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Original work

PREOPERATIVE HIGH-SENSITIVE TROPONIN T AND N-TERMINAL PRO B-TYPE NATRIURETIC PEPTIDE IN PREDICTION OF SHORT-TERM MORTALITY AFTER NON-CARDIAC SURGERY (HIGH-SENSITIVE TROPONIN T AND N-TERMINAL PRO B-TYPE NATRIURETUC PEPTIDE IN PREDICITON OF MORTALITY AFTER NON-CARDIAC SURGERY)

Nenad Savić[1], Ilija Golubović[2], Milena Stojanović[1], Anita Vuković[1], Danica Marković[1], Radmilo Janković[1]

1Clinic for anesthesia and intensive therapy, Blvd. dr. Zorana Đinđića 48, Clinical Center Niš, 18000 Niš, Serbia
2Department of General surgery, Clinical Center Niš, Blvd. dr. Zorana Đinđića 81, 18000 Niš, Serbia

Summary

Background and Aims: *The aim of this study was to evaluate potential of prognostic cardiac biomarkers by predicting fatal events during perioperative period and the significance of their increased values in all patients and with coronary artery disease (CAD).* ***Methods:*** *The study included 87 patients who underwent major abdominal and vascular surgery. Blood samples were taken from all patients prior to surgery and levels of high-sensitive troponin T (hsTnT) and N-Terminal Pro B-type natriuretic peptide (NT-proBNP) were measured. It was analyzed how their increased values (above the predefined cut-offs of > 14 ng/L and > 300 pg/mL respectively) was associated with perioperative mortality in both all subjects and in patients with CAD.* ***Results:*** *Median value of hsTnT in survival group was 11.29 ng/L (interquartile range – IQR, 6.03–18.57) vs. 26.62 ng/L (IQR, 21.48–76.31) in non-survival group, p = 0.045 and for NT-proBNP in survival group was 259.05 pg/mL (IQR, 93.03–447.45) vs. 759.2 pg/mL (IQR, 433–6095) in non-survival group, p = 0.017. The odds ratio of mortality was presented in the form of direct association for both measured biomarkers - not only in patients with CAD but also in all included patients.* ***Conclusions:*** *Preoperatively increased hsTnT and NT-proBNP indicate high mortality risk during perioperative period. Because of the association between increased cardiac biomarker and mortality events in patients with CAD, special attention is necessary in preparation for major surgery.*

Key words: *cardiac biomarkers; short-term mortality; perioperative risk; non-cardiac surgery; coronary artery disease*

Introduction

Non-cardiac surgery is usually performed on elective basis. However, this type of surgery can be associated with significant cardiovascular morbidity and mortality. One of the most important predictors of complications is Coronary Artery Disease (CAD)[1,2]. When a patient with ischemic cardiac disease undergoes a high-risk surgery, the risk of cardiac complications rises almost tenfold[3]. There are powerful biomarkers that reflect myocardial injury, specifically heart failure, valvular heart disease, as well as CAD. From a group of potential biomarkers, B-type Natriuretic Peptide (BNP) and N-Terminal Pro B-type natriuretic peptide (NT-proBNP), and troponins seem to be the most important[4, 5].

Several studies have demonstrated that BNP and NT-proBNP provide strong prognostic information in both documented cardiovascular patients and apparently healthy individuals[6,7]. Cardiac troponins have also been used for a long time as a golden standard for diagnosing myocardial infarction. However, since the implementation of high-sensitive troponin T (hsTnT) assays, they proved to be useful for the detection of minor cardiovascular injuries and these markers can be used for providing significant prognostic information[8, 9].

The aim of this study was to investigate the association between preoperative levels of hsTnT and NT-proBNP and short-term mortality events in patients who underwent major non-cardiac surgery. Additionally, we performed an analysis to determine the mortality risk in a subgroup of pa-

Corresponding author: Milena Stojanović, Dr. Milutina Ivkovića 8, 18000 Niš, Serbia, Telephone: +381606240788, E-mail: milenastojanoviclaci@gmail.com

tients with documented CAD according to cut-offs of these cardiac biomarkers values.

Subjects and methods

The study was conducted as a single-center, prospective, observational study. It included 87 patients who underwent major abdominal and vascular surgery under general anesthesia. All patients were recruited in 2008 and 2009 at the Department of Surgery, The Clinical Center of Niš. The surgeries were performed according to clinical standards of our hospital. Besides the type of surgery, other inclusion criteria were age >55 years, and the presence of at least one of cardiovascular risk factors – arterial hypertension, family history of cardiac disease, hyperlipidemia, active smoking status or diabetes mellitus. Inabilities to understand or sign an informed consent as well as emergency surgery, were taken as exclusion criteria.

Each patient had to sign an informed consent that included biomarker analysis. The study was approved by the local Ethical Committee of Clinical Center Niš.

Follow-up period for postoperative mortality, as the primary clinical outcome of our study, was within 30 days. All-cause mortality was included following: acute myocardial infarction, ventricular fibrillation, cardiac arrest, cardio-pulmonary resuscitation, and acute cardiac decompensation. Coronary artery disease was defined on the basis of positive laboratory tests, clinical risk factors, prior bypass surgery, coronary intervention or prior myocardial infarction. Acute myocardial infarction was diagnosed according to universal definition of myocardial infarction[7].

Laboratory analysis

Blood samples for laboratory assessment were taken no more than seven days before the surgery. Immediately after venipuncture from antecubital region, tubes with blood were processed without additives. Prior to analyses, serum was separated and frozen to -70°C. The samples were sent to predefined investigating laboratory center at the University of Basel, Switzerland.

Cardiac TnT was measured by a newly developed highly-sensitive electrochemiluminescence-immunoassay (hsTnT) on an Elecsys analyzer (Roche Diagnostics, Mannheim, Germany). The lower limit of detection for this assay was 3 ng/L, the 99th percentile of a healthy reference population was 14 ng/L, and the concentration with a coefficient of variation (CV) of 10% was 13 ng/L. NT-proBNP was measured by an electrochemiluminescence-immunoassay (ElecsysproBNP, Roche Diagnostics, Mannheim, Germany). The analytical range extended from 5 to 35 000 pg/mL. The total CV was 3.3% (n ¼ 28) at a level of 252.6 pg/mL and 3.7% (n ¼ 25) at a level of 6130.8 pg/mL of NT-proBNP.

Statistical analysis

Values are expressed as the mean ± SD (standard deviation), median with interquartile range, odds ratio (OR) or hazard ratio (HR). Because there was no normal distribution of some variables in the subjects with CAD, differences in survival were tested with the Mann-Whitney U test for independent samples. Also, Z-test and Students t-test were used as appropriate and Chi-square test was used for categorical variables. Differences of laboratory parameter between two groups were assessed with Students t-test and median test. To evaluate test performance for NT-proBNP and hsTnT, an area under the curve (AUC) for the receiver operating characteristics (ROC) was calculated. OR and 95% confidence interval (CI) was measured for all patient to determine risk of mortality in relation to cut-off values of biomarkers. HR for all variables were analyzed with multivariant Cox regression analyses. A value of $P \leq 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS software (version 10) and Comprehensive Meta-Analysis (version 3; Biostat Inc, Englewood, NJ).

Results

Out of 87 patients, 39 (45%) were women. Mean age of our patients was 68. Nine of all included patients (10%) had history of CAD. Most of our patients – 65 (75%) underwent abdominal surgery and the rest 22 (25%) had major vascular surgery. Majority of the patients were on cardiovascular medical treatment and had one or more cardiovascular risk factors. General features of the patients are presented in Table I.

The median value of high-sensitive troponin levels for entire cohort was 11.45 ng/L, with IQR

Table I: General features

	All patients	Survivors	Deceased	p-value survivors vs. deceased
n (%)	87 (100)	80 (92)	7 (8)	
Gender (female), n (%)	39 (44.83)	37 (46.25)	2 (28.57)	0.178
Age (years) ± SD	67.95 ± 7.97	68.04 ± 7.94	67.02 ± 8.88	0.749
BMI (kg/m^2) median (IQR)	24.77 (23.091–27.68)	24.80 (2.36–27.68)	22.66 (19.60–27.78)	0.694
CAD, n (%)	9 (100)	7 (8.75)	2 (28.57)	< 0.001
Dyspnoea, (NYHA II-IV) n (%)				
1	56 (64.37)	54 (667.5)	2 (28.57)	0.053
2	27 (31.03)	22 (27.5)	5 (71.43)	
3	4 (4.6)	4 (5)	0 (0)	
Angina pectoris, n (%)				
1	69 (78.75)	66 (82.55)	3 (42.86)	0.032
2	17 (16.25)	13 (16.25)	4 (57.14)	
3	1 (1.25)	1 (1.25)	0 (0)	
Atrial fibrillation, n (%)	1 (1.25)	1 (1.25)	0 (0)	0.006
Diabetes mellitus, n (%)	25 (31.25)	25 (31.25)	0 (0)	< 0.001
Hyperlipidemia, n (%)	22 (27.5)	20 (27.5)	2 (28.57)	0.908
Active smokers, n (%)	20 (21.25)	17 (21.25)	3 (42.86)	0.007
Beta blocker, n (%)	45 (51.25)	41 (51.25)	4 (57.14)	0.677
ACE inhibitor/AT antagonist, n (%)	49 (57.5)	46 (57.5)	3 (42.86)	0.318
Diuretics, n (%)	22 (27.5)	19 (23.75)	3 (42.86)	0.027
Nitrates, n (%)	7 (6.25)	5 (6.25)	2 (28.57)	< 0.001
BMI > 27	26 (30)	24 (30)	2 (28.57)	0.885
Age > 65	50 (58.75)	47 (58.75)	3 (42.86)	0.282
Hb (g/dL) median (IQR)	11.7 (10.1–13)	11.65 (10.1–13)	12.6 (11.1–14.7)	0.874
Creatinine (mg/dL) median (IQR)	0.85 (0.7–1)	0.84 (0.7–1.01)	0.9 (0.75–0.98)	0.924
hsTNT (ng/L) median (IQR)	11.45 (6.28–19.5)	11.29 (6.03–18.57)	26.62 (21.48–76.31)	0.045
NT-proBNP (pg/mL) median (IQR)	280.3 (99.71–450.1)	259.05 (93.03–447.45)	759.2 (433–6095)	0.017
hsTNT > 14 ng/L, n (%)	34 (39.08)	28 (35)	6 (85.71)	0.008
NT-proBNP > 300 pg/mL, n(%)	40 (41.25)	33 (41.25)	7 (100)	< 0.001

Abbreviations: *hsTnT* – high-sensitive troponin T; *NT-proBNP* – N-Terminal Pro B-type natriuretic peptide; *BMI* – Body Mass Index; *NYHA* – New York Heart Association; *ACE* – Angiotensin Converting Enzyme; *AT* – Angiotensin; *SD* – Standard Deviation; *IQR* - Interquartile Range

6.28–19.5, and the median value for NT-proBNP was 280.3 pg/mL (Interquartile Range - IQR 99.71–450.1). There were statistically significant differences between levels of hsTnT and NT-proBNP in group of survivors (S) and non-survivors (NS). Median value of hsTnT in S group was 11.29 ng/L (6.03–18.57) vs. 26.62 ng/L (21.48–76.31) in NS group, p = 0.045 and for NT-proBNP in S group was 259.05 pg/mL (93.03–447.45) vs. 759.2 pg/mL (433–6095) in NS group, p = 0.017. Thirty-four of all included patients (39%) in study were with hsTnT values above 14 ng/L while NT-proBNP values were above 300 pg/mL in 40 patients (41%). Patients with diagnosed angina pectoris, atrial fibrillation, diabetes mellitus, as well as active smokers, had increased mortality events. Other tested parameters showed no statistical significance for survival.

The OR of mortality was presented in the form of direct association for both measured biomarkers, not only in patients with CAD, but also in all included patients. The OR in all patients with measured hsTnT was 11.14 (95% CI, 1.28–97.23; p = 0.03), and in patients with CAD was 75.00 (95% CI, 1.15–4868.64; p = 0.04). For all patients with measured NT-proBNP, the OR was 21.27 (95% CI,

1.17–385.25; p = 0.04), and for patients with documented CAD was 75.00 (95% CI, 1.15–4868.64; p = 0.04) (Table II – Mortality events and OR in patients with baseline cut-offs of > 14ng/L for hsTnT and of > 300pg/mL for NT-proBNP).

age of 65 have statistically significant values of hsTnT. Other comorbidities were not in association with values of hsTnT.

ROC curve (Figure 1 – ROC curves for hsTNT and NT-proBNP for the mortality rate) and AUC

Table II: Mortality events and OR in patients with baseline cut-offs of > 14 ng/L for hsTnT and of > 300 pg/mL for NT-proBNP

Mortality	hsTnT (> 14 ng/L) and NT--proBNP (> 300 pg/mL)		hsTnT (< 14 ng/L) and NT--proBNP (< 300 pg/mL)		Odds ratio and 95% CI	p-Value
	Events	Total Number	Events	Total Number		
Measured hsTnT in all patients	6	34	1	53	11.14 (1.28–97.23)	0.03
Measured hsTnT in CAD patients	2	2	0	7	75.00 (1.15–4868.64)	0.04
Measured NT--proBNP in all patients	7	40	0	47	21.27 (1.17–385.25)	0.04
Measured NT--proBNP in CAD patients	2	2	0	7	75.00 (1.15–4868.64)	0.04

Abbreviations: *hsTnT* – high-sensitive troponin T; *NT-proBNP* – N-Terminal Pro B-type natriuretic peptide; *CI* – Confidence Interval; *CAD* – Coronary Artery Disease

Table III (High-sensitive troponin T related to comorbidities) presents the values of hsTnT as a prognostic indicator in accord with comorbidities. From this data, we can see that patients over the

analysis (Table IV – Area under the curve analysis of hsTNT and NT-proBNP for the mortality rate) was used to evaluate specificity and sensitivity of both values of hsTNT (p = 0.004) and NTproBNP

Table III: High-sensitive troponin T related to comorbidities

	hsTnT (ng/L)		
	Median	IQR	P-value
Creatinine > 1.2 mg/dL			
yes	31.88	11.54–70.50	0.251
no	11.28	6.25–19.15	
diabetes			
yes	11.8	5.73–19.98	0.588
no	11.29	6.71–19.6	
smoker			
yes	12.02	8.12–21.31	0.183
no	11.08	5.9–19.38	
hypertension			
yes	11.55	7.84–20.82	0.883
no	11.45	5.72–19.7	
Age > 65			
yes	15.35	8.46–25.94	0.003
no	8.11	4.91–12.02	
BMI > 27			
yes	8.35	4.61–19.16	0.117
no	11.93	7.38–21.13	

Abbreviations: *hsTnT* – high-sensitive troponin T; *BMI* – Body Mass Index

Table IV: Area under the curve analysis of hsTNT and NT-proBNP for the mortality rate

Test Result Variables	Area	Std. Errora	Asymptotic Sig.b	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
hsTNT (ng/L)	0.834	0.076	0.004	0.686	0.982
NT-proBNP (pg/ml)	0.862	0.046	0.002	0.772	0.953

Abbreviations: *hsTnT* – high-sensitive troponin T; *NT-proBNP* – N-Terminal Pro B-type natriuretic peptide

(p = 0.002) as indicators for increased mortality risk. All the patients with values equal to or higher than cut-offs of measured biomarkers were considered as positive.

Discussion

During the perioperative period of major surgery, patients are prone to the significant physiological changes and stress[10]. Cardiovascular system

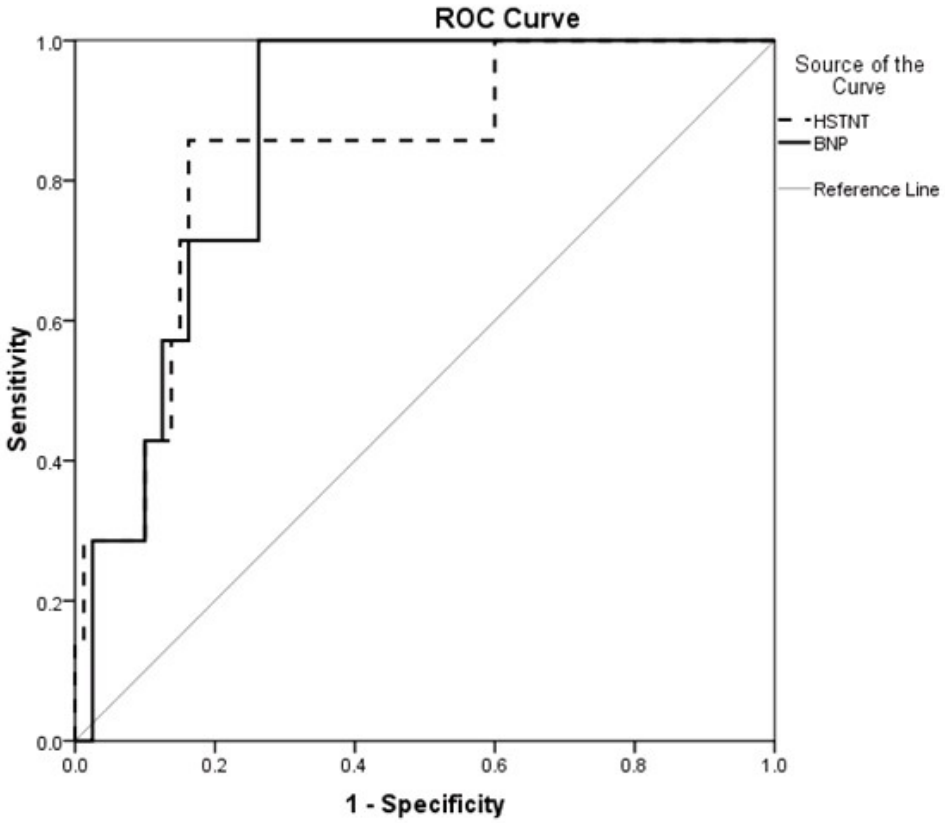

Figure 1: ROC curves for hsTNT and NT-proBNP for the mortality rate
Abbreviation: *hsTnT* – high-sensitive troponin T; *NT-proBNP* – N-Terminal Pro B-type natriuretic peptide; *ROC* – receiver operating characteristic

Table V (Results of Cox regression analyses) presents the summary statistics for multivariant Cox regression analysis of tested parameters. The mortality risk for values of hsTNT was 1.050 with statistical significance (p = 0.010). We found no evidence of increased mortality risk among others tested parameters.

is probably under the highest risk, especially for those who already have some type of cardiovascular disease. Although CAD is a well-established risk factor for perioperative complications[11–13] so far there has not been published a research examining the significance of CAD in relation to cardiac biomarkers in a patient undergoing major surgery.

For predicting surgical risk, CAD is usually observed as a part of composed risk scores[3,14]. This

Table V: Results of Cox regression analyses

	B	p-value	Wald	df	Sig.	Exp (B)
Systolic blood pressure (mmHg)	-0.008	0.021	0.164	1	0.685	0.992
Heart rate (/min)	-0.038	0.039	0.961	1	0.327	0.962
NT-proBNP (pg/ml)	0.000	0.000	1.720	1	0.190	1.000
hsTnT (ng/L)	0.049	0.019	6.633	1	0.010	1.050
Lee score ≥ 2	-0.043	1.012	0.002	1	0.966	0.957
NYHA II-IV	0.970	1.251	0.601	1	0.438	2.637
Angina pectoris CCS II-IV	1.067	1.122	0.905	1	0.341	2.907

Abbreviations: *hsTnT* – high-sensitive troponin T; *NT-proBNP* – N-Terminal Pro B-type natriuretic peptide; *NYHA* – New York Heart Association; *CCS* – Canadian Cardiovascular Society

scoring has gained popularity recently, but the specific role of CAD in predicting complications during the perioperative period is still unclear. Our study included 87 subjects from which about 10% had positive history of CAD, and one of the main purposes of the paper was to evaluate whether values of cardiac markers may be used for identifying high perioperative mortality risk in patients suffered from CAD.

Both markers examined in the present study are used as a proof of myocardial damage. Although most publications showed biomarker elevation in postoperative period, we could find only several that evaluated the significance of their increase before the operation[15,16]. This is especially true for hsTnT, since only Weber et al. demonstrated that increased level of this marker in preoperative period indicated significant risk for the fatal cardiovascular complications both during and after the surgery[17].

Using highly sensitive essays, we were able to detect even minor elevations in troponin T levels. Furthermore, such increased values of this marker may be detected even in population of apparently healthy individuals. It is well documented that significant elevation of this biomarker is in direct association to patients with either CAD or other cardiovascular diseases, and it provides important prognostic information.[8,9,18] Thus, detected in this way, troponin T seems to become strong prognostic marker, not only for the acute coronary syndrome, but also for apparently stable CAD and other non-acute states in patients with various cardiovascular disorders.

The most interesting finding was that levels of hsTnT above the predefined margin (> 14ng/L) were significantly associated with unwanted events. More than one third of our patients (39%) had increased levels of hsTnT, and there was a clear difference between survivors and deceased. The levels of this marker were increased in more than 85% in subjects deceased. Similar trends noted for NT-proBNP. Its levels were above cut-off value in 41% of the patients from the entire cohort, and in all the subjects who did not survive, follow/up period had increased values. The most important clinically relevant finding was the possibility of applying these biomarkers to predefined protocols for risk stratification that may help to identify subjects with high risk for fatal complications. However, measurements of hsTnT and NT-proBNP for all patients undergoing major surgery into routine biochemical profiles, would be both impractical and very expensive. For this reason we searched for the group of patients who could benefit the most from such analysis.

Although neither Mangano nor Lidsky in their studies found the association between preoperative CAD and both major cardiac events and subsequent mortality after surgical intervention[2,19], our results showed statistically significant association with fatal events in short-term follow-up. However, with a small sample size, caution must be applied. This observational study suggests that measuring of hsTnT and NT-proBNP in a patient with documented CAD or without it, may help prevent the risk of mortality events. Additionally, our findings

suggest that hsTnT was more prognostic for subjects age over 65, as well as statistically significance only for hsTnT among other tested parameters in multivariant regression analysis. Furthermore, these findings lead to debate about the criteria for detecting CAD. Since we defined positive laboratory tests, clinical risk factors, prior bypass surgery, coronary intervention or prior myocardial infarction as only necessary criteria for diagnosing CAD, it is possible to apply more lenient criteria, which are not only known from the history or medical management, and that may give different results. This is an important issue for future research.

The study would have been more interesting if it had included an analysis of coronary intervention in patients with CAD prior to an elective major surgery. There is a number of publications that evaluate this problem[20–23]. The CARP trial concluded that preoperative coronary revascularization did not improve perioperative or long-term outcomes. The rates of postoperative myocardial infarction and mortality were similar in all included patients, and they were not dependent on prior revascularization[22]. Indeed, percutaneous or surgical coronary procedures delayed elective vascular surgery[22,23]. Moreover, the delay may cause very serious consequences in both vascular and major abdominal surgery, and a definite need for balance between risks and benefits of potential delay is important for every single patient. A reasonable approach to tackle this issue could be to potentiate the significance of risk stratification for patients with documented CAD before a non-cardiac surgery.

This study has several important limitations. The major limitation of this study was the small sample size. Second, this research was conducted in one center and included patients that were prepared for major surgery according to local protocols. Third, more comprehensive survey would deserve strict preoperative stratification of CAD based on cardiac catheterization and/or echocardiography, but such stratification was out of the scope in this study. Fourth, we did not measure hsTnT and NT-proBNP levels after the operations and it was not possible to evaluate whether these values would have been more prognostic for the same patients than these perioperative measures. Fifth, the study design requires that included subjects must have minimum one cardiovascular risk factor and age over 55, so that our results cannot be generalized to patients who are undergoing a major non-cardiac surgery, but without those criteria. Also, the mortality was followed-up for a period of 30 days and our findings may be useful only for prognosis of short-term mortality risk. Finally, our results could not have been affected by selection bias, because of absence of marker levels during the study.

Conclusion

In summary, this study has shown that preoperatively increased levels of cardiac biomarkers are positively associated with short-term mortality in postoperative period after major abdominal or vascular surgery, and they can serve as important predictors of fatal events. The research has also shown that patients with CAD benefit the most from determination of hsTnT and NT-proBNP levels before the surgery. These findings suggest that increased values of examined markers denote significant risk for this group of patients. In case of a such increase, patients deserve more detailed examination before the surgery and careful balancing between potential delay of the surgery and the risk that it carries with it. Although the current study is based on a small sample of participants, the findings suggest potentially prognostic biomarkers for patients undergoing major non-cardiac surgery. Large randomized controlled trials could provide more definitive evidence.

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