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The correlation between IDH-1 mutation and overall survival in Iranian patients with high grade gliomas

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ABSTRACT

Introduction: Despite advances in diagnostic procedures and treatment modalities, high grade gliomas have poor prognosis and low overall survival (OS) time. Novel prognostic biomarkers such as mutations in metabolic enzyme of isocitrate dehydrogenases-1 (IDH1) were linked to cancer patient prognosis and therapeutic response. The aim of this study was to investigate the frequency of IDH1 mutation and its associations with OS in patients with high-grade gliomas.

Methods: A total of 75 patients with histologically confirmed high-grade gliomas (WHO grades III and IV) were retrospectively recruited from patients referred to the clinical oncology department of Ahvaz Golestan Hospital, Iran from 2013 to 2020. All patients received the standard treatment (surgery, radiotherapy and chemotherapy with temozolomide). Immunohistochemical method was used to determine the mutation in IDH-1 gene. The overall survival distributions were estimated using Kaplan-Meier method and compared between subgroups by Log-rank test.

Results: The patients included 17 (22.7%) grade III and 58 (77.3%) grade IV tumors. IDH1 mutant Type was found in 24 patients (32%), including 12 case (70.59%) in grade III and 12 case (20.69) in grade IV glioma (P<0.0001). Furthermore, IDH1 mutant was more likely to exhibit in secondary gliomas other than primary tumors (71.43% vs. 27.94%; P=0.019). The number of death patients in the IDH1 mutation group was lower than in the wild type (26.23% vs. 73.77%; P=0.030). In the survival analysis, patients with IDH1 mutations had better OS compared to those with wild-type IDH1 (median 21 vs. 12 months; P=0.017).

Conclusion: According to our results, IDH1 mutant is more likely to exhibit in grade III and secondary gliomas. Patients with IDH1 mutations had longer life compared to those with wild-type IDH1**.** This finding suggest that IDH-1 mutation was a positive prognostic factor for OS in high grade gliomas.

KEYWORDS

IDH1 mutation, High-grade glioma, Overall survival, Prognosis

Introduction

Gliomas are the most common tumors of the central nervous system (CNS), with high-grade gliomas (grades III and IV according to the World Health Organization (WHO) classification) being the most common primary malignant brain tumors (1). Despite significant advances in diagnostic methods and therapeutic strategies, including surgery, radiotherapy, chemotherapy, and immunotherapy, they still have a poor prognosis and short overall survival (OS) (2, 3).

Today, changes in cancer cell metabolism are considered an important marker of carcinogenesis and tumor progression. Therefore, cellular biomarkers are crucial for understanding the biology and behavior of cancer cells and for adopting new therapeutic strategies (1). In 2016, WHO introduced molecular and genetic markers for the first time to classify gliomas to aid in better diagnosis and treatment (4), with a greater emphasis on them in 2021

(5). Currently, the fifth edition of the classification of CNS tumors by the World Health Organization (WHO CNS5) is the international standard for the classification and diagnosis of gliomas. This system fundamentally changes the classification of gliomas and includes numerous molecular biomarkers; one of the most important early genetic markers for gliomas is the mutation status of isocitrate dehydrogenase (IDH1/IDH2) (5, 6), which has been suggested as a useful tool for predicting prognosis and survival in glioma patients (7, 8).

IDH1 is a cellular metabolism-regulating enzyme located in the cytoplasm, responsible for the epigenetic regulation of redox states and DNA repair (9). The neomorphic activity of mutant IDH1 leads to the production of the oncometabolite D-2-hydroxyglutarate (D-2-HG), which contributes to gliomagenesis and has major autonomous cellular and non-cellular effects (10, 11). The broad effects of IDH1 mutations on epigenetic, differentiation, and metabolic programs, combined with their high prevalence, early presence in tumorigenesis, and uniform expression in tumor cells, make mutant IDH1 an ideal therapeutic target and prognostic marker (11). IDH1 mutation has been observed in 32% of CNS tumors, particularly in primary brain tumors, especially in diffuse astrocytoma (64%), anaplastic astrocytoma (49%), and glioblastoma (9%) (12). The role of mutant IDH1 in assessing the prognosis of patients with various types of gliomas has been reported in some studies (13-16). IDH1 mutations, compared to wild-type IDH1, have been associated with longer survival in glioma and glioblastoma patients (16, 17).

Since IDH1 mutation is an early event in gliomagenesis, occurring before other genetic alterations and having high prognostic value (6, 11), it appears that assessing IDH1 genotype as a positive prognostic marker can be useful in predicting survival and determining subsequent therapeutic strategies in these patients. However, studies on the association of IDH1 mutation with survival in high-grade glioma patients are limited. Therefore, the present study aims to investigate the incidence of IDH1 mutation in high-grade gliomas and determine its relationship with survival parameters in patients referred to the Radiation Oncology Department of Golestan Hospital in Ahvaz.

Methodology

This retrospective study was based on hospital and clinic data and was conducted on patients with confirmed high-grade glioma who were referred to the Radiation Oncology Department of Golestan Hospital in Ahvaz from 2013 to 2020. The study was conducted after obtaining approval from the Research Council and the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Ethics Code: IR.AJUMS.HGOLESTAN.REC.1401.202). Throughout the study, the ethical guidelines of the Helsinki Declaration and principles of patient confidentiality were observed

Sample Characteristics

Inclusion criteria included patients with confirmed high-grade glioma (WHO grades III and IV) through histopathology; availability of complete and reliable clinical and imaging data; tumor samples accessible for analysis and immunohistochemistry (IHC); and receipt of standard treatment, including surgery, radiotherapy (with a minimum radiotherapy dose of 50 Gy), and concurrent chemotherapy with temozolomide. Patients with a history of other malignancies, those who did not receive chemoradiotherapy or radiotherapy at a dose lower than 50 Gy, those with inaccessible patient information or pathology samples, and any cases with a questionable diagnosis of high-grade glioma were excluded from the study.

Initially, 91 patients with high-grade glioma were identified, but 16 cases were excluded based on the inclusion and exclusion criteria. Ultimately, 116 patients were selected, and their data were collected and analyzed.

Data Collection

Necessary information was gathered by reviewing patients' medical records and, if needed, through telephone contact. Baseline characteristics of the patients, including age, gender, tumor information such as size and location based on MRI findings, glioma type (primary/secondary), and treatment details, were collected and recorded. Histopathological assessment, tumor type, and grading were performed by an experienced neuropathologist according to the World Health Organization (WHO) classification of CNS tumors. Grade III tumors, including those with mitotic activity and anaplasia, were classified as anaplastic astrocytomas, while Grade IV tumors, characterized by microvascular proliferation and necrosis, were classified as glioblastomas (4). The exact date of death was obtained from the civil registration office. Overall survival (OS) was calculated from the onset of the disease until death.

IDH1 Gene Mutation

The mutation or wild-type status of the IDH1 gene was assessed using histopathological techniques. Initially, formalin-fixed, paraffin-embedded tissue blocks from the archives of surgical samples of patients with high-grade gliomas (grade III and IV) were prepared for immunohistochemical analysis. Four-micrometer sections were cut and stained with hematoxylin and eosin (H&E) to examine the tumor. The test was considered positive or negative based on the staining results. Finally, the frequency of IDH1 mutation and its association with overall patient survival was evaluated.

Statistical Analysis

For statistical analysis, SPSS software (SPSS Inc., Chicago, IL, U.S.A.) version 22 was used. To describe the data, mean, median, standard deviation, interquartile range (IQR), frequency, and percentage were utilized. The normality of the data was assessed using the Kolmogorov-Smirnov test. To compare qualitative variables between groups, the chi-square test was employed. Kaplan-Meier analysis was used to estimate survival, and the Log-Rank test was applied to compare survival curves across subgroups. Univariate and multivariate Cox regression models were used to control for potential confounding factors and identify independent predictors of patient mortality, with hazard ratios (HR) calculated at a 95% confidence interval. A significance level of 0.05 was considered in the tests

Findings

In this study, 75 patients with a mean age of 46.32 ± 16.22 years (ranging from 5 to 78 years) participated, including 46 men (61.3%) and 29 women (38.7%) (Table 1). According to the WHO classification, 17 patients (22.7%) had grade III glioma, and 58 patients (77.3%) had grade IV glioma. Based on immunohistochemical findings, the frequency of IDH1 mutation in high-grade glioma patients was 24 cases (32%).

Table 1 - Baseline Characteristics of the Patients Under Study

Variable	Group	
Age (years), S.D ± Mean Median (IQR))		22/16 ± 32/46 47 (60 - 37)
Age (years), n (%)	> 50	43 (3/57)
	≤ 50	32 (7/42)
Gender ,n (%)	Male	46 (3/61)
	Female	29 (7/38)
Findings MRI		
Tumor Location, n (%)	Frontal Lobe	12 (0/16)
	Parietal Lobe	7 (3/9)
	Temporal Lobe	16 (3/21)
	Occipital Lobe	2 (7/2)
	Frontoparietal	8 (7/10)
	Temporoparietal	8 (7/10)
	Parietooccipital	5 (7/6)
	Frontotemporal	4 (3/5)
	Brain Stem	4 (3/5)
	Bilateral	3 (0/4)
	Missing	6 (0/8)

02/11 ± 57/45 44 (50 - 40)	Maximum Diameter (Length)	Tumor Size (mm), S.D ± Mean Median (IQR)
13/7 ± 60/37 37 (7/44 – 32)	Minimum Diameter (Width)	
	Pathology	
68 (7/90)	Primary	Type of Glioma, n (%)
7 (3/9)	Secondary	
17 (7/22)	Grade III	Glioma WHO grade, n (%)
58 (3/77)	Grade IV	
51 (0/68)	Wild Type	IDH1
24 (0/32)	Mutant Type	

IDH1: Isocitrate dehydrogenase-1

Surgical and Treatment Characteristics

Partial surgery was performed in 35 patients (46.7%), while complete surgery was conducted in 17 patients (22.7%). Concurrent chemotherapy was administered to 70 patients (93.3%), and adjuvant chemotherapy (either before or after radiotherapy) was given to 64 patients (85.3%). The mean total dose of radiotherapy was 59.22 Gy (± 1.85). The minimum dose received was 50 Gy, and the maximum dose was 63 Gy. The mean duration of radiotherapy was 46.13 days (± 5.64). Tumoral disease recurrence was observed on MRI in 63 patients (84%), and the need for salvage treatment and re-radiotherapy was reported in 14 patients (18.7%) (Table 2).

Table 2 - Treatment Characteristics of High-Grade Glioma Patients

Variable	Group	
Surgery		
Extent of surgery, n (%)	Extended biopsy	17 (7/22)
	Partial resection	35 (7/46)
	Complete resection	17 (7/22)
Concurrent Chemotherapy		
Chemotherapy	Total	70 (3/93)
Chemotherapy Agent, n (%)	TMZ	68 (1/97)
	TMZ+VCR	2 (9/2)
TMZ Cumulative Dose (mg), Mean±S.D		62/1199 ± 35/4754
Adjuvant Chemotherapy		
Chemotherapy, n (%)	Total	64 (3/85)
Regimen, n (%)	TMZ	61 (3/81)
	TMZ+VCR	2 (7/2)
	TMZ+Bevacizumab	1 (3/1)

TMZ Cumulative Dose S.D±Mean ،(mg)		00/5064 ± 70/8003
Radiotherapy		
Treatment Characteristics, S.D ± Mean	Dose (Gy)	85/1 ± 22/59
	Duration (days)	64/5 ± 13/46
Salvage Therapy		
Type of Treatment, n (%)	Total	14 (7/18)
	Surgery	4 (3/5)
	Biopsy	4 (3/5)
	Chemotherapy	11 (7/14)
	Reradiation	4 (3/5)

In the present study, during a median follow-up of 17 months (IQR: 10–31 months), 61 out of 75 patients with high-grade glioma (81.3%) died. The mean overall survival (OS) from the onset of the disease to death was 17.15 ± 12.62 months (median 17.15 months; IQR: 13.98–20.31). This included 12 cases (70.59%) in patients with grade III glioma and 12 cases (20.69%) in grade IV ($P < 0.0001$).

According to the results of the Kaplan-Meier survival analysis, the survival duration in patients with IDH1 mutation was significantly longer than in wild-type patients ($P = 0.017$) (Table 3 and Figure 1).

Table 3 - Median Overall Survival (Months) of High-Grade Glioma Patients Based on IDH1 Mutation

IDH1	Estimate mean (lower-upper Range)	Estimate median (lower-upper Range)	Chi-Square	* P-value
Mutant	50/24 (63/30 – 36/18)	00/21 (88/26 – 12/15)	715/5	017/0
Wild	53/14 (95/17 – 11/11)	00/12 (28/15 – 71/8)		

* آزمون Log-Rank

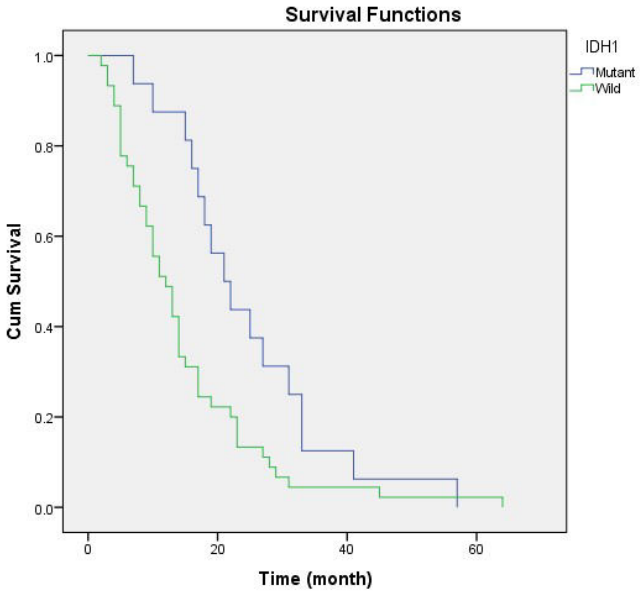

Figure 1 - Overall Survival (OS) of Glioma Patients Based on IDH1 Mutation

The results indicated that the frequency of IDH1 mutations was higher in patients with secondary gliomas (P = 0.019), WHO grade III (P < 0.0001), and deceased patients (P = 0.030). However, the IDH1 mutation did not show a significant correlation with the age and gender of patients with high-grade glioma (Table 4**).**

Table 4 - Relationship Between IDH1 Mutation and Various Variables in Patients with High-Grade Glioma

* P-value	(case 51) Wild	(case 24) Mutant	Group	Variable
105/0	26 (0/51)	17 (8/70)	> 50 year	Age
	25 (0/49)	7 (2/29)	≤ 50 year	
887/0	31 (8/60)	15 (6/62)	Male	Gender
	20 (2/39)	9 (5/37)	Female	
0001/0>	5 (41/29)	12 (59/70)	WHO Grade III	Grade glioma
	46 (31/79)	12 (69/20)	WHO Grade IV	
019/0	49 (05/72)	19 (94/27)	primary	
	2 (57/28)	5 (43/71)	Secondary	
030/0	8 (0/50)	8 (0/50)	alive	survival
	45 (77/73)	16 (23/26)	died	

The chi-square test; P-values less than 0.05 are considered statistically significant.

The results of the Cox survival regression model for evaluating the impact of independent variables on predicting the risk of death during follow-up are presented in Table 5. The univariate analysis indicated that the variables of age, gender, WHO grade, type of glioma, and type of surgery were not predictors of patient survival. The only effective factor in predicting patient mortality was the wild type of IDH1. The hazard ratio (HR) for death in individuals with IDH1 mutations compared to the wild type was 0.508 (95% CI: 0.910 - 0.283; P = 0.023). In the multivariate analysis, none of the variables studied were significant predictors of mortality in patients with high-grade gliomas.

Table 5 - Influential Factors on the Survival of High-Grade Glioma Patients

Cox Multivariate analysis	Cox Univariate analysis	Group	Variable

P-value	HR (95% CI)	P-value	HR (95% CI)		
132/0	605/0 (163/1 – 315/0)	023/0	508/0 (910/0 – 283/0)	Mutant(Ref)	Mutation IDHD
				Wild Type	
341/0	347/1 (485/2 – 730/0)	730/0	913/0 (532/1 – 544/0)	> 50 (Ref)	Age
				≤ 50	
506/0	798/0 (552/1 – 411/0)	135/0	664/0 (135/1 – 388/0)	Male (Ref)	Gender
				Female	
685/0	846/0 (896/1 -378/0)	098/0	560/0 (113/1 -282/0)	Grade III (Ref)	WHO grade
				Grade IV	
				Yes	
539/0	421/1 (362/4 – 463/0)	528/0	389/1 (856/3 –،	primary (Ref)	Type of glioma
				ثانویه Secondary	
569/0	321/1 (856/3 – 500/0)	066/0	129/2 (772/4 – 950/0)	Partial resection	Type of surgery
324/0	467/1 (441/3 – 507/0)	197/0	588/1 (207/3 – 787/0)	Extended biopsy	Complete resection (Ref)

HR: Hazard ratio; CI: Confidence Interval; IDH1: Isocitrate dehydrogenase-1; WHO: World Health Organization.

Discussion

The results of the present study indicated that IDH1 mutation was present in 24 cases (32%) of patients with high-grade gliomas. Additionally, the frequency of IDH1 mutation in patients with grade III gliomas was higher than in grade IV patients (59.70% versus 20.69%), and in secondary gliomas, it was higher than in primary gliomas (71.43% versus 27.94%). Other studies have also reported that IDH1 mutation is more prevalent in grade III gliomas and secondary glioblastomas compared to grade IV gliomas and primary glioblastomas (18-21). For instance, in July et al.'s study, the frequency of IDH1 gene mutation in patients with grade III gliomas was 42%, while in grade IV it was 3.4% (18).

The frequency of IDH1 mutation in grade III and IV gliomas was reported to be 50% in Pandith et al.'s study (20) and 27.63% in Kramár et al.'s study (22). In Polivka et al.'s study, IDH1 mutation was observed in 45.5% of glioblastoma patients, most of whom had secondary tumors (89.9%), while only 15.3% had primary glioblastomas (15). According to the findings of Zou et al., the highest frequency of IDH mutation was found in grade II and III gliomas (59.5%) and secondary glioblastomas (63.4%), while primary glioblastomas had the lowest frequency of mutated IDH (13.7%) (13). In Myung et al.'s study (2012) in South Korea, the frequency of IDH1 mutation in patients with low-grade gliomas (grade I and II) was 73.2%, in patients with grade III gliomas it was 82.9%, and in glioblastoma patients (grade IV) it was 6.5% (19).

It is noteworthy that some differences in the prevalence of IDH1 mutation in various studies may be attributed to differences in sample size, study population, and mutation assessment methods. For instance, the present study examined only patients with grade III and IV gliomas and utilized immunohistochemistry for mutation evaluation. Nevertheless, IDH1 mutation has become one of the most important genetic markers considered in the diagnosis and classification of central nervous system tumors since 2016 (4). Given its high prevalence in glioma patients, it can assist in predicting clinical outcomes and disease prognosis.

In the present study, the survival duration in patients with IDH1 mutation was significantly longer than in patients without mutation (Wild type IDH1) (an average of 21 months versus 12 months). Moreover, the frequency of deceased patients in the Wild type group was higher than in the IDH1 mutation group (73.77% versus 26.23%). Additionally, in univariate analysis, the hazard ratio (HR) of death in individuals with wild type IDH1 compared to those with IDH1 mutation was greater. These results suggest that IDH1 mutation is associated with longer survival in glioma patients and could serve as a positive prognostic marker for glioma patients.

Many other studies have also reported that patients with gliomas carrying IDH mutations have significantly better prognoses compared to gliomas with wild type IDH (6, 23-29). Large meta-analyses have shown that IDH1

mutations are associated with longer overall survival (OS) and progression-free survival (PFS), regardless of tumor grade (13, 30). In Shen et al.'s study (2020) in China, overall survival (OS) of glioma patients with mutated IDH1 was significantly higher than that of wild type IDH1 patients. Additionally, IDH1 mutation was a predictor of longer survival and better prognosis (31).

The important role of mutated IDH1 in assessing the prognosis of patients with astrocytomas and glioblastomas has been demonstrated in several studies. In Hartmann et al.'s study, anaplastic astrocytomas and glioblastomas with IDH1 mutation had the best prognosis and longest survival, while anaplastic astrocytomas and glioblastomas without IDH1 mutation had the lowest survival rates (32). In Aktan et al.'s study, the presence of IDH1 mutation was a predictor of overall survival and disease-free survival. The average OS and DFS in high-grade glioma patients with IDH1 mutation were 37.9 and 29.8 months, respectively, compared to 12.4 and 70.4 months in patients without mutation (14). In Polivka et al.'s study, glioblastoma patients with IDH1 mutation had longer overall survival compared to patients without mutation (270 days versus 130 days) (15). The findings of July et al. also indicated that high-grade glioma patients (grades III and IV) with IDH1 mutation had higher overall survival compared to patients with wild type IDH1 (21 months versus 13 months) (18). In Pandith et al.'s study, mortality rates in low and high-grade glioma patients with IDH1 mutation were lower compared to wild type (46.87% versus 67.74%), and the survival duration was longer (56.8 months versus 22.7 months) (20). Consistent with the current study, the findings of studies by Kramár et al. (22) and Van den Bent et al. (33) showed that glioma patients carrying IDH1 mutation are associated with favorable prognostic outcomes and prolonged survival, indicating that IDH1 mutation is a positive prognostic factor for predicting mortality in these patients.

A meta-analysis comprising the analysis of 24 different studies reported that glioblastoma patients with IDH1 mutation are associated with improved OS (HR: 0.35) and PFS (HR: 0.32) (34). Recently, a large cohort study reported that IDH1 mutation occurs in 34% of glioma patients and its occurrence is a predictor of better overall survival (OS) and progression-free survival (PFS) (21). Therefore, due to the high prognostic importance of IDH mutation in both high-grade and low-grade glioma patients, it should be evaluated primarily.

IDH1 utilizes nicotinamide adenine dinucleotide phosphate (NADP +) as a cofactor to catalyze the conversion of isocitrate to alpha-ketoglutarate (α-KG). Thus, IDH1, by producing α-KG, leads to an increase in NADPH, which plays a crucial role in the cell cycle (10). Mutations in IDH1 disrupt the enzyme's ability to bind to isocitrate and result in a neomorphic activity that increases the conversion of α-KG to D-2-hydroxyglutarate (D-2-HG) (35). The excess D-2-HG, often referred to as an "oncometabolite," fosters gliomagenesis; it alters cancer metabolism and induces oxidative stress (10). Furthermore, NADPH production is disrupted in IDH1 mutated gliomas, which may render tumors more sensitive to radiotherapy and chemotherapy, explaining why patients with IDH-mutated neoplasms have longer survival (8, 36). Therefore, the occurrence of mutations in IDH1 prevents tumor growth by altering the enzyme's function, improving patient survival.

Molecular and cellular research in gliomas has significantly enhanced our understanding of the genetic pathogenesis of gliomas. Numerous molecular and cellular biomarkers are currently recognized, which assist in the diagnosis, prognosis, and prediction of the behavior and outcomes of gliomas. One of the most important positive prognostic markers is IDH1 mutation, which, based on the results obtained in the present study and previous studies, its clinical application can contribute to improving patient management. Additionally, the development of IDH1 antibodies for specific mutations involved in high-grade gliomas may hold promise for treatment and improved prognosis for these patients.

Finally, it should be noted that the present study also faced limitations: the single-center nature of the study and the relatively small sample size (especially among grade III glioma patients) may lead to statistical weaknesses in the study. This study was conducted retrospectively, making it difficult to maintain consistency in specific treatment regimens across all patients. The use of semi-quantitative assessment methods and immunohistochemical staining for mutation evaluation were other limitations. Therefore, future studies on larger sample sizes and employing quantitative reverse transcription polymerase chain reaction (RT-PCR) methods could yield more accurate results**.**

Conclusion

The results of the present study indicated that IDH1 mutation was present in 32% of patients with high-grade gliomas. The frequency of IDH1 mutation was higher in patients with grade III gliomas compared to grade IV gliomas and in secondary gliomas compared to primary gliomas. Moreover, overall survival in high-grade glioma patients with IDH1 mutation was significantly greater than in patients without mutation (Wild type IDH1). These

results suggest that IDH1 mutation may serve as a promising therapeutic target and a strong prognostic biomarker in high-grade gliomas.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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