

# The Neural Network Technology Application for Prediction of Preeclampsia in Pregnant Women with Chronic Arterial Hypertension

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**The aim of the study** was to assess biomedical risk factors for preeclampsia in pregnant women with chronic arterial hypertension (CAH) and on this basis to create the neural network system for calculating the probability of developing preeclampsia in these women.

**Materials and Methods.** Pregnancy and delivery outcomes were analyzed in 548 patients with pre-existing arterial hypertension (AH): 318 with CAH and 230 with preeclampsia secondary to CAH. Risk factors were calculated using the OpenEpi program (UK). A combined method of global optimization and neural network method of information compression were used when training the developed neural network system.

**Results.** There were identified the main risk factors for developing preeclampsia in pregnant women with CAH: hereditary burden of hypertension; hypertensive disorders in previous pregnancies; hypertension during more than five years; the initial diastolic blood pressure being more than 80 mm Hg; body mass index more than 30; tobacco smoking; nulliparity; chronic pyelonephritis and gastritis; hypertensive disease stage II; degree II and III AH; hypertensive retinal angiopathy; left ventricular hypertrophy; lack of regular antihypertensive therapy before and during pregnancy; late treatment initiation. The data obtained were used to train and test the neural network software and to develop the "Neuro\_Chronic — neural network system for predicting secondary preeclampsia in pregnant women with chronic arterial hypertension". The system includes two modules. The first module is designed to train the neural network software model using a given set of images, the second module provides evaluation of preeclampsia developing during pregnancy in a particular patient in the form of five probability options — from very low to very high — after entering the parameters obtained during the anamnestic and clinical examination into the corresponding fields.

**Conclusion.** Revealing the proposed predictors of preeclampsia in pregnant women with CAH and entering these data into the developed computer program will enable physicians to determine the probability of preeclampsia developing during gestation at the outpatient stage and to take timely preventive measures in pregnant women at high-risk.

**Key words:** risk factors in pregnant women; arterial hypertension; hypertensive disease; complications in pregnancy; preeclampsia; neural network system.

## Introduction

Arterial hypertension (AH) in pregnancy is one of the most common and dangerous medical disorders. According to the Ministry of Health of the Russian Federation, edema, proteinuria, and hypertensive disorders accounted for 15.1% of all causes of maternal death in the Russian Federation in 2014 and 10.1% in

2015, being classified as potentially preventable [1, 2]. In pregnant women, the prevalence of chronic arterial hypertension (CAH) has increased by almost one-third over the past 10–15 years due to an increase in the average age of parturient women [3]. According to the literature data [4], in patients with pre-pregnancy AH, preterm birth rate is 10–12%, stillbirth rate is 3.8%, intrauterine growth restriction accounts for 16.6%,

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while the level of perinatal mortality reaches 11.4%. Preeclampsia exacerbates the perinatal outcomes in particular: the incidence of adverse outcomes associated with this complication amounts to 22% [5]. According to foreign literature, preeclampsia complicates 78% of pregnancies in women with severe CAH and 20–25% of pregnancies in women with degree I AH [6]. Domestic scientists show that 36–52% of patients with CAH develop this pathology during gestation [5, 7].

Preeclampsia can develop in any pregnancy, but the probability of this complication risk is associated with a combination of several factors in one woman [8]. At the same time, there is evidence that preeclampsia does not always develop in the presence of certain risk factors, and, by contrast, this complication may develop even in the absence of predictors [9–11] — all this makes it difficult to predict and prevent preeclampsia.

The research [8, 12–15] has revealed risk factors likely to increase the probability of preeclampsia in pregnancy: nulliparity; the inter-pregnancy interval of more than 10 years; family history of preeclampsia; hypertensive disorders in previous pregnancies; age over 35 years; increased body mass index (BMI>25); diastolic blood pressure (DBP) being more than 80 mm Hg on the date of registration; multiple pregnancy; insulin-dependent diabetes; kidney diseases; hypertensive disease (HD); thrombophilia in past history and autoimmune diseases; antiphospholipid syndrome. However, there are few works in the scientific literature devoted to studying the risk factors for secondary preeclampsia in pregnant women with CAH and the possibility to predict this complication development by identifying the disease predictors in the given category of individuals.

HD is known to increase many times the risk of developing preeclampsia during pregnancy (especially, its severe forms) [8, 14]. Pre-pregnancy degree I AH increases the risk of preeclampsia by 2 times even without target organ damage [16]. There is some information about such risk factors for preeclampsia in women with CAH as obesity (Quetelet index  $\geq 30$ ), hereditary burden of hypertension and life-threatening cardiovascular diseases, pre-pregnancy smoking [7]. It should be noted that there are findings in the literature denying the risk of preeclampsia in women smokers [17–20], although the authors fail to explain thoroughly the mechanism of this process. They suggest that carbon dioxide produced while smoking inhibits the synthesis of placental proteins sFlt1, reduces placental apoptosis and necrosis.

Preeclampsia secondary to CAH depends on many factors that may occur in combination or be unrelated to each other and have individual influence. In this regard, a trained artificial neural network is likely to be the best solution for predicting this complication in pregnancy. Neural network technologies are advantageous in solving problems under uncertainty, when working with fuzzy data, such conditions being typical for many tasks in the field of medicine [21].

**The aim of the study** was to assess biomedical risk factors for preeclampsia in pregnant women with chronic arterial hypertension (CAH) and on this basis to create the neural network system for calculating the probability of developing preeclampsia in these women.

## Materials and Methods

Pregnancy and labor outcomes were analyzed retrospectively in 548 patients with CAH whose labor took place at Ivanovo Research Institute of Motherhood and Childhood named after V.N. Gorodkov in the period from 2013 to 2017. Depending on the course of pregnancy (secondary preeclampsia), they were divided into two groups: group 1 consisted of 318 pregnant women with CAH (ICD-X code O10.0), group 2 included 230 patients who developed preeclampsia against the background of CAH (ICD-X code O11).

The diagnosis was made in accordance with the clinical guidelines “Hypertensive disorders during pregnancy, the intrapartum and postpartum periods. Preeclampsia. Eclampsia” dated 2016, approved by the Ministry of Healthcare of the Russian Federation, where the classification of hypertensive disorders in pregnancy is as follows [22]:

- preeclampsia and eclampsia (ICD-X codes O14, O15);

- preeclampsia and eclampsia secondary to chronic AH (ICD-X code O11);

- gestational (pregnancy induced) AH (ICD-X code O13);

- chronic AH existing prior to pregnancy (ICD-X code O10) and including two nosological forms: HD and secondary (symptomatic) AH.

The study complies with the Declaration of Helsinki (2013) and was approved by the Ethics Committee of Ivanovo Research Institute of Motherhood and Childhood named after V.N. Gorodkov. All the patients gave informed consent to participate in the study.

Exclusion criterion was secondary (symptomatic) AH (ICD-X codes O10.1, O10.2, O10.3, O10.4).

Preeclampsia secondary to CAH was diagnosed in pregnant women if there was proteinuria for the first time after 20 weeks of pregnancy (urinary protein in amounts exceeding 0.3 g in a 24-hour urine collection) and in case of AH in the women whose BP had been controlled prior to week 20 of pregnancy.

The data for investigation were copied from medical records (medical histories of pregnant and parturient women and labor case histories).

When training the neural network system, a combined method of global optimization was used which involved the use of gradient, memory gradient, advanced random search, inertial and genetic algorithms at different search iterations. The method enables overcoming local extrema of the objective function and finding the global optimum. Neural network compression method makes it possible to reduce the dimensions of the analyzed

information and highlight the main components of images.

Computer program "Neuro\_Chronic — neural network system for predicting secondary preeclampsia in pregnant women with chronic arterial hypertension" was created and tested using processor x86 Family 6 Model 23 Stepping 6 Genuine Intel ~2999 MHz with Microsoft Windows XP Professional, Microsoft Office Excel 2007 software.

Statistical analysis was carried out using variation statistics methods with applied licensed software package Microsoft Office 2010, Statistica 6.0 and methods of clinical epidemiology (calculation of relative risk values — RR, confidence interval — CI at the significance level of 95%) using the OpenEpi program (UK). Quantitative values were expressed as mean and standard error of mean ( $M \pm m$ ) for normal distribution and as a median with the 25<sup>th</sup> and 75<sup>th</sup> percentiles (Me [25; 75]) if distribution was different from normal. Significance of differences between the indexes was evaluated using Student t-criterion and Mann–Whitney U-test (significance level  $p < 0.05$  was regarded as statistically significant).

## Results and Discussion

Analysis of both groups showed that there were almost no differences in the average age of women, it was  $33.1 \pm 0.5$  years in patients with CAH and  $32.1 \pm 0.6$  years in patients with CAH and secondary preeclampsia ( $p = 0.06$ ). Social characteristics of patients of both groups were also comparable. Tobacco smoking occurred in women with CAH and secondary preeclampsia statistically significantly more often than in group 1 — 4.3 and 1.9%, respectively (RR=3.6; 95% CI 1.4–10.3;  $p = 0.005$ ). Earlier registration at the women's clinic was more often observed in women of group 1 as compared to group 2 (55.03 and 46.9%, respectively;  $p = 0.04$ ). At the same time, at the first visit to the clinic pregnant women had higher BMI ( $31.5 \pm 0.7$ ) in group 2 than in group 1 ( $28.6 \pm 0.7$ ) ( $p = 0.001$ ). There were no significant differences in the average levels of systolic and diastolic BP on registration and these parameters amounted to 137.5 (120–140) and 80 (80–90) mm Hg in group 1 and 132.5 (120–140) and 86 (80–90) mm Hg in group 2 ( $p > 0.05$  in all cases). However, it is remarkable that at the first visit DBP above 80 mm Hg was more often reported in patients of group 2 (60.4%) than in group 1 (48.4%) (RR=1.6; 95% CI 1.2–2.3;  $p = 0.003$ ). The average AH duration in patients of both groups was practically unchanged and amounted to  $7.2 \pm 0.5$  and  $7.5 \pm 0.2$  years ( $p = 0.06$ ); however, 57.4% of patients in group 2 suffered from this pathology for more than five years, while they were only 48.1% in group 1 (RR=1.5; 95% CI 1.1–2.1;  $p = 0.02$ ). Stage II HD with target organ damage was more often diagnosed in women of group 2 — 39.6 vs. 23.3% of pregnant women in group 1 (RR=2.2; 95% CI 1.5–3.1;  $p = 0.0001$ ); in other patients, stage I HD was diagnosed. Pre-pregnancy degree I

AH was established in group 1 more frequently than in group 2 (80.5 vs. 62.6%;  $p = 0.001$ ). At the same time, women in group 2 were more likely to have degree II AH (29.1%) (RR=1.9; 95% CI 1.3–2.9;  $p = 0.001$ ) and degree III AH (8.3%) (RR=4.7; 95% CI 1.9–12.9;  $p = 0.001$ ). Comparison of the maximum levels of systolic BP in the first half of pregnancy showed that it was higher (150 (140–160) mm Hg) in women of group 2 than in pregnant women of group 1 (140 (130–150) mm Hg) ( $p = 0.01$ ). The maximum DBP level in women of group 2 was also higher and amounted to 100 (90–105) mm Hg, while in group 1 it equaled 95 (90–100) mm Hg ( $p = 0.002$ ).

According to Order of the Ministry of Healthcare of the Russian Federation No.572n dated 12.11.2012 "Approval of the procedure for healthcare delivery in the field of obstetrics and gynecology (but not including the use of assisted reproductive technologies, Annex No.1-4)", all pregnant women were examined by a therapist, an ophthalmologist and underwent ECG in the first trimester. Examination by the therapist confirmed the presence of CAH in patients of both groups. Ophthalmological examination of the eye fundus in the first trimester of pregnancy revealed hypertensive angiopathy of the retina in most patients of group 2 — 69.6 vs. 41.3% in group 1 (RR=3.7; 95% CI 2.5–5.5;  $p = 0.001$ ). Retinal angiopathy degree I B was diagnosed in 29.6% of these patients in group 2 vs. 9.4% in group 1 (RR=4.1; 95% CI 2.5–6.5;  $p = 0.0001$ ). According to ECG data obtained in the first trimester, left ventricular hypertrophy was recorded in 18.3% of pregnant women in group 2 and 4.7% in group 1 (RR=4.5; 95% CI 2.5–8.6;  $p = 0.0001$ ).

The analysis of previous diseases revealed that all examined patients had come through different infectious childhood diseases (measles, rubella, scarlet fever, chickenpox), each woman had suffered acute respiratory viral infection at least once ( $p > 0.05$  in all cases). The study of family medical history found hereditary burden of HD and cardiovascular disease to be more often present in pregnant women of group 2 (66.3%); in group 1 it was 47.1% (RR=2.2; 95% CI 1.3–3.9;  $p = 0.001$ ). Hypertensive disorders in previous pregnancies were observed in 19.1% of patients in group 2 and 11.0% in group 1 (RR=1.9; 95% CI 1.2–3.1;  $p = 0.01$ ).

In terms of extragenital pathology, fat metabolism disorders were observed more often in patients of group 2 compared to group 1 and accounted for 56.6 and 36.1% (RR=2.3; 95% CI 1.3–4.0;  $p = 0.01$ ); chronic pyelonephritis made 34.7 and 17.3% (RR=2.5; 95% CI 1.7–3.8;  $p = 0.0001$ ); chronic gastritis — 16.0 and 13.0% (RR=1.2; 95% CI 1.1–2.1;  $p = 0.04$ ), respectively.

Analysis of gynecological and obstetric history of patients in the two groups revealed no significant differences. It was remarkable that almost half of women in group 2 (44.8%) were expecting their first labor and this percentage was only 36.2% in group 1 (RR=1.4; 95% CI 1.1–2.1;  $p = 0.02$ ); in group 2 the patients were more likely to be primiparous: 31.7 vs. 22.6%, respectively (RR=1.6; 95% CI 1.1–2.3;  $p = 0.01$ ).

Before pregnancy, women in group 1 received regular antihypertensive therapy significantly more often than in group 2 ( $p=0.01$ ) where occasional symptomatic therapy prevailed ( $p=0.01$ ), which increased the risk of preeclampsia 1.9 times (95% CI 1.2–3.0). During pregnancy, antihypertensive therapy was more common in group 1 patients ( $p=0.001$ ). It was mainly initiated in the first trimester in both groups ( $p=0.05$ ), but in group 1 it began earlier — at  $9.3\pm 1.3$  weeks, on average, while in group 2 — at  $13.4\pm 1.2$  weeks ( $p=0.02$ ). The absence or late initiation (in the third trimester) of antihypertensive therapy in pregnancy increased the risk of preeclampsia in women with CAH ( $p=0.001$  and  $p=0.04$ , respectively) by 2.8 (95% CI 1.8–4.5) and 1.7 times (95% CI 1.1–2.7), respectively.

Thus, according to our data, the risk of preeclampsia in pregnant women with CAH is increased in patients with hereditary burden of HD by 2.2 times, in those with hypertensive disorders in previous pregnancies by 1.9 times, with AH duration of more than five years by 1.5 times, with baseline DBP of more than 80 mm Hg by 1.6 times, with body mass index of more than 30 by 2.3 times, in smoking patients by 3.6 times, in nulliparous patients by 1.4–1.6 times, in those with chronic pyelonephritis by 2.5 times, with chronic gastritis by 1.2 times. The presence of stage II HD increases the risk of developing preeclampsia by 2.2 times, degree II AH by 1.9 times, degree III AH by 4.7 times. Target organ damage such as hypertensive retinal angiopathy increases the risk of this complication by 3.7 times, retinal angiopathy degree I B by 4.1 times, left ventricular hypertrophy (according to ECG) by 4.5 times. The absence of regular antihypertensive therapy before pregnancy increases the risk of preeclampsia by 1.9 times, the lack of therapy during gestation by 2.8 times, late treatment initiation (III trimester) by 1.7 times.

Investigations carried out in this field [23–26] allowed us to formulate the main risk factors for preeclampsia in pregnant women with CAH: age over 36 years; hypertensive disorders in previous pregnancies; the

presence of polymorphisms of vascular tone regulating genes (renin-angiotensin system and endothelial nitric oxide synthase); closed craniocerebral trauma in medical history; chronic pyelonephritis in history and its exacerbation during gestation; pelvic inflammatory diseases; early gestosis during pregnancy; increased BMI; smoking.

The data obtained should be evaluated as specific risk factors for the development of preeclampsia in pregnant women with CAH, used by us for training and testing the neural network software in the form of images represented by number sequences reflecting the clinical and anamnestic data of the patient. The input parameters (the data concerning medical history and examination of a pregnant woman) correspond to the predictors obtained in the mathematical analysis: 1<sup>st</sup> pregnancy, 1<sup>st</sup> labor, hereditary burden of HD, smoking, stage II HD, retinal angiopathy, chronic gastritis, chronic pyelonephritis, body mass index more than 30, baseline DBP more than 80 mm Hg.

The structure of the neural network includes an input layer for distribution of training image signals and two layers of sigmoid neurons, associative (hidden) and effector (output) layers, respectively (Figure 1). The input layer contains ten cells corresponding to the number of parameters in each image, the hidden layer contains seven neurons. Due to a smaller number of cells in the hidden layer, data is compressed using neural network funnel technology that allows selecting the main uncorrelated information. Neural network information compression is the preferred substitute for principal component analysis containing such costly operations as finding eigenvalues and eigenvectors of matrices [27]. The output layer of the network consists of one neuron determining the probability of complications.

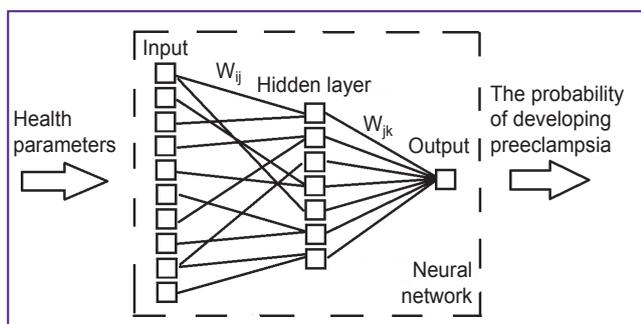
Training neural network implies finding the optimal weighting factors of connections between neurons in which the error of the network response tends to zero. A series of numerical experiments were performed to determine the best training algorithm in this task. Training was carried out by the method of error back-propagation, random search, genetic algorithm. However, the combined method of global optimization proved to be the most effective [28]. Using this algorithm, we managed to achieve high quality of network operation — more than 90% of correct answers. While operating the neural network, there is a possibility of its additional training.

Introduction of adjustment coefficient for each neuron on the hidden and output layers according to the Golovko scheme allows forming the neuron response at the most productive area of the activation function curve [29]. With commonly accepted notations, this appears as follows:

$$T_{upd}[j]=T_{cur}[j]+\eta\cdot O_i[i]\cdot\delta_j'[j],$$

$$O_j[j]=1/(1+e^{T_{cur}[j]-S_j[j]/H_j}),$$

where  $T_{upd}$ ,  $T_{cur}$  are adjustment coefficient values updated and current, respectively;  $\eta$  is neural network



**Figure 1. The structure of a neural network with a compressive hidden layer to predict preeclampsia developing**

$W_{ij}$  — a set of weights of connections between receptor and associative layers;  $W_{jk}$  — a set of weights of connections between associative and effector layers

training rate constant;  $O_i$ ,  $O_j$  are values of neuron output signals at the receptor and associative layers, respectively;  $\delta_j'$  is derived function of associative layer neuron error;  $i$  is the number of receptor layer neuron;  $j$  is the number of associative layer neuron;  $S_j$  is the sum of signals at the input of hidden layer neuron;  $H_j$  is the parameter determining the form of neuron activation function;  $e$  is Euler's transcendental constant.

This measure allows us to accelerate neural network training process and increase the level of recognition.

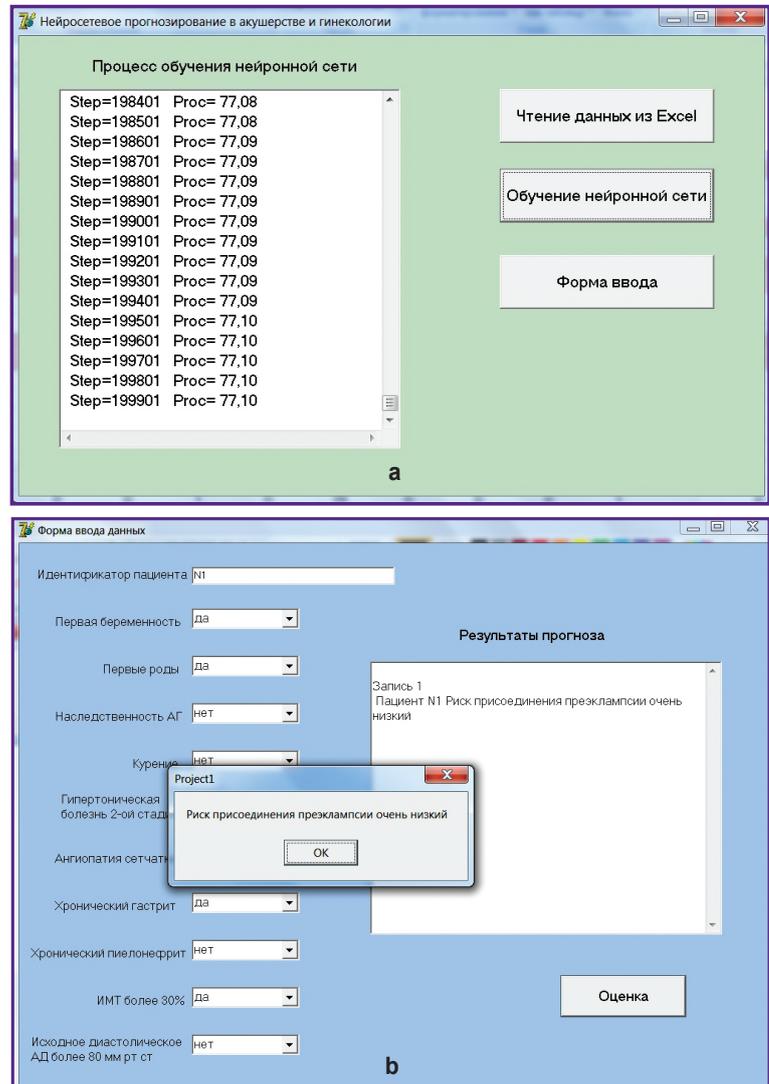
After training and testing the system, there was developed an intelligent program system "Neuro\_Chronic — neural network system for predicting secondary preeclampsia in pregnant women with chronic arterial hypertension" to determine the probability of developing preeclampsia in pregnant women with CAH. The system includes two modules. In the first module, the neural network software model is trained using a given set of images (Figure 2 (a)).

After training, the option of initiating the operating mode of the program is activated in the interface form (the second module). In the interface form of the operating mode, there are fields for entering the appropriate parameters obtained while collecting medical history data and making clinical examination of a pregnant woman with CAH. After filling them, the probability of developing preeclampsia during gestation in a particular patient is evaluated (Figure 2 (b)). As a result, there are five possible options to mark the probability of developing preeclampsia — from very low to very high.

The intelligent predicting system comes complete with a user manual with a detailed description of program operation procedure developed by the authors. The system has been tested using a database of pregnant women with hypertensive disorders admitted to Ivanovo Research Institute of Motherhood and Childhood named after V.N. Gorodkov in the period from 2013 to 2017.

The computer program "Neuro\_Chronic — neural network system for predicting secondary preeclampsia in pregnant women with chronic arterial hypertension" has undergone state registration, certificate No.2018612460 dated 16.02.2018.

The use of the proposed neural network system enables practical doctors to evaluate the risk of preeclampsia in pregnant women with CAH at the outpatient stage based on patient medical history and primary examination data, to develop an individual monitoring program, take timely preventive measures and administer additional examination.



**Figure 2. The on-screen form of "Neuro\_Chronic — neural network system for predicting secondary preeclampsia in pregnant women with chronic arterial hypertension":**

(a) 1<sup>st</sup> module: training the neural network; (b) 2<sup>nd</sup> module: evaluating the risk of developing preeclampsia

## Conclusion

Revealing the proposed predictors of preeclampsia in pregnant women with CAH, applying the computer program "Neuro\_Chronic — neural network system for predicting secondary preeclampsia in pregnant women with chronic arterial hypertension" makes it possible to evaluate the probability of this dangerous complication developing during gestation at the outpatient stage and to take timely preventive measures in high-risk pregnant women.

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**Conflict of interests.** The authors have no conflict of interests to disclose.

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