



Analysis of Predictors of 30-Day Mortality for Patients Undergoing Surgical Repair of Post-Myocardial Infarction Ventricular Septal Defect

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Authors' contributions

This work was carried out in collaboration among all authors. Author YL wrote the first draft of the manuscript. Author CLF was responsible for the study design and concept. Author RA analysis and interpretation of data, critical revision of article. Author MG performed the data cleaning and analysis, and all authors contributed to the writing of the paper. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Despite the existence of numerous studies devoted to predictors of 30-day mortality in patients with post-myocardial infarction (MI) ventricular septum defect (VSD), the choice of surgical treatment tactics for post-MI VSD remains an item of discussion. The purpose of the research was to determine the most significant risk factors of 30-day mortality in patients with post-MI VSD in order to optimize the tactics of such patients' surgical repair.

Study design: The retrospective analysis of the results of a comprehensive examination and surgical treatment of 88 in-patients with post-MI VSD for the period of 2002-2019 was carried out.

Results: As follows of the research findings, independent predictors of 30-day mortality in patients

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with post-MI VSD were determined. The predictors identified were combined into a Scoring system to stratify the risk of surgical failure in patients with post-MI VSD. Modelling the surgery outcomes makes it possible to optimize the tactics of surgical treatment of patients with post-MI VSD.

Conclusion: we have identified the most significant predictors of 30-day mortality in patients with post-MI VSD. The Score designed for mortality risk assessment is easy in use compared to other existing tools used in clinical practices when planning the surgical intervention in post-MI VSD patients. This Score may allow the stratification of post-MI VSD patients.

Keywords: Ischemic heart disease; myocardial infarction; ventricular septum defect; ventricular septum; mortality.

1. INTRODUCTION

Post-myocardial infarction (MI) ventricular septum defect (VSD) involve tearing or rupture of acutely infarcted myocardial tissue and is one of the most life-threatening mechanical complications due to acute MI. The Prevalence of post-MI VSD makes up 0,2-3,0% of the total number of patients with previous acute MI [1,2]. Post-MI VSD is characterized by rather poor prognosis always leading to severe heart failure. Surgical repair of post-MI VSD is the only efficient method since the possibilities of drug therapy for this complication of acute MI are extremely limited and ineffective. However, despite success attained in cardio surgery and pharmacology, the repair of post-MI VSD is associated with high rate of hospital mortality and high frequency of complications especially while repairing VSD in early time after development of acute MI [3-5].

Scientific literature reports a great number of references to the impact of different predictors on the survival rate and risk of mortality among post-MI VSD patients [6-9]. Preoperative hemodynamic status of a patient and the time from the development of acute MI to surgical intervention are the most significant factors to determine the prognosis for the postoperative outcome of post-MI VSD surgical repair [10,11]. Notably, discussions on the tactics of surgical treatment of post-MI VSD patients on early stages after the development of acute MI are still on. So far as the risk stratification is an important component of quality health care delivery to ischemic heart disease patients, it seems advisable to study the factors having a high predictive value in relation to the risk of hospital mortality in post-MI VSD patients.

Purpose of the Research: To determinate the most significant predictors of 30-days mortality risk in patients with post-MI VSD with the view of such patients surgical repair tactics optimization.

2. MATERIALS AND METHODS

In the study presented we have retrospectively analyzed the data of 88 post-MI VSD patients admitted for surgical intervention within the period of 2002-2019. Among such patients it was men who prevailed (72,3%). The age of the patients admitted ranged from 29 to 81 ($59,9 \pm 9,6$ years; $Z=0,729$, $p=0,663$). Depending on the outcome of clinical treatment all patients were divided in two groups: the survived and the deceased. Among the deceased patients the above-mentioned pre-surgical repair mortality rate made up 17,4%. Demographic and anthropometric indicators, data of generally accepted clinical and laboratory-instrumental methods of research and comorbidity had been analyzed. The surgical repair involved the VSD plastics implementation along with the left ventricular aneurysmectomy and the coronary artery bypass grafting in line with existing protocol [7,12]. Functional class of chronic heart failure has been established in accordance with the New York Heart Association (NYHA) classification.

Categorical variables have been presented as a proportion (number or percentage), while continuous variables – as median (interquartile range, quartiles). Binary variables have been compared using Fisher's exact test, whilst continuous variables – using Wilcoxon rank sum test. The correlation has been identified through univariate and multivariable logistic regression methods.

The variables that statistically differed significantly between the survived and the dead patients have been entered into univariate logistic regression analysis. The odds ratio (OR) with 95% confidential interval (CI) and p-value have been obtained. The continuous variables affecting mortality have been converted into a binary value with a cut-off point determined by operating curve analysis (ROC) in order to calculate the area under the curve (AUC, c-

statistic) and identify the highest predictive value. Statistically significant variables have been entered into multivariable logistic regression model to identify the predictors independently associated with mortality. While using the ORs obtained within multivariable regression model, the predicted mortality rate had been assessed. The predictive value of the Scoring system indicators for assessing the death probability in patients have been analyzed using ROC-analysis and C-statistics. The statistical value was taken at $p < 0,05$ level. The statistical analysis has been performed with GraphPad PRISM 9.0. software.

3. RESULTS AND DISCUSSION

Among 88 post-MI VSD patients, within 30 days after admission, most of these patients did not undergoing primary revascularization by percutaneous coronary intervention ($n=14$) at the prehospital stage, deaths were registered in 26,1% ($n=23$) of cases. Apart from that, the mortality rate of post-MI VSD patients has been analyzed depending on the surgery schedule, given the 2-week interval. The rate of mortality after surgical repair of post-MI VSD in the first 2 weeks after acute MI development made up 42,1%, starting from 3rd week - 10,5-15,8%. Subsequently, with an increase in the period from the development of acute MI, no significant changes in the mortality rate have been observed.

The deceased were elder than the survived ($63,3 \pm 9,9$ and $58,9 \pm 9,3$ ages, respectively). In the group of the deceased the proportions of patients with chronic kidney disease history (CKD) (47,8%) was more than 2 times higher than the proportion of such patients among those who survived (20,0%). Analysis of the hemodynamic profile on admission highlighted the differences in the values of shock index, heart rate (HR), NYHA class IV between the deceased and survived post-MI VSD patients. Furthermore, there were differences observed between the patients groups in terms of systolic blood pressure (SBP), the left ventricular end-diastolic volume, presence of pulmonary edema and surgical intervention timing from acute MI development (Table 1).

For the purposes of identifying the factors having prognostic significance in relation to surgical failures (predictors of 30-day mortality), the indicators of the target groups of patients with post-MI VSD have been analyzed which have statistically significant differences on patients' admission (Table 2).

Univariate logistic regression analysis followed by ROC-analysis of continuous variables to determine the optimal cut-off point made it possible to identify factors of the highest risk of postsurgical deaths in patients with post-MI VSD. The age met the AUC 0,659 with an optimal cut-point of 69 years, the period of surgical intervention after acute MI development – AUC 0,761 with optimal cut-point of 17 days, shock index - AUC 0,784 with optimal cut-point of 1,2, HR – AUC 0,746 with optimal cut-point of 100 beat/min, the left ventricular end-diastolic volume – AUC 0,663 with optimal cut-point of 171 ml, SBP – AUC 0,692 with optimal cut-point < 95 mmHg, NYHA class IV – AUC 0,716, pulmonary edema – AUC 0,531 and CKD history – AUC 0,639. The variables with poor prognostic ability ($p > 0,05$) according to the AUC analysis results (Table 2) were not used for further analysis.

Thus, six indicators were chosen as risk predictors of postsurgical deaths in patients with post-MI VSD. The variables with statistically significant prognostic ability were introduced into multivariable logistic regression model (Table 3).

The analysis revealed statistically significant variables that were subsequently identified as risk factors for post-surgical procedure deaths in patients with post-MI VSD. According to the results of multivariable logistic regression analysis, the time of surgery after development of acute MI, HR, history of CKD, NYHA class IV, values of shock index and SBP were independent predictors of 30-day mortality in post-MI VSD patients (Table 3).

The variables which were independent predictors of 30-days mortality within multivariable logistic regression analysis were combined into a Score for assessing the mortality risk (DH2NS2) in patients with post-MI VSD. The Score was designed based on the values of the ORs of multivariable logistic regression analysis to simplify their application in clinical practice. Based on the above, the variables of shock index and NYHA class IV were given a value of 2 scores, and the surgery time from the development of acute MI, HR, CKD history and SBP – 1score (Table 4).

High risk of post-surgical procedure mortality in patients with post-MI VSD is tightly interrelated with surgical intervention in the early time after acute MI development, with hemodynamic status when admitted, as well as with patients' comorbidity – with CKD in history. According to our data, the accumulation of DH2NS2 scores is

actually accompanied by an increase in the risk of mortality in the post-surgical procedure term (Fig. 1; Table 5).

DH2NS2 Score had AUC 0,882 (95% CI 0,800 – 0,965) for predicting postsurgical mortality rate in patients with post-MI VSD. The optimal cut-off point with the highest combined sensitivity and specificity was at the score ≥ 5 points with 52,0% of sensitivity and 98,5% of specificity, with positive predictive value of 79,0% and negative predictive value of 94,9% (Table 6).

The analysis results signal a high risk of 30-day mortality in patients with post-MI VSD with a score ≥ 4 points when admitted (79,0%). In patients with post-MI VSD with a score ≥ 5 points we have a higher OR of 8,355 (95% CI 65,98% - 80,0%, $p < 0,001$) compared to the score < 5 points. Moreover, patients with a score < 4 points have a high probability (94,9%) of a favorable outcome in the post-surgery period.

Along with the prevalence of ischemic heart disease and incidence of acute MI, as well as

given the high rates of hospital mortality during surgical treatment of post-MI VSD, it's imperative to assess the prediction of mortality risk in postsurgical period for such patients. Numerous works are devoted to the research of risks of postsurgical complications and mortality in patients with post-MI VSD [6-9]. However, it is kind of hard to assess the risk for an individual patient with merely descriptive characteristics used; therefore, a simple model is needed to predict the risk in clinical practice. Besides, such model for predicting postsurgical mortality in patients with post-MI VSD can be used by various medical institutions as a means of assessing the effectiveness of specialized medical aid. Thus, there exists no doubt about the relevance of carrying out full-fledged therapeutic examination and completeness of correction of a complex of cardiac morphological changes for improving the quality of life given the problem of predicting the risk of postoperative mortality in surgical treatment of post-MI VSD [7,12].

Table 1. Patients characteristics and comorbidities according to post-surgical intervention outcome of post-MI VSD repair (n=88)

Group	Survived patients (n=65)	Non-survived patients (n=23)	P
Indicator			
Age (years)	58,9 \pm 9,3	63,3 \pm 9,9	0,011
Males	48 (73,8%)	15 (65,2%)	0,433
Body mass index (kg/m ²)	26,9 \pm 3,9	29,1 \pm 6,5	0,169
Cardiac index (l/min/m ²)	1,9 \pm 0,6	2,0 \pm 0,8	0,182
Cardiac power index (W/m ²)	0,38 \pm 0,2	0,37 \pm 0,2	0,364
Days from AMI to surgery	75,7 \pm 74,6	33,1 \pm 37,7	<0,001
GFR (ml/min/1,73 m ²)	80,3 \pm 47,9	62,3 \pm 40,4	0,068
History of CKD (GFR < 60 ml/min/1,73 m ²)	13 (20,0%)	11 (47,8%)	0,015
History of COPD	8 (12,3%)	3 (14,0%)	1,0
History of diabetes mellitus	19 (29,2%)	12 (52,1%)	0,074
History of arterial hypertension	18 (27,6%)	3 (13,0%)	0,254
NYHA class IV	30 (46,1%)	20 (87,0%)	<0,001
LV EF (%)	43,4 \pm 9,7	45,1 \pm 12,7	0,413
LV EDV (ml)	203,1 \pm 47,1	188,3 \pm 70,2	0,011
Size of post-MI VSD (mm)	17,8 \pm 9,9	20,1 \pm 14,1	0,463
Presence of LV aneurysm	16 (24,6%)	4 (17,3%)	0,640
Pulmonary edema by lung USG	4 (6,1%)	7 (30,4%)	<0,001
Presence of ST elevation	16 (24,6%)	7 (30,3%)	0,591
HR on admission (bpm)	81,5 \pm 13,4	94,5 \pm 14,2	0,002
SBP (mmHg)	116,4 \pm 19,1	106,1 \pm 17,7	0,003
Pulse pressure (mmHg)	40,7 \pm 13,1	34,8 \pm 14,7	0,052
Shock index (HR/SBP)	0,9 \pm 0,2	1,2 \pm 0,2	<0,001

Note: AMI – acute myocardial infarction; GFR – glomerular filtration rate; HR – heart rate; CKD – chronic kidney disease; COPD – chronic obstructive pulmonary disease; LV – left ventricular; LV EF – LV ejection fraction; LV EDV – LV end-diastolic volume; NYHA – The New York Heart Association functional classification; USG – ultrasonography; SBP – systolic blood pressure; post-MI VSD – post myocardial infarction ventricular septum defect. Cardiac power index was obtained by the formula: cardiac index (L/min/m²) (obtained by trans thoracic ultrasound) x mean arterial pressure divided by 451

Table 2. The results of univariate logistic regression analysis indicators of patients with post-MI VSD

Indicator	Group	OR	95% CI	p
Age (years)		0,988	0,966 – 1,004	0,051
Days from AMI to surgery		1,119	0,983 – 1,338	<0,001
HR on admission (bpm)		4,079	1,032 – 18,98	<0,001
History of CKD		2,721	0,833 – 14,20	0,013
LV EDV (ml)		0,015	1,516e-008 – 399,7	0,268
NYHA class IV		0,937	0,840 – 1,009	0,003
Pulmonary edema by lung USG		0,988	0,966 – 1,004	0,601
Shock index (HR/SBP)		1,119	0,983 – 1,338	<0,001
SBP (mmHg)		4,079	1,032 – 18,98	0,030

*Comment: AMI – acute myocardial infarction; HR – heart rate; CKD – chronic kidney disease; LV – left ventricular; LV EDV – LV end-diastolic volume; NYHA – The New York Heart Association functional classification; SBP – systolic blood pressure; USG – ultrasonography; CI – confidence interval; OR – odds ratio

Table 3. Multivariable logistic regression analysis of patients with post-MI VSD indicators

Indicator	Group	OR	95% CI	P
Days from AMI to surgery		0,988	0,966 – 1,004	<0,001
HR on admission (bpm)		1,119	0,983 – 1,338	
History of CKD		4,079	1,032 – 18,98	
NYHA class IV		2,721	0,833 – 14,20	
Shock index (HR/SBP)		0,015	1,516e-008 – 399,7	
SBP (mmHg)		0,937	0,840 – 1,009	

Note: AMI – acute myocardial infarction; HR – heart rate; CKD – chronic kidney disease; NYHA – The New York Heart Association functional classification; SBP – systolic blood pressure; CI – confidence interval; OR – odds ratio

Table 4. 30-days mortality prediction Score system (DH2NS2) in patients with post-MI VSD

Indicator	Value	Score
Days from AMI to surgery	<17	1
HR on admission (bpm)	>100	1
History of CKD	Yes	1
NYHA class IV	Yes	2
Shock index (HR/SBP)	>1,2	2
SBP (mmHg)	<95	1

Note: AMI – acute myocardial infarction; HR – heart rate; CKD – chronic kidney disease; NYHA – The New York Heart Association functional classification; SBP – systolic blood pressure

Table 5. Prognostic DH2NS2 Score of 30-days mortality risk in patients with post-MI VSD.

DH2NS2	Prognostic 30-days mortality	95% CI
0	2,0%	1,8% – 2,2%
1	5,2%	3,9% – 6,0%
2	12,8%	10,9% – 14,0%
3	28,2%	25,9% – 30,0%
4	51,2%	45,9% – 60,0%
5	73,7%	65,9% – 80,0%
6	88,2%	85,9% – 90,0%
7	95,2%	92,9% – 97,9%
8	98,2%	98,0% – 100,0%

Comment : CI – confidence interval

Table 6. Assessment of the prognostic significance of the DH2NS2 Score for predicting 30-day mortality in patients with post-MI VSD

Score	Sensitivity	95% CI	Specificity	95% CI	PPV	95% CI	NPV	95% CI
≥0	100,0	86,3-100,0	0	0-5,5	10,0	10,0-10,0		
>1	96,0	79,6-99,9	47,69	35,1-60,5	16,9	13,8-20,7	99,1	93,9-99,9
>2	96,0	79,6-99,9	52,31	39,5-64,9	18,3	14,6-22,6	99,2	94,4-99,9
>3	84,0	63,9-95,5	66,15	53,4-77,4	21,6	15,9-28,7	97,4	93,7-98,9
>4	72,0	50,6-87,9	90,77	81,0-96,5	46,4	28,0-65,9	96,7	93,9-98,2
>5	52,0	31,3-72,2	98,46	91,7-100,0	79,0	34,1-96,5	94,9	92,5-96,5
>6	36,0	18,0-57,5	100,0	94,5-100,0	100,0		93,4	91,3-95,0
>7	0	0-13,7	100,0	94,5-100,0	100,0		90,0	90,0-90,0
>8	0	0-13,7	100,0	94,5-100,0	100,0		90,0	90,0-90,0

Comment: CI – confidential interval; PPV – positive predictive value; NPV – negative predictive value

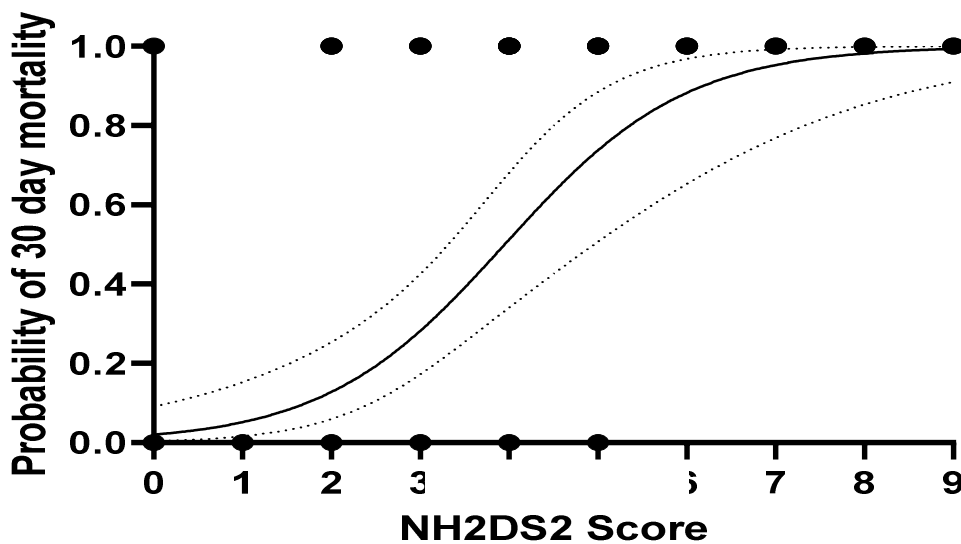


Fig. 1. Logistic curve (DH2NS2) of 30-days mortality predictors in patients with post myocardial infarction ventricular septum defect

In the course of the research, six most significant clinical factors have been identified as independent predictors of postoperative deaths in patients with post-MI VSD (time of surgery after development of acute MI, HR, NYHA class IV, shock index, CKD in medical history and SBP). The data obtained are consistent with the literature report on the high risk of death in patients with post-MI VSD during surgery at the early stages after the development of acute MI, against the hemodynamic instability and comorbidity [8,13,14,15], and CKD as an early mortality risk factor [16].

Given the high mortality rate in patients with post-MI VSD, separate studies have identified the factors influencing survival of patients after surgical repair of post-MI VSD [6-9,13]. Among

them, arterial hypertension, high Killip class on admission and cardiac rate are specified as independent predictors of mortality. [10,11]. Nonetheless, in spite of a large body of research devoted to surgical treatment of post-MI VSD, the choice of treatment strategies remains unsettled. In our research, a lethal outcome within 30 days after admission was registered in 26,1% (n=23) of cases, which correlates with the findings of numerous research works devoted to study of mortality in patients after surgical repair of post-MI VSD [3,8].

Notably, Prêtre R.et al. reported mortality in the early post-surgery period in 26,0% of patients (n=54) who underwent surgical repair of post-MI VSD [8], results also obtained by Cinç-Mars et al, with 65% of mortality in patients who undergone

surgical repair under the first 7 days from AMI event [17]. The high mortality rate of such surgeries is associated with initial severity of clinical condition and comorbidity in patients, as well as with their elderly age. There is no doubt about the idea that the most indicative prognostic factor determining the postoperative outcome is the patient's preoperative hemodynamic status. This is confirmed by the conclusions of a great number of authors, indicating the prognostic significance of cardiogenic shock (CS) at admission. Literature suggests that, the development of CS may depend on the volume and area of ischemic lesions [8]. Shock index and cardiac power index has been proposed as strong predictors of in-hospital mortality, short-term and long-term adverse outcomes after AMI, however, shock index showed to have a stronger correlation with fatal outcomes in patients complicated with VSD [18,19]. In the SHOCK study, in patients with CS, hospital mortality after surgical correction of post-MI VSD was 87,0%, while for patients without CS it was 59,0%. At the same time, the 30-day mortality rate of operated patients with post-MI VSD in this study was about 47,0% [20].

There is ample research which testifies that early survival in patients with post-MI VSD can show significant improvement through surgical delay. In the other extreme, the recommendations of the American Heart Association highlight the need for emergency surgery regardless of patient's clinical condition [21]. Thus, the ideal timing of operation remains a matter of argument. In the Score designed for clinical assessment of the risk of mortality in patients with post-MI VSD, an independent predictor of mortality, specifically, the time from the development of acute MI to the surgery date, has a cut-off point of 17 days. The analysis of mortality in patients with post-MI VSD signifies the advisability of applying the wait-and-see tactics in surgical treatment, on the assumption of hemodynamic stability of such patients. These findings are evidenced by the decrease in operative mortality from 42,1% to 10,5-15,8% starting from 3 weeks after the acute MI development. As the data show, no further wait-and-see tactics justifies itself, since it does not reduce the surgical mortality in patients with post-MI VSD who received surgical repair in early time after the development of acute MI. Yet, the decision on the need for emergency surgery in patients with post-MI VSD should be also based on the possibility to stabilize systemic

hemodynamics through medication and endovascular techniques.

Actually, the EuroSCORE II calculator is available to assess the risk of surgical intervention failure [17,22]. The post-MI VSD patients mortality risk factors obtained are consistent with many those presented in the EuroSCORE II. Notably, the Score presented by us demonstrates a high separating ability in predicting a 30-day lethal outcome in patients with post-MI VSD and is easier to use. Moreover, the Score proposed by us takes account of independent predictors of 30-day mortality and their "weight" specifically for patients with post-MI VSD.

4. CONCLUSION

As a result of our research, we have identified the most significant predictors of 30-day mortality in patients with post-MI VSD. The Score designed for mortality risk assessment is easy in use compared to other existing tools used in clinical practices when planning the surgical intervention in post-MI VSD patients. This Score allows stratifying the post-MI VSD patients, even the risk of post-surgical repair mortality, and the ability of modelling the outcomes of surgery will help to optimize the tactics of surgical treatment of patients with post-MI VSD. In consideration of the mortality risks involved and according to our research findings, in terms of post-MI VSD patient's surveillance it seems viable to perform surgical intervention 2 weeks after acute MI development.

5. LIMITATIONS

Some authors suggest that location of the VSD may play a role in mortality [8,14], however We did not take into account post-MI VSD localization in the study because we did not get significant differences in mortality. In 20.8% (n = 10) of cases, a lethal outcome was registered in patients with anterior and in 25.0% (n = 9) - with posterior localization of post-MI VSD ($\chi^2(1, n = 84) = 0.035; p = 0.851$), reason why was not included in the analysis. Also, as the present study at the date of publication, have the largest sample collected for this subject, larger multicentric studies may be necessary to validate the suggested score.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.”

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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