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PERSONALIZED MATHEMATICAL MODEL OF OUTCOME IN PATIENTS WITH TRAUMATIC BRAIN INJURIES

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Abstract

Introduction. Previously, determining the prognosis based on epidemiological data was the key to informing about the treatment of patients [1,2], but modern prognostic models based on demographic data, clinical examination, radiological imaging have limited prognostic ability [3,4]. At the same time, a reliable prognosis of the outcome of the disease with modern highly specific and sensitive markers is of great clinical importance [5,6].

Aim. Developing a method for mathematical modeling of the outcome of acute traumatic cerebral injuries based on complex clinical, laboratory, and neuroimaging studies with integral scales for assessing neurological status.

Materials and methods. The studies were conducted in 79 patients with various acute traumatic brain injuries. All patients underwent a detailed clinical and neurological examination using the Glasgow Coma Scale (GCS), computed tomography, X-ray, ultrasound, hematological and biochemical examinations. To identify dependent and independent risk factors for death in the acute period of injury, a one-dimensional and multidimensional regression analysis was performed. To determine the predictive variables, an analysis of the receiver's performance characteristics (ROC) was performed with the calculation of sensitivity and specificity.

The results obtained. We found that the strongest predictors of a poor outcome were - AVDO2 > 52% of the left side (OR) - 9.01 (95% CI: 3.45 - 23.51), p<0.0001; AVDO2 >52%, right side (OR) - 5.71 (95% CI: 2.31-14.16), p=0.0002. Lactate level >3.3 mmol/l (OR) - 4.30 (95% CI: 1.61-11.51), p=0.0036. With an increase in S100ß 0.1 mcg/l> (OR) - 3.77 (95% CI:1.63-8.73), p=0.0020 and NSE ng/ml>12.5 (OR) - 2.69 (95% CI:1.14-6.36), p=0.0240; SAD>169 mmHg (OR) - 3.27 (95% CI:1.26-8.48), p=0.0146; at the age of > 65 years (OR) - 2.43 (95% CI: 1.04-5.68), p=0.0406. The measure of reliability of the model obtained by the criterion of pseudo R2, Nagelkerke - 627.3% and logLikelihood - 112.7.

Conclusion. These data were used to develop a mathematical model that allows predicting the outcome of the disease. The best predicted value of the model had a cut-off point of 99.13%, AuROC-0.912; Se-93.26%; Sp-80.00%; NPV-94.55%; PPV-76.15%.

Keywords: *brain injury, forecasting, mathematical model.*

Резюме

ПЕРСОНАЛИЗИРОВАННАЯ МАТЕМАТИЧЕСКАЯ МОДЕЛЬ ИСХОДА У БОЛЬНЫХ С ТРАВМАТИЧЕСКИМИ ПОВРЕЖДЕНИЯМИ ГОЛОВНОГО МОЗГА

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Введение. Раннее определение прогноза на основе эпидемиологических данных является ключом к информированию о лечении пациентов [1,2]. Но современные прогностические модели, основанные на демографических данных, клиническом обследовании, радиологической визуализации, имеют ограниченную прогностическую способность [3,4]. В тоже время надежный прогноз исхода заболевания с современными высокоспецифичными и чувствительными маркерами имеет большое клиническое значение [5,6].

Цель. Разработка метода математического моделирования исхода острых травматических церебральных повреждений на основе комплексных клинических, лабораторных, нейровизуализационных исследований с интегральными шкалами оценки неврологического статуса.

Материалы и методы. Исследования проведены у 79 пациентов с различными острыми травматическими поражениями головного мозга. Все пациенты прошли подробное клиническое и неврологическое обследование с использованием шкалы комы Глазго (GCS), компьютерную томографию, рентгенологические, ультразвуковые, гематологические и биохимические исследования. Для выявления зависимых и независимых факторов риска летального исхода в остром периоде травмы был проведен одномерный и многомерный регрессионный анализ. Для определения прогнозных переменных был проведен анализ рабочих характеристик приемника (ROC) с расчетом чувствительности и специфичности.

Полученные результаты. Мы обнаружили, что самыми сильными предикторами плохого исхода были - AVDO2 > 52% левой стороны (ОШ) - 9,01 (95% СИ: 3,45 - 23,51), p<0,0001; AVDO2 >52%, правой стороны (ОШ) - 5,71 (95% СИ: 2,31-14,16), p=0,0002. Уровень лактата >3,3 ммоль/л (ОШ) - 4,30 (95% СИ: 1,61-11,51), p=0,0036. При увеличении S100β 0,1 мкг/л> (ОШ) - 3,77 (95% СИ:1,63-8,73), p=0,0020 и NSE нг/мл>12,5 (ОШ) - 2,69 (95% СИ:1,14-6,36), p=0,0240; САД>169 мм. рт. (ОШ) - 3,27 (95% СИ:1,26-8,48), p=0,0146; при возрасте > 65 лет (ОШ) - 2,43 (95% СИ: 1,04-5,68), p=0,0406. Мера надежности модели, полученной по критерию псевдо R2, Nagelkerke - 627,3% и logLikelihood - 112,7.

Вывод. Эти данные были использованы для разработки математической модели, позволяющей прогнозировать исход заболевания. Наилучшее прогнозируемое значение модели имели точку отсечения 99,13%, AuROC-0,912; Se-93,26%; Sp-80,00%; NPV-94,55%; PPV-76,15%.

Ключевые слова: *травма головного мозга, прогнозирование, математическая модель.*

Түйіндеме

МИДЫҢ ТРАВМАТИКАЛЫҚ ЗАҚЫМДАНУЫ БАР НАУҚАСТАРДАҒЫ НӘТИЖЕНІҢ ЖЕКЕ МАТЕМАТИКАЛЫҚ МОДЕЛІ

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Кіріспе. Бұрын эпидемиологиялық деректерге негізделген болжамды анықтау пациенттерді емдеу туралы хабардар етудің кілті болып табылады [1,2], бірақ демографиялық деректерге, клиникалық тексеруге, рентгенологиялық бейнелеуге негізделген заманауи болжамдық модельдердің болжау қабілеті шектеулі [3,4]. Сонымен қатар, қазіргі заманғы жоғары спецификалық және сезімтал маркерлері бар аурудың нәтижесінің сенімді болжамы үлкен клиникалық мәнге ие [5,6].

Мақсаты. Неврологиялық жағдайды бағалаудың интегралды шкалалары бар кешенді Клиникалық, зертханалық, нейробейнелеу зерттеулері негізінде жедел травматикалық церебральды зақымданулардың нәтижесін математикалық модельдеу әдісін жасауға бағытталған.

Материалдар мен әдістер. Мидың әртүрлі жедел травматикалық зақымданулары бар 79 пациентте зерттеулер жүргізілді. Барлық пациенттер Глазго кома шкаласын (GCS), компьютерлік томографияны, рентген, ультрадыбыстық, гематологиялық және биохимиялық зерттеулерді қолдана отырып, егжей-тегжейлі клиникалық және неврологиялық тексеруден өтті. Жарақаттың өткір кезеңінде өлімге тәуелді және тәуелсіз қауіп факторларын анықтау үшін бір өлшемді және көп өлшемді регрессиялық талдау жүргізілді. Болжалды айнымалыларды анықтау үшін сезімталдық пен ерекшелікті есептей отырып, қабылдағыштың жұмыс сипаттамаларына (ROC) талдау жүргізілді.

Алынған нәтижелер. Нашар нәтиженің ең күшті болжаушылары - AVDO2 > 52% сол жақ (ОШ) - 9,01 (95% СИ: 3,45 - 23,51), p<0,0001; AVDO2 >52%, оң жақ (ОШ) - 5,71 (95% СИ: 2,31-14,16), p=0,0002. Лактат деңгейі >3,3 ммоль / л (ОШ) - 4,30 (95% СИ: 1,61-11,51), p=0,0036. S100β 0,1 мкг/л> (ОШ) - 3,77 (95% СИ:1,63-8,73), p=0,0020 және NSE нг/мл>12,5 (ОШ) - 2,69 (95% СИ:1,14-6,36), p=0,0240; ОАҚ>169 мм.сын. бағ. (ОШ) - 3,27 (95% СИ:1,26-8,48), p=0,0146;

> 65 жаста (ОШ) - 2,43 (95% СИ: 1,04-5,68), p=0,0406. Жалған R2 критерийі бойынша алынған модельдің сенімділік өлшемі, Nagelkerke-627,3% және logLikelihood - 112,7.

Қорытынды. Бұл деректер аурудың нәтижесін болжауға мүмкіндік беретін математикалық модель жасау үшін пайдаланылды. Модельдің ең жақсы болжамды мәні кесу нүктесі 99,13%, AuROC-0,912; Se-93,26%; Sp-80,00%; NPV-94,55%; PPV-76,15% болды.

Түйін сөздер: *ми жарақаты, болжау, математикалық модель.*

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Introduction

Increased interest in various traumatic events. The increased interest in various traumatic injuries is due to the high frequency of adverse outcomes, large economic costs and an annual increase in the number of victims [5,6]. Today, various severe injuries are both a medical, economic, and social problem for society. Based on such problems, researchers are constantly searching for ways to improve the effectiveness of treatment, possible risk factors and ways to objectively predict the outcome of the disease in victims. Answers to these questions would allow doctors to develop measures to prevent possible complications, carry out timely necessary therapeutic correction, thereby reducing the likelihood of an adverse outcome [9,8,11].

The development of multifactorial models using independent outcome predictors makes it possible to personalize the forecast [7,15,28]. Unfortunately, there is not enough such research on injuries. In clinical practice, it is of great importance to determine the early outcome of long-term treatment in such severe patients [22,25].

The aim. To study significant predictors that determine the clinical course of severe traumatic injuries with a personalized mathematical model of outcome.

Materials and methods.

79 adult patients were included in a prospective, continuous cohort study. Of these, combined severe traumatic brain injuries - 45 (56.9%) patients – group 1; combined injuries without severe damage to the skull and brain – 34 (43.03%) – group 2. All patients were treated in a Multidisciplinary regional hospital for the period from 2020 to 2021. The study was conducted in accordance with the standards of Good Clinical Practice, the principles of the Helsinki Declaration and in accordance with the principles of the Ethical Commission of the Marat Ospanov West Kazakhstan Medical University No. 12 dated January 30, 2018 [15].

The criteria for inclusion: patients with multiple injuries of two or more different anatomical parts of the body with concussion and brain contusion (mild, moderate, severe), intracerebral hematomas and hygromas, subarachnoid hemorrhages, confirmed by clinical and computer data, the integral GCS scale of the disease.

Exclusion criteria: patients with brain death confirmed by the EEG method and GCS below 3 points (11 patients), with severe decompensated somatic diseases (6 patients). According to the outcome of the disease, regardless of the diagnosis, patients were divided into groups: survivors – 62.3% (n=47) and deceased – 37.7% (n=32). The total population was 587544. The prevalence was 13.7%, the sample size was 79 patients. The distribution of patients by age (years) and diagnosis is shown in Table 1.

Demographic and clinical characteristics stratified by neurological outcome in deceased and surviving patients are presented in table 2.

Table 1.

Distribution of patients by age (years) and diagnosis.

Groups	General. number. patients, абс. (%)	before 49,%	50 – 59,%	60 – 69,%	70 and more ,%	P
Group 1	45 (56,9)	22(48,8)	13 (28,8)	5 (11,1)	5 (11,1)	<0,0001[1]
Group 2	34(43,03)	14(41,1)	10 (29,4)	5 (14,7)	5 (14,7)	<0,0001[1]
Total	79 (100)	36 (45,5)	23(29,1)	10 (12,6)	10 (12,6)	

Notes: Kraskel-Wallis 1[1] - between groups

Patients were not comparable in terms of disease outcome (p=0.3904), age (p=0.4287) and gender (p = 0.8921 according to Table 2). The degree of impaired consciousness of the patients participating in the study was assessed by GCS.

Research methods. Laboratory studies were carried out in dynamics on the 1st (initial) – 3 – 5 – 7- e days of the patient's stay in the hospital. Serum levels of NSE and S100 were determined using the human ELISA kit (DiaMetraSrl, cat. No.:DKO073, ZI Paciana, Italy). Brain gas exchange

studies determined the ratio of oxygen delivery/consumption in the cerebral cortex (rSO2), which was performed on the INVOS - 5100 device, SOMANETICS, USA. The study of brain metabolism (lactate and glucose, LDH) using a Beckman-680 analyzer (Japan), hemodynamics using NIHON KONDEN operating monitor systems (Japan) and IMEC 15S (Mindray, China). Dynamic and systematic monitoring of the main body parameters and clinical and laboratory data was carried out in patients. The patients received complex necessary therapy. Differences in the 2 groups studied by outcome in clinical and bioimmunological parameters of the neuron-specific proteins enolase and calcium binding protein, data on gas exchange and brain metabolism, as well as hemodynamics with the determination of AVDO2, rSO2, lactate, glucose and mean blood pressure. These results were later used as countfounding factors for correction in multivariate statistical analyses.

Table 2.

Demographic and clinical characteristics stratified by neurological outcome in deceased and surviving patients.

Characteristic Demographic characteristics	Cohorts, 100% (N=79)	Survivors, 59,4% (N=47)	Deceased, 40,5% (N=32)	p
Age, years Me [Q1; Q3]	40,00 (42,00; 69,00)	42,24 ± 12,33	30,34± 15,04	0,4287[2]
Gender (%) men	57(72,1%)	32 (56,14%)	25 (43,8%)	0,8921[1]
women	22 (27,8%)	14 (63,6%)	8 (36,4%)	
Basic score GCS Me [Q1; Q3]	11,07±2,65 (10,72; 11,43)	12,04 ± 2,28	9,66 ± 2,52	<0,0001[2]
Group 1	45 (56,9)	21 (46,6%)	24 (53,3%)	0,3905[1]
Group 2	34(43,03)	26 (76,4%)	8 (23,6%)	0,3905[1]
Symptoms of hyperglycemia	64	34 (53,1%)	30 (46,8%)	0,0231[1]
Arterial hypertension + coronary heart disease	27	17 (62,9%)	10 (37,03%)	0,0231[1]
Arterial hypertension + Diabetes mellitus	21	10 (47,6%)	11 (52,38%)	0,0231[1]
Other diseases	10	3 (30%)	7 (69,98%)	0,0231[1]
Pneumonia, yes	32	12 (37,5%)	20 (62,5%)	<0,0001[1]

Notes: 1[1] - χ2 Pearson
2[2] - Mann-Whitney U-test

The obtained research results were subjected to **statistical processing** by Microsoft Excel 2020 and SPSS Statistics programs. The Pearson method with a coefficient of agreement χ2 was used to determine the significance of frequencies. Spearman's nonparametric method with an indication of the R coefficient was used for correlation analysis. The evaluation and interpretation of the diagnostic significance of the signs was carried out with the determination of the area under the curves of the ROC analysis with a 95% confidence interval. The cut–off point was set - cut-off. The mathematical equations of the influence of several variables on the probability of detecting a dependent predictor were obtained by logistic regression multiple analysis. Mathematical processing of the results obtained constants with significance, Wald coefficients and relative risk. As a result, the final equations were determined indicating sensitivity, specificity according to the chi-square criterion. The Nigelkirk coefficient (R2) was used to evaluate the quality of a mathematical model with the calculation of the variance of the dependent variable. The Hosmer-Lemeshov criterion of agreement allowed us to determine the degree of agreement of our model with the initial data and the level of statistical significance of the results corresponded ($p < 0.05$).

Results. Discriminant analysis revealed the main statistically significant predictors for the development of the matrix of the basic model. The model specifies the coefficient weight and constant for different groups of results. The model formula we have compiled allows us to determine the discriminant function for each outcome of the disease.

At the stage of multiple logistic regression (LR), the risk of increasing the level of the target variable poor outcome was found to be related to the indicators obtained during laboratory and instrumental examination methods. The results of the analyses are presented in Table 3.

Table 3.

Prediction of outcome/death risk.

Factor	AuROC	Stand error	CR	95% CI for CR		χ^2	Regression coefficient	P
				Upper	lower			
Constant		0,7956				45,5206	-5,3676	<0,0001
$AVDO_2$[1], right. >52	0,823	0,4629	5,71	2,31	14,16	14,1795	1,7430	0,0002
S100β[2]>0,1	0,868	0,4288	3,77	1,63	8,73	9,5773	1,3269	0,0020
$AVDO_2$, left. >52	0,887	0,4893	9,01	3,45	23,51	20,1866	2,1985	<0,0001
Lactate >3,3	0,902	0,5018	4,30	1,61	11,51	8,4633	1,4597	0,0036
GCS[4] <9	0,905	0,4855	3,27	1,26	8,48	5,9660	1,1857	0,0146
NSE[3]>12,5	0,906	0,4387	2,69	1,14	6,36	5,0930	0,9900	0,0240
Age >65	0,912	0,4333	2,43	1,04	5,68	4,1906	0,8870	0,0406

Notes: 1 AVDO2 - arteriovenous difference
2 NSE - neuron-specific enolase
3 S100ß - Calcium binding protein
4 GCS – Glasgow Coma Scale

The following predictors were strongly associated with an unfavorable outcome: AVDO2 > 52% of the left side (OR) - 9.01 (95% CI: 3.45 - 23.51), p<0.0001; AVDO2 >52%, of the right side (OR) - 5.71 (95% CI: 2.31-14.16), p=0.0002. Lactate level >3.3 mmol/l (OR) - 4.30 (95% CI: 1.61-11.51), p=0.0036. With an increase in S100ß mcg/l>0.1 (OR) - 3.77 (95% CI:1.63-8.73), p=0.0020 and NSE ng/ml>12.5 (OR) - 2.69 (95% CI:1.14-6.36), p=0.0240;

GCS <9 score (OR) - 3.27 (95% CI:1.26-8.48), p=0.0146; at the age of > 65 years (OR) - 2.43 (95%

CI: 1.04-5.68), p=0.0406. The measure of reliability of the model obtained by the criterion of pseudo R2, Nagelkerke - 627.3% and logLikelihood - 112.7.

These data were used to develop a mathematical model that allows predicting the outcome of the disease. The resulting logistic regression equation of the model has the form:

P = 1 / (1 + Exp (- (-5.368 + 1.743 * AVDO$_2$ + 1.327 * S100β>0 + 2.198 * AVDO2+ 1.46 * Lactate >3 + 1.186 * GCS <9+ 0.99 * NSE >12 + 0.887*age >65)

where P is the probability of a risk of increased outcome/mortality; e is the base of the natural logarithm (e = 2.72), - 5.3676431 is constant. The best predicted value of the model is the cut-off point of 99.13%, AuROC - 0.912; Se - 93.26%; Sp - 80.00%; NPV-94.55%; PV - 76.15%, where shown in Figure 1.

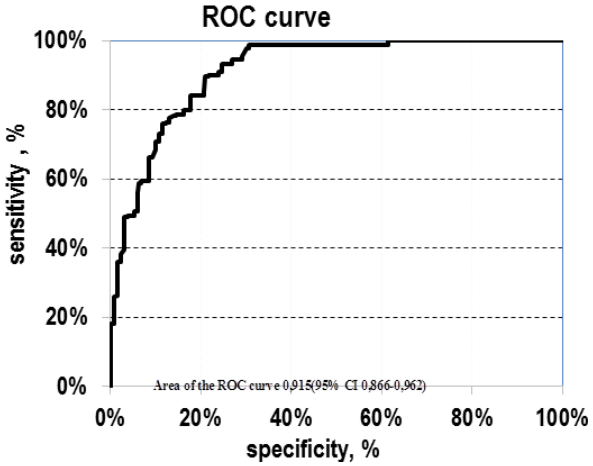

Figure 1. Sensitivity and specificity of the predictive model

Discussion

The results of our research have shown that the method of mathematical equation is quite simple to work with, allows you to quickly and fully determine the prognosis of the disease [25,12,1]. The availability of the used predictors of outcome in most medical institutions, the possibility of widespread use of the database and various application packages with the possibility of extensive mathematical calculations make it possible to widely use the developed prognosis model. Similar prognostic models of outcomes have been described by other researchers [14,35,34].

By predicting the outcome of the disease, we will be able to establish a basic risk profile for each patient, thereby providing primary information and pre-evaluating the volume of medical care. Predictive mathematical models are important for the analysis of subsequent large studies in order to obtain a covariative correction of the treatment [16,17,18] and to consider other markers that increase statistical significance [23].

Authors Fernando Zanela Areas et al. It is indicated that variables such as old age, GCS score of pupil diameters and CT data with displacement of median brain structures, hypotension, the presence of subarachnoid hemorrhages can determine the outcomes of severe injuries of traumatic genesis [27,13,33].

Li X., Lü C., Wang J. et al. It is also claimed that the development of multifactor models using well-known independent forecasts makes it possible to personalize the forecast [15,21,26]. Various calculators for mathematical predictions of the clinical course of traumatic diseases in adults, based on CRASH and IMPACT studies, are currently one of the most popular and affordable models of individual forecasting. Our conclusions coincide with the opinions of Badjatya N., Carney N., Croco T.J. et al. that predicting the outcome of brain damage is one of the main factors of a poor outcome or death of a patient. These provisions can identify possible complications and introduce early preventive measures into therapy. And such cohort prospective studies are currently insufficient. In the studies *of Perel. P.,* 2018, devoted to the study of data on the prediction of various outcomes, recommendations are made that predictors of disease prognosis should be constantly reviewed and supplemented. According to the author, this is due to the fact that new data and knowledge about the mechanisms of pathogenesis of severe injuries are constantly being updated, diagnostic capabilities are expanding, and new treatment methods are being introduced. Our opinions coincide with the researcher that with the current availability of a wide range of patient monitoring data, they cannot all be used in routine clinical practice. The problem is related to the fact that heterogeneity of material and technical support and staff qualifications is noted at different levels of medical institutions [2,32].

However, we note that personal mathematical models can only complement, not replace, clinical judgments, but such models are based on the systematic experience of the results of several hundred patients that underlie our models [24].

The disadvantages of our model, as in other models, are that there is not enough external validation, which is necessary to recommend the model for widespread distribution. The validity and applicability of predictive models are influenced by various factors. Many models, like ours, include data obtained after admission, and most of them were developed on small sample sizes of patients from one medical center [10]. The level of diagnostic research and medical care may vary depending on the location and equipment of medical institutions, which may lead to different results [29,30,31].

The coded data of the studied patients on the Excel platform is entered into the mathematical model developed by us. Age, gender, the results of assessment scales of general condition, data from instrumental laboratory studies were taken into account. The final point of the prognostic analysis was the indicator of the outcome of the disease (favorable and unfavorable). According to the obtained research results, such parameters as age over 65 years (OR) - 2.43 (95% CI: 1.04-5.68), p=0.0406 had a significant impact on the adverse outcome of the disease in patients with traumatic brain injuries; neurological deficit according

to GCS less than 9 points (OR) - 3.27 (95% CI:1.26-8.48), p=0.0146; circulatory insufficiency with an increase in serum lactate of more than 3.3 mmol/l (OR) - 4.30 (95% CI: 1.61-11.51), p=0.0036. At 40.5% of the studied patients showed an increase in the parameters of cerebral oximetry, reflecting a violation of cerebral perfusion, oxygen transport and predetermining the unfavorable course of the disease. Also, an unfavorable prognosis for the degree of influence on the outcome was increased levels of serum neurochemical markers – neuron-specific enolase NSE and protein S100ß. These markers of brain damage had high sensitivity - 91.30%; 51.59% and specificity - 95.06%;72.09 The resulting model adequately differentiates patients with favorable and unfavorable outcomes. The model quickly allows the doctor to obtain data on the prognosis of the disease, make timely changes in management and treatment tactics in order to improve the patient's prognosis.

Conclusions. Thus, the developed personalized mathematical model with risk factor coefficients makes it possible to predict the outcome of the disease with high probability in patients with acute traumatic brain injuries. The proposed calculator of the individual risk of an adverse outcome of the disease is recommended to be integrated into the electronic medical record of the patient upon admission to the hospital. Patients with a high coefficient of adverse outcome need individual preventive measures to correct the identified risk factors.

The contribution of the authors. The work was carried out within the framework of a scientific and technical project on the topic "Development of modern scientifically based technologies for predicting and preventing secondary brain damage in order to improve the effectiveness of treatment in patients with acute traumatic and vascular lesions." All the authors participated equally in the research and in writing the sections of the article.

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