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Determining Subgroups of Significant Correlation in Analyzing Relation between NR2 Antibodies and Factor VIII in Acute Neurological Diseases

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Abstract. The paper considers a new method for finding correlations distorted by the influence of a third factor. In other words, the method is designed to search for effects consisted in the existence a significant correlation between two variables in a group of observations received from the main sample by removal of the observations with extremal values of a third factor. Testing for such effects should include both an assessment of the statistical significance of the correlation in the subgroup and the significance of the influence of the third factor. Potentially, this can be done using the previously developed method of valid conditional linear regularities (VCLR). The statistics used in the VCLR method is the maximum of the functional, which depends on the correlation coefficients in the subgroups identified using the threshold for the third factor and the sizes of these subgroups. The disadvantage of this method is that it cannot be used if the maximum of the functional corresponds to a threshold value that cuts off a small group. This drawback did not allow to adequately assess the significance of the effect associated with the existence of a significant negative correlation between the serum levels of antibodies to factor VIII and NR2 in the group of patients with ischemic stroke and transient ischemic attack after excluding patients with abnormally high levels of vascular endothelial growth factor. An alternative method was proposed, which is based on a permutation test. At that the statistics of the test is a minimum p-value from those characterizing the correlation coefficients calculated using the normal approximation of the Fisher z-transform corresponding to all possible threshold values for the third factor. The use of the new criterion made it possible to adequately assess the significance of the observed effect.

Key words: *correlation significance, optimal partitioning, permutation test, ischemic stroke, Factor VIII, NR2 antibodies.*

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INTRODUCTION

Biological effects can often be a complex interplay of several factors. An example is the effects where the linear correlation between two variables X and Y is skewed by a third factor, Z. In other words, the effect consists in the existence of a subgroup of observations for which the variables X and Y deviate from the linear dependence that is present for them in the main group. At that the value of the third factor Z in this subgroup of observations exceeds a certain threshold value. Such a combined effect can be considered significant only if two statements are statistically significant:

- variables X and Y mutually correlate in a subsample of the initial sample;
- this subsample can be extracted from the initial sample by the factor Z.

This approach to assessing statistical significance is consistent with the concept of fully significant regularities discussed earlier in the works [1, 2, 3]. Ignoring the requirement to achieve full significance can lead to an erroneous conclusion about the existence of combined effects on data configurations arising from of simpler effects [1].

Standard statistical tools are found to be insufficient to assess full statistical significance. In the works [2, 3], an approach is used in which the estimation of the statistical significance of the combined effect considered above should be reduced to the refutation of three null hypotheses:

1. the null hypothesis H_0^1 about the independence of X from the combination of Y and Z;
2. the null hypothesis H_0^2 about the independence of Y from the combination of X and Z;
3. the null hypothesis H_0^3 about the independence of Z from the combination of X and Y.

A universal way to test null hypotheses about the independence of one of the variables from combinations of other variables is the increasingly widespread permutation test [4, 5]. This approach requires no additional assumptions. It was also used in the works [2, 3] in the method of valid conditionally linear regularities(VCLR). At that, the maximum of the functional depending on the values of the correlation coefficients in the subgroups corresponding to the values of the third factor to the sides of the threshold and the sizes of these subgroups was used as the statistics of the test. The disadvantage of this method is the impossibility of using it if the maximum of the functional corresponds to a threshold value that cuts off a small group. Research carried out in the work [2] showed that the maximum size of a cut-off group is 25 objects. This drawback did not allow adequately assessing the significance of the effect considered in present work, associated with the existence of a significant negative correlation between the serum levels of Factor VIII (FVIII) and levels of antibodies to NR2 subunits of the N-methyl-D-aspartate (NMDA) receptor, referred hereinafter to as ABNR2, in the group of patients with ischemic stroke (IS) and transient ischemic attack (TIA) after removal of 8 cases with an abnormally high vascular endothelial growth factor (VEGF).

It is known that increases in ABNR2 levels are closely connected to occurrence of IS or TIA. The connection is proved by significant dissimilarity of ABNR2 levels in groups with IS or TIA and its levels in the control groups [6] as well as strong correlation of ABNR2 levels and the sizes of the affected brain area [7, 8]. At the same time, the cause of stroke is the process of thrombus formation affected by the FVIII. Its connection to the stroke risk was noted in [9, 10]. In this regard, it is of interest to study the relationship between the two indicators: ABNR2 and FVIII.

Coefficient of correlation between ABNR2 and Factor VIII serum levels in the group of patients with IS and TIA was -0.195, while its significance reached only the trend level ($0.05 < p < 0.1$) $p = 0.06$. This value is completely insufficient for a confident conclusion about the

existence of a statistically significant relationship. At the same time, the reason for the decrease in the correlation coefficient and the loss of statistical significance is often the existence of outliers in the data. In this case, the deviation from the main dependence is often closely related to a third factor. A preliminary analysis suggested that hypoxia may act as such an indicator. It can be estimated by the partial pressures of O2 and CO2, CO-oximetry parameters as well as closely connected to them the vascular endothelial growth factor (VEGF). Conventional correlation analysis does not allow to reasonably conclude that each of the two correlating variables and the factor controlling the correlation is significant for the individual contribution to the observed effect. One of the possible ways to take into account the influence of the third factor is to analyze the partial correlation coefficient, that is, the correlation coefficient between the residuals of linear regressions that approximate each of the first two indicators with the third factor. It turned out that, with the allowance for the impact of VEGF, the absolute value of the partial coefficient of correlation between ABNR2 and FVIII is significantly higher compatively red to the initial coefficient. The disadvantage of partial correlation coefficients [11] is the need to assume the linearity of all three relationships.

Besides conventional methods for verifying partial correlation coefficients are based on the assumption that the joint distribution of three variables is a multivariate normal distribution.

Previously [2] introduced VCLR approach was used to prove the effect of hypoxia on the interrelations between VEGF and s100, between VEGF and the complement component c4. However VCLR approach did not allow the researches to assess the effect significance properly. This served as a prerequisite to search for new approaches.

DATA

We analyzed the data of two patient groups: patients with transient ischemic attack (n = 33) and patients with ischemic stroke (n = 55). A patient's age ranged from 33 to 88 years. Data included blood serum levels of ABNR2, FVIII, neuropeptides VEGF and S100, CO oximetry parameter, O2 and CO2 partial pressures. The levels of ABNR2, FVIII and neuropeptides VEGF and S100 were determined using an enzyme-linked immunosorbent assay (ELISA). Venous CO-oximetry was measured with an ABL80 FLEX CO-OX analyzer. The average values of indicators in the groups with TIA and IS are shown in Table 1.

PRELIMINARY ANALYSIS

Further analysis showed that excluding a single object from the sample increases the correlation coefficient to -0.36, which is significant at the level of $p = 0.03$. In addition, the partial correlation coefficient between the levels of logarithms of ABNR2 and FVIII without taking into account the influence of VEGF ($log(ABNR2)$ vs. $lof(FVIII)$, $log(VEGF)$ correlation) turns out to be -0.45, $p < 0.0001$. The use of the binary indicator f_{bin} significantly increases the statistical significance. It is calculated according to a simple rule: $f_{bin} = 1$ if FVIII above 120, $f_{bin} = 2$ if FVIII less than 120. The results obtained using a variant of the optimal partitions method described in the work [9] are shown in Fig. 1.

The following notation is used: green circles correspond to $f_{bin} = 2$, red squares correspond to $f_{bin} = 1$. To the left of the 3.11 border (roughly the median) there are 35 cases with a high FVIII and only 15 with a low one, to the right of the border there are only 12 cases with high and 26 with low levels. The age located along the Y axis is used for unfolding the image and does not participate in the pattern shown in the figure. Statistical significance is assessed using a permutation test at the $p = 0.0083$ level. The pattern shown in Fig. 1 is statistically significant evidence of a relationship between ABNR2 and FVIII. The purpose of this work is, among other things, to prove the existence of a pronounced correlation between ABNR2 and FVIII in a group of patients, which can be distinguished by the values of the third factor, which in our

Table 1. Average factor levels in groups with IS and TIA

	TIA	IS	p-value (Student)
Age	63.5 ± 11.9	63.8 ± 11.6	0.93
pCO2	54.45 ± 5.9	51.84 ± 8.9	0.14
pO2	24.6 ± 7.8	27.4 ± 10.6	0.19
sO2	48.4 ± 17.5	50.43 ± 19.1	0.63
FO2Hb	46.44 ± 16.6	47.9 ± 17.7	0.7
FCOHb	0.85 ± 1.0	0.75 ± 0.9	0.62
FMetHb	1.32 ± 0.39	1.26 ± 0.35	0.46
FHHb	49.6 ± 15.2	48.4 ± 16.5	0.73
S100	91.65 ± 34.7	151.95 ± 154.7	0.03
ABNR2	3.1384 ± 2.38	3.8475 ± 4.14	0.37
VEGF	496.5 ± 281.02	906.8 ± 831.5	0.0075
FVIII	121.47 ± 49.4	124.2236 ± 59.42	0.82

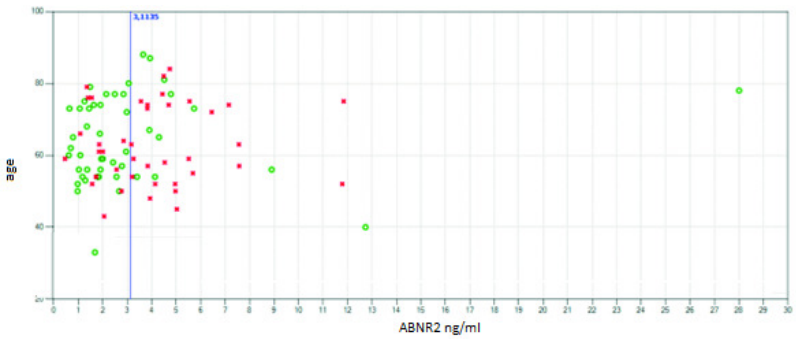

Fig. 1. Relationship of the binary factor to ABNR2.

case is VEGF. The use of the VCLR variant of the method of optimal valid partitions [2, 3] to assess the significance of such a combined effect did not allow us to assess the significance of the combined effect at a sufficient level. The analysis of the shortcomings of this option, carried out in the next section, allowed us to develop a new modification of the VCLR method, which makes it possible to obtain estimates in broader conditions.

THE MODIFICATION OF THE METHOD OF VALID CONDITIONALLY LINEAR REGULARITIES (VCLR)

1. The VCLR method

In [2], a method was proposed for assessing the statistical significance of the effect associated with the existence of significance of differences between the correlation coefficients of the Y and X indicators in the S_l and S_r groups formed from the initial sample S by the values the third

indicator Z. Groups are formed using a threshold rule. An object $s_j \in S$ described by values (x_j, y_j, z_j) is included into S_l if $z_j \leq b$ and into $S_r$if $z_j > b$.

In our case, the variable X corresponds to the serum level of FVIII, the variable Y corresponds to the serum level ABNR2, and the variable Z corresponds to the serum level of VEGF.

In the works [2, 3] the boundary b was selected so that the special quality functional Q, which characterizes the presence of a high degree of correlation between the variables X and Y on one side of the boundary and at the same time the difference between the correlation coefficients to the left and right of the border reached the maximum possible value. The following functional was used:

$$Q = \frac{||\varrho_l| - |\varrho_r||m_l m_r}{\sqrt{1 - \max \varrho_l, \varrho_r}}, \tag{1}$$

where m_l, ϱ_l are number of objects and correlation coefficient to the left of the threshold, m_r, ϱ_r are number of objects and correlation coefficient to the right of it. The maximum value of Q attained at the optimal boundary b_{opt} will be further denoted by Q_{max}.

Verification of the existence of the effect was reduced to an attempt to refute null hypotheses H_0^1, H_0^2 and H_0^3. Each hypothesis is tested by comparing the value of Q_{max} at S with the value of Q_{max} at the set of random samples $S_1^r, \ldots, S_N^r$, which are generated from the original sample by random permutations of one of the three variables X, Y, Z relative to the fixed positions of the other two variables. In this case, the shares of objects $S_1^r, \ldots, S_N^r$ for which the value of Q_{max} exceeds the value reached at S are used as p-values. The use of nonparametric permutation tests is becoming more and more widespread due to the absence of the need for a priori assumptions about the nature of distributions or the validity of asymptotic approximations [4, 5].

The use of the Q functional (1) allowed us to describe the effect associated with the existence of a correlation between VEGF and the complement component C4 in the hypoxic group. The disadvantage of the functional is the impossibility of an adequate assessment of the significance of the differences in the correlation coefficients if one of the S_l or S_r groups includes less than 25 objects. The latter is associated with an increase in the variance of the sample correlation coefficients at small sample sizes. As a consequence, there is a high probability of a random occurrence of data configuration for which the absolute value of the correlation coefficient will be close to 1. As a result, the value of Q_{max} at a random sample from $S_1^r, \ldots, S_N^r$ often turns out to be higher than Q_{max} at S, which leads to a significant overestimation of p-values. The use of a technique based on the Q functional does not allow us to draw a statistically significant conclusion about the existence of a combined effect. While the null hypothesesH_0^1 and H_0^2 were rejected with significance $p < 0.05$, the null hypothesis H30, at the use of functional Q, was not rejected even at the level $p < 0.1$.

2. New verification method based on Fisher's z-transform

The need to introduce new functional is related to the need to remove the above-mentioned restriction on the size of the S_l and S_r groups. This can be achieved by the following functional, based on the well-known Fisher's z-transform, first proposed by him back in 1915 [12]. Suppose that the sample objects to the left and to the right of the boundary b for the third factor Z are independently generated from bivariate normal distributions with the correlation coefficients between the variables X and Y equal to ϱ_l and ϱ_r, respectively. Suppose that to the left of the boundary b there is a subsample S_l of m_l objects with the correlation coefficient $r(S_l)$; to the right of the b border there is a S_r subsample of m_r objects with the correlation coefficient $r(S_r)$. Fisher's transformation for the correlation coefficients $r(S_l)$ and $r(S_r)$ are $z_l = \frac{1}{2} \ln \left(\frac{1+r(S_l)}{1-r(S_l)} \right)$ and $z_r = \frac{1}{2} \ln \left(\frac{1+r(S_r)}{1-r(S_r)} \right)$, respectively. Fisher has shown that values z_l and z_r are distributed

close to normal with mathematical expectations $\frac{1}{2}\ln\left(\frac{1+\varrho_l}{1-\varrho_l}\right)$ and $\frac{1}{2}\ln\left(\frac{1+\varrho_r}{1-\varrho_r}\right)$ and standard deviations $\sqrt{m_l-3}$ and $\sqrt{m_r-3}$ respectively. Variables $Z_l = \frac{1}{2}\ln\left(\frac{1+r(S_l)}{1-r(S_l)}\right)\sqrt{m_l-3}$ and $Z_r = \frac{1}{2}\ln\left(\frac{1+r(S_r)}{1-r(S_r)}\right)\sqrt{m_r-3}$ if the null hypothesis $\varrho_l = \varrho_r = 0$ is true have distribution close to normal distribution $N(0,1)$. Values $p_l = 1 - F_s^N(Z_l)$ and $p_r = 1 - F_s^N(Z_r)$, where F_s^N is the standard normal distribution function, are p-values for the specified null hypothesis. The monotonically increasing with $r(S_l)$ and $r(S_r)$ values $-\ln(p_l)$ and $-\ln(p_r)$ can be used instead of p-values with fixed sample S_l and S_r sizes. It should be noted that there is a low probability of high values of $-\ln(p_l)$ and $-\ln(p_r)$ for small sizes of S_l and S_r if the null hypothesis is valid due to the very definition of p-values.

Instead of the functional Q (1), it is proposed to use the functional Φ, which for a fixed boundary b is calculated by the formula

$$\Phi = \max(-\ln(p_l), -\ln(p_r)) . \tag{2}$$

The boundary is chosen to maximize Φ.

The verification of null hypotheses H_0^1, H_0^2 and H_0^3 when using the Φ functional is carried out in the same way as in valid conditionally linear regularities, that is, each hypothesis is tested by comparing the maximum values of the functional Φ_{max} at S with the value Φ_{max} at the set of random samples $S_1^r, \ldots, S_N^r$, which are generated from the original sample by random permutations of one of three variables X, Y, Z relative to the fixed positions of the other two variables. In this case, the shares of objects $S_1^r, \ldots, S_N^r$ for which the value of Φ_{max} exceeds the value reached at S are used as p-values. At the same time, relatively low probability of high values of Φ_{max}, if the null hypothesis is true, arising from the Φ definition, allows us to hope for the effectiveness of the method for small samples. The presented method for searching and verifying the effects associated with the influence of third factors on the correlation of two indicators is focused not on searching for partitions with maximum differences in correlation coefficients, but on identifying subgroups with the most significant coefficients according to the third factor Z.

Despite the explicit use of normal distributions in calculating the Φ_{max} value, which is the statistics of the test, the estimation of statistical significance is based on nonparametric permutation tests and does not require assumptions about normality. Higher efficiency of the new method was demonstrated with the problem of assessing the influence of VEGF on the correlation between FVIII and ABNR2, considered in this work.

RESULTS

In the analyzed sample, the optimal b boundary for VEGF turned out to be 1726 ng/ml with an average value of 753 ng / ml. In this case, the size of S_l is 79, and the size of S_r is 9. The correlation coefficient between FVIII and ABNR2 is -0.513 in the S_l group and 0.038 in the S_r group. The value of the functional Φ for the optimal bound is 14.78. The observed effect is shown in Fig. 2.

In the figure, the blue circles correspond to 79 cases from the S_l group; red squares correspond to 9 cases from the S_r group. It can be seen that the decrease in the absolute value of the correlation coefficient is associated with four outliers from the S_r group, highlighted in the figure, which distort the negative correlation between FVIII and ABNR2, which exists in the main part of the studied sample.

The null hypothesis H_0^1 is rejected at the level $p = 0.00039$ when using a variant of the permutation test with random permutations of the positions of FVIII with fixed positions of ABNR2 and VEGF. The null hypothesis H_0^2 is rejected at the level $p = 0.00056$ when using

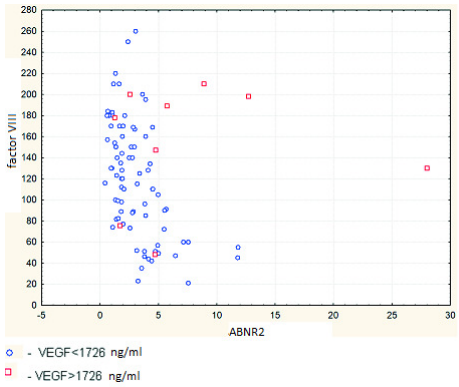

Fig. 2. The relationship between factor VIII and ABNR2. Cases with VEGF> 1726 ng/ml are highlighted in red.

a variant of the permutation test with random permutations of positions ABNR2 with fixed positions of FVIII and VEGF. The null hypothesis H_0^3 is rejected at the level of $p = 0.00778$ when using a variant of the permutation test with random permutations of VEGF positions at fixed positions of FVIII and ABNR2.

The significance was somewhat higher when calculating the correlation coefficients between the logarithms of FVIII and ABNR2. In this case, the optimal limit for VEGF also turned out to be 1726 ng/ml. The coefficient of correlation between the logarithms of FVIII and ABNR2 is -0.543 in the S_l group and 0.156 in the S_r group. The value of the functional Φ for the optimal bound is 16.69. The observed effect is shown in Fig. 3. Similar to Fig. 2 blue circles correspond to 79 cases from the S_l group; red squares correspond to 9 cases from the S_r group. It can be seen that the decrease in the absolute value of the correlation coefficient is associated with four outliers from the S_r group, highlighted in the figure, which distort the negative correlation between the logarithms, which exists in the main part of the study sample. At the same time, the linearity of the relationship is seen from the figure.

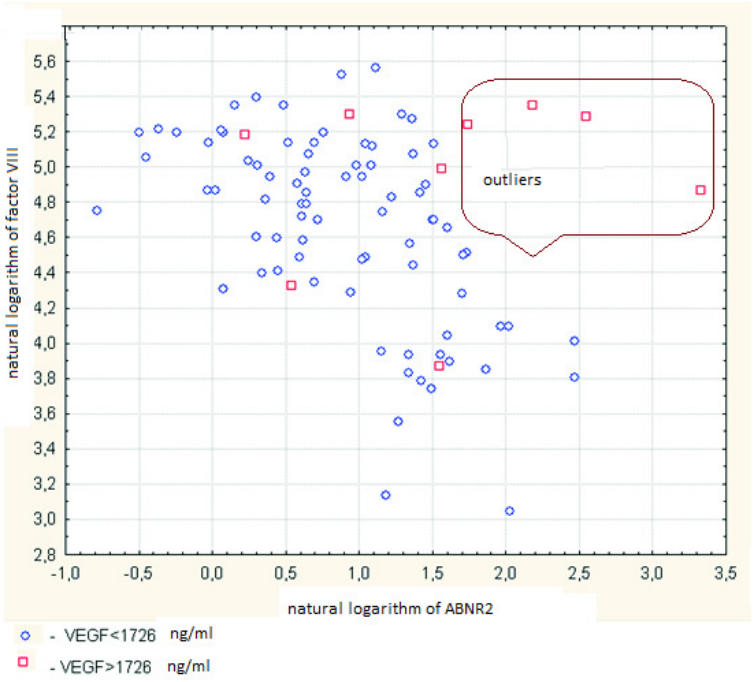

Fig. 3. The relationship between logarithm of factor VIII and ABNR2. Cases with VEGF> 1726 ng/ml are highlighted in red.

The null hypothesis H_0^1 about the independence of the logarithm of FVIII from the combination of the logarithm of ABNR2 and VEGF is rejected at the level $p = 0.00014$. The null hypothesis H_0^2 about the independence of the logarithm of ABNR2 from the combination of the logarithm of FVIII and VEGF is rejected at the level $p = 0.0002$. The null hypothesis H_0^3 about the independence of VEGF from the combination of the logarithm of FVIII and the logarithm of ABNR2 is rejected at the level $p = 0.00738$.

In addition to high (above 1726 ng/ml) serum levels of VEGF for the four isolated cases, acute hypoxia can also be noted: sO2 in venous blood is 37%, partial pressures of pO2 and pCO2 no more than 20 and no less than 56 mm Hg, respectively. The correlation coefficient between the logarithms of FVIII and ABNR2 in the general group, excluding four outliers, is -0.532, which is slightly lower in absolute value than the value of the similar correlation coefficient for the S_l group, equal to -0.543.

3. Discussion of the medical outcome

Thus, the null hypothesis of the absence of a relationship between FVIII and the combination of VEGF and ABNR2 is rejected at the level of $p < 0.001$. The null hypothesis that VEGF is not associated with a correlation between ABNR2 and FVIII is rejected at the level of $p < 0.01$. At the same time, there is a certain contradiction between the found negative relationship between ABNR2 and FVIII (I.e. the higher the ABNR2 index, the less the activity of Factor VIII.) and existing views about the relationship between the levels of factor VIII or ATNR2 and the occurrence of a stroke [7, 8, 9, 10]. An explanation of this phenomenon can be found in the publications [13, 14], which show that the activation of FVIII causes the rapid appearance of antibodies (Factor VIII Inhibitors) that block its activity. At the same time, the faster and more strongly FVIII is activated, the more antibodies to it are generated. This may explain the negative relationship we obtained between these two parameters. We have not determined antibodies to FVIII and therefore this assumption is still a working hypothesis that needs to be validated in further studies.

CONCLUSION

Thus, a new method has been developed for describing, searching and evaluating the statistical significance of combined effects, which consist in the influence of the third factor on the correlation between two variables. This method is based on the use of Fisher's z-transformation. The advantage of the developed method over the previously developed method of valid conditionally linear regularities, which is similar in purpose, is the ability to take into account distortions introduced by small groups of observations associated with extreme values of the third factor.

The use of a new modification of the optimal partitioning method, when constructing the statistics of the criterion, allowed us to reveal a statistically significant ($p < 0.001$) negative correlation between the serum levels of ABNR2 and Factor VIII in the group from which cases with abnormally high (> 1726 ng/ml) serum VEGF level were omitted.

The developed method also made it possible to assess the statistical significance of the effect of VEGF on the correlation between ABNR2 and FVIII at the level of $p < 0.01$. The likely reason for the negative correlation is the rapid generation of antibodies to FVIII upon its activation, which, however, requires confirmation in further studies.

The developed statistical method can be used in various biomedical or other studies related to the search for mutual correlations between two indicators in subgroups formed according to the third factor.

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