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Risk Factors for Unfavorable Outcome in Aneurysmal Subarachnoid Hemorrhage Revisited; Odds and Ends

Abdolkarim Rahmanian[1], Nima Derakhshan[1], Alireza Mohsenian Sisakht[1, 2], Najme Karamzade Ziarati[3], Hadi Raeisi Shahraki[4], Soheil Motamed[5]

[1]*Department of Neurosurgery, Shiraz University of Medical Sciences, Shiraz, Iran*
[2]*Student Research Committee, Iran University of Medical Sciences, Tehran, Iran*
[3]*Student Research Committee, Tehran University of Medical Sciences, Tehran, Iran*
[4]*Department of Biostatistics, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran*
[5]*Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran*

***Corresponding author:** Nima Derakhshan*
Address: Neurosurgeon, Shiraz University of Medical Sciences, Neurosurgery Office, Nemazee Hospital, Nemazee Square, Postal Code: 71937-11351, Shiraz, Iran.
Tel/Fax: +98-71-36474259; **Cellphone:** +98-917-7161290
e-mail: nima_med83@yahoo.com

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ABSTRACT

Objectives: To evaluate the odds for unfavorable outcome of each risk factor and a combination of them in patients with aneurysmal subarachnoid hemorrhage (SAH) undergoing surgical clipping in Southern Iran
Methods: A total of 367 patients who were operated between March 2007 and March 2016 due to aneurysmal SAH were analyzed according to patients' factors, aneurysm characteristics and intra-operative data. Correlation between outcomes of patients measured by modified Rankin Scale at 6-months with each factor were analyzed. Market Basket analysis was also used to identify the odds of unfavorable outcome for combinations of factors.
Results: A total of 367 patients, including 199 females and 168 males with a mean age of 47.27±11.53 years, who underwent operation between March 2007 and March 2016 due to aneurysmal SAH were analyzed. Unlike gender, higher age was associated with unfavorable outcome. Ischemic heart disease, Duration of operation and amount of bleeding were also found to increase the odds of unfavorable outcome (p=0.01, 0.02, 0.04 respectively). DM, Cigarette smoking and opium addiction as well as the location and multiplicity of aneurysms did not have an adverse effect on outcome ($p \geq 0.05$).
Conclusion: Among the numerous risk factors presumed to result in unfavorable outcome in aneurysmal SAH, only older age, duration of operation more than 60 minutes, previous known history of ischemic heart disease, poorer clinical grade and intra-operative bleeding more than 500 mL were found to be significant factors.

Keywords: Cerebral aneurysm; Risk factors; Market basket analysis; Outcome.

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Introduction

Rupture of cerebral aneurysms is the most common cause of spontaneous subarachnoid hemorrhage (SAH) worldwide [1]. Despite recent advancements in the domains of surgical technique and critical care, SAH is still devastating and associated with high rates of mortality and morbidity [2]. However, based on natural history and cohort studies which provided long term follow-up in aneurysmal SAH patients, several risk factors have been defined to be related with functional outcome of these patients [3]. Risk factors can be classified into three main groups; patient factors, aneurysm features and operation-related factors.

Patients have variable outcomes due to their differences in age [4], gender [5, 6], neurological state on admission [7, 8] (in terms of clinical grades like Hunt and Hess grading and Glasgow coma scale), medical conditions (hyperlipidemia [9], IHD, HTN [7, 10, 11], vasculitis [7], etc.) and a positive history of similar comorbidities in their close relatives [12]. Behavioral factors such as heavy alcohol consumption [13], cigarette smoking [5, 14] and addiction to opioids [15] and other recreational drugs such as cocaine and methamphetamine [16-18] also contribute to a poorer prognosis according to several studies. On the other hand, non-significant protective role was also suggested for Caucasian ethnicity [19], hormone replacement therapy [5, 20], diabetes mellitus [18] and higher body mass index [21].

Aneurysm characteristics have also been identified as important predictors of functional outcome, considering their size (very small [22], small, large and giant), location (anterior versus posterior circulation), shape (fusiform, blister-like, saccular, etc.) and certain anatomic considerations (azygos, fenestrated [23] or duplicated parent vessel, proximity to parent vessels and branching of vessels from aneurysm dome, etc.) as well as dome-to-neck ratio. Several operative factors have been associated with post-operative outcome of patients undergoing aneurysm clipping. Early surgery, amount of bleeding, operative time, familiarity and experience of surgeon with microsurgical techniques, use of certain neuro-anesthetic agents, circulatory arrest and hypothermia were all proposed to be associated with outcome of these patients [24]. Overall most authorities agree that older age, poorer neurological state on admission and aneurysms located in the posterior circulation were associated with unfavorable outcome in those who sustain aneurysmal SAH.

Here in, providing a large population of patients with aneurysmal SAH who were operated between 2007 and 2016 in a tertiary referral center in southern Iran, we sought the co-occurrence of certain combination of risk factors that lead to unfavorable outcome using Market Basket analysis. Prevention through addressing modifiable risk factors is still the mainstay of focus in the outnumbered research projects, surveying the outcome of patients with SAH.

Materials and Methods

Study Population

This cross-sectional study was conducted during a 9-year period between March 2007 and March 2016 in Nemazee hospital, a referral tertiary neurovascular center in southern Iran, affiliated with Shiraz University of Medical Sciences. The study protocol was approved by the institutional review board (Reference number: 13292-01-01-95) and medical ethics committee of Shiraz University of Medical Sciences (IR.SUMS.MED.REC. 1396. s98). All patients with diagnosis of SAH due to a ruptured anterior circulation cerebral aneurysm who underwent surgical clipping of aneurysm during the mentioned timeframe were included in the study. Patients who did not survive the prehospital course were excluded from the studied population. Patients with incomplete hospital records or those who were unavailable with the provided phone number and address and lost to follow-up individuals were excluded from this survey. A total number of 367 patients met the criteria to enter this analysis.

Data Collecting

The data for this study were obtained from the hospital-based registry in Namazi hospital. A data form was designed and for each patient demographic data including age, sex, and place of residence, past medical and surgical history, drug history and history of social habits such as cigarette smoking, addiction and alcohol consumption and family history of similar events. GCS (Glasgow Coma Scale) and Hunt and Hess (H&H) grade was also obtained from admission notes for each patient. Intra-operative data were obtained from the hospital records with focus on duration of surgery, amount of bleeding and the days of interval between SAH and operation. Aneurysm characteristics including number (one, two, three or more) and location (ACom versus Non-ACom) were also obtained from op-notes according to description by the surgeon.

Functional Outcome

Functional outcome at 6-months after operation was also made available from outpatient records as well as calling the patients utilizing modified rankin scale (mRS). We further categorized outcome to favorable (mRS2) versus unfavorable (mRS>2). The assessment was based on asking the patient and his or her guardians about arousability and awareness and the level of independence in feeding, grooming, toileting, ambulation and return of the patient to previous employability status.

Statistical Analysis

All the statistical analyses were performed using statistical package for social sciences (SPSS Inc., Chicago, Illinois, USA) version 24.0. Data are reported as mean±SD as appropriate. In order to compare

the parametric variables with normal distribution between patients with favorable versus unfavorable outcome, independent t-test was utilized. One-way ANOVA and Mann-Whitney tests were utilized to compare the means and medians, respectively between study groups. Non-parametric data were compared using chi-square test. A 2-sided *p*-value of less than 0.05 was considered statistically significant. To identify certain combinations of presumed risk factors which leads to unfavorable outcome, Market Basket analysis was carried out for 31 combinations.

Results

A total of 367 patients, including 199 females and 168 males with a mean age of 47.27±11.53 years, who underwent surgical clipping due to aneurysmal SAH and had at least 6-month of follow-up were eligible to enter this analysis. Patient's follow-up ranged from 6 to 118 months with a mean of 28.6±11.1 months. A slight female preponderance was observed in the studied population (54.2%). Most of the patients belonged to the 40 to 60-year age group (53.7%) and an inverse association between age and favorable outcome was observed. as patients with higher age had lower proportion of favorable outcome. Both Chi-square and independent T-test (for categorical age group and continuous age respectively) confirmed that this association was statistically significant ($p<0.001$) (Table 1).

Table 1. Demographics, clinical features, location and number of aneurysms and the outcome (mRS).

Variable	Subgroups	Follow up mRS		*p* value
		Favorable (n=307)	Unfavorable (n=60)	
Sex	Male	143 (85.1)	25 (14.9)	0.49
	Female	164 (82.4)	35 (17.6)	
Age	<20	8 (100)	0 (0)	<0.001
	20-40	51 (87.9)	7 (12.1)	
	40-60	176 (89.3)	21 (10.7)	
	60-70	52 (70.3)	22 (29.7)	
	70<	20 (66.7)	10 (33.3)	
Clinical Grade (H&H)	1	165(93.8)	11(6.2)	<0.001
	2	103(89.6)	12(10.4)	
	3	1(50)	1(50)	
	4	24(57.1)	18(42.9)	
	5	14(43.8)	18(56.2)	
HTN[a]	No	162 (87.1)	24 (12.9)	0.07
	Yes	145 (80.1)	36 (19.9)	
DM[b]	No	289 (84.8)	52 (15.2)	0.05
	Yes	18 (69.2)	8 (30.8)	
IHD[c]	No	265 (85.8)	44 (14.2)	0.01
	Yes	42 (72.4)	16 (27.6)	
Smoking	No	206 (82.4)	44 (17.6)	0.34
	Yes	101 (86.3)	16 (13.7)	
Opium addiction	No	250 (83.9)	48 (16.1)	0.80
	Yes	57 (82.6)	12 (17.4)	
Aneurysm location	A.Com[d]	102 (85.0)	18 (15.0)	0.63
	Non A.Com	205 (83.0)	42 (17.0)	
Aneurysm number	One	245 (84.2)	46 (15.8)	0.61
	Two	42 (79.2)	11 (20.8)	
	Three or more	20 (87.0)	3 (13.0)	
Duration of operation	<60 minutes	139 (89.7)	16 (10.3)	0.02
	60-120 minutes	126 (78.3)	35 (21.7)	
	120 or more	42 (82.4)	9 (17.6)	
Amounts of Bleeding	<100	73 (91.3)	7 (8.8)	0.04
	100-300	165 (84.2)	31 (15.8)	
	300-500	38 (72.1)	10 (20.8)	
	500 or more	31 (72.1)	12 (27.9)	
SAH-Op[e]	One day or less	89 (76.1)	28 (23.9)	0.18
	2 or 3 days	62 (86.1)	10 (13.9)	
	4-7 days	54 (83.1)	11 (16.9)	
	8-14 days	27 (93.1)	2 (6.9)	
	More than 14 days	23 (85.2)	4 (14.8)	

[a]HTN: Hypertension; [b]DM: Diabetes Mellitus; [c]IHD: Ischemic heart disease; [d]A.Com: Anterior communicating artery; [e]SAH-Op: Duration between SAH and surgical clipping, Due to missing total sample size was 310 (255 for favorable and 55 for unfavorable)

Patients' GCS and H&H grade had a mean of 12.43 and 2.33 respectively and as shown in Table 1, poor clinical grades were significantly correlated with unfavorable outcome. Based on medical history of SAH patients in this study, about half of cases (49.3%) had hypertension, but only 15.8% and 7.1% had IHD and DM, respectively. Chi-square test also suggested that IHD and DM could increase the odds of unfavorable outcome; however, this increase was not significant for diabetes (p=0.01, 0.05, respectively). History of cigarette smoking and opium addiction was positive in 117(31.9%) and 69(18.8%) cases, respectively. Neither cigarette smoking nor opium addiction had any significant effect on the outcome (Table 1).

The location of aneurysm in most of the patients (n=247, 67.3%) was non-A.Com. Furthermore, most cases (n=291, 79.3%) had only one aneurysm. Neither the location nor the number of aneurysms were associated with the outcome of patients (Table 1). Based on the surgical information, the duration of operation (the time between opening dura matter and confirmation of successful clipping by intra-operative video-angiography) was less than 60 minutes for 155 patients (42.2%). Additionally, the amount of bleeding was less than 100 mL in 80 patients (21.8%) and it seems that duration of operation and amount of bleeding can increase the odds of unfavorable outcome (p=0.02, 0.04 respectively). The duration between SAH and operation did not show any effect on patients' outcome (p=0.18).

According to mRS at 6-months post-operatively, 307 patients (83.7%) had favorable outcome and 60 (16.3%) had unfavorable outcome. Available mRS at 6-months follow-up was summarized in Table 2 in each group of patients. Utilizing multiple logistic regression analysis, patients' age, duration of operation and bleeding amount were found the most powerful factors affecting the outcome. The proposed model revealed that for every 10 years increase in age, the odds of unfavorable outcome increase 1.04-fold and the odds of unfavorable outcome was more than 2 folds for duration of operation of 60-120 minutes compared to less than 60 minutes of operation (p=0.04). Even though duration above 120 minutes was associated with 1.28-fold increase in unfavorable outcome (compared to that of the baseline group), this was not significant (p= 0.66). Furthermore, odds for unfavorable outcome was 3.72-fold for bleeding amount more than 500 mL bleeding, compared to those with100 mL or less. (p=0.03) (Table 3). To indicate the most common scenarios which lead to unfavorable outcome, the presumed risk factors were analyzed via Market Basket Analysis. The extracted combinations are reported in Table 4, sorted by support percentage. It should be mentioned that all the detected combinations were established in at least 5 patients.

Discussion

In the current study, we investigated the epidemiological and clinical features of 367 patients with aneurysmal SAH who were operated in Shiraz Namazi hospital, the main referral neurovascular center in Southern Iran [24]. An updated review of risk factors in SAH patients was provided, focusing on the patient's age and gender, history of opium

Table 2. Modified Rankin Scale (mRS) at 6-month.

Modified Rankin scale at 6-month follow up						
Favorable outcome=307(83.7%)			**Unfavorable outcome=60 (16.3%)**			
0	1	2	3	4	5	6
276(89.9%)	15(4.9%)	16(5.2%)	6(10%)	1(1.7%)	2(3.3%)	51(85%)

Table 3. Multiple logistic regression analysis of risk factors leading to unfavorable outcome.

Variable	**Subgroup**	**Follow up mRS**		
		Coefficient (SE)	**Odds Ratio**	***p* value**
Age		0.04 (0.01)	1.04	0.004
HTN	No	Baseline	---	---
	Yes	0.03 (0.33)	1.03	0.94
DM	No	Baseline	---	---
	Yes	0.63 (0.51)	1.87	0.21
IHD	No	Baseline	---	---
	Yes	0.24 (0.40)	1.29	0.53
Duration of operation	<60 minutes	Baseline	---	---
	60-120 minutes	0.74 (0.36)	2.09	0.04
	120 or more	0.25 (0.55)	1.28	0.66
Amount of bleeding	<100	Baseline	---	---
	100-300	0.60 (0.48)	1.82	0.21
	300-500	0.71 (0.59)	2.04	0.23
	500 or more	1.31 (0.62)	3.72	0.03

Table 4. The extracted combinations based on market basket analysis.

#	Combinations of risk factors	Support (%)	Confidence (%)
1	SAH-Op£one, age=60-70, HTN=yes, Duration≥60	1.90	70.0
2	SAH-Op£one, age=60-70, HTN=yes, Duration≥60, SMOKING=no	1.90	70.0
3	HTN=yes, DM=no, IHD=yes, Bleeding³300	1.63	75.0
4	LOC=A.Com, HTN=yes, IHD=yes, Duration≥60	1.63	75.0
5	SAH-Op£one, age=60-70, HTN=yes, DM=no, SMOKING=no, Duration≥60	1.63	75.0
6	SAH-Op£one, age=60-70, Num=two	1.36	83.3
7	age≥70, SMOKING=no, Bleeding≤300, Duration≥60	1.36	100
8	SAH-Op£one, age=60-70, Num=two, DM=no	1.36	100
9	SAH-Op£one, Num=two, HTN=yes, DM=no	1.36	83.3
10	Num=one, HTN=yes, IHD=yes, Bleeding≥300	1.36	71.4
11	LOC=A.Com, IHD=yes, SMOKING=no, Duration≥60	1.36	83.3
12	age=60-70, LOC=A.Com, HTN=yes, Duration≥60	1.36	71.4
13	age=60-70, LOC=A.Com, Bleeding≤300, Duration≥60	1.36	71.4
14	age≥70, SMOKING=no, ADDICTION=no, Bleeding≤300, Duration≥60	1.36	100
15	SAH-Op£one, Num=two, HTN=yes, DM=no, SMOKING=no	1.36	83.3
16	Num=one, HTN=yes, IHD=yes, Bleeding≥300, Duration≥60	1.36	71.4
17	HTN=yes, DM=no, IHD=yes, ADDICTION=no, Bleeding≥300	1.36	71.4
18	LOC=A.Com, HTN=yes, IHD=yes SMOKING=no, Duration≥60	1.36	83.3
19	LOC=A.Com, IHD=yes, SMOKING=no, ADDICTION =no, Duration≥60	1.36	83.3
20	SAH-Op£one, age=60-70, IHD=no, Bleeding≥300, Duration≥60	1.36	71.4
21	SAH-Op£one, age=60-70, HTN=yes, IHD=no, Duration≥60	1.36	83.3
22	age=60-70, LOC=A.Com, HTN=yes, SMOKING=no, Duration≥60	1.36	71.4
23	age=60-70, LOC=A.Com, HTN=yes, DM=no, Duration≥60	1.36	71.4
24	age=60-70, LOC=A.Com, DM=no, Bleeding≥300, Duration≥60	1.36	71.4
25	SAH-Op£one, Num=two, HTN=yes, DM=no, SMOKING=no, ADDICTION =no	1.36	83.3
26	LOC=A.Com, HTN=yes, IHD=yes, SMOKING=no, ADDICTION =no, Duration≥60	1.36	83.3
27	SAH-Op£one, age=60-70,IHD=no, SMOKING=no, Bleeding≥300, Duration≥60	1.36	71.4
28	SAH-Op£one, age=60-70, HTN=yes, IHD=no, SMOKING=no, Duration≥60	1.36	83.3
29	age=60-70, LOC=A.Com, HTN=yes, DM=no, SMOKING=no, Duration≥60	1.36	71.4
30	SAH-Op£one, age=60-70, IHD=no, SMOKING=no, ADDICTION =no, Bleeding≥300, Duration≥60	1.36	71.4
31	age=60-70, LOC=A.Com, HTN=yes, DM=no, SMOKING=no, ADDICTION =no, Duration≥60	1.36	71.4

addiction and cigarette smoking, history of HTN, type 2 DM and IHD, Aneurysm location and number, interval between SAH and operation, duration and amount of bleeding of operation. According to the follow-up mRS at sixth month, patients were categorized as favorable versus unfavorable. Only older age, longer duration of operation, poorer clinical grade, previous known history of ischemic heart disease and intra-operative bleeding more than 500mL were found to be significant factors

Neuro-epidemiology is a recently established science dedicated to epidemiologic analysis of certain neurological disorders and has helped the health policy makers to manage resources in the appropriate direction to prevent and cure the diseases. Outcome of centers with expertise in surgical management of aneurysmal SAH are varied due to their knowledge, attitude and experience in this field. Identifying risk factors contributes largely to outcome especially for the modifiable factors. Market Basket analysis is a well-known concept in statistics which we used to define the odds of an outcome when several factors co-occur in a certain subset of patients [25]. Although female gender was recognized as a risk factor for occurrence of aneurysmal SAH [5, 6], such finding was not seen in our study population (female-to-male ratio of 1.2). Furthermore, female gender was not associated with unfavorable outcome as well (p=0.49).

Our data confirms that incidence of SAH is lower in elderly. Although older age was found not to impose any further risk for unfavorable outcome in some studies [26], most authorities believe that elderly individuals with SAH will have poorer functional outcomes [27]. However, in this study we observed a correlation between patients' age and unfavorable outcome, i.e. mRS of 3 and higher was seen in none of those aged younger than 20 but in almost a third of patients aging older than 70 years. Among medical comorbidities, HTN had the greatest prevalence in SAH patients (49.3%) and ischemic heart disease (15.8%) was ranked the second with odds ratio for unfavorable outcome of 1.04 and 1.87, respectively. Although this finding is consistent with most previous studies but some investigations have questioned this issue [28].

Cigarette smoking and opium addiction were the two important modifiable risk factors for SAH in many series. Current cigarette smokers had 3 to 4-fold greater risk to develop SAH.[3, 14] In our series, the percentage of current cigarette smokers and opium addicts among cases were 31.9% (117 cases) and 18.8% (69 cases) respectively, but neither of these factors were found to affect the follow up mRS at 6 months (P=0.34 and 0.8, respectively). Several studies have demonstrated that interval between SAH and operative management can affect the outcome [29]. Ohman *et al*., [30] reported that surgical intervention within 3 days of SAH is associated with increased cerebral infarction. Others emphasize on early surgery including a case series previously reported from our center. These variable findings are probably due to two factors; cerebral edema and natural selection. Proponents of early surgical intervention recommend the benefits from operating on a lax brain with less cerebral edema before its evolution days after SAH, and those who supports late surgery have the bias of operating on healthier subjects who survived the early phase following death of those who suffered early complications of SAH (e.g. re-bleeding, hydrocephalus and vasospasm) through natural selection.

Moreover, duration of operation significantly affected the follow up mRS of patients (p=0.02). Patients with duration of operation between 60-120 minutes had more than 2-folds odds of unfavorable outcome compared to those with less than 60-minute operation time. For aneurysm location, non-anterior communicating arteries were the most common sites (67.3%) in aneurysmal SAH patients in this study. These results are consistent with those of previous studies. The majority (79.3%) of cases in our study had one aneurysm. However, the location and number of aneurysm did not have a significant effect on the outcome of patients.

To evaluate the odds of unfavorable outcome in patients sustaining several presumed risk factors, we utilized a novel statistical model of data mining, Market Basket analysis. This is among the few of Market Basket analysis in neuro-epidemiology with presenting the odds and confidence of unfavorable outcome for 31 different combinations. According to this model, patients sustaining a combination of hypertension, age between 60 to 70 years and with operation durations more than 60 minutes, had the highest risk to end in an unfavorable outcome. A considerable limitation of this study is its retrospective nature which makes some biases inevitable. Another limitation to be mentioned is that neuro-radiologic intervention was not routinely practiced in our center in the first 4 years of this study and patients were selected for this intervention thereafter and we excluded them from this cohort and only addressed the surgically treated individuals.

Another strength of the current study is the large number of patients with available long-term follow-up, which has made a reliable data pool for this single-center analysis. Limitations of this study can be listed as lost to follow-up individuals, incomplete hospital records and also no information regarding patients' drug history which theoretically might affect their outcome. Among the numerous risk factors presumed to result in unfavorable outcome in aneurysmal SAH (Table 5), we only found older age, duration operation more than 60 minutes, poorer clinical grade, previous known history of ischemic heart disease and intra-operative bleeding more than 500 mL to be significant contributors to poor outcome. Also, Market Basket analysis revealed that a hypertensive patient aging between 60 and 70 years with operative duration of more than 60 minutes sustain the combination of risk factors with highest probability for unfavorable outcome.

In conclusion, among the numerous risk factors presumed to result in unfavorable outcome in aneurysmal SAH, only older age, duration of operation more than 60 minutes, previous known history of ischemic heart disease, poorer clinical grade and intra-operative bleeding more than 500 mL were found to be significant factors

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Conflicts of Interest: None declared.

Table 5. Risk Factors of Poor Functional Outcomes after SAH.

Author	Year	Risk Factors
Germanson TP, *et al*., [31]	1998	Age, Female gender, Premorbid HTN, Aneurysm size and location, Clot thickness, GCS
Juvela S, *et al*., [32]	2005	Hyperglycemia, Obesity, Premorbid HTN, Rebleeding, Alcohol
Rosengart AJ, *et al*., [33]	2007	Age, Neurological grade, Clot thickness, Aneurysm Size, Posterior circulation location, Premorbid HTN
McGirt MJ, *et al*., [34]	2007	Age, Neurological grade, Clot thickness, "Persistent" hyperglycemia, Premorbid HTN, Caucasian race
Risselada R, *et al*., [35]	2010	Age, Neurological grade, Clot thickness, Aneurysm Size
Jaja BN, *et al*., [36]	2013	Age, Neurological grade, Clot thickness, Aneurysm Size

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