# DEVELOPMENT OF A MATHEMATICAL MODEL FOR PREDICTING POSTOPERATIVE PAIN AMONG PATIENTS WITH LIMB INJURIES

*Розроблено математичну модель прогнозування ймовірності розвитку післяопераційного болю у пацієнтів молодого віку, оперованих в плановому порядку з приводу травм кінцівок. В якості предикторів моделі обрані: рівень болю до операції, визначений за візуальною аналоговою шкалою, результат оцінки когнітивних здібностей за Монреальською шкалою та рівень середнього артеріального тиску*

*Ключові слова: післяопераційний біль, травма кінцівок, пацієнти молодого віку, анестезія, прогнозування, логістична регресія*

*Разработана математическая модель прогнозирования вероятности развития послеоперационной боли у пациентов молодого возраста, оперированных в плановом порядке по поводу травм конечностей. В качестве предикторов модели выбраны: уровень боли до операции, определенный по визуальной аналоговой шкале, результат оценки когнитивных способностей по Монреальской шкале и уровень среднего артериального давления*

*Ключевые слова: послеоперационная боль, травма конечностей, пациенты молодого возраста, анестезия, прогнозирование, логистическая регрессия*

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## 1. Introduction

It is known that the limb injuries comprise a significant share in the structure of morbidity among the persons of young age, and the results of surgical treatment to a large degree depend on the chosen method for the provision of anesthesiology, as well as on the quality of postoperative analgesia [1]. In order to effectively control the postoperative pain, it is better to use multimodal analgesia, which is attained by combining a few analgesics, acting through a variety of mechanisms (for example, opioids, NSAIDs) and local anesthetics), and predetermines development of fewer side effects [2].

According to the scientific literature, from 30 to 75 % of patients suffer from pronounced pain in the post-surgical period, and 40.7 % of patients who underwent scheduled and emergency operations, expressed dissatisfaction with the quality of postoperative analgesia [3]. The tasks for postoperative pain relief include improving life quality of patients during the postoperative period, acceleration of postoperative functional rehabilitation, reducing the frequency of postoperative complications, accelerating the discharge of patients from clinic.

Given the complexity of constructing an adequate mathematical description that might be used to predict the probability of pain development after surgery, we find it relevant to define independent predictors and modeling technique, which would make it possible, under conditions of multifactoriality and uncertainty of parameters, to build a quality

predictive model to prevent the development of pain, as well as its early quenching.

## 2. Literature review and problem statement

Assessment of pain is an important element of the post-operative analgesia. In a daily clinical practice, visual scales are commonly used [4], of which the most wide-spread one is the 10-point (or 100-point) visual-analog scale (VAS). This scale is a line segment of length 10 cm (100 mm) whose beginning is denoted as "no pain" and the end as "excruciating pain." A patient makes a mark in this section at the point that reflects the intensity of his/her pain [5].

To determine prediction in the development of postoperative pain syndrome, neural network models are employed that are based on the Kohonen self-organizing maps, which enables to identify the most meaningful indicators and determine their position in a general structure of a multi-dimensional feature space [6]. In this case, however, the postoperative pain syndrome is not assessed.

Comprehensive evaluation of the nature and intensity of the patient's pain is possible by using special questionnaires [7] and scales [8]. Their application may help to quantitatively correct assess pain severity of the patient in the current moment, but none of the questionnaires is aimed at predicting the level of pain after the operation.

Many researchers who study the issue of algology, tried to predict pain syndrome to ensure adequate analgesia in postoperative period.

The distinctiveness of postoperative pain syndrome [9] is determined based on the index of nociception (IN):

$$IN = \frac{S}{L}, \qquad (1)$$

where S is the surface area of the body, L is the length of the operating wound.

The surface area of the body $S$ is calculated by formula:

$$S = 71{,}84 \cdot V^{0,425} \cdot Z^{0,725}, \qquad (2)$$

where V is the weight, Z is the height.

When the values of IN exceed 20, a low level of pain by VAS in the postoperative period is predicted. Values of IN=20 and lower indicate a high level of pain after the operation. However, this method allows determining the pain syndrome only after the end of operational intervention.

There are data on the existence and distinctiveness of such psychological characteristics as apathetic and sensitive type of attitude towards the disease, reaction of social protection in the structure of situational anxiety and phobic component of personal anxiety [10], which allow prediction of the pain syndrome severity in the early postoperative period.

The prognostically unfavorable factors in the development of intensive postoperative pain syndrome are the duration of operation, physiological status by ASA and the fear of future operational intervention [11].

Distinctiveness of preoperative pain, anxiety, age of the patient, as well as the type of surgery, are the four essential determinants in the prediction of postoperative pain [12]. The type of operation, patient's age and the presence of psychological stress, according to these researchers, were important for the postoperative analgesic consumption.

However, despite all of the aforementioned, the effectiveness of models proposed for the pain prediction amounted to 54 % only, that is, they did not work out for practically every second patient. Thus, despite a significant number of factors that correlate with pain, there is no a unified approach to address the issue of predicting pain yet. This state of things necessitates conducting research that is more energetic and employs convincing methods.

To predict the level of pain in the postoperative period, it is possible to use the methodology for the verbal analysis of solutions [13], as well as various statistical methods that demonstrated their robustness when solving similar medical tasks, in particular discriminant [14] and [15] regression analyses. Despite the achievements in the field of classification and analysis of the informativeness of medical data by the means of discriminant analysis [16], there are a number of restraining factors. Certain measurement may be closely related (correlated). All this leads to the degeneration or poor conditionality in the ratings of covariance matrices (poorly conditioned problems). Poor conditionality is a restraining factor when using the methods of discriminant analysis, as well as a number of other similar mathematical methods [17].

One of the appropriate methods for analysis of such links is the method of logistic regression. Compared with the discriminant analysis, this approach has the advantage that is in much less stringent restrictions, and therefore has a wider scope of application.

Thus, determining the factors that significantly affect the probability of development of postoperative pain, as well as their predictive significance, should be addressed employing the method of binary logistic regression.

## 3. The aim and tasks of the study

The aim of present research is to devise a mathematical model for predicting the probability of development of postoperative pain and to assess effectiveness of its application for young patients with limb injuries.

To achieve the set aim, the following tasks were formulated:

– to explore the current state of postoperative pain development, depending on the method of anesthesiological provision;

– to determine predictors that affect pain after the operation, and to assess contribution of each of them to the probability of development of postoperative pain among young patients with limb injuries;

– to identify possibilities for the implementation of the developed mathematical model for predicting the probability of development of postoperative pain among young patients with limb injuries into clinical practice and to evaluate the prospects of its application.

## 4. Materials and methods of research

The research was conducted based on anesthesiology and intensive therapy unit at KZOZ "Kharkiv Regional Clinical Traumatological Hospital" (Ukraine), Department of Pediatrics Anesthesiology and Intensive Therapy at the Kharkiv Medical Academy of Postgraduate Education (Ukraine) during 2013–2015 in conjunction with the Department of

Biomedical Engineering of the Kharkov National University of Radioelectronics (Ukraine).

After receiving consent to participate in the study, we invited 102 patients, 72 men (70.6 %) and 30 women (29.4 %), of average age 33.5±0.7 years, who were treated with the planned operation for metal osteosynthesis caused by the traumatic limb injuries (38 patients had injuries on the upper limb, 64 – on the lower limb).

The criteria for inclusion in the study were as follows: age from 18 to 45; planned surgery on the upper and lower limbs (metal osteosynthesis) caused by injuries; duration of surgical intervention exceeding 60 minutes; the type of anesthesia (regional anesthesia, regional anesthesia with sedation, intravenous anesthesia); informed consent to participate in the study and comprehension of the essence of psychometric techniques and VAS.

The exclusion criteria were as follows: diabetes mellitus, myocardial infarction, lung disease, neurological disorders, impaired vision and hearing; repeated surgery; the use of tranquilizers, antidepressants, nootropics; alcoholism, medicinal and drug addiction; pain syndrome, not associated with trauma and surgery.

By age, gender, anthropometric characteristics, educational level, amount and duration of surgical intervention, patients in groups did not differ (p>0.05). All the examined patients belonged to the classes I–II by ASA (American Society of Anesthesiologists).

Among the accompanying pathology, the examined patients had hypertensive disease (5.9 %), obesity (11.8 %), duodenal ulcer in remission (2.0 %), and chronic gastritis (1.0 %). By the concomitant pathology, patients in the groups did not vary much (p>0.05).

All patients were exposed to the premedication in the hospital room the night before the surgery: per os phenazepam 0.03±0.001 mg/kg, and on the operating table atropine was intravenously applied – 0.006±0.001 mg/kg, diphenhydramine – 0.13±0.004 mg/kg, diazepam – 0.13± ±0.002 mg/kg, omnopon – 0.3±0.005 mg/kg.

The mean duration of surgical intervention was 96.07± ±4.53 min.

In the perioperative period, for the purpose of anesthesia, dexketoprophenum was prescribed in the dose of 50 mg intramuscularly; optionally, a 2 % omnopon was added (in the postoperative period) in the dose of 20 mg intramuscularly.

Perioperative monitoring included control of systolic (APs), diastolic (APd) and mean arterial blood pressure (MAP) by the non-invasive method, the heart rate (HR), electrocardiography and pulseoximeter ($SpO_2$) using the monitor G3L (Heaco, United Kingdom).

The level of pain by VAS was estimated before the surgery and on the first recovery day. In the postoperative period, in each group of patients, we calculated the total dose of the introduced non-narcotic (dexketoprophenum) analgesics and registered the number of patients who required the introduction of narcotic analgesics (omnopon).

The testing of cognitive functions among the patients was carried out using a Montreal scale of cognitive assessment (MOCA), method of "short-term memory" (SM) and "numerical square" (NS) in the first half of the day before the surgery and on the first day after the operation. MOCA is designed for rapid screening of mild cognitive impairment and consists of subtests, which assess a variety of cognitive functions: attention and concentration, executive functions, memory, speech, optical-spatial activities, abstract thinking, counting and orientation.

In order to detect predictors of pain development after the operation, we employed a method of logistic regression with the calculation of ratio of chances (RC), the 95 % limit of confidence interval (CI) and the value of criterion of statistical significance. To explore quality of the synthesized mathematical model, we performed a ROC-analysis (receiver operating characteristic, analysis of operating characteristic curve).

## 5. Mathematical modeling of probability of pain development after surgery

When carrying out logistic regression analysis, we included the following predictors: APs, APd, MAP, HR, $SpO_2$, level of pain by the VAS scale, testing results of cognitive functions using the MOCA scale, methods of SM and NS, which were defined prior to the operation.

All patients were divided into two groups:

– the first group of patients whose level of pain after the operation amounted to not more than 3 points by VAS – 14 people;

– the second group of patients whose level of pain after the operation by VAS exceeded 3 points – 88 persons.

We identified the following parameters before the surgery as the factors associated with the risk of pain development after the operation: MAP, VAS, MOCA (Table 1).

Table 1

Independent predictors of logistic regression binary equation for determining individual risk of pain development after surgery

| Risk factors of pain development after surgery | Regression coefficient | RC (95 % CI) | P |
|---|---|---|---|
| MAP before operation | −0.006 | 0.904 (0.805−0.994) | 0.048 |
| MOCA before operation | 1.250 | 3.492 (1.893−6.440) | 0.001 |
| VAS before operation | 0.172 | 1.664 (1.050−2.640) | 0.030 |

The negative coefficient of regression related to MAP before operation characterizes it as a factor that reduces the probability of pain development. Not a less important fact is that we detected high statistically significant relation between the pain development after the operation and result of the MOCA test before the operation (RC=3.492, p<0.001). It should be noted that RC of all the selected independent predictors is statistically significant because the 95 % CI for RC did not include unity: values of the lower and upper limits of DI predictors of MOCA before the operation are larger than 1, and both limits of DI of the MAP predictor before the operation is less than 1.

Therefore, our equation takes the form:

$$\hat{P} = \left[ 1 + e^{-(-0,006 \cdot x_1 + 0,172 \cdot x_2 + 1,250 \cdot x_3 - 28,716)} \right]^{-1}, \qquad (3)$$

where $\hat{P}$ is the probability of development of postoperative pain, $x_1$ is the MAP before operation, $x_2$ is the VAS before operation, $x_3$ is the MOCA before operation.

It is established that all the predictors affect the pain development after the operation at the level of p<0.05 (Table 1).

The Cox and Shell, Nigelkerk indicators (Table 2) are the measures of certainty. They point to the part of variance that can be explained using logistic regression.

Table 2

Characteristics of binary logistic regression model devised for determining the risk of pain development after operation

| −2 Log Credibility | The Cox and Shell R square | The Nigelkerk R square |
|---|---|---|
| 33.774 | 0.374 | 0.680 |

A measure of certainty by Cox and Shell has the disadvantage in that the value equal to 1 is theoretically not attainable; this shortcoming was resolved due to the modification of this event by the Nigelkerk method. Part of the dispersion, understandable with the help of logistic regression, in our case is 68.0 %.

The Cox and Shell indicator was determined as:

$$R^2 = 1 - \left(\frac{-2LL_{null}}{-2LL_k}\right)^{2/n}. \qquad (4)$$

A problem of using the Cox and Shell indicator is in the fact that its maximum can be less than 1.0, which is difficult to interpret as the result. That is why the Nigelkerk indicator is designed as a modified version of Cox and Shell, which varies from 0 to 1 and is usually larger than the measure of Cox and Shell.

The Nigelkerk indicator was found as:

$$R^2 = \frac{1 - \left(\frac{-2LL_{null}}{-2LL_k}\right)^{2/n}}{1 - \left(-2LL_{null}\right)^{2/n}}. \qquad (5)$$

Fig. 1 shows a classification diagram.

Symbols: 1 – no pain after operation (VAS≤3); 2 – pain after operation (VAS>3). Division point was the value of p=0.5.
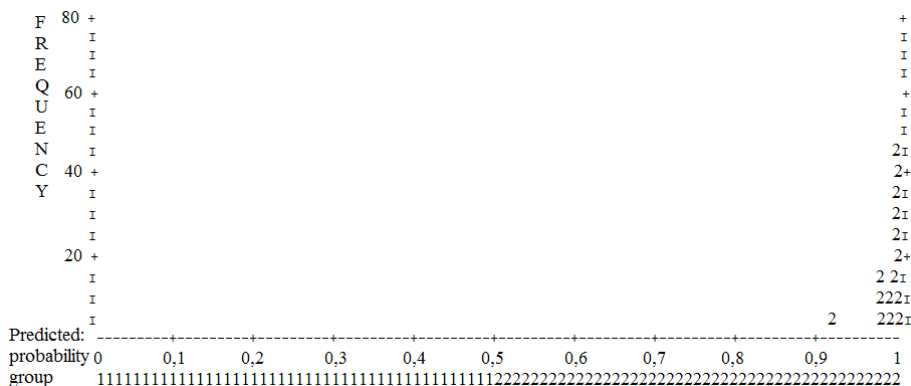


Fig. 1. Classification diagram

Along the horizontal axis we pointed the values of predicted probability that are calculated by the regression equation, along the vertical axis – frequency. Thus, each column in the diagram corresponds to a particular predicted probability, and its height – to the number of objects, for which this possibility is predicted. The closer the values of the predicted probability to unity, the more probable is the

development of postoperative pain syndrome among the traumatological patients of young age.

The number of correct and incorrect predictions can be considered by the classification Table 3.

Table 3

Classification results of the binary logistic regression model created for determining the risk of pain development after operation

| Observed | | Predicted | | |
|---|---|---|---|---|
| | | Group | | Percent of correct |
| | | 1.00 | 2.00 | |
| Group | 1.00 | 10 | 4 | 71.4 |
| | 2.00 | 2 | 86 | 97.7 |
| Total | | 12 | 90 | 94.1 |

We can conclude from Table 3 that out of total number of patients of the first group who did not feel pain after the operation, equal to 14, 10 were determined by the test and 4 were mistakenly attributed to the group of patients who experienced pain after the operation. Out of the total number of patients who experienced pain after the operation, equal to 88, 86 were determined by the test while 2 were mistakenly attributed to the group of patients who did not experience pain after the operation. In general, 96 cases out of 102 were detected correctly and it is equal to 94.1 %.

Overall assessment of the alignment between the effect of risk factors found in the model and actually registered occurrence of adverse outcome was carried out using the Hosmer-Lemeshow goodness of fit test ($H_L$), in which the value of p is the higher the less are the differences between frequency of the observed and predicted results based on data of the regression model.

The Hosmer-Lemeshow criterion that shows the degree of difference between the estimated and actual values of the dependent variable for both groups (the values of binary variable 0 and 1) is determined as:

$$H_L = \sum_{j=1}^{g} \frac{\left(O_j - E_j\right)^2}{E_j \cdot (1 - E_j / n_j)}, \qquad (6)$$

where $n_j$ is the number of observations in the jth group; $O_j = \sum_i y_{ij}$ is the observed number of cases in the jth group; $E_j = \sum_i \hat{p}_{ij}$ is the expected number of cases in the jth group.

In accordance with the obtained $O_j$ and $E_j$, for each step we calculated the values of the Hosmer-Lemeshow criterion (Table 4).

The resulting low value of $H_L = 8.251$, at the significance level p>0.05 (p=0.409), indicates acceptable quality of the selected model.

Table 4

The Hosmer-Lemeshow criterion

| $H_L$ | Degrees of freedom | Significance, p |
|---|---|---|
| 8.251 | 8 | 0.409 |

In order to assess effectiveness of the model, we also used a ROC-analysis. The value of area under the curve AUC (Area Under Curve) amounted to 0.950.

Roc-analysis of the received model (Fig. 2, Table 5) revealed its characteristics, which are an indicator of excellent quality of the examined model.

Table 5

ROC-analysis results

| Area | Standard error | Signifi-cance, p | 95 % credibility interval | |
|------|----------------|------------------|-----------|-------------|
| | | | Lower limit | Upper limit |
| 0.950 | 0.034 | 0.001 | 0.883 | 1.000 |

The test sensitivity is 97 %, specificity – 71 %, value of the area under the ROC-curve, which allows assessing the diagnostic (predictive) value of this model, was 0.95 (0.88; 1.00) that testifies to the excellent quality of the model.
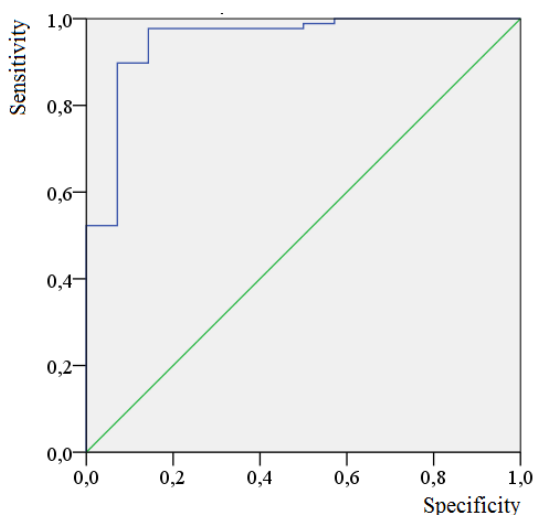


Fig. 2. ROC-curve

In Fig. 2, green diagonal line corresponds to the "vain" classificator, that is, complete indistinguishability between two groups; blue curve is the ROC-curve.

Thus, determining the level of pain by VAS, the MAP measurement and evaluation of cognitive functions by the MOCA-test before operation allows the prediction of probability of pain development after the operation. The developed model, which assesses individual risk of pain development after operation, will make it possible to improve tactics for treating the patients, assess the need for medical anesthetizing.

**6. Discussion of results of applying the devised mathematical model for the prediction of postoperative pain syndrome development**

The developed mathematical model (3) was applied to predict the level of pain by VAS in the postoperative period among the patients of young age before conducting planned operations of metal osteosynthesis caused by the traumatic limb injuries at KZOZ "Kharkiv Regional Clinical Traumatological Hospital".

The VAS, MOCA and MAP indicators were determined for all patients.

According to the results of mathematical modeling, the patients were given appropriate anesthesiological provision in the perioperative period.

After the operation, we also determined the level of pain by VAS. Results of comparison between the predicted and observed level of pain after the operation are given in Table 6.

Table 6

Classification results of the model on the test sample

| Observed level of pain | Predicted level of pain | | Per cent of predicted correctly |
|------------------------|-------------|-------------|---------------------------------|
| | VAS≤3 | VAS>3 | |
| VAS≤3 | 9 | 0 | 100.0 |
| VAS>3 | 1 | 21 | 95.2 |

Thus, results of predicting the pain level by VAS in the postoperative period among patients of young age were confirmed in 96.7 % of the patients. In other words, the application of the developed model allows predicting the level of pain after operation by the values of VAS, MOCA and MAP indicators before the operation, which makes it possible to improve quality of providing the patients with anesthesiological assistance.

The results obtained allow us to understand better the peculiarities of development of postoperative pain among patients of young age with limb injuries. Promising tasks are to determine important factors and to synthesize mathematical models for predicting the level of pain among patients after operations of different types and in different age groups.

The results obtained will be used in the development of information decision support system for a physician-anaesthesiologist for the objectification and automation of the process of determining the probability of development of postoperative pain syndrome. The implementation of such a system into clinical practice will enhance quality of anesthesia for patients, operated on for limb injuries, due to the personalization of treatment, reduction of load and side effects of medicines among patients whose VAS value after the operation does not exceed 3 points, and conducting more adequate analgesia among patients with a higher value of VAS.

**7. Conclusions**

1. It was found that the problem of predicting development of postoperative pain among patients is very serious and there are serious obstacles on the way towards its effective solution. They are related primarily to the large number of factors that correlate with the pain, and the lack of uniform mathematical approach to the prediction of pain.

2. Here we proved the possibility to predict probability of development of postoperative pain by using visual analog scale, MOCA-test and the level of the mean blood pressure in traumatological patients of young age when conducting planned operations, with the possibility of subsequent adjustment of doses of analgesics.

3. The implementation into clinical practice of the developed mathematical model whose predictors are the indicators of VAS, MOCA and MAP, determined before operation, revealed that the probability of correct prediction of the level of pain by VAS in the postoperative period among patients of young age with limb injuries is 96.7 %.

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