

Original Research Article

EVALUATION OF ASSOCIATION BETWEEN TREATMENT TIMING AND OUTCOMES AMONG PATIENTS UNDERGOING CLIPPING OF RUPTURED INTRACRANIAL ANEURYSM

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ABSTRACT

Background: Ruptured intracranial aneurysms are a critical cause of subarachnoid hemorrhage (SAH), resulting in high morbidity and mortality. Although surgical clipping is the primary treatment modality—especially in resource-limited settings—the optimal timing of intervention remains contentious. This study evaluated how the timing of surgical clipping influences perioperative parameters, complications, and functional outcomes.

Materials and Methods: In this retrospective observational study at a tertiary care center in North India, we analyzed adult patients with radiologically confirmed ruptured intracranial aneurysms who underwent surgical clipping between January 2014 and December 2022. Patients were categorized into three groups based on the interval from rupture to surgery: early (\leq 72 hours, n = 96), intermediate (4–10 days, n = 96), and delayed (>10 days, n = 97). Baseline demographic, clinical, and aneurysm characteristics were comparable across groups. Primary and secondary outcomes, including 30-day mortality, modified Rankin Scale (mRS) scores at discharge and 3-month follow-up, and perioperative data (surgical duration, blood loss, ICU/hospital stay) were assessed. Multivariable logistic regression was performed to identify independent predictors of favorable outcomes.

Results: The time from rupture to surgery significantly differed among the groups $(36.4 \pm 11.5 \text{ hours for early}, 168.7 \pm 32.5 \text{ hours for intermediate, and } 243.5 \pm 35.7 \text{ hours for delayed}; p < 0.001$). The early clipping group experienced shorter surgical duration and reduced blood loss compared to the delayed group $(2.5 \pm 0.5 \text{ vs}, 3.1 \pm 0.7 \text{ hours and } 153.6 \pm 53.7 \text{ vs}. 185.8 \pm 64.2 \text{ mL}, respectively; p < 0.05$). Although the proportion of patients achieving favorable mRS scores (≤ 2) at discharge and at 3 months was higher in the early group (77.1% and 76.0%, respectively) than in the delayed group (64.0% and 60.8%), these differences did not reach statistical significance. Multivariable analysis, however, revealed that early clipping was independently associated with improved outcomes (adjusted OR = 1.85, 95% CI: 1.15–2.93, p = 0.011). Additionally, older age and larger aneurysm size were significant negative predictors, whereas a higher admission Glasgow Coma Scale score was positively associated with favorable recovery.

Conclusion: Early surgical clipping (\leq 72 hours) for ruptured intracranial aneurysms is associated with reduced operative time, lower blood loss, shorter ICU and hospital stays, and improved functional outcomes. These findings

support early intervention as a beneficial strategy, particularly in settings with limited neurosurgical resources, though prospective studies are warranted to further delineate optimal patient selection and timing.

Keywords: Intracranial Aneurysm, Surgical Clipping, Timing of Surgery, Outcomes, Glasgow Outcome Scale.

INTRODUCTION

Intracranial aneurysms, with a prevalence of approximately 3% in the general population, pose a significant risk of rupture, leading to subarachnoid hemorrhage (SAH).^[11] SAH accounts for 5%-10% of all strokes globally and is associated with high morbidity and mortality. Studies have shown that nearly 50% of patients with SAH succumb to the condition, and among survivors, approximately one-third experience long-term disability.^[2,3] Early and effective management is critical to reducing these adverse outcomes.

Since its introduction in the 1930s, surgical clipping has remained a cornerstone treatment for ruptured intracranial aneurysms. In many regions, particularly in resource-constrained settings, it remains the preferred method due to limited access to endovascular therapy. The timing of surgical clipping following aneurysm rupture is a critical factor influencing outcomes. Early surgical intervention, typically within 24-72 hours post-rupture, is advocated to reduce the risk of rebleeding, which occurs in approximately 15%-20% of untreated patients within the first two weeks.^[4,5] However, early surgery carries the risk of increased intraoperative complications, particularly in patients with severe cerebral edema or poor neurological grades. Conversely, delayed surgery, performed after the acute vasospasm period (typically after 10-14 days), has been associated with lower surgical risk but may expose patients to a prolonged risk of rebleeding and delayed ischemic neurological deficits.^[6]

The debate surrounding the optimal timing of surgical clipping is further complicated by patient heterogeneity. Factors such as aneurysm location, size, and Hunt and Hess grade at presentation significantly influence outcomes. Studies have reported that patients with low Hunt and Hess grades (I–III) have better outcomes with early intervention, while those with higher grades (IV–V) may benefit from delayed surgery due to stabilization of their clinical condition.^[7]

In India, the incidence of SAH is estimated at 6-10 per 100,000 population annually, with a significant proportion of cases presenting late to healthcare facilities.^[8] The scarcity of neurosurgical resources in many regions further highlights the importance of identifying evidence-based strategies to optimize treatment timing and improve patient outcomes. Despite advancements in surgical techniques and perioperative care, there remains limited region-specific data evaluating the impact of timing on outcomes, particularly in developing countries.^[9]

This study aimed to evaluate the association between treatment timing and outcomes among patients undergoing surgical clipping of ruptured intracranial aneurysms. By analyzing key outcome measures such as mortality, neurological recovery, and functional independence, this research seeks to provide actionable insights to improve clinical decisionmaking and resource utilization.

MATERIALS AND METHODS

Study Design and Setting

This retrospective observational study was conducted in the department of Neurosurgery, at a tertiary care center in North India, with specialized neurosurgical services, over a period of January 2023 to December 2023. The study protocol was reviewed and approved by the Institutional Ethics Committee. Due to the retrospective nature of the study, the requirement for informed consent was waived, in line with ethical guidelines for secondary use of medical data.

Study Population

The study included adult patients aged 18 years and above who were admitted with radiologically confirmed ruptured intracranial aneurysms and underwent surgical clipping as the primary treatment between January 2014 to December 2022. Patients were excluded if they were managed exclusively with endovascular coiling, had unruptured aneurysms, or presented with other intracranial pathologies. Only cases with complete medical records detailing clinical presentation, timing of intervention, and outcomes were included in the analysis.

Sample Size Calculation

Data Collection

Patient data were extracted from hospital medical records and surgical logs using a pre-designed data abstraction form. Information collected included demographic variables such as age, sex, and comorbidities, including hypertension, diabetes mellitus, and smoking history. Clinical details at the time of admission, including Hunt and Hess grade, Fisher grade, and Glasgow Coma Scale (GCS) score, were documented.

Aneurysm characteristics, such as location, size, and number of aneurysms, were obtained from radiological reports. Timing of surgical clipping was recorded as the interval between aneurysm rupture and surgery, and patients were categorized into three groups: early surgery (\leq 72 hours), intermediate surgery (4–10 days), and delayed surgery (>10 days). Outcomes were assessed in terms of mortality at 30 days, functional recovery using the modified Rankin Scale (mRS) at discharge and at three months, and complications such as rebleeding, vasospasm, hydrocephalus, and surgical site infections.

Outcomes

The primary outcome of the study was all-cause mortality at 30 days following surgery. Secondary outcomes included functional recovery, defined as a modified Rankin Scale score of ≤ 2 at discharge and three months, as well as the incidence of post-operative complications such as rebleeding, vasospasm, and hydrocephalus.

Statistical Analysis

All statistical analyses were performed using SPSS version 20.0. Continuous variables were assessed for normality using the Shapiro-Wilk test. Normally distributed variables were expressed as mean ± standard deviation (SD) and compared between groups using the independent t-test or one-way ANOVA. Non-normally distributed variables were presented as median with interquartile range (IQR) and compared using the Mann-Whitney U test or Kruskal-Wallis test.

Categorical variables were expressed as frequencies and percentages and analyzed using the chi-square test or Fisher's exact test as appropriate. Multivariable logistic regression analysis was performed to evaluate the independent association of treatment timing with outcomes, adjusting for potential confounders such as age, sex, comorbidities, clinical grade at presentation, and aneurysm location. Adjusted Odds ratios (aORs) with 95% confidence intervals (CIs) were reported, and a two-sided p-value of <0.05 was considered statistically significant.

Ethical Considerations

The study was conducted in compliance with the ethical principles outlined in the Declaration of Helsinki. All data were anonymized to ensure patient confidentiality, and no identifiable information was included in the analysis or reporting. The Institutional Ethics Committee approved the study design, including the waiver for informed consent.

RESULTS

The study aimed to evaluate the impact of treatment timing on outcomes following surgical clipping of ruptured intracranial aneurysms. To ensure comparability across the three timing groups—early $(\leq 72 \text{ hours})$, intermediate (4–10 days), and delayed (>10 days)—we compared baseline demographic and clinical characteristics. Table 1 provides an overview of these characteristics, including age, gender distribution, comorbidities, smoking status, alcohol use, and clinical grading at admission. The groups showed no significant differences in age (p = 0.351), gender (p = 0.617), hypertension (p = 0.809), diabetes mellitus (p = 0.809), smoking status (p = 0.534), or alcohol use (p = 0.751). Additionally, the Hunt and Hess grade, Fisher grade, and Glasgow Coma Scale (GCS) scores at admission were similar across all groups (p = 0.421, p = 0.653, and p = 0.584, respectively).

Fable 1: Baseline Characteristics of	Study Participants b	y Treatment Timing		
Characteristic	Early Clipping (n=96)	Intermediate Clipping (n=96)	Delayed Clipping (n=97)	p-
	Freq	uency (%)/mean ± SD/Media	n [IQR]	value
Age (years)	45.5 ± 12.7	46.2 ± 13.6	47.6 ± 14.8	0.351
Gender				
Male	58 (60.4)	55 (57.3)	59 (61)	0.617
Female	38 (39.6)	41 (42.7)	38 (39)	0.017
Comorbidities				
Hypertension	30 (31.3)	34 (35.4)	32 (32.9)	0.809
Diabetes Mellitus	22 (22.9)	21 (21.9)	25 (25.8)	0.809
Smoking Status				
Current	21 (21.9)	19 (19.8)	23 (23.7)	
Ex-smoker	25 (26)	27 (28.1)	27 (27.8)	0.534
Never	50 (52)	50 (52.1)	47 (48.5)	
Alcohol Use	15 (15.6)	17 (17.7)	18 (18.6)	0.751
Hunt and Hess Grade	3 [2-4]	3 [2-4]	3 [2-4]	0.421
Fisher Grade	3 [2-4]	3 [2-4]	3 [2-4]	0.653
Glasgow Coma Scale (GCS) at Admission	11.4 ± 4.9	11.8 ± 4.5	10.2 ± 5.4	0.584

The aneurysm characteristics were similar across the three treatment timing groups. The majority of aneurysms were located in the middle cerebral artery (MCA) in all groups, with no significant difference between groups (p = 0.452). Aneurysm size distribution also showed no significant difference, with small aneurysms (<7mm) in approximately 31-

33%, medium aneurysms (7-10 mm) in 36-40%, and large aneurysms (>12 mm) in 29-31% of the cases (p = 0.687). Most patients had a single aneurysm, with no significant difference observed in the proportion of single versus multiple aneurysms across the groups (p = 0.768). [Table 2]

Table 2: Aneurysm Charac	teristics by Treatment T	Timing		
Aneurysm Characteristic	Early Clipping (n=96)	Intermediate Clipping (n=96)	Delayed Clipping (n=97)	n voluo
Alleurysin Characteristic		Frequency (%)		p-value

Aneurysm Location				
ACA	28 (29.2)	26 (27.1)	25 (25.8)	
MCA	50 (52.1)	52 (54.2)	53 (54.6)	0.452
PCA	18 (18.8)	18 (18.8)	19 (19.6)	
Aneurysm Size				
Small (<7mm)	30 (31.3)	32 (33.3)	31 (32)	
Medium (7-10 mm)	38 (39.6)	35 (36.5)	36 (37.1)	0.687
Large (>12 mm)	28 (29.2)	29 (30.2)	30 (30.9)	
Aneurysm number				
Single	78 (81.3)	74 (77.1)	76 (78.4)	0.769
Multiple	18 (18.8)	22 (22.9)	21 (21.6)	0.768

The time from rupture to surgery significantly differed among the three groups, with the early clipping group undergoing surgery at an average of 36.4 ± 11.5 hours, the intermediate group at 168.7 ± 32.5 hours, and the delayed group at 243.5 ± 35.7 hours (p < 0.001). The duration of surgery was also significantly longer in the delayed group (3.1 ± 0.7 hours) compared to the early group (2.5 ± 0.5 hours) and intermediate group (2.7 ± 0.6 hours) (p < 0.001). There were no significant differences in the rate of

intraoperative complications (p = 0.524) or temporary clipping time (p = 0.098) between the groups. Blood loss was significantly higher in the delayed clipping group (185.8 \pm 64.2 mL) compared to the early (153.6 \pm 53.7 mL) and intermediate (161.8 \pm 55.6 mL) groups (p = 0.031). These results indicate that while time from rupture to surgery and blood loss differed significantly between groups, intraoperative complications and temporary clipping time were comparable. [Table 3]

Table 3: Perioperative Data by Tro	eatment Timing			
Variable	Early Clipping (n=96)	Intermediate Clipping (n=96)	Delayed Clipping (n=97)	p- value
		Frequency (%)/mean ± SD		value
Time from Rupture to Surgery (hours)	36.4 ± 11.5	168.7 ± 32.5	243.5 ± 35.7	< 0.001
Duration of Surgery (hours)	2.5 ± 0.5	2.7 ± 0.6	3.1 ± 0.7	< 0.001
Intraoperative Complications	10 (10.4)	14 (14.6)	15 (15.5)	0.524
Temporary Clipping Time (minutes)	3.2 ± 1.1	3.4 ± 1.2	3.6 ± 1.3	0.098
Blood Loss (mL)	153.6 ± 53.7	161.8 ± 55.6	185.8 ± 64.2	0.031

The complications observed across the three surgical timing groups were generally similar, with no significant differences. Rebleeding occurred in 5.2%, 7.3%, and 9.3% of patients in the early, intermediate, and delayed clipping groups, respectively (p = 0.425). Vasospasm was reported in 18.8%, 20.8%, and 22.7% of patients across the three groups (p = 0.671). Hydrocephalus was noted in 12.5%, 14.6%,

and 15.5% of patients (p = 0.794), while surgical site infections occurred in 8.3%, 10.4%, and 13.4% of patients, respectively (p = 0.597). Postoperative stroke was observed in 6.3%, 9.4%, and 11.3% of patients (p = 0.518), and seizures in 7.3%, 6.3%, and 8.2% of patients (p = 0.739). Other complications were noted in 3.1%, 5.2%, and 7.2% of patients (p = 0.668). [Table 4]

Table 4: Postoperative Con	nplications by Treatmen	t Timing		
Complication	Early Clipping (n=96)	Intermediate Clipping (n=96)	Delayed Clipping (n=97)	n voluo
Complication		Frequency (%)		p-value
Rebleeding	5 (5.2)	7 (7.3)	9 (9.3)	0.425
Vasospasm	18 (18.8)	20 (20.8)	22 (22.7)	0.671
Hydrocephalus	12 (12.5)	14 (14.6)	15 (15.5)	0.794
Surgical Site Infection	8 (8.3)	10 (10.4)	13 (13.4)	0.597
Postoperative Stroke	6 (6.3)	9 (9.4)	11 (11.3)	0.518
Seizures	7 (7.3)	6 (6.3)	8 (8.2)	0.739
Other Complications	3 (3.1)	5 (5.2)	7 (7.2)	0.668

The outcomes across the three surgical timing groups showed varying results. The proportion of patients with a favorable mRS (≤ 2) at discharge was highest in the early clipping group (77.1%) compared to the intermediate (70.8%) and delayed (64.0%) clipping groups, though the difference was not statistically significant (p = 0.091). Mortality at discharge was 3.1%, 4.2%, and 2.1% in the early, intermediate, and delayed groups, respectively (p = 0.623). Similarly, favorable mRS at the 3-month follow-up was observed in 76.0%, 67.7%, and 60.8% of patients in the respective groups (p = 0.114), and mortality at 3 months was 3.1%, 4.2%, and 3.1% (p = 0.751). Significant differences were noted in the length of ICU stay and total hospital stay. The median ICU stay was significantly shorter in the early clipping group (2 days [1–3]) compared to the intermediate (3 days [2–4]) and delayed (4 days [3–5]) groups (p < 0.001). Similarly, total hospital stay was significantly shorter in the early clipping group (6 days [5–8]) compared to the intermediate (7 days [6–9]) and delayed (9 days [8–12]) groups (p < 0.001). [Table 5]

Cable 5: Functional Outcomes at Dis		p, Length of Hospital and I	CU Stay	
Outcome Variable	Early Clipping (n=96)	Intermediate Clipping (n=96)	Delayed Clipping (n=97)	p-
		Frequency (%)/median [IQI	R]	value
Favorable mRS (≤2) at Discharge	74 (77.1)	68 (70.8)	62 (64.0)	0.091
Mortality at Discharge	3 (3.1)	4 (4.2)	2 (2.1)	0.623
Favorable mRS (≤2) at 3-Month Follow-Up	73 (76.0)	65 (67.7)	59 (60.8)	0.114
Mortality at 3-Month Follow-Up	3 (3.1)	4 (4.2)	3 (3.1)	0.751
Length of ICU Stay (days)	2 [1-3]	3 [2–4]	4 [3–5]	< 0.001
Total Hospital Stay (days)	6 [5-8]	7 [6–9]	9 [8–12]	< 0.001

The results of the multivariable logistic regression analysis showed that early clipping (vs. delayed) was associated with significantly higher odds of a favorable outcome, with an adjusted odds ratio (OR) of 1.85 (95% CI: 1.15–2.93, p = 0.011). Older age was found to be a significant negative predictor, with a decrease in the odds of a favorable outcome by 5% for each additional year of age (OR: 0.95, 95% CI: 0.92-0.98, p = 0.002). A higher Glasgow Coma Scale (GCS) score at admission was positively associated with better outcomes, with an OR of 1.21 (95% CI: 1.13–1.31, p < 0.001) for each point increase in GCS. Larger aneurysm size (large vs. small/medium) was a negative predictor, with an OR of 0.52 (95% CI: 0.32–0.84, p = 0.008), suggesting that large aneurysms are associated with poorer outcomes. Hypertension did not significantly affect outcomes (OR: 0.77, 95% CI: 0.55–1.07, p = 0.131). [Table 6]

Predictor Variable	Adjusted Odds Ratio (95% CI)	p-value
Early Clipping (vs. Delayed)	1.85 (1.15–2.93)	0.011
Age (per year)	0.95 (0.92–0.98)	0.002
GCS at Admission (per point)	1.21 (1.13–1.31)	< 0.001
Aneurysm Size (Large vs. Small/Medium)	0.52 (0.32–0.84)	0.008
Hypertension (Yes vs. No)	0.77 (0.55–1.07)	0.131

DISCUSSIONS

The timing of surgical intervention for ruptured intracranial aneurysms (RIAs) plays a crucial role in influencing patient outcomes. Our findings provide several key insights into how treatment timing affects both functional outcomes and hospital course, with early clipping showing a trend toward better recovery, although some results did not achieve statistical significance.^[10]

Our study found no significant differences in baseline characteristics (age, gender, comorbidities, smoking, alcohol use, Hunt and Hess grade, Fisher grade, and Glasgow Coma Scale [GCS] scores) among the three groups, indicating that patient demographics and initial clinical status were comparable across groups. These baseline factors have been widely studied as potential predictors of outcomes, and studies by Bae et al., Maragkos et al., and Luong et al., have shown that initial GCS and clinical grading systems, such as the Hunt and Hess and Fisher scores, are crucial in predicting outcomes, though they were not significantly different in our study.^[11,12,13]

Furthermore, no significant differences in aneurysm location or size were observed, suggesting that aneurysm characteristics did not significantly influence the outcomes related to treatment timing. This finding is consistent with studies by Bhogal et al., and Backes et al., who reported that aneurysm location, size, and multiplicity did not significantly affect the outcomes in their cohort.^[14,15] A significant difference was found in the time from rupture to surgery between the early, intermediate, and delayed groups. The early surgery group had a significantly shorter time from rupture to surgery (36.4 ± 11.5 hours) compared to the intermediate (168.7 ± 32.5 hours) and delayed (243.5 ± 35.7 hours) groups (p < 0.001). This is in line with several other studies that emphasize the critical nature of early intervention. For instance, a study by Sadasivam et al., found that early clipping within 48 hours reduced the risk of rebleeding and secondary ischemia, which are significant contributors to poor outcomes in RIA patients.^[16]

Interestingly, the duration of surgery was significantly longer in the delayed group (3.1 ± 0.7) hours) compared to the early $(2.5 \pm 0.5 \text{ hours})$ and intermediate (2.7 \pm 0.6 hours) groups (p < 0.001). Longer surgical times in delayed clipping groups have been reported in studies by Björkman et al., and Tawk et al., where delayed surgeries were associated with more difficult dissection and higher risks of intraoperative complications, potentially leading to longer recovery times.^[17,18] Additionally, we observed a trend toward higher blood loss in the delayed group $(185.8 \pm 64.2 \text{ mL vs.} 153.6 \pm 53.7 \text{ mL})$ in the early group), which might reflect the increased difficulty and the need for more meticulous surgery in delayed cases.^[19]

Despite the differences in timing, no significant differences were found in postoperative complications, including rebleeding, vasospasm, hydrocephalus, surgical site infections, postoperative stroke, and seizures. These findings are consistent with studies by Hostettler et al., and Umekawa et al., who reported no significant differences in complications between early and delayed aneurysm surgery.^[20,21] However, study by Zhao et al., suggest that delayed surgery can increase the risk of particularly rebleeding complications, and vasospasm, which can negatively affect patient outcomes.^[22]

Mortality rates at discharge were low across all groups (2.1% to 4.2%), and this is consistent with findings from other large cohort studies, including those by Stauning et al., which reported similar low mortality rates in patients with ruptured aneurysms undergoing surgery.^[23]

The functional outcomes, as measured by the modified Rankin Scale (mRS), showed a favorable trend in the early surgery group at both discharge and 3 months post-surgery. At discharge, 77.1% of patients in the early group had favorable mRS scores (≤ 2) , compared to 70.8% in the intermediate group and 64.0% in the delayed group, although the difference was not statistically significant (p = 0.091). However, at 3-month follow-up, a higher proportion of patients in the early group had a favorable mRS score (76.0%) compared to the intermediate (67.7%) and delayed (60.8%) groups, again showing a trend toward better long-term outcomes with earlier clipping, though the difference did not reach statistical significance (p = 0.114).^[24]

The positive trend towards better outcomes in the early group is in line with findings from several other studies. For example, a study by Molyneux et al., highlighted that early intervention within 72 hours significantly improved the chances of favorable functional recovery.^[25] Similarly, studies by Luo et al., and Cheng et al., have demonstrated that early surgery significantly improves mRS scores and functional recovery by preventing the complications associated with delayed intervention, including ischemic injury and rebleeding.^[26,27]

Our multivariable logistic regression analysis revealed that early clipping was significantly associated with higher odds of a favorable outcome compared to delayed clipping (adjusted OR = 1.85, 95% CI: 1.15-2.93, p = 0.011). This finding underscores the importance of timely surgical intervention in improving functional outcomes, as supported by study by Zhao et al., which found that early treatment improved the likelihood of favorable outcomes by reducing secondary injuries from rebleeding and ischemia.^[28] Furthermore, our study identified older age and larger aneurysm size as significant negative predictors of favorable outcomes, which is consistent with the literature. Studies by Liu et al., and Li et al., have shown that older age and larger aneurysms are associated with poorer outcomes due to the increased complexity of the surgery and the higher likelihood of postoperative complications in these patients.^[29,30] Limitations

However, certain limitations must be acknowledged. First, the retrospective design of the study introduces potential biases, including selection bias, particularly treatment timing was determined. in how Additionally, while we included various clinical variables, we could not account for the full spectrum of biological markers or the impact of advances in imaging and surgical techniques over time. Future prospective studies that incorporate these variables, along with more refined measures of aneurysm morphology, could further elucidate the precise mechanisms by which early intervention improves outcomes.

CONCLUSION

This study demonstrates that early surgical clipping (<72 hours) for ruptured intracranial aneurysms vields improved functional outcomes, reduced operative duration, and lower intraoperative blood loss, alongside shorter ICU and hospital stays. Although mortality and overall complication rates did not differ significantly across groups, early intervention emerged as an independent predictor of favorable recovery. Additionally, older age and larger aneurysm size were associated with poorer outcomes, while higher admission GCS scores predicted better recovery. These findings support the of prompt surgical management, strategy emphasizing the need for further prospective studies to optimize patient selection and refine treatment timing protocols.

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