity and consistency of data,
- the accordance between ICD-10 codes in patients' records and in statistical forms as a measure of accuracy of data,
- the number and kinds of procedures recorded in statistical forms as a measure of completeness of data.

No statistical analyses (except calculating mean ± SD) was performed because of small groups of patients with identical diagnoses, and discrepancies between diagnoses in almost each patient's documentation.

Results

Medical documentation and statistical forms

The medical record should accurately reflect the course of disease and indicate the probable cause of disease. This concept of Hippocrates, developed 2500 years ago, is still valid, as referred to medical documentation. The majority of information collected during patient's stay at a hospital is placed into the medical documentation, namely – the patient's record. Those are mainly medical data: results of medical examination (interview – anamnesis, and physical examination), laboratory tests, X-ray images, consultations, medical procedures, medications and their side-effects, complications etc. According to SNOMED-CT (Systematized Nomenclature of Medicine – Clinical Terms), the total number of terms (named "concepts") related to medicine exceeds one million. ICD-10 (International Statistical Classification of Diseases and Related Health Problems 10th Revision) covers 14 400 codes of diseases, which can be expanded up to 16 000 by subclassifications. US national version of ICD contains over 155 000 codes. Moreover, ICD-10 must not be mismatched with ICD-10-PCS (Procedure Coding System) which covers 72 081 procedures.

It seems reasonable to use those codes in everyday practice. However, ICD-10 does not fully reflect the processes and relationships between different diseases in different cases. For example codes I10-I15 (hypertensive diseases) exclude hypertension complicating pregnancy (O10-O11) and pul-

monary hypertension (I-27.0). It is a quite different condition when a woman suffering from idiopathic hypertension becomes pregnant as compared with pregnancy complicated by hypertension. The etiology, therapy and courses of those diseases are different. Pulmonary hypertension is treated with sildenafil (Viagra) and it is easy to look for a mistake or malpractice when sildenafil is prescribed for an old man. Also the economic and legal consequences of such mismatches may be serious. It is clear, that the medical data may be used in structured form, but it is easier for a doctor to describe a complex condition in unstructured form (narrative text) than to look for appropriate codes.

Diagnosing process is based on the signs and symptoms, it may last some time (even weeks) in those complex cases when different diseases reveal the same symptoms, and the number of medical data may increase almost exponentially. So called differential diagnosis is the result of several processes including laboratory tests and specialists consultations. The final diagnosis – at the discharge – may differ from the preliminary (initial) diagnosis stated at the admission. Actually, a doctor sometimes has to manage several kinds and numbers of diagnoses during one patient's stay at the hospital. It is assumed that the final diagnosis is more accurate than the initial diagnosis. For example, "cardiac arrhythmia" may be diagnosed at the admission but the final diagnosis is "Wolf-Parkinson-White syndrome". From the medical point of view, there is no mistake. WPW syndrome is a kind of cardiac arrhythmia. But the ICD-10 codes for these conditions are different. The number of diagnoses in one patient may range from one to over a dozen. The average European above 40 suffers from at least one of chronic diseases. This number is doubled at the age above 50.

So it is essential which diseases are recognized as the main cause of hospitalization. Some problems may emerge here e.g. if the patient suffering from perforation of gastric ulcer and hypertension (not related one with another) is admitted to the surgical ward the main diseases is gastric ulcer treated with surgery. But when the same patient after successful surgery has to be treated because of hypertension at the department of internal medicine hypertension will be the main disease. So we have to manage with one patient's record, two diseases and two hospitalizations with two final diagnoses. Moreover, the final diagnosis is the base for DRG (disease related group) – a classification system in which patients are grouped into medically and economically consistent entities. The diagnoses and surgery codes are the main medical data used by DRGs.

The implementation of the ordinance on medical documentation issued by the Ministry of Health (Dec 21th, 2010) evoked the expectations on new

quality of health care system in Poland. The possibility of analyzing almost all data collected in all (approx. 16 000) health care units, wards, clinics, and hospitals (approx. 700) etc. seems to be promising – from managerial point of view. However, the enthusiastic opinion of an expert [22] should be confirmed in an ordinary hospital practices. One may have rather serious objections to the results of the unification and combined system of medical and statistical information. First of all, according to § 10. 1 of the ordinance the information on health status and disease, diagnostic, therapeutic and rehabilitation processes should be placed into medical documentation. In detail these mean:

- description of health services provided to the patient;
- diagnosis/diagnoses of the disease, condition, injury or pregnancy;
- orders and advices;
- information about medical statements and opinions
- information about prescriptions, prescribed drugs and medicines
- other information

At the discharge from the ward (§ 19) also the final diagnoses, comorbidities, complications should be described as well as their ICD-10 codes. The description of medical procedures, surgical operations and their ICD-9 codes, epicrisis (a summing up of a medical case history), date and cause of discharge from the ward. So the medical documentation according to the regulations of the Ordinance contains a series of pictures reflecting a dynamic process.

The most important difference between medical data and statistical ones may be described as the medical data refer mainly to an individual and the statistical data should reflect the status of population. Moreover, the requirements of statistical offices differ from those of medical clinics. Statistical data should be aggregated in a uniform way to enable the comparison of population, and to create the measures and indicators referring to large number of patients. Differing from a dynamic, clinical form (MZ/Szp-26) a "snapshot" approach is represented by the statistical information completed by the hospital. The form MZ/Szp-11 should contain the information extracted from inpatient documentation.

Statistical data are collected according to the Public Statistics Act by the use of standard forms. 39 forms are used by the Ministry of Health. The MZ/Szp-11 form (The Statistical, General, Hospital Chart) contains the following information about each individual patient's stay at the hospital (all wards):

- one main (final) diagnosis,
- one additional diagnosis

- one diagnosis from ICD blocks V-Y – external causes of morbidity and mortality (accidents; event of undetermined intent; legal intervention and operations of war; complications of medical and surgical care; sequelae of external causes of morbidity and mortality; supplementary factors related to causes of morbidity and mortality classified elsewhere)
- 3 co-morbidities,
- 6 procedures

Each diagnosis should be named, and its ICD-10 code should be also used. 4-digit standard is obligatory. The codes of medical procedures must be in accordance with the 2nd edition of International Classification of Medical Procedures. Data of all patients hospitalized in Polish hospitals are sent to the National Institute of Public Health – National Institute of Hygiene where the annual reports on hospital morbidity rate are prepared.

Comparing the medical and statistical forms one can conclude that the patient's stay at the hospital is the unit of healthcare services in medical documentation. The number of diagnoses and procedures is not limited here. In the statistical form the units are diagnoses (1 to 5) and procedures (up to 6). So, as the result of legal regulation on medical and statistical documentation one may expect the underreporting of diseases and procedures which are not recognized as important enough to be placed in MZ/Szp-11. So the reports on hospital morbidity have to be limited to main diseases and underreporting may be enhanced by aggregation of simplified data. Different approach to medical data is used for billing purposes with National Health Fund, but this problem should be investigated and discussed in a separate report.

Diagnoses and ICD-10 codes

According to the opinion of a Medical University expert, the evaluated clinical documentation was correct, and no important differences in describing the clinical status of all patients could be found. However, the final diagnoses were described mostly in unstructured way, i.e. using different terms for the same disease. For example, in one patient the chronic ischemic heart diseases was recognized as acute transmural myocardial infarction of anterior wall. Actually these are different conditions but the acute infarction may be the result of chronic ischemic heart disease. In a given example the problem was that the final diagnosis of chronic disease (I25.0) did not precede the acute infarction (I21.0), as could be expected in classical history of that disease. The analysis of medical documentation revealed that the initially observed signs and symptoms of acute infarction were not confirmed during hospitalization. This way of thinking was confirmed by the number

and kinds of procedures applied to this patient: ECG, Holter's monitoring and chest x-ray are more likely used in chronic ischemic diseases than in acute heart infarction. However, no trace of differential diagnosing was found in the statistical form. That is the result of "snapshot" information collected in a statistical form.

Another problem is illustrated by the case of a patient with the following final diagnoses and ICD-10 codes found in his record (medical documentation / statistical documentation)[1]:

1. Wolff-Parkinson-White syndrome / Wolff-Parkinson-White syndrome – I45.6.
2. Paroxysmal tachycardia / Paroxysmal atrioventricular tachycardia – I47.1.
3. Status post cholecystectomy / no diagnosis – no ICD code.
4. Status post electrical cardioversion / no diagnosis – no ICD code.

The main diagnosis was the WPW syndrome, and that was reported also in MZ/Szp-11, but the status post cholecystectomy and status post cardioversion were omitted in the statistical form. It should be stressed here that the past history of the patient (anamnesis) contains important information: some time ago (not determined) the patient had the episode of cardiac arrest successfully treated with cardioversion. Such an episode may appear also in future, and probably it could be the indication for implanting a pacemaker. No information about such a risk can be found in statistical form. Similar diagnostic and prognostic problems could appear when the status of patient's liver and alimentary tract were analyzed.

The results of the documentation analysis are summed up in [Tab. 1]. In 31 patients' medical documentation 127 initial diagnoses, 148 final diagnoses were stated, but only 73 of them were presented as ICD-10 codes. The identical initial and final diagnoses were noted in 57 cases. In 19 out of 31 cases the diseases of circulatory system (codes I00-I99) were main final diagnoses in both statistical and medical documentation. Only in two cases the preliminary and final diagnoses were fully identical. i.e. noted exactly in the same words. The average number of initial diagnoses per patient in medical documentation was 4.09 ± 1.97 as compared with final diagnoses 4.77 ± 1.81. The average number of diagnoses identical at admission and at discharge was 1.84 ± 1.67. This indicates the changing diagnoses and/or the rank of each diagnosis (main or co-morbidity).

[1] Only one diagnosis is exactly the same in both types of documentation.

Tab. 1. The content of medical and statistical forms – number of diagnoses, ICD-10 codes in each studied documentation

Patient's number	Medical documentation				Statistical documentation	Comparison of data	
	The number of diagnoses at admission (initial diagnoses)	The number of diagnoses at discharge (final diagnoses)	The number of diagnoses identical at admission and at discharge	The number of ICD-10 codes at discharge (MZ/Szp-26)	The number of diagnoses in MZ/Szp-11	The number of identical diagnoses in medical and statistical forms	The number of identical ICD-10 codes in medical and statistical forms
1.	2	4	1	2	2	0	2
2.	5	5	1	0	2	0	0
3.	5	4	0	3	3	1	1
4.	4	5	3	3	2	0	2
5.	4	5	0	4	2	0	0
6.	4	4	4	2	2	0	2
7.	5	5	4	0	3	0	0
8.	1	4	1	2	3	1	2
9.	8	5	1	5	3	0	0
10.	5	6	3	0	4	1	0
11.	6	6	5	6	4	1	4
12.	3	5	1	3	3	0	3
13.	1	4	1	0	3	0	0
14.	2	1	0	0	1	1	1
15.	4	8	2	0	3	0	0
16.	9	7	6	0	4	0	0
17.	3	3	2	0	4	0	0
18.	6	4	4	0	3	2	0
19.	1	1	1	0	1	0	1
20.	6	5	3	0	3	0	0
21.	2	4	2	4	4	0	4
22.	4	5	1	3	4	0	0
23.	5	8	2	6	4	0	2
24.	3	6	2	4	4	0	0
25.	7	7	5	6	4	0	0
26.	2	6	1	5	4	0	3
27.	2	1	1	1	1	0	1
28.	5	6	0	1	3	0	0
29.	5	5	0	4	4	0	0
30.	5	2	0	2	2	3	2
31.	3	7	0	7	4	0	0
Mean	**4.09**	**4.77**	**1.84**	**2.35**	**3**	**0.32**	**0.97**
SD	**1.97**	**1.81**	**1.67**	**2.22**	**0.98**	**0.69**	**1.25**

The statistical forms of the same patients contained only 93 diagnoses and 93 ICD-10 codes. It is easy to see that 55 diseases were not reported in statistical forms. The accordance in ICD-10 codes in medical and statistical documentation was noted only in 30 cases (out of 148 in clinical and out of 93 in statistical documentation). The diagnoses were identically written down in the medical and statistical forms only in 10 cases. All of this means poor completeness of statistical data presented as MZ/Szp-11.

It is obvious, that no rule nor any regularity could be found when each patient's documentation was analyzed. In some cases the number of final diagnoses was greater than the initial ones – in other patient quite opposite phenomena were noted. The only exception is MZ/Szp-11 in which all parameters (diagnoses and codes) are fully in accordance one with another, but not with the medical documentation.

Procedures

Both, the names of procedures and their ICD-9 codes were placed into statistical forms with different frequency (mean $3{,}00 \pm 0{,}98$ per case). In two fatal cases no procedures were noted in the statistical form. In the rest 29 forms the number of procedures ranged from 1 to 5. However, it should be stressed that the actual number of procedures performed should be many times higher. First of all, the International Classification of Medical Procedures contains the routine procedures performed every day at every ward. Here are the most often of them:

89 Interview, evaluation, consultation, and examination
- 89.0 Diagnostic interview, consultation, and evaluation
- 89.7 General physical examination
- 89.6 Circulatory monitoring

99 Other non-operative procedures
- 99.0 Transfusion of blood and blood components
- 99.1 Injection or infusion of therapeutic or prophylactic substance
- 99.2 Injection or infusion of other therapeutic or prophylactic substance
- 99.6 Conversion of cardiac rhythm

It is impossible to diagnose the patient without examination and to treat her/him without injections at the hospital. The lack of such procedures in statistical form strongly indicates that the medical personnel did not register all procedures, but chose some of them to write down in MZ/Szp-11. The following procedures were noted there:

1. Electrocardiogram 93% of patients
2. Routine chest x-ray, so described – 45% of patients
3. Electrographic monitoring – 24% of patients

4. Diagnostic ultrasound of heart – 18% of patients
5. Diagnostic ultrasound of abdomen and retroperitoneum – 12% of patients
6. Computerized axial tomography of thorax – 12% of patients
7. Cardiovascular stress test using treadmill – 9% of patients
8. Cardioversion – 6% of patients
9. Diagnostic ultrasound of head and neck – 3% of patients
10. Diagnostic ultrasound of peripheral vascular system – 3% of patients
11. Electrographic monitoring of blood pressure Holter's type – 3% of patients
12. Gastric lavage – 3% of patients
13. Injection or infusion of therapeutic or prophylactic substance – 3% of patients

All these are the cases of serious underreporting of the procedures independently from the types of patients and their diseases.

Discussion

According to WHO guidelines (2007) the purposes of medical documentation are as follows: communication, accountability, fulfilling legislative requirements, research, quality improvement, funding and resources management [28]. The quality of medical information is well documented condition indispensable for patient safety, effective treatment, good practices, effective management and health policies [5, 9, 26]. Twenty years ago Burnum stated that "medical record information has become less reliable than ever before despite the electronic information revolution in medical care and the authority medical records have been accorded in our society" [2]. In contrast to such skeptical but well documented opinion, at present some Polish experts strongly believe in the revolutionary changes in Polish health care system caused by the Ordinance on Medical Documentation issued by the Minister of Health on December 2010 [22, 24]. Six years ago Hillestad et al. were suggesting that electronic medical record system may transform health care [10]. Similar opinion was presented by Wright et al. who proposed a method for automated inference of patient problems from electronic medical record if the data were structured and knowledge-based [29]. In spite of numerous guidelines and standards on medical documentation [1], evaluation of electronic health records [21], the quality of medical data still should be improved.

Medical documentation according to the National Council of Quality Assurance (NCQA) may be a crucial factor for evaluating the quality of

services [28]. The following 6 (out of 21) parameters are core components of a medical record for quality assurance:

- Significant illnesses and medical conditions are indicated on the problem list.
- Medication allergies and adverse reactions are prominently noted in the record.
- Past medical history.
- Working diagnoses are consistent with findings.
- Treatment plans are consistent with diagnoses.
- There is no evidence that the patient is placed at inappropriate risk by a diagnostic or therapeutic procedure.

All of this information may be retrieved from electronic or paper patient's record if it is structured in a correct way. However, narrative text may be also a good source of information [18]. Pullen and Loudon present 17 purposes of the clinical record [23]:

- To act as a working document for day-today recording of patient care
- To store a chronological account of the patient's life, illnesses, its context and who did what and to what effect
- To enable the clinician to communicate with him- or herself
- To aid communication between team members
- To allow continuity of approach in a continuing illness
- To record any special factors that appear to affect the patient or the patient's response to treatment
- To record any factors that might render the patient more vulnerable to an adverse reaction to management or treatment
- To record risk assessments to protect the patient and others
- To record the advice given to general practitioners, other clinicians and other agencies
- To record the information received from others, including carers
- To store a record to which the patient may have access
- To inform medico-legal investigations
- To inform clinical audit, governance and accreditation
- To inform bodies handling complaints and inquiries
- To inform research
- To inform analyses of clinical activity
- To allow contributions to national data-sets, morbidity registers, etc.

Corrao et al. strongly advised to test the electronic health or medical record system before implementation [4]. However, if the correct and precise data are provided to an electronic system of information the results may be very effective in clinical terms [17, 19]. On the other hand, defi-

cit or lack of appropriate communication and information transfer between medical institutions and doctors may worsen the quality of care and patient safety [15]. Also Kaczmarek et al. claim the poor quality of medical records from the perspective of social security institution [13]. In this case insufficient information meets the overload of information in medical records. Both are not supporting the decision making in individual cases of patients at the Institution of Social Securities. Several years ago, in a study of the influence of specialists supervision on the quality of medical documentation in occupational medicine, Kacprzak et al. postulated that the supervision improves the quality more than legal regulations [12]. According to results presented here, the author may only confirm this controversial opinion, as the quality of medical documentation was higher than the statistical information. Medical documentation was carefully reviewed by the senior doctor in a ward. Statistical forms were simply delivered to statistical offices.

Medical records and statistical forms in presented material seem to function independently one from another. The completeness of information is much better in medical record than in statistical forms, but the consistency seems to be better in statistical documentation. As the result, we may obtain at least two different pictures of hospitalization: statistical – with clear and consistent but not complete information, and clinical – (more complete, valid and accurate) representing more dynamic approach to the processes of diagnosing and therapy. Those two pictures overlap one another only in minor extend. However, similar problems on the inaccurate and incomplete data obtained from common structured sources like patient problem list and billing data were discussed by Wright et al. [29]. Jordan et al. also stated the varied quality of morbidity coding, even in computerized general practices [11]. Fontaine et al. concluded that the potential for health information exchange to reduce costs and improve the quality of health care in ambulatory primary care practices is well recognized but needs further empiric substantiation [6].

The quality of primary data is an important factor influencing the healthcare organization, health policy and/or evaluation of effectiveness of health care. Serden et al. connected the prospective payment system with the primary and secondary diagnoses in health care [25]. They suggested that introduction of DRG-based systems, irrespective of use, focuses on recording diagnoses and therefore increases the number of diagnoses. This makes the value of accurate reporting of primary diagnoses for administrative purposes. However, collecting the valid, accurate and complete data is the problem even in big computerized systems.

Good quality data enable the evaluation of geographic variation in diagnosis frequency as well as the risk-adjustment. Among fee-for-service Medicare beneficiaries, there is an inverse relationship between the regional frequency of diagnoses and the case-fatality rate for chronic conditions [27]. That opinion may radically change the approach of decision makers to the diagnoses in medical documentation.

However, the problem is difficult to solve. In recent publication, Hansen et al. concluded: documentation of discharge process components in the medical record may not reflect actual discharge process activities [8]. Alternatively, mandated discharge processes are ineffective in preventing readmission. The observed absence of an association between discharge documentation and readmission indicates that discharge quality improvement initiatives should target metrics of discharge process quality beyond improving rates of documentation.

So the problem of quality of medical and statistical data persists irrespectively from the country and experience in paper forms, electronic forms of patient record, electronic medical record, electronic health record or so. The development of document-centered electronic patient record (EPR) or the more conventional approach – data-centered EPR would lead to the solution combining both of them [18]. Similar actions should be undertaken to combine medical and statistical data in a tightly linked system. Further investigations on the causes of discrepancies between medical and statistical forms and reports are required to elaborate the most effective legislative, organizational and informatics solutions.

Conclusions

1. The quality of medical and statistical data in patients' documentation should be improved, as the remarkable portion of diagnoses stated in medical documentation are not present in statistical forms.
2. Serious underreporting of procedures was observed in statistical forms.
3. Medical data are of high completeness, validity and accuracy but of relatively low consistency in contrast to statistical data representing poor completeness but high consistency.
4. Further investigations are needed to reveal the most important reasons of discrepancies between medical and statistical data.

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The effectiveness of education with the use of e-learning platform at the Faculty of Health Sciences, Medical University of Bialystok

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Abstract. The publication presents the analysis of education results in the subject "Obstetrics, Gynecology and Obstetrics-Gynecological Care" within the years 2006–2011 at the Faculty of Health Sciences, Medical University of Bialystok. A comparison of effectiveness between traditional and distance teaching methods with the use of e-learning platform introduced for scientific research was performed. An attempt to assess the usefulness of on-line learning with respect to student education was made.

Introduction

Dynamic development of distant education contributes to a greater interest in this form of acquiring knowledge. Better access to the computer and the Internet attracts more and more participants to distant learning. It can be observed in both educational institutions (schools, universities) and companies which use e-learning platforms to educate employees.

Currently, acquisition of knowledge is crucial as it is connected with improving professional qualifications, education and exploring interests. Traditional forms of teaching are gradually becoming insufficient. Therefore, teachers start to search for new forms of transferring knowledge to students as well as checking their abilities. Thus, people learn through the Internet more frequently and more willingly [1–5].

Despite the convenience of distant learning (possibility of learning at any time and place), it will never replace traditional education. Direct contact between students and teachers is irreplaceable. Therefore, we can observe occurrence of offers combining both forms (b-learning), which provides numerous opportunities for both students and teachers [1, 4, 12–13, 16].

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Currently, many programs supporting distant learning can be found on the market. They allow for compilation of complete e-learning courses which might be placed directly on educational platforms in SCORM, AICC and IMS standards [6–8]. Moreover, these tools give an opportunity to create modern tests, various quizzes and interactive tasks for checking students' knowledge.

The most efficient educational process involves traditional teaching supported by e-learning methods. In other words, classes conducted in traditional educational facilities are supplemented with virtual lessons. Teachers provide various materials, clues and instructions by the use of distant teaching. This method is perfect for students who find it problematic to deal with a particular part of material. Due to blended learning, the student has a possibility of having numerous revisions of a particular issue [12, 26].

An attempt of introducing distant learning at the Medical University of Bialystok was commenced by Wiesław Półjanowicz MSc, Eng who has been dealing with this method since 2001 [9–10] and Robert Latosiewicz, MD, PhD. In the academic year 2008/2009 both scientists prepared a pilot e-learning course in "Therapeutic massage" in the Rehabilitation Clinic, [11] implemented in LMS/LCMS-Moodle system [Fig. 1]. MOODLE stands for Modular Object-Oriented Dynamic Learning Environment and is a LMS/LCMS system based on GNU GPL (Open Source) [16, 29].

In the academic year 2009/2010 a cooperation between the Department of Obstetrics, Gynecology and Obstetrics/Gynecological Care and Independent Department of Sight Rehabilitation was commenced while in 2010/2011 – with the Department of Integrated Medical Care. Currently, five subjects are conducted in a complementary system (b-learning) with the use of the Moodle e-learning platform. Implementation of the study was approved by the Bioethical Committee of Medical University of Bialystok (regulation no R-I-002/338/2009).

Virtual environment of distant education

Currently used technical tools (modern e-learning platform, e.g. Moodle, server system, databases, broadband Internet access) allow for using mictrotechnology achievements as a new approach to design virtual education. The following mobile devices might be used: notebooks, palmtops (PDA), smart phones and mobile phones. Modern development of professional education should be taken into consideration in designing virtual courses for particular students. Its core is creating the shortest possible pathway of

professional competence development for a student of virtual educational space. The most significant elements are optimal form and amount of knowledge transferred in proper modules by the lecturer as well as student's activity connected with it.

A discrete model of virtual environment in distant teaching (VLE – virtual learning environment) within one or more universities in a city or country ought to contain various information which would complement each other on many levels of theoretical and practical knowledge and would be available for students after logging in and authorization on the e-learning platform. This would raise the attractiveness of studying various courses as students could easily and independently choose subjects they would like to study in a particular semester among a wide range of different thematic issues. With unlimited Internet access the best students would be able to do extra subjects within distant learning and thus gain additional specialties.

Exemplary model of a *blended learning* course

Complementary courses use methods and working styles from both – e-learning and traditional education. An exemplary schedule of the course comprises of three stages:

- electronic training in basic theoretical information,
- traditional training which is based on the knowledge acquired during the first stage and allows for gaining practical skills (direct participation in the educational process),
- e-learning training aimed at strengthening the acquired knowledge, revising and supplementing information, experience exchange in discussion as well as checking the knowledge by means of tests and tasks. This is aimed at determining future objectives and final grade of a particular student.

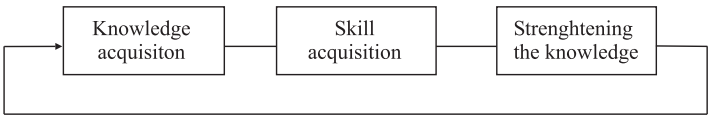


Fig. 1. Model of a three-stage complementary training

Also, models of a five-stage training can be found. The first stage, which is conducted in form of a direct contact between students and the teacher involves presentation of aims and organization of the training. The second,

third and fourth stages are a classic form of *blended learning* course which was presented in the previous model. The last stage is conducted in form of a direct meeting. It is aimed at evaluation of the didactic process as well as handing in certificates of course completion [26].

Organization of b-learning education to students of the Medical University of Bialystok

Blended learning applied in the didactic process constitutes a fully controlled time proportions of mutual and independent work of the teacher with students. Other crucial aspects are as follows: education individualization emerging from the proportions of information conveyed in both distant and traditional ways, the number of students in a group, student activation and the possibility of motivating students in form of both direct contact and distant education (interactive lectures supported by multimedia elements, tests of knowledge, tasks to perform, forum).

Work time organization in the case of traditional classes is an imposed lesson while in the case of distant education – it is flexible. Part of distant classes involves completion of tasks designated for individual performance. As they are placed on the platform in smaller portions, students do them more often, which leads to the development of a habit of dutifulness in completing objectives, provides the opportunity of improving skills and deepening knowledge as well as improves professional and social activeness [12, 26].

The subject "Obstetrics, Gynecology and Obstetrics-Gynecological Care" has been taught in the blended learning system for two years – lectures are given on-line while practical activities and self-education are conducted only in form of traditional classes. Students who decided to learn electronically are given free access to the educational platform and to the course (subject) completed in distant method. While completing a module students have constant (24 hours a day) access to didactic materials while the order of particular topics and period of their availability are determined by the academic teacher responsible for the subject.

Positive aspects of this method include fairly flexible class hours – education of particular modules might be completed in the time suitable for students. The student has the opportunity of choosing the form of classes, traditional or e-learning (Internet access is a necessary condition). Exams and credits take place in "traditional" form upon the rules provided by Study Regulations of Medical University of Bialystok.

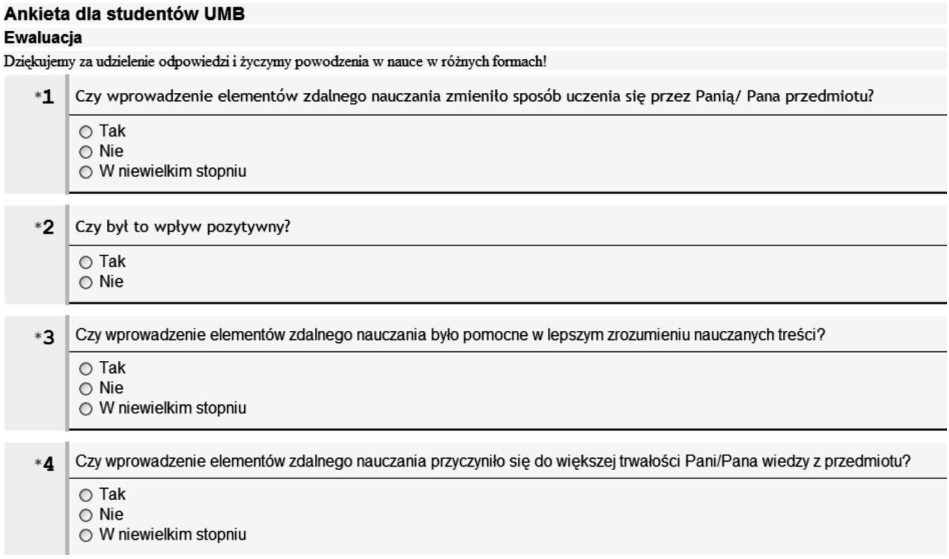
Material and methods

The study included a group of 132 students at the III-rd year of the first-degree full-time course in nursing, subject: "Obstetrics, Gynecology and Obstetrics-Gynecological Care" within the academic year 2010–2011. The students were divided into two groups. The study group attended lectures in the e-learning form with the use of LMS/LCMS (MOODLE platform) [16–17] [Fig. 2]. The control group attended lectures in the traditional form.

Fig. 2. The main window of e-learning platform

The final exam in the subject was conducted in the form of multiple choice test with one correct answer in a traditional way in both groups simultaneously. Test results of both groups were compared with consideration of final grades (i.e. level of professional knowledge). Upon the completion of lectures and prior to the final exam both groups were asked to fill in a questionnaire on the classes and the effectiveness elements of education. Exam results were compared with final exam outcomes from previous years (2006–2009) in which the classes were conducted in the traditional method exclusively.

A fundamental element following the completion of this e-course was the evaluation of the questionnaire placed on the e-learning platform connected with elements of the education and satisfaction from the classes (course of learning, access to materials, opinion on the on-line learning) compared with the traditional model [Fig. 3].


Ankieta dla studentów UMB

Ewaluacja

Dziękujemy za udzielenie odpowiedzi i życzymy powodzenia w nauce w różnych formach!

*1 Czy wprowadzenie elementów zdalnego nauczania zmieniło sposób uczenia się przez Panią/ Pana przedmiotu?

- ○ Tak
- ○ Nie
- ○ W niewielkim stopniu

*2 Czy był to wpływ pozytywny?

- ○ Tak
- ○ Nie

*3 Czy wprowadzenie elementów zdalnego nauczania było pomocne w lepszym zrozumieniu nauczanych treści?

- ○ Tak
- ○ Nie
- ○ W niewielkim stopniu

*4 Czy wprowadzenie elementów zdalnego nauczania przyczyniło się do większej trwałości Pani/Pana wiedzy z przedmiotu?

- ○ Tak
- ○ Nie
- ○ W niewielkim stopniu

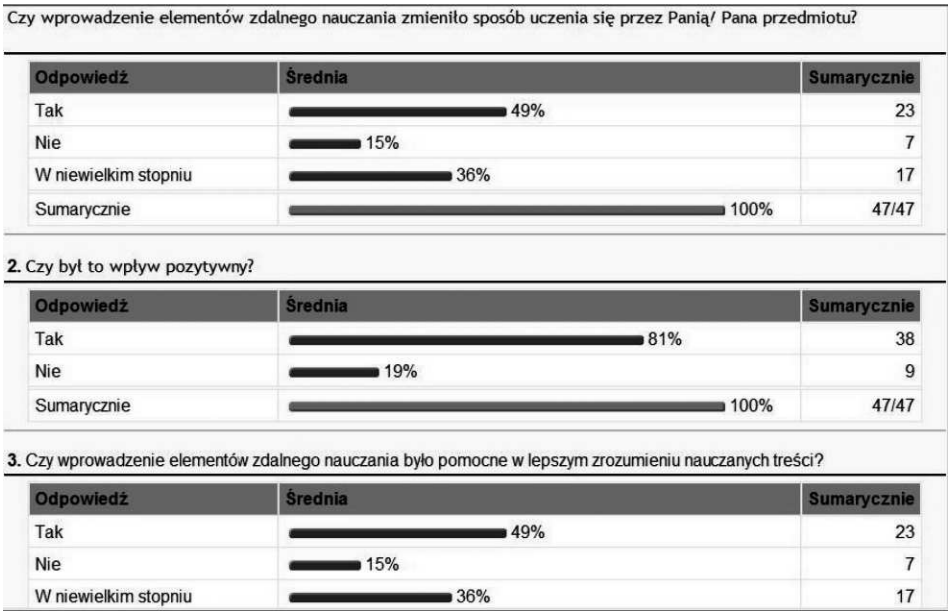
Fig. 3. Part of the evaluation questionnaire placed on the e-learning platform (questions 1–4)

Evaluation of e-learning effectiveness might be presented with respect to two aspects: didactic and financial. The former refers among others to a realistic indicator of both: deepening e-student's knowledge with visible effect during practical classes – e-course students remembered theoretical knowledge better (79%) as well as the level of implementation of the didactic e-process due to lecturer's efforts (93%). As regards to the financial aspect, it involves costs of implementing didactic e-process and a ratio of measureable acquired knowledge of the e-student to education cost (no accurate analysis in this respect has been performed yet) [21–22, 27–30].

Results

In the years 2010–2011 women constituted vast majority in both groups of e-learning students – 126 persons – 96% (data from the e-learning platform). As regards to the questionnaire evaluation of the level of students' satisfaction from education course and effectiveness elements, no statistically significant differences were found between the years 2010/2011 [Fig. 4, 5] and 2009/2010 [Fig. 6].

In the evaluation questionnaire students answered many questions. One of them was: "What was the most valuable element in this form of learning?". One of the answers was: possibility of comfortable studying at home,



Czy wprowadzenie elementów zdalnego nauczania zmieniło sposób uczenia się przez Panią/ Pana przedmiotu?

Odpowiedź	Średnia	Sumarycznie
Tak	49%	23
Nie	15%	7
W niewielkim stopniu	36%	17
Sumarycznie	100%	47/47

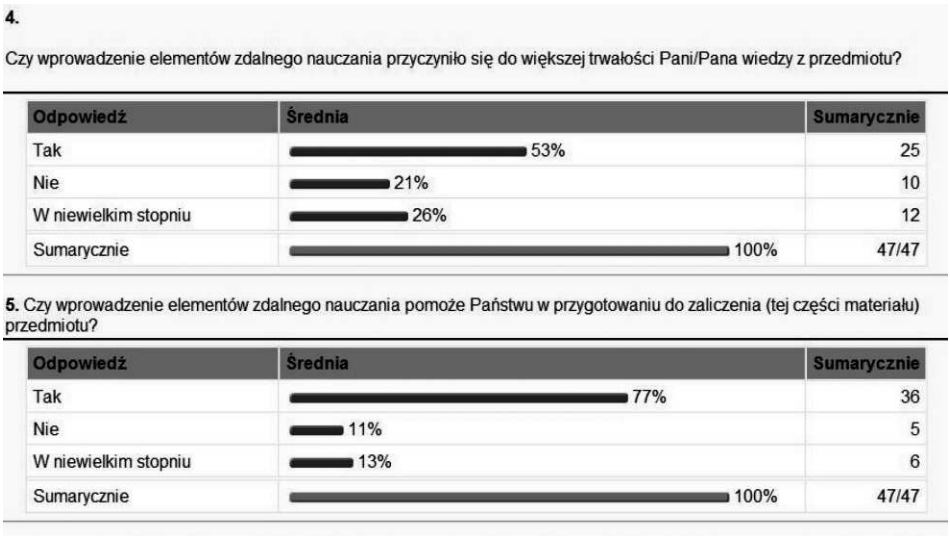
2. Czy był to wpływ pozytywny?

Odpowiedź	Średnia	Sumarycznie
Tak	81%	38
Nie	19%	9
Sumarycznie	100%	47/47

3. Czy wprowadzenie elementów zdalnego nauczania było pomocne w lepszym zrozumieniu nauczanych treści?

Odpowiedź	Średnia	Sumarycznie
Tak	49%	23
Nie	15%	7
W niewielkim stopniu	36%	17

Fig. 4. Results of the evaluation questionnaire placed on the e-learning platform (questions 1–3), 2010/2011



4.

Czy wprowadzenie elementów zdalnego nauczania przyczyniło się do większej trwałości Pani/Pana wiedzy z przedmiotu?

Odpowiedź	Średnia	Sumarycznie
Tak	53%	25
Nie	21%	10
W niewielkim stopniu	26%	12
Sumarycznie	100%	47/47

5. Czy wprowadzenie elementów zdalnego nauczania pomoże Państwu w przygotowaniu do zaliczenia (tej części materiału) przedmiotu?

Odpowiedź	Średnia	Sumarycznie
Tak	77%	36
Nie	11%	5
W niewielkim stopniu	13%	6
Sumarycznie	100%	47/47

Fig. 5. Results of the evaluation questionnaire placed on the e-learning platform (questions 4–5), 2010/2011

saving time, the possibility of reading lectures and taking achievement test is a convenient time (a few days for completion), mobilization for regular studying. According to the opinion of certain students, they acquired greater

1.

Czy wprowadzenie elementów zdalnego nauczania zmieniło sposób uczenia się przez Panią/ Pana przedmiotu?

Odpowiedź	Średnia	Sumarycznie
Tak	81%	25
W niewielkim stopniu	19%	6
Sumarycznie	100%	31/31

2. Czy był to wpływ pozytywny?

Odpowiedź	Średnia	Sumarycznie
Tak	100%	31
Sumarycznie	100%	31/31

3. Czy wprowadzenie elementów zdalnego nauczania było pomocne w lepszym zrozumieniu nauczanych treści?

Odpowiedź	Średnia	Sumarycznie
Tak	71%	22
Nie	10%	3
W niewielkim stopniu	19%	6

Fig. 6. Window of particular results of the evaluation questionnaire placed the on e-learning platform, 2009/2010

7. Co było najbardziej wartościowe w tej formie kształcenia?

nr	Odpowiedź
1	możliwość wygodnej nauki we własnym domu, oszczędność czasu możliwość czytania wykładów i rozwiązywania quizu w dogodnym dla siebie czasie (kilka dni na rozwiązanie) -quiz mobilizuje do systematycznej nauki -jestem pewna, że zdobyłam większą wiedzę niż byłoby to możliwe uczęszczając na tradycyjne wykłady, podczas, których nie zapamiętuje części materiału, tutaj mogłam zapoznać się dokładnie z tematami, a mając możliwość ponownego ich przeczytania przed egzaminem, nie będzie problemu z brakami w tradycyjnych notatkach
1	-możliwość przeanalizowania całego wykładu
1	.
1	Brak konieczności chodzenia na wykłady
1	Brak pośpiechu w ich czytaniu.
1	brak zdania
1	Dodatki do wykładów.
1	domowy dostęp do kursu.
1	dowolny czas na naukę
1	duża ilość informacji, sprawdzanie wiedzy po każdej przeczytanej stronie
1	Fakt ze mogłam we własnym tępie czytać slajdy i dobrym pomysłem sa pytania sprawdzajace znajomość materiału

Fig. 7. Window of answers to the 7th question in the evaluation questionnaire, 2010/2011

knowledge compared with traditional lectures as during the latter students fail to remember part of the material. The educational platform provides opportunity to revise the material before an exam. Other answers are as

Tab. 1. Mean final exam grade in the subject "Obstetrics, Gynecology and Obstetrics/Gynecological Care" in 2006–2011

Academic year	Lectures – traditional method	Lectures – e-learning method	Number of students taking re-sit exam – traditional method lectures	Number of students taking re-sit exam – e-learning lectures
2005–2006	3.10	lack	13%	lack
2006–2007	3.64	lack	3%	lack
2007–2008	4.09	lack	5%	lack
2008–2009	4.14	lack	0%	lack
2009–2010	3.26	3.49	15%	4.65%
2010–2011	lack	3.73	lack	0%

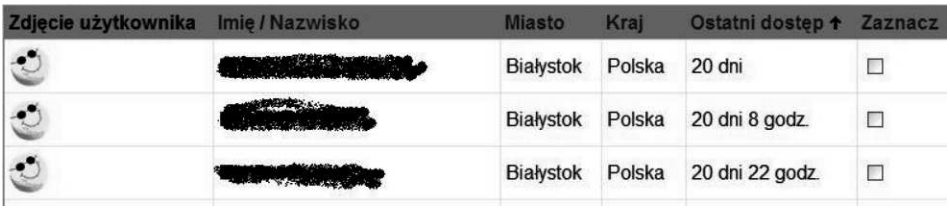


Fig. 8. Window of the last log – in to the e-learning platform in 2010/2011

follows: no necessity to attend lectures, no rush in reading lectures, multimedia extras to the lectures, flexible learning time, own reading pace and good idea of checking knowledge after each part of the material [Fig. 7].

Mean final exam grade in "Obstetrics, Gynecology and Obstetrics-Gynecological Care" in 2001/2011 among students from both groups, traditional and e-learning, as well as exam results in 2006–2009 are presented in [Tab. 1]. It can be assumed that mean exam grade in 2006–2009 had an increase tendency from 3.10 to 4.14 while in 2010 it decreased to 3.26. Standard deviation in this study of final exam grades in 2006–2011 amounts to SD = 4.47 in traditionally learning group. The comparison of study results in this subject based on mean final exam grade in 2010–2011 shows an increase by 0.24 points from 3.49 to 3.73. Standard deviation in e-learning amounts to SD = 0.17.

The highest exam grade (4.5) was received by a person who participated in distant education in 2009/2010 while the highest grade obtained by traditionally learning students was 4.0. In 2010/2011 also an on-line student received the highest exam grade – 4.5. This person was the last from the whole e-learning group to log in on the platform, most probably to gain ac-

cess to didactic materials for the final exam [Fig. 8]. This might suggest that students used the e-learning platform regularly and read didactic materials placed there in order to prepare to the exam.

Discussion

The studies were connected with the effectiveness of teaching the subject "Obstetrics, Gynecology and Obstetrics-Gynecological Care" to students of the third year of nursing course at the Medical University of Bialystok based on both traditional and e-learning methods within the years 2006–2011. Didactic materials prepared in the e-learning form were well received by the students. Almost 92% (43) of the e-learning students stated that introduction of distant learning elements contributed to greater acquisition of knowledge in this subject in 2009/2010 compared with 2010/2011 – 79% (37) students. As regards the question: "Will implementation of distant learning elements help you in preparation to passing the subject (particular part of the material)?" – 94% (90) students answered "yes", while only 6% – "no".

The said opinions prove high level of preparation to the classes. The authors believe that high popularity of distant education might result from interactive access to the knowledge included in the on-line course (lesson, quiz, task, forum) or simply website substantial content. The student might revise preciously analyzed issues many times, learn them better, acquire knowledge on a particular topic as well as check his/her knowledge in a particular field [11, 16, 25, 28].

A significant issue is the change in the role of the academic teachers in on-line education. Using previously prepared tests, they can check students' knowledge in a convenient way and the results are available immediately after checking [16–17]. This increases learning effectiveness while the cost of preparation and implementation of e-learning classes are high only in the first stage of compiling didactic materials. However, they do not exceed costs of traditional methods [19–20, 27].

The study included a group of 90 students of the nursing course who learnt by both traditional and distant methods and a group of 331 students who learnt by the traditional method in a classroom. This comparison confirms an assumption that implementation of e-learning methods would not decrease the level of professional knowledge, students' satisfaction from education or the effectiveness of the educational process compared with traditional methods. It was comparable.

Therefore, it can be assumed that possibilities provided by e-learning tools enrich the education model on the in-class courses. Thus, it is rationally justified to enrich the syllabus with a greater number of subjects which at Medical Universities would be taught in a complementary way (*blended learning*). These should include all lectures and seminars conducted in the distant form while typically practical classes ought to be conducted in the traditional form.

Studies on students' attitudes and expectations as regards to traditional education and e-learning were conducted among students of the Economy University of Poznan during the Economy course as well as in the Institute of Mathematics and Computer Science of Vilnius University. The outcomes confirm positive opinions on e-learning methods applied in the didactic process [15, 18].

The answers to the questionnaire indicate that the development of distant education might be a great form of supplementing traditional education and blended learning. The authors emphasize the need to continue studies in this field, especially as regards to enriching educational offer for a wider range of students of medical courses. A crucial element is the use of methods by part-time students who often work and concurrently wish to broaden their professional knowledge.

Conclusions

1. The results indicate that the e-learning method is as good as the "traditional" method of teaching vocational subjects during a nursing course.
2. Distant education is considered by students as slightly easier in acquiring knowledge due to constant access to materials.
3. E-learning platform tools for automatic knowledge check, systems of questionnaires and voting as well as systems of communication between students and academic teachers increase students' motivation for regular and independent studying which in final effects gives comparable and slightly better results than traditional methods.
4. Didactic materials compiled in electronic form, placed in LMS/LCMS system are available 24 hours a day, seven days a week, which provides more flexible conditions of learning and preparing for the final exam and thus revising knowledge in a particular scope.
5. Virtual register built in the content management system LMS (e-learning platform) allows for control of study results for both the student and academic teacher, which contributes to regular work of most of the students.

Student satisfaction level in the case of virtual courses depends on many factors. Positive view of experience in distant learning is typical for students possessing a particular set of features crucial for success. Most of all, a person registering for distant education should have a desire to learn and acquire new knowledge or skills for his/her own needs or for the purpose of future professional carrier. The motivation of a student, who makes his/her own decisions on what, how, when and where to learn, is one of the most significant self-regulators of student's behavior in distant education process. The aim of every student should be acquisition of knowledge without teacher's supervision rather than receiving certificates. A more independent student should show more responsibility to manage the self-learning process as it decides on when and how much to learn [14, 23–25].

To conclude, it can be assumed that distant education, which is desired by most students (91% – the questionnaire data) and which is successfully implemented in many countries, should not be overlooked. Its crucial element is proper preparation not only in terms of technical matters but also intellectually. "Distant learning is actually an educational issue, not technical" [23–24]. Particularly universities, but also private companies entering the educational market should consider the issue of offering virtual courses in order to avoid situations when an institution offers this form of learning with no proper preparation just because other companies do it or for financial benefits [1, 5].

Knowledge of different impressions of students on particular stages of the distant learning process might help the organizers to adjust the form of material presentation, message content and frequency of contact with course participants to students' needs and possibilities and thus increase their satisfaction and knowledge.

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Pasat Package Program in the evaluation of perinatal care quality in the Podlasie province in the light of the World Health Organization guidelines

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Abstract. Evaluation of health care quality in perinatal period based on particular statistical data and Pasat package program might be a good measure of a particular hospital's functioning. In order to evaluate the level of perinatal care, WHO guidelines ought to be implemented. Patients' satisfaction is considered the main criterion in this evaluation. Thus, the aim of the study was individual evaluation of perinatal care at a particular obstetric facility in the Podlasie province taking into account WHO guidelines. The study was implemented with the use of: questionnaire interview compiled for the study and standardized tool compiled by Health Care Quality Monitoring Center in Cracow – PASAT package. WHO guidelines are implemented to a limited extent. In the province the number of C-sections refers to 1/3 of the participants (35%). Less than a half of the women (45%) had induced labor. The level of patients' satisfaction from perinatal care in the Podlasie province is satisfactory. Improvement and educational–organizational actions are required as regards to WHO guidelines implementation in terms of: decreasing the percentage of C-sections, decreasing medical interventions by the reduction of induced labor percentage and encouraging pregnant women to go into physiological labor in vertical positions.

Introduction

In the modern world health care system requires new directions in obstetric actions. Perinatal interdisciplinary care, most of all effective perinatal care, ought to be carried out by specialized obstetric and neonatology staff. The actions are aimed at meeting biological and psychical needs of the mother and the baby. This assumption requires implementation of actions in accordance with current medical knowledge and standard procedures by health care providers of the pregnant woman and her family. A new era in obstetrics is a time of implementing standards and procedures of perinatal care which are a great chance in obstetrics but also a threat due to lack of

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professionalism in performing obstetrician's work. Quality evaluation of perinatal care based on particular statistical data is a commonly acknowledged measure of health protection in a particular country and thus an indicator of economic and health conditions as well as a reflection of society's background.

Aim

Perinatal care in the Podlasie province is implemented according to the system of regional reference. Most labors (81.9%) are performed in facilities of I and II level. Study on the quality of services and determination of potential differences depending on hospital referral level are considered as basic actions in the complex system of reproduction health care. Patients' satisfaction is considered to be the main criterion in this evaluation. Therefore, the aim of the study was individual evaluation of perinatal care at a particular obstetric facility within the Podlasie province taking into account World Health Organization's guidelines. Particular elements referred to are:

1. Implementation of WHO guidelines (difference evaluation depending on referral level)
2. Quality and course of prenatal care (difference evaluation depending on referral level)

Materials and methods

The study was conducted upon the approval of Bioethical Committee of Medical University of Bialystok (R-I-003/310/2006).

The study was performed by means of:

A. questionnaire interview compiled for the study in the Department of Obstetrics, Gynecology and Obstetrics/Gynecological Care,
B. standardized questionnaire interview compiled in the Health Care Quality Monitoring Center (CMJ) in Cracow, called PASAT package.

PASAT package is a tool that uses a questionnaire compiled and tested in CMJ allowing for the analysis of patients' expectations and satisfaction from medical care. The questionnaire comprises of two parts: part I – PASAT package questionnaire, part II – own questionnaire.

The questionnaire was completed by patients of public health care facilities of randomly chosen 6 hospitals of I° referral level within the Podlasie province:

1. Independent Public Healthcare Center in Hajnowka
2. Independent Public Healthcare Center in Monki
3. Independent Public Healthcare Center in Bielsk Podlaski
4. General Hospital in Grajewo
5. Independent Public Healthcare Center in Siemiatycze
6. Independent Public Healthcare Center in Sokolka

and 3 hospitals of II° referral level:

1. Cardinal Stefan Wyszynski Provincial Hospital in Lomza
2. Independent Public Provincial Hospital in Suwalki
3. Independent Public Healthcare Center, J. Sniadecki Provincial Hospital Complex in Bialystok

from May 1st 2003 to August 31st 2006. The study included 1000 women chosen randomly during puerperium on obstetric wards who filled in the questionnaire on the day of discharge, put it into an envelope and next put sealed envelopes to a specially labeled box. After completion of the questionnaire stage 942 intact (sealed) envelopes were obtained.

Statistical data

Data obtained from 942 properly filled questionnaires was transferred to specially prepared application forms of MS ACCESS database. The results were analyzed statistically by CMJ by means of PASAT, a licensed program.

The comparison was presented on diagrams in form of graphic presentation of answer distribution in pie, doughnut and bar charts as well as histograms.

The presentation of answer distribution in form of histogram is one of the graphic ways of presenting distribution of a particular property. It consists of many rectangles placed on coordinate axis. On one side the rectangles are determined by class intervals of property value while their height is determined by the number (or frequency) of elements included in a particular class interval. This type of graphic presentation was used for the evaluation of nurse and doctor care over the woman and the newborn on the scale from 1 to 10.

Results

Mean age of all the participants (942 persons) was 27.6 years. The youngest patient for labor was 16 years old, the oldest – 48. The most numerous group were mothers aged 26–30 years (35.04%, i.e. 330) [Tab. 1].

Tab. 1. Patient age range

Patient age range	Number of people	Percentage of people
16–20	68	7.21%
21–25	279	29.62%
26–30	330	35.04%
31–35	186	19.74%
36–40	63	6.69%
> 41	16	1.69%
Overall	**942**	100%

1/3 of the participants had higher education, i.e. 300 (32%) and the same number of patients had secondary education – 32%, i.e. 304 women. 87 (9%) had primary education while 160, i.e. 17% completed vocational school [Fig. 1].

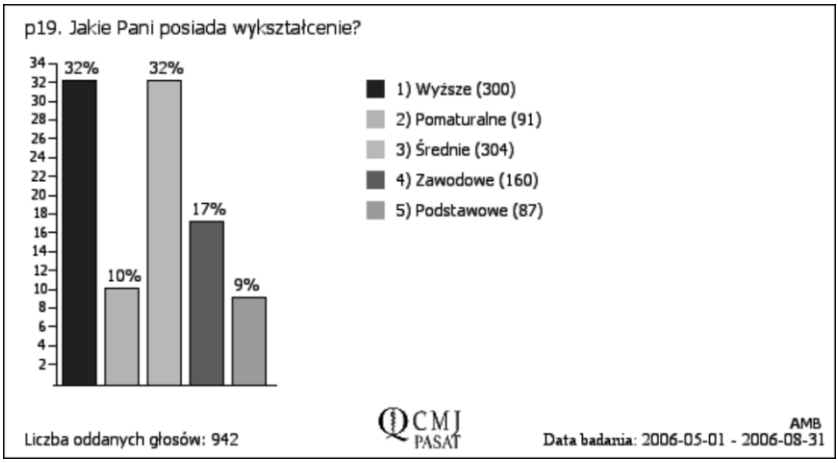

Fig. 1. Education

Implementation of WHO guidelines – evaluation of differences depending on referral level. Type of labor in hospital

In the Podlasie province in the studied period the most numerous group – 604 (64%) were women who gave birth physiologically, in a natural way. In 191 women (20%) C-section was performed due to emergency reasons. A planned C-section (elective) was performed on 139 women (15%). Obstetric forceps and cephalotractor cup were used in 8 pregnancies [Fig. 2].

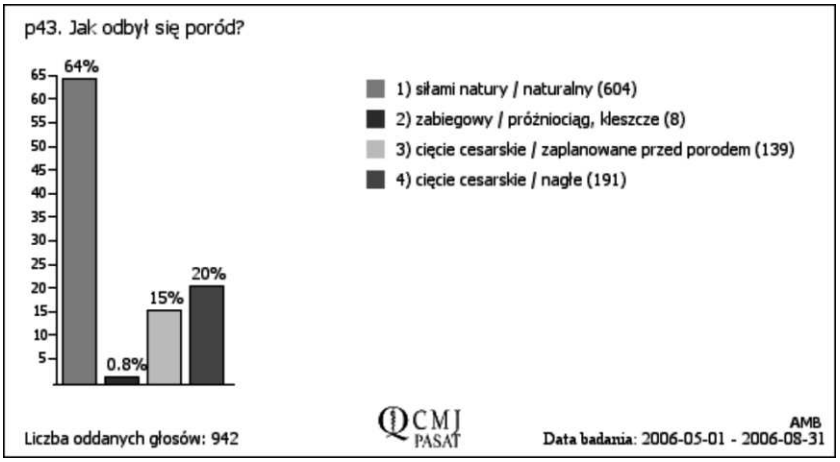

Fig. 2. Type of labor in hospital

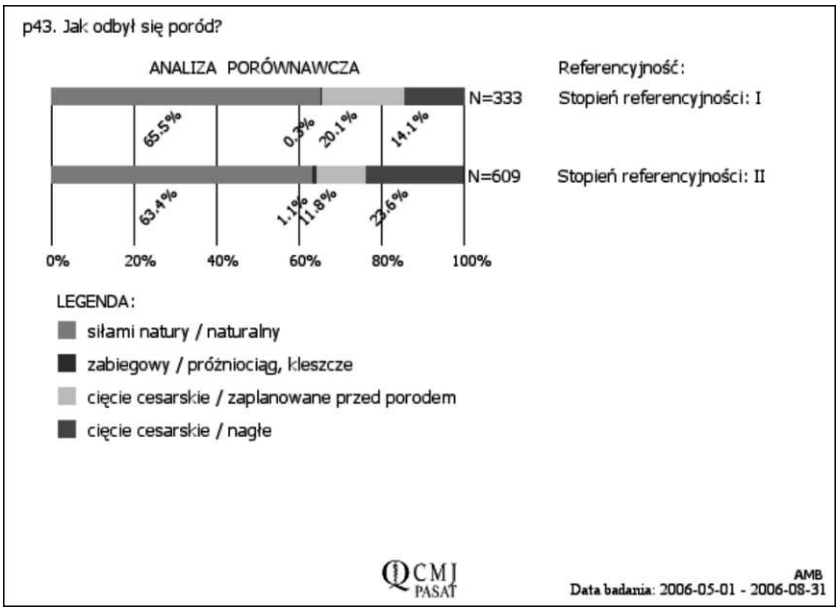

Fig. 3. Hospital referral level and type of labor

Emergency C-sections were considerably more numerous (23.6%) in II° hospitals. Percentage of natural labors is similar: I° referral level – 65.5%, II° – 63.4% [Fig. 3].

Labor medicalization. Inducement – "bringing about" labor

According to the participants, labor induced by an intravenous oxidoxin infusion was performed in 368 (39%) women in labor. Amniocentesis

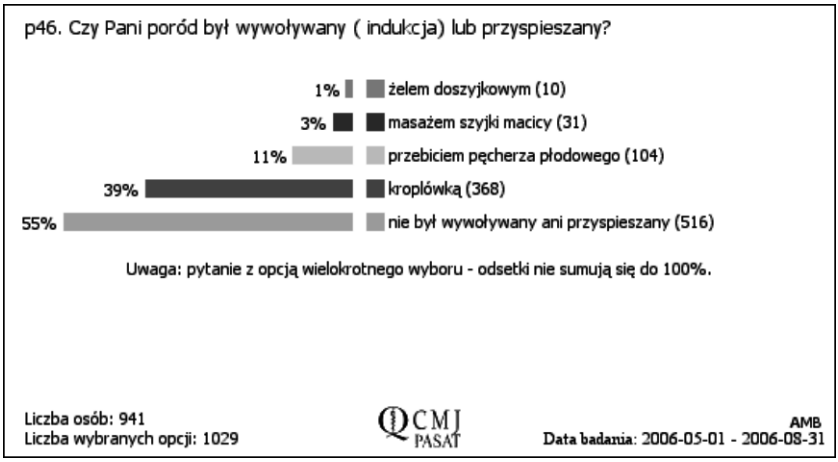

Fig. 4. Inducement – "bringing about" labor

was performed in 104 patients (11%). Other methods of inducing labor were applied in 41 (4%) women (cervical massage, intracervical gel). No actions influencing the labor were undertaken in the case of 516 women (55%) [Fig. 4].

In II° referral level hospitals intravenous oxidocin infusion was used more frequently to induce the labor (42%). In I° referral level hospitals 61% of labors were carried out with no pharmacological action while in II° level hospitals – 52%. Other options lack significant differences in both types of hospitals.

Position during II labor stage

462 women (75%) lied flat on the back during the labor. In certain hospitals the participants gave birth in knee-elbow position which referred to 66 women (10.78%). 74 women (12.09%) gave birth sitting on a labor chair. Questionnaire indicated also other positions (on the side, squatting, half-sitting) yet they referred only to 10 cases (1.63%).

In I° hospitals 37.9% of women went into labor in different vertical positions while in provincial hospitals – 17.3% [Fig. 5].

Routine episiotomy

The women in labor were asked: "did you have episiotomy?". Among women who went into labor in a natural way, 449 (74%) had episiotomy. The question did not include differentiation between primparae and multiparae. Primparae amounted to 491 women in the whole group [Fig. 6]. Episiotomy was performed more frequently in II° hospitals (77.3%) compared to district hospitals (67.6%) [Fig. 7].

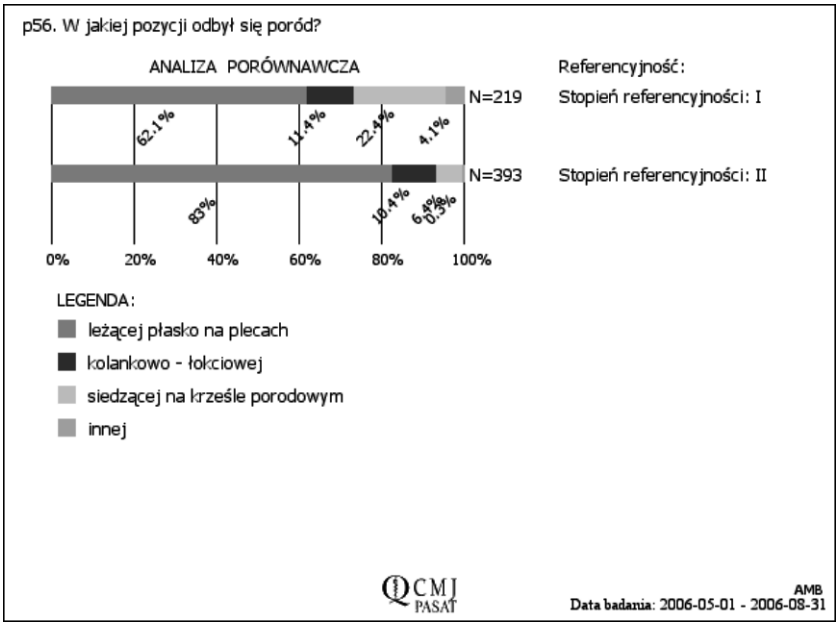

Fig. 5. What was the labor position? – comparative analysis of hospitals

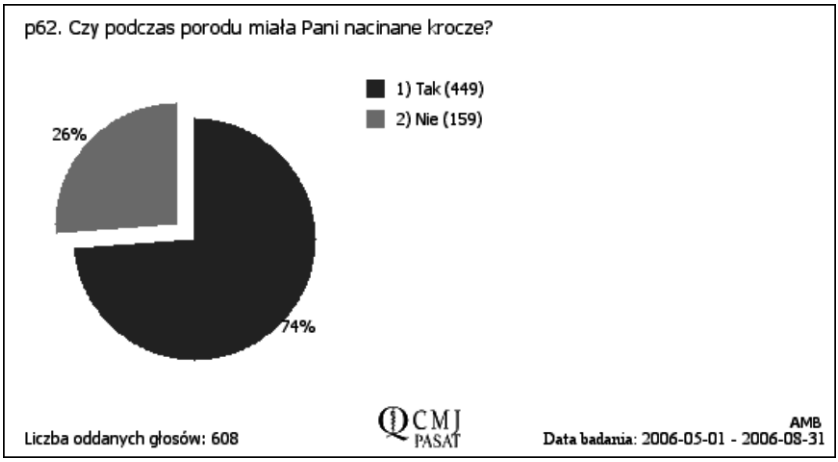

Fig. 6. Episiotomy

Skin-to-skin contact of a mother and a newborn following physiological labor and Caesarian section

Direct skin-to-skin contact was implemented in the case of 573 labors (61%). 3 mothers (0.3%) decided that postpartum condition of the baby did not allow for the contact [Fig. 8].

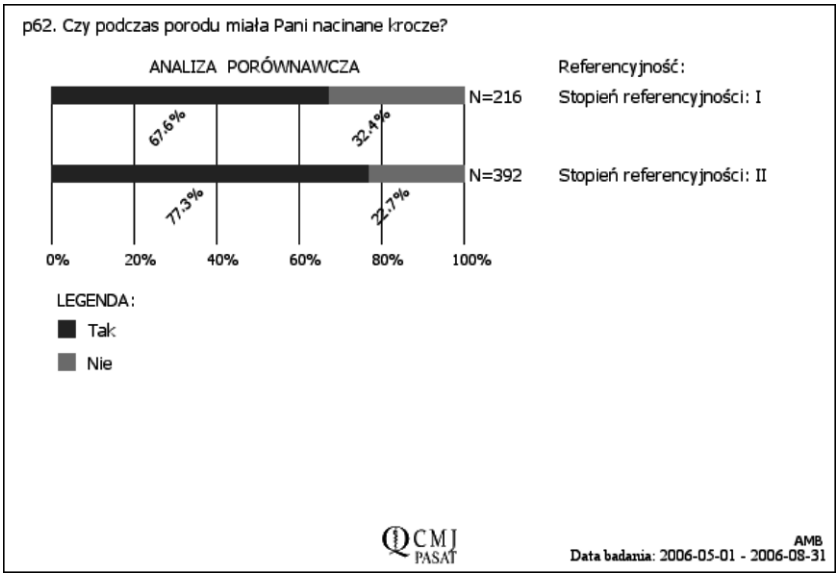

Fig. 7. Episiotomy in I° and II° referral level hospitals

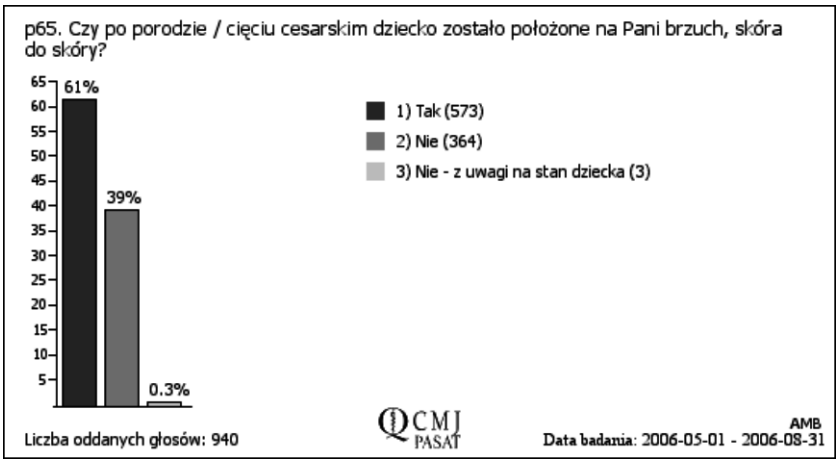

Fig. 8. Skin-to-skin contact

In I° hospitals newborns were placed on mother's abdomen in 67% of the cases while in II° hospitals in 57.7% [Fig. 9].

Duration of skin-to-skin contact

As regards to the question "how long was a newborn held by the mother", 274 participants (48%) answered "only for a moment", 213 (37%) "only for a few – a dozen or so minutes", 84 women (15%) were with the baby for the whole time [Fig. 10].

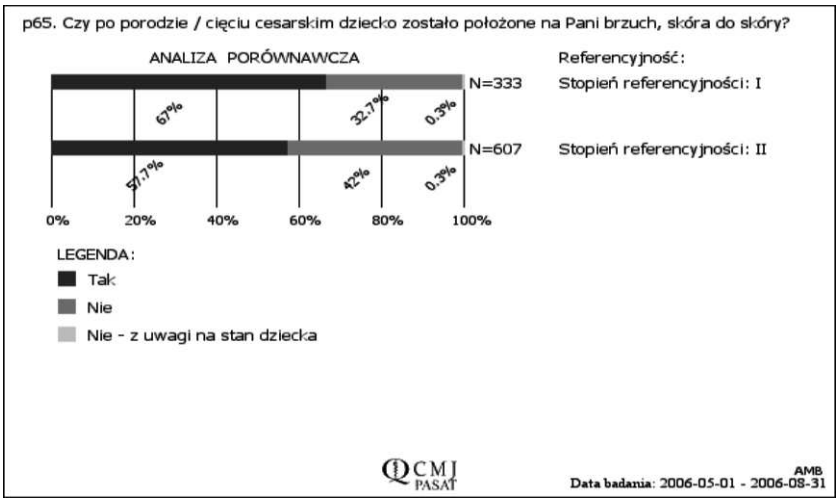

Fig. 9. Placing a newborn on mother's abdomen in I° and II° referral level hospitals

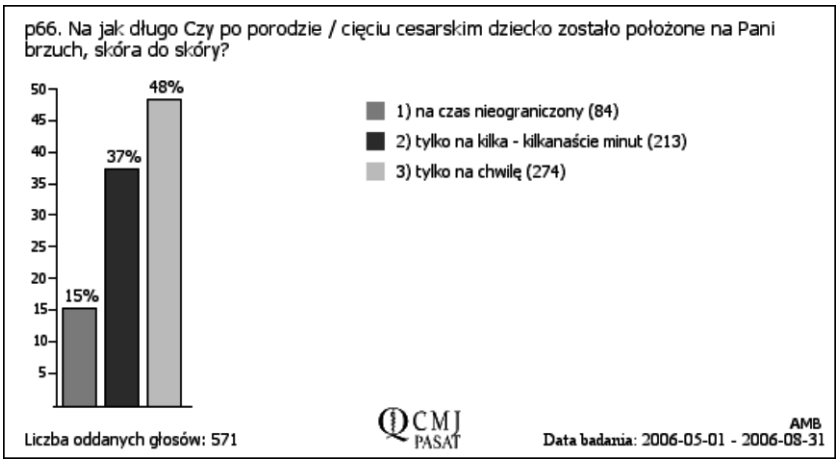

Fig. 10. Duration of leaving the baby on mother's abdomen

In I° level hospitals the baby was on mother's abdomen without limitations in 17.6% of patients while in II° hospitals – 12.9%. Percentage of mothers who held their babies only for a moment was similar in I° and II° hospitals and amounted to 48.6% and 47.6% respectively [Fig. 11].

Pre-labor enema

On admission to obstetric wards pre-labor enema was not performed in 614 patients (66%). The procedure was performed in the other 322 women [Fig. 12].

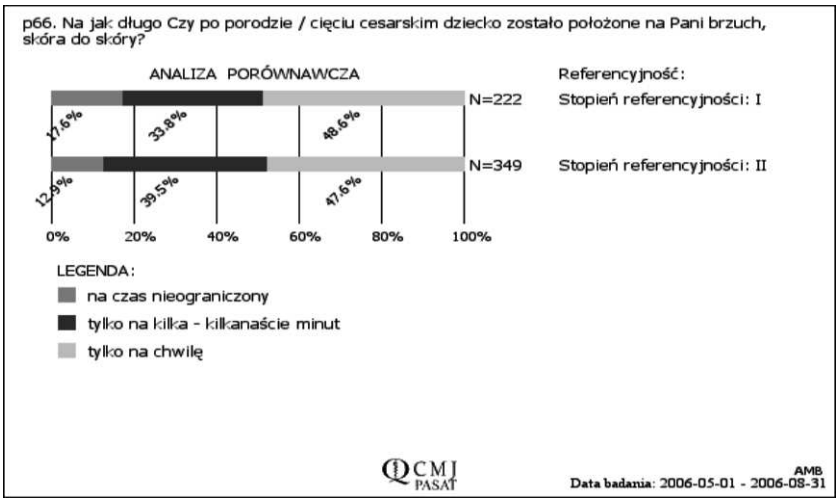

Fig. 11. Duration of leaving the baby on mother's abdomen in I° and II° referral level hospitals

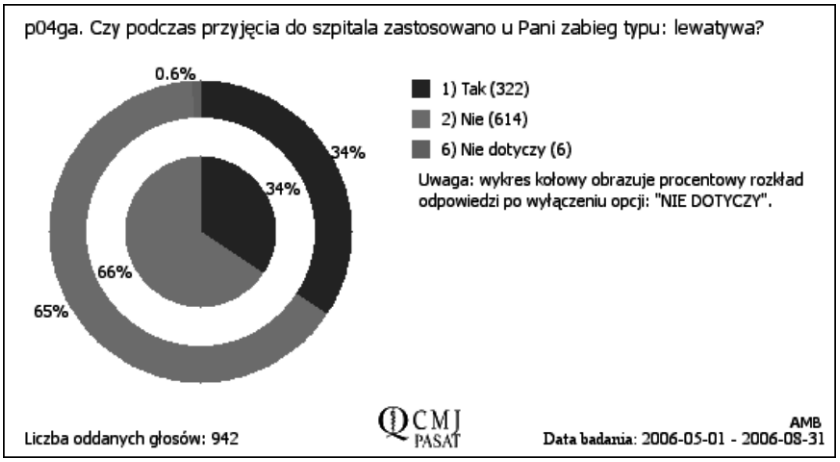

Fig. 12. Enema on admission for labor

In I° hospitals the procedure was performed in 23.2% of women in labor while as regards II° facilities, the percentage is higher and amounts to 40.6% [Fig. 13].

Pre-labor pubic area shaving

Labor shaving was performed in 471 women (50%). About 0.5% of patients did it at home [Fig. 14]. According to comparative analysis, II° level hospitals perform this procedure in 53.2% while I° hospitals in 44.9% [Fig. 15].

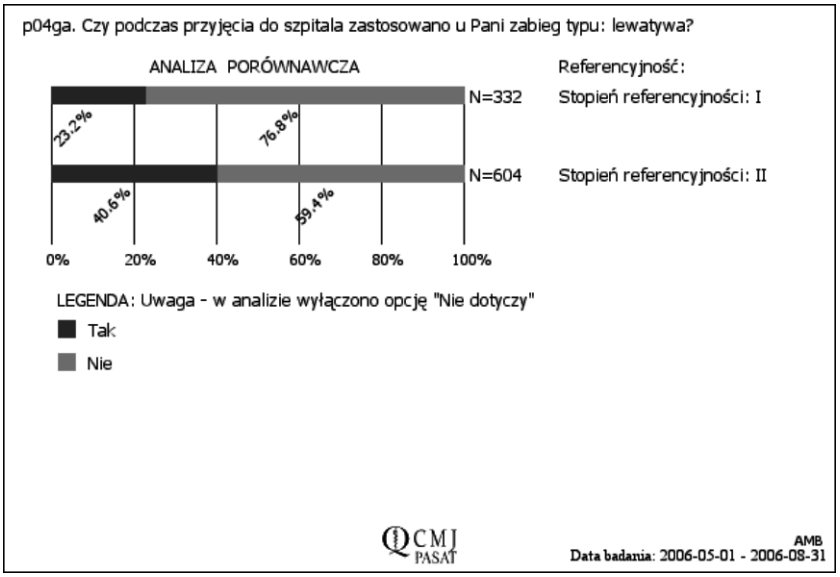

Fig. 13. Enema on admission for labor in I° and II° referral level hospitals

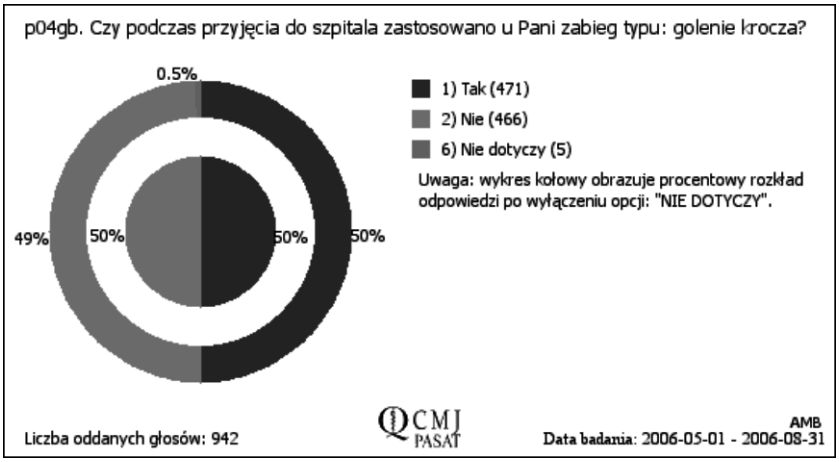

Fig. 14. Pubic area shaving on admission for labor

Quality and course of prenatal care – evaluation of differences depending on referral level

The questionnaire included an issue of patients' satisfaction from prenatal care. The question was: "did you attend ante natal clinic in the current pregnancy?". A group of 805 women (85%) answered "yes" while 137 (15%) did not attend the clinic at all [Fig. 16].

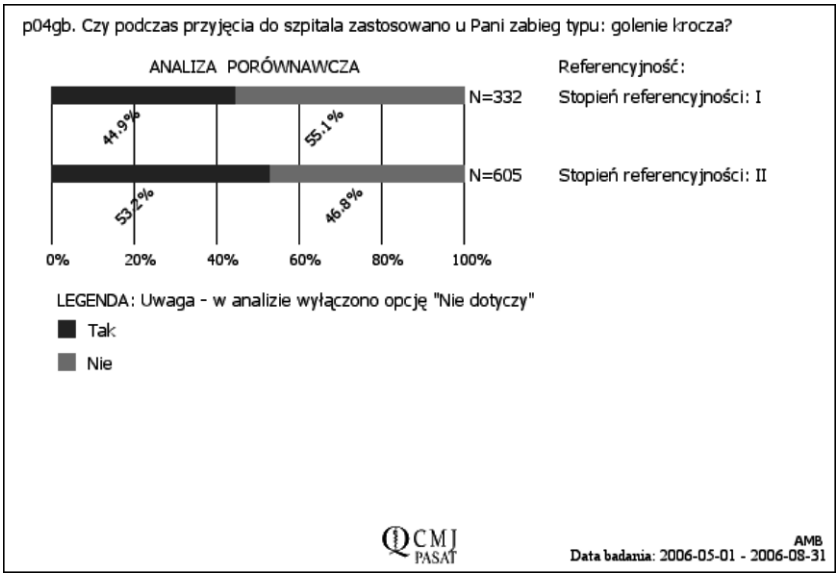

Fig. 15. Pubic area shaving on admission for labor in I° and II° referral level hospitals

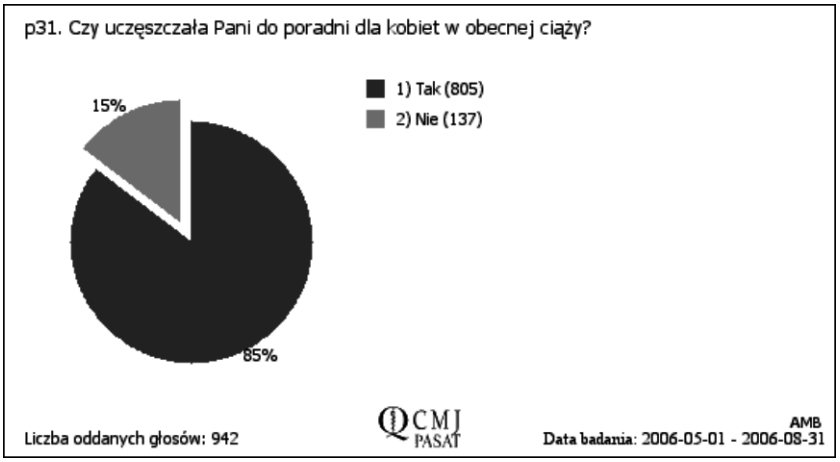

Fig. 16. "Did you attend ante natal clinic in the current pregnancy?"

As regards to women attending Woman's Health Center, 705 (87%) reported to the gynecologist regularly – every month. A group of 71 women (9%) reported to the center every two months while 35 (4%) every three months [Fig. 17].

As regards public / free clinic, its services were used by 564 women (67%) while 277 (33%) went to private paid facilities [Fig. 18].

Fig. 17. Frequency of visits in Woman's Health Center

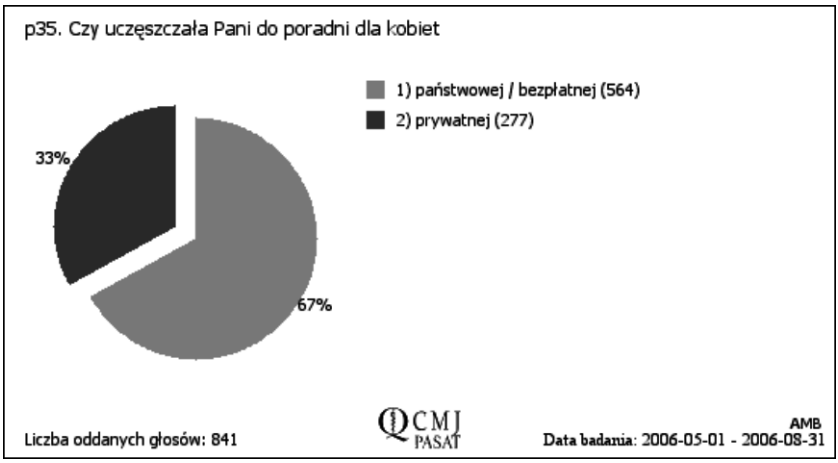

Fig. 18. Type of woman's clinic – public or private?

Discussion

According to WHO, the highest goal is the right of a unit to the best possible health and thus the right to the best possible health care. On one hand, it means that everybody ought to have access to medical services. On the other hand, the services should have proper quality.

In 1991 member states of WHO European Region accepted a regional program within the program "Health for everyone in 2000" which includes point 31 of the following content: "until 200 all the member states ought to prepare procedures and structures that will provide a constant increase in

quality of medical services as well as development and better use of medical technologies". For the said purpose, regular monitoring, evaluation and promotion of service quality are necessary [1–2].

The concept of constant quality improvement was reflected in a document compiled by WHO European Regional Committee called: "Health 21 – health for all in 21st century". The main goal is point 16 – management of medical care quality – of the following content: *"until 2010 management of health sector in member states should be oriented at health outcomes starting with health population programs to individual clinical care over a patient"* [2–3].

Attempts to evaluate the quality of health care in Poland arouse various emotions. Importantly, service quality is becoming a popular subject, improvement actions are undertaken and this is related to the increased commercialization of health service.

The term *quality* (gr. poiotes) was first defined by Plato as "certain level of perfection". In those times it was a philosophical term and is has remained this way until modern times. To put it differently, quality is a particular standard or level of perfection which constitutes a border between intentions (willingness) and possibilities (reality). Numerous philosophical disputes established the following: quality has objective and measurable features, such as mass and shape, as well as subjective which are evaluated differently by everyone, such as color or smell [4].

Quality is strictly connected with the level of satisfaction. Patient's satisfaction depends on differences between what they receive and their subjective expectations. If the difference is positive, the patient is satisfied while if it is negative – dissatisfied.

In the process of providing health services, mutual relations between a woman in labor and obstetrician/nurse might be defined according to Marć in the so called soft aspects which are: cooperation and aid in care, explaining the procedures, kindness, patience and sufficient information, which results in the expected satisfaction [5].

Labor conducted in a direct way might have impact on the evaluation of obstetric staff work. Standard procedures compiled by numerous scientific associations enable application of the most suitable solutions according to medical data which is based on evidence.

In 1985 WHO decided that optimal percentage of C-sections for saving the life and health of mothers and newborns is between 10% and 15%. One of the main arguments for the legitimacy of the increase in Caesarian sections is a decrease in perinatal mortality. However, many worldwide studies do not confirm this dependency [6].

According to Lech et al., the percentage of C-sections in the nineties of the previous century amounted to 15% in Poland, about 23% in the United States while in the years 1999–2005 in Poland it was 18.2–27.2% [7]. Wróblewski et al. show that the number of C-sections within the years 1994–2001 in Poland increased and oscillated between 13.8 and 21.1% [8]. In our material 35% of women out of 942 individuals had C-section (both not planned / emergency and planned before the labor – elective).

According to Kubicka-Kraszyńska and Otfinowska, data obtained by Childbirth with Dignity Foundation from 2003 indicate that episiotomy was performed approximately in 57.5% of labors, in 79% of primparae and 36% of multiparae [6]. In 82% of departments the percentage limit of C-sections established by WHO is exceeded. According to data from 2006, the procedure was performed in 80% [6, 9–11].

Eason et al. evaluated the influence of routine episiotomy on development of its severe damage based on Medline database from 1966–1999 [12]. They showed that episiotomy failś to both protect anal sphincter and prevent incontinence as well as that it is the cause of pain. A great study by Szamotulska and Mierzejewska conducted in 1999 on a large group of women in labor (2600) showed that routine episiotomy was performed in 72% of individuals [13]. Our material indicates similar results. Routine episiotomy was performed in 74% of all the physiological labors.

A significant problem in modern medicine is the inducement of labor. Poniedziałek-Czajkowska et al. believe that the percentage of induced labors in Poland might amount to 9.5–33%. In the United States the number of induced labors has doubled [14]. According to the participants, in the Podlasie province hospitals in 2006 a pharmacologically induced labor was performed in 39% of cases while 11% of patients had amniocentesis.

The possibility of going into labor in various positions proves high quality of obstetric care. The 17th point of WHO guidelines refers to woman's free choice of labor position [10]. Szamotulska and Mierzejewska claim the performance of metaanalysis of 19 studies which included 5764 women from different countries. The best body position in labor was studied (upright, sitting with the use of stools or labor chair, squatting or lying). The outcomes showed that upright or side-lying positions shortes the second labor stage compared with back-lying or litotomic position (lying on the back with legs up) [13].

According to the study by "Childbirth with Dignity Foundation" from 2006, women were positioned supine in 32% [6]. Suchocki et al. claim that in 71.5% women went into labor in a traditional supine position [15]. In the Podlasie province hospitals of I° and II° referral level women gave birth in

a traditional way (supine) in 75% while the other percentage referred to vertical positions. Similar data is indicated by Kubicka-Kraszyńska, Otfinowska as well as Grabarczyk et al. in studies by "Childbirth with Dignity Foundation". In 2000 49.3% of women in labor were imposed lying flat on the back position while in 2006 – 50% [6, 16].

Next analyzed aspect referred to post-labor skin-to-skin contact with a newborn. For the last decades separating newborns from mothers as well as limiting and controlling their further contact were a routine procedure. "Baby Friendly Hospitals', an initiative by WHO and UNICEF, were aimed at changing it. WHO guideline is as follows: "the mother and the baby should be in body-to-body contact immediately after the labor or within 5 minutes after it; the contact should last at least 1 hour unless medical reasons for delaying the contact occur" [6].

In hospitals within the Podlasie province 61% of women could hold the newborn immediately after the labor. The babies remained with their mothers for "unlimited time" only in 15% of cases, "for a dozen or so minutes" in 37% of the cases while in the other cases "only for a moment". It was observed that early skin-to-skin contact of mothers and their healthy babies has a positive influence of the newborn in further hours of life, on breastfeeding in 1–3 months after the labor and on better interactions between a mother and the baby [13, 17]. Mikiel-Kostyra et al. in the study of dependencies between newborn feeding and post-labor procedures in hospitals evaluated implementation of skin-to-skin contact indications which in the studied group amounted to 77.2% [18].

Conclusions

1) The analysis confirms that patients' level of satisfaction from perinatal care in the Podlasie province is satisfactory.
2) Improvement and educational actions are necessary as regards to the implementation of WHO guidelines in terms of:
   a) decreasing the percentage of Caesarian sections
   b) decreasing medical interventions by reduction in the percentage of induced labors
   c) encouraging pregnant women to go into physiological labor in vertical positions.

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Clinical department information system's internal structure

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Abstract. The construction of an advanced information system supporting the work of a clinic is a great challenge. Particularly, after the initial determination of the functionality of the system, its internal structure must be designed. For the major elements of the system their interaction must be also accurately determined.

Introduction

In the middle of the 20$^{\text{th}}$ century the first modern general-purpose computing machines were created. The first computers were much more bulky than those used today and had a low computational speed. Since then, computers underwent tremendous, almost exponential evolution. With the new capabilities of hardware its software is also subject to the process of development. In today's world the computer has become a tool for everyday use. The ongoing process of computerization and the growth of user requirements force the development of information systems of increasing complexity.

Many modern fields of human activity, including medicine, benefit from the ongoing process of computerization. Modern hospital information systems (HIS) [2] are the example of this. The task of the described here JeNaK system (from Polish "Jednostka Naukowo-Kliniczna" – "Clinical Science Unit") is a comprehensive management of the medical university's selected clinical unit. Creation of such a complex system poses a great challenge, therefore, during work on each of the elements of the system, modern software engineering tools, including UML modeling language, were used. The aim of this article is to describe the internal structure of the proposed system. Selected class diagrams of key system elements will be described in detail.

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Application in medicine and engineering systems

Informatics systems engineering took shape thanks to the development of hardware capabilities which induce the evolution and growth of software complexity. It was quickly noted that the creation of such systems, possible thanks to the work of many programmers, but without an adequate methodological background, often leads to failure [5]. This led to the emergence of software engineering. Standardization of the software creation process had found its culmination in the establishment of the Universal Modeling Language (UML). UML version 2.2 [1] describes informatics system by means of 14 diagrams representing various aspects of the modeled system.

With the software development, first systems, supporting the work of hospitals emerged. They were used for cost accounting and hospital management by *stricte* economic mean [6]. Since then, these systems have undergone a profound evolution. Most modern HIS focuses its attention around medical and organizational information flow, crucial to hospital operation as a therapeutic unit. They allow for e.g. to store patient information, his/her medical history, or treatments. Nowadays, there are many hospital information systems. Most of them supports the standard methods for exchanging information such as DICOM [4] or HL7 [3].

Despite the diversity of available HIS, there is no system so far that would support the clinical aspect of the specified hospital unit. In contrast to the typical HIS, the JeNaK system not only assists the work of doctors and hospital, but also takes into account the presence of scientists, teachers and technical workers of the clinic, and also taught students. Due to the nature of the clinical unit, the JeNaK system includes collection, storage and processing of various data relevant to this unit type.

JeNaK system structure

After a detailed analysis of potential user's requirements through the use case diagrams [8], the next step is to build class diagrams – the basic components of the system. These diagrams describe the internal, static fabric of the proposed system. Actual structure of the clinical unit, internal dependencies, relationships and functions should be directly reflected in classes.

Concepts of class and object are key issues in modern software engineering. They define the paradigm of object-oriented programming (OOP), with its many consequences. The class, often identified simply as a type, is

a description, which allows creating its representation (instances) – objects, that exists in the computer machine memory. Class binds information related to the current state of an object with its functionality, which allows for internally consistent change of that state. The state is described by the so-called class fields and functionality through the methods.

Typically, most of the fields and class methods that can be used need an object to operate on it. Most classes have special methods that are executed when an instance is created or is destroyed. These special methods are the constructor (in C++ it has the same name as class) and the destructor (in C++ it has name of the class presided with tilde). There are usually a number of constructors, but only one destructor is defined. In addition, some classes have fields or methods that are shared by all objects of the class, without affecting their internal state. They are called static fields/methods. To read/execute them, an object is not needed, only the class itself. UML represents a class with a rectangle divided into three smaller sections by horizontal lines [Fig. 1]. Upper section defines class name, the middle – all fields of the class, the bottom – all of its methods. Depending on the level of detail, a description of the types of fields and types of values returned by the method (after the colon) and the arguments of the method (as a comma separated list, each argument is described by its name and type after the colon) can be presented as well. Static methods/fields are underlined.

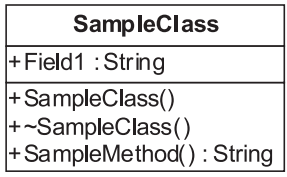

Fig. 1. Simple class diagram

In addition to the class concept, an important part of OOP is data encapsulation (hiding). Typically, the internal state of the object and part of its functionality should be protected from outside access. This makes the management of information flow within the program significantly easier. Three types of access specifications [Fig. 2] are defined (UML designation in parentheses):

- public (+) – a method or field is available for other objects from the outside
- protected (#) – a method or field is available for objects whose class is derived (inherits) from the current class

- private (–) – a method or field is available only to the methods of the class.

The C++ language, which was chosen by the authors as the target programming language of the JeNaK system, allows for the weakening of this mechanism, when it is preferred due to the readability of the code and its performance. A class can grant access to protected or private methods to another class by declaring it as a "friend" [Fig. 2].

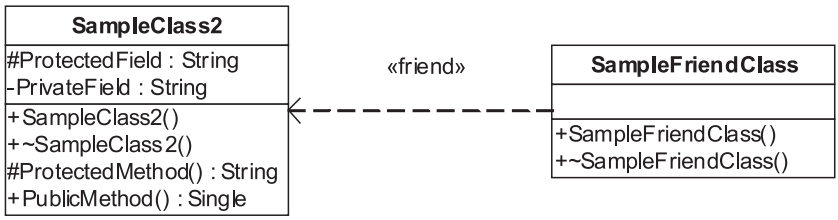

Fig. 2. Simple class diagram with friend and different function/members kinds

Another important OOP issue is interdependence of classes and objects. This relationship is (usually) a logical consequence of the real dependence of the modeled system. Dependence at the class level (the fact of inheritance), and at the object level (relation or inclusion) is distinguished.

Inheritance – "is a" dependency – occurs in arrangement of two classes, when one of them – subclass – is extended or specialized form of another – a super class [Fig. 3a]. Languages supporting OOP allow to treat each child class object (the car in [Fig. 3a]) as the parent class object (vehicle in [Fig. 3a]) – this is polymorphism mechanism. The above mentioned specialization may involve redefining some methods, or changeing their action in relation to the original class. Borderline case of such dependency are the so-called abstract classes, which represent only the method names (that is, the expected functionality), without defining their actions. Instances of such classes cannot be created, but objects, which class derives from it, can be treated as representatives of these classes, according to the mechanism of polymorphism. C++ allows the inheritance from multiple base classes. The fact of inheritance is depicted on class diagram by an arrow with a blank tip directed from the sub class to a super class. The name of an abstract class is written in *italics*.

A link represents a loose association between objects [Fig. 3b]. Usually, it is a functional relationship. A more specialized form of link is inclusion. Two kinds of objects inclusion – composition and aggregation can be listed. Aggregation [Fig. 3c] occurs when an object holds references to other objects, but the lifetime of those objects is independent. Composi-

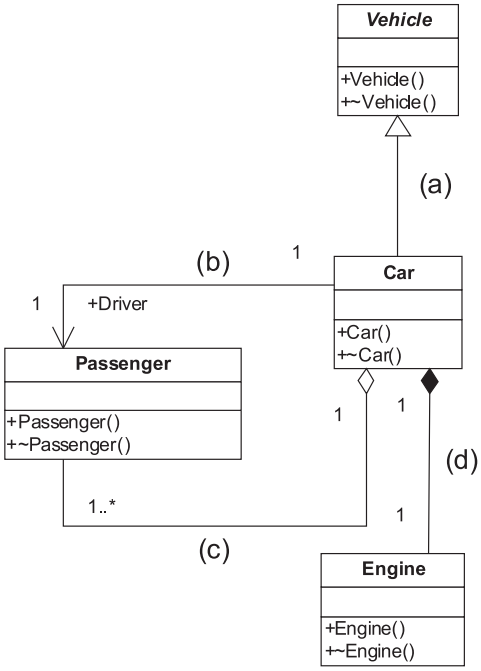

Fig. 3. (a) Inheritance (b) Dependence (c) Aggregation (d) Composition Example

tion [Fig. 3d] is inclusion with a strong dependence of the lifetime of the objects. This means that with the destruction of the container object, contained instances are also destroyed.

The link between objects is represented as a line (or arrow) connecting class boxes. If necessary, higher order associations (not binary) can be drawn with more than two ends by connecting all lines to the central diamond. If named, the line can be adorned with a brief description of relation. The aggregation is determined by adding the hollow diamond-like sign at the container-class end of the line. The composition is similar, but the sign is filled. In case of aggregation and composition, usually quantities of associated objects are determined. Numbers inserted near description of a class means a count of instance occurrence. Frequencies are presented in the following forms (n and m are numbers, $n \leq m$):

- $n..m$ – opposite object contain from n to m instances of this object
- $n..*$ – opposite object contain n or more instances of this object
- n – opposite object contain exactly n instances of this object
- * – opposite object contain 0 or more instances of this object (same as 0..*)

As it has been already mentioned, the class diagram translates real relationships and dependencies to the internal structure of the system. There are many rules for handling such translation. One of the easiest is to treat each noun within the use case diagram as a potential class, and a verb as a method of this class. Class diagrams presented below were developed after a detailed analysis of the system use cases.

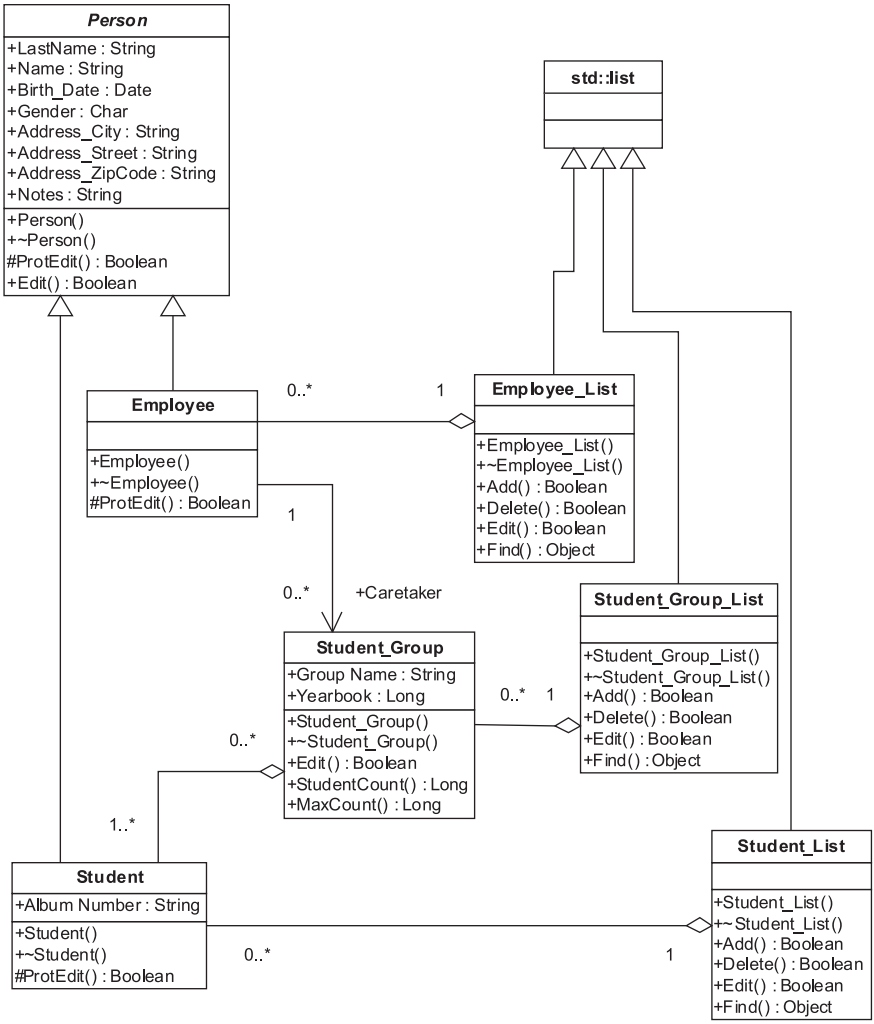

Fig. 4. Class diagram of list containers

On the first diagram [Fig. 4] the structure of the list containers is presented. Abstract class *Person* is created to store basic personal data of students and employers. Two specialized classes – *Student* and *Employee*

inherit from it. In addition, the *Student_Group* class, which stores the information about the student-in-group organization is presented. All of these 3 classes have their list containers (*Employee_List*, *Student_List* and *Student_Group_List*) which are used to manage the whole sets of it. These classes are derived from one standard C++ class named std::list. Worth noticing is the fact that each student can belong to many groups. This situation is necessary to reflect that a student can be a participant of many courses (including the elected ones) that can spread across many years of study.

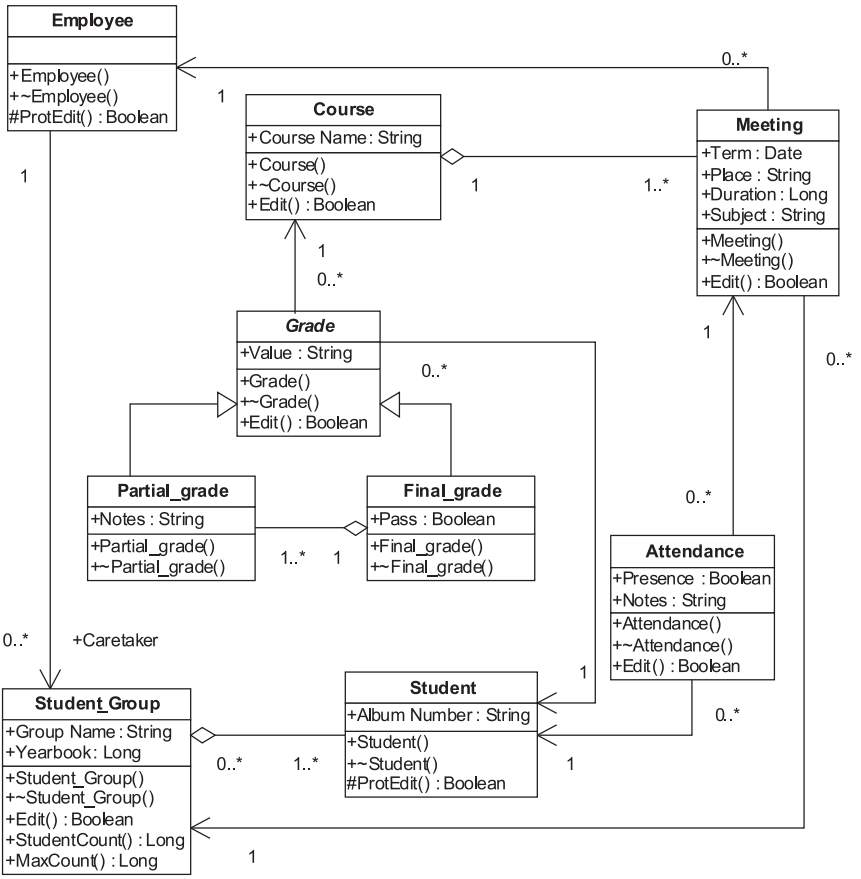

Fig. 5. Class diagram of student evaluation data

Diagram presented on [Fig. 5] shows the dependencies between classes responsible for the storage of student evaluation data. Students participate in courses organized in groups. Each course consists of many meetings during which course material is presented to students. The presence of each student at each meetings is recorded by means of a special class called

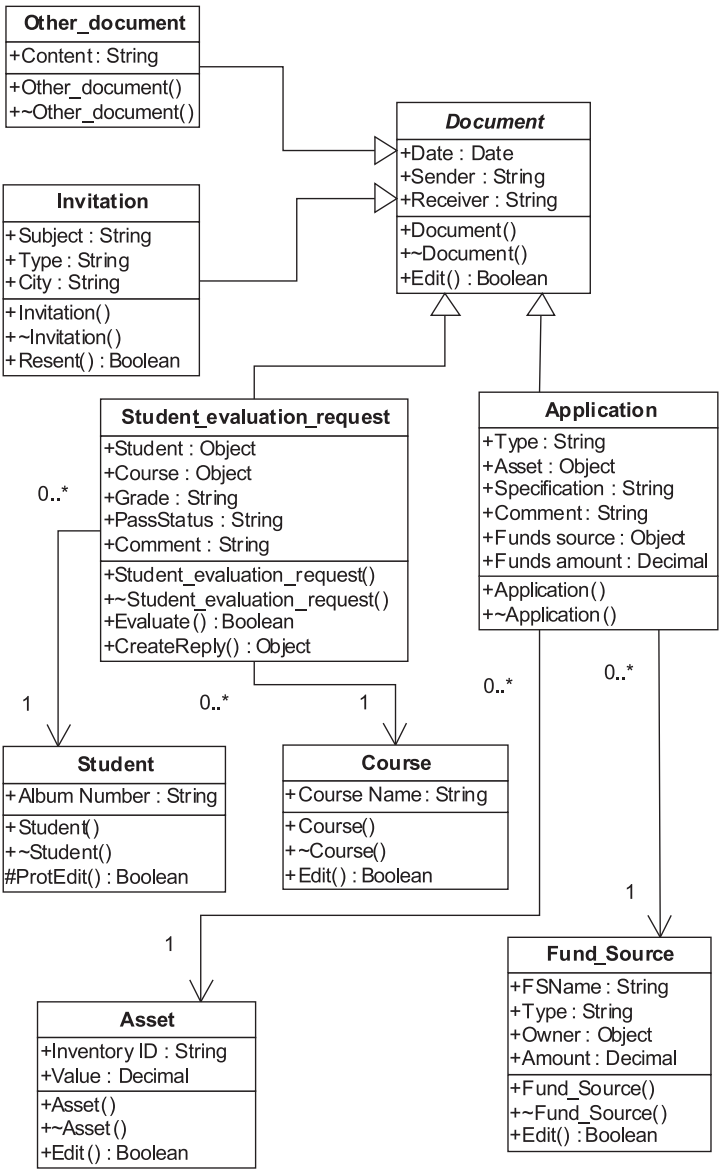

Fig. 6. Class diagram of the mail document derived classes

Attendance. Abstract class *Grade* is used by derived classes *Partial_Grade* and *Final_Grade* to hold respectively partial and final evaluation results. Every grade is related to a course and a student which shows which of them it concerns. The final grade consists of many partial grades and contains additional field that determines if the student passed the course or not.

[Fig. 6] presents many particular classes that derive from one abstract class *Document*. This class is used to support any ingoing and outgoing paper mail documents. Most specialized classes that inherit from it is the *Student_Evaluation_Request* which can be used to obtain, handle and prepare a replay for requests about particular students' results. A pecial method called *Evaluate* can be used to provide adequate reply data and comment to the document. Another method, called the *CreateReply* is able to create a new document containing the reply for the request and fill it with provided earlier data. The class itself is related to the Student and Course classes which enable to point particular student and course which relate to the question.

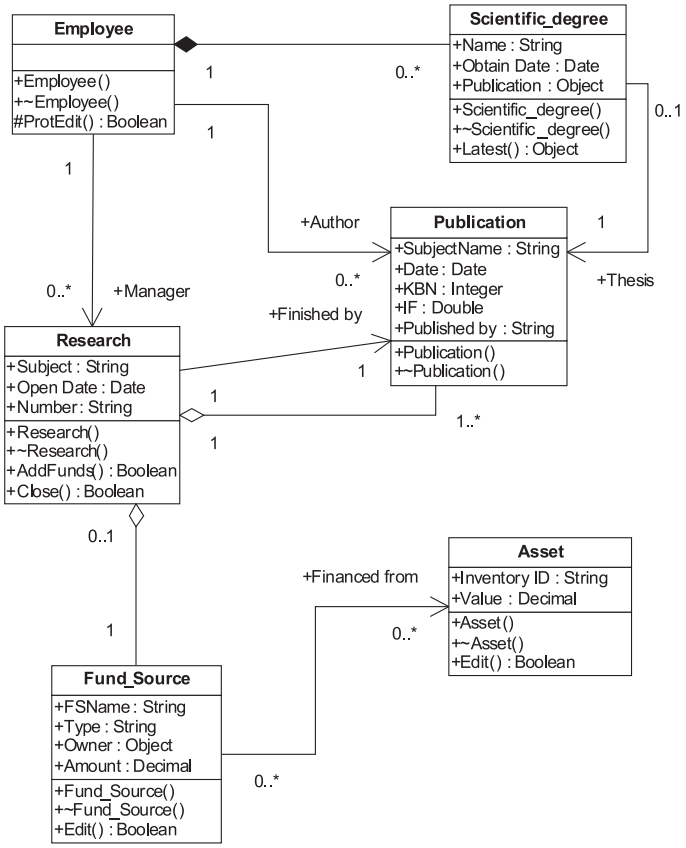

Fig. 7. Class diagram of scientific data

Last diagram [Fig. 7] shows the structure used to store the scientific achievement data of each employee. The composition between *Employee*

and *Scientific_degree* classes perfectly reflects the life-time dependency that forces all degrees to be deleted in case of employee deletion. Any publication can be linked to the research but only one can be used as a settlement and finish it.

Conclusions

The JeNaK system was designed to supplement the typical HIS with the administrative, scientific and didactic aspects of the clinical unit. In the paper, a technical draft of selected modules of the system was outlined. Efforts have been made to make it compatible to the user's requirements described in previous articles [7–8]. Further research is required to create class diagrams for the communication with HIS using standard DICOM and HL7 protocols module. In the longer term, ongoing work will focus on the implementation of the system and its deployment in selected clinical units of the Medical University of Bialystok.

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