Multiphasic arterial spin labeling imaging to predict early recurrent ischemic lesion in acute ischemic stroke

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In acute ischemic stroke (AIS), the hemodynamics around the lesion are important because they determine the recurrence or prognosis of the disease. This study evaluated the effects of perfusion deficits in multiphasic arterial spin labeling (ASL) and related radiological parameters on the occurrence of early recurrent ischemic lesions (ERILs) in AIS. We assessed AIS patients who underwent multiphasic ASL within 24 h of symptom onset and follow-up diffusion-weighted imaging within 7 days. ASL perfusion deficit, arterial transit artifact (ATA), and intra-arterial high-intensity signal (IAS) were manually rated as ASL parameters. A total of 134 patients were evaluated. In the multivariable analyses, ASL perfusion deficit [adjusted odds ratio (aOR) = 2.82, 95% confidence interval = 1.27–6.27] was positively associated with ERIL. Furthermore, when ATA was accompanied, the ASL perfusion deficit was not associated with ERIL occurrence. Meanwhile, IAS showed a synergistic effect with ASL perfusion deficit on the occurrence of ERIL. In conclusion, we demonstrated the association between perfusion deficits in multiphasic ASL with ERIL in patients with AIS. This close association was attenuated by ATA and was enhanced by IAS. ASL parameters may help identify high-risk patients of ERIL occurrence during the acute period.

The recurrence of stroke increases the risk of disability and mortality, making it an important concern in patients with acute ischemic stroke (AIS)1,2. However, it is difficult to distinguish clinical recurrence through neurological examination in AIS patients with neurological deficits1,2. Although the reported clinical recurrence rate was < 5%1,2, early recurrent ischemic lesions (ERILs), defined as radiological recurrence on diffusion-weighted imaging, occurs up to 40% of patients within the first week after AIS2,4. Since the presence of symptoms in stroke is determined by the lesion size, location, and number, ERIL is considered a pathology such as clinical recurrence4–6. Therefore, as a surrogate of recurrent stroke, studies have identified various clinical, laboratory, and radiological predictors of ERIL6–8.

AIS is a vascular disease, in which the hemodynamics of the lesion area determine the disease prognosis or recurrence8–12. Therefore, it is important to accurately measure perfusion deficits or collateral flow in patients with AIS. Arterial spin labeling (ASL) is a noninvasive magnetic resonance imaging (MRI) technique that uses magnetically labeled blood as an endogenous contrast agent8,10. In previous studies, the perfusion deficit area on ASL was well correlated with the perfusion deficit area on conventional imaging techniques (e.g., MRI, computed tomography)11–16, and it was closely related to stroke prognosis and recurrence16,17,18.

In ASL imaging, not only the perfusion deficit but also the accompanying parameters are important19. When the time for labeled blood to reach the tissue (= arterial transit time, ATT) is longer than that of post-label delay (PLD) due to slow arterial flow, this delayed blood flow appears as a hyperintense signal on the ASL

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These are called arterial transit artifact (ATA) (= cortical ATA) or intraarterial high-intensity signal (IAS) (= proximal ATA), depending on where they are found, indicating leptomeningeal collateral flow and stagnant flow by arterial occlusion, respectively.\textsuperscript{20–26} ATA and IAS are frequently found in AIS patients, and their pathology has been clarified in several experimental studies.\textsuperscript{13,22–24,26} However, studies on their effects on clinical prognosis are lacking.

Conventional ASL is a good technology, but, there are limitations in using it in the area where the ATT is normally long.\textsuperscript{22,27} Multiphase ASL has addressed some of the issues with long-ATT areas by acquiring PLDs of multiple time points allowing the images both the early and late label arrival.\textsuperscript{13,22,27–30} In this study, we attempted to demonstrate that ASL perfusion deficit has a positive correlation with ERIL occurrence in patients with AIS. Furthermore, we examined how other accompanying ASL parameters affect the association between perfusion deficits and ERIL. Since previous studies showed that the occurrence of ERIL differed according to the stroke mechanism,\textsuperscript{31} we also compared the patterns of ASL parameters according to the stroke mechanism and the resulting ERIL occurrence.

### Results

A total of 134 AIS patients were assessed (mean age, 71 ± 13 years; male sex, 62.7%); mean initial NIHSS score, 6 ± 6). ERIL occurred in 59 (44.0%) patients, including 30 (22.4%) cases of ERIL-local and 29 (21.6%) cases of ERIL-distant. We identified ASL perfusion deficits in 87 (64.9%) patients, ATA in 37 (27.6%) patients, and IAS in 27 (20.1%) patients. Other detailed baseline characteristics are presented in Supplementary Table 1.

### Table 1. Baseline characteristics of patients with and without ERILs.

|                        | No ERIL (n=75) | ERIL (n=59) | P value |
|------------------------|---------------|------------|---------|
| Age, years [IQR]       | 71 [61–79]    | 74 [65–80] | 0.218   |
| Sex, male, n (%)       | 47 (62.7)     | 37 (62.7)  | 0.996   |
| Follow-up MRI time, days [IQR] | 2 [1–4]    | 3 [2–4]    | 0.520   |
| Hypertension, n (%)     | 52 (69.3)     | 44 (74.6)  | 0.504   |
| Diabetes, n (%)         | 29 (38.7)     | 24 (40.7)  | 0.813   |
| Hyperlipidemia, n (%)   | 33 (44.0)     | 31 (52.5)  | 0.326   |
| Atrial fibrillation, n (%) | 23 (30.7)  | 19 (32.2)  | 0.849   |
| Ischemic heart disease, n (%) | 16 (21.3) | 14 (23.7)  | 0.741   |
| Smoking, n (%)          | 14 (18.7)     | 8 (13.6)   | 0.428   |
| History of stroke, n (%) | 19 (25.3)   | 14 (23.7)  | 0.831   |
| Mechanism, n (%)        |               |            | 0.843   |
| Intracranial-LAA        | 18 (24.0)     | 13 (22.0)  | 0.789   |
| Extracranial-LAA        | 11 (14.7)     | 12 (20.3)  | 0.387   |
| Cardioembolism          | 27 (36.0)     | 21 (35.6)  | 0.961   |
| Cryptogenic             | 19 (25.3)     | 13 (22.0)  | 0.657   |
| Initial NIHSS score [IQR] | 4 [2–8]  | 3 [1–7]    | 0.091   |
| IV thrombolysis, n (%)  | 11 (14.7)     | 5 (8.3)    | 0.272   |
| HbA1c, % [IQR]          | 5.9 [5.5–6.5] | 5.9 [5.7–6.9] | 0.407   |
| Fasting blood sugar, mg/dL [IQR] | 98 [87–116] | 98 [85–113] | 0.857   |
| Total cholesterol, mg/dL [IQR] | 161 [142–182] | 162 [137–202] | 0.898   |
| LDL cholesterol, mg/dL [SD] | 97 ± 36  | 100 ± 37   | 0.659   |
| HDL cholesterol, mg/dL [SD] | 48 ± 14  | 46 ± 14    | 0.439   |
| Triglyceride, mg/dL [IQR] | 92 [67–124] | 98 [76–153] | 0.389   |
| White blood cell, × 10^3/μL [IQR] | 7.15 [5.69–8.94] | 6.97 [5.68–9.95] | 0.761   |
| High-sensitivity CRP, mg/dL [IQR] | 0.11 [0.06–0.40] | 0.11 [0.05–0.26] | 0.655   |
| ASL perfusion deficit, n (%) | 43 (57.3) | 44 (74.6)  | 0.038   |
| ATA, n (%)              | 24 (32.0)     | 13 (22.0)  | 0.200   |
| IAS, n (%)              | 7 (9.3)       | 20 (33.9)  | <0.001  |
| Recanalization, n (%)   | 12 (16.0)     | 16 (27.1)  | 0.116   |
confidence interval [CI] = 1.27–6.27) and age (aOR = 1.03, 95% CI = 1.00–1.06) were positively associated with ERIL after adjusting for confounders (Table 2).

Similarly, additional multivariable analyses showed opposite effects on ERIL between ATA and IAS. For ATA, the [ASL deficit (+) ATA (−)] group showed the highest frequency of ERIL (62.0%) and had the highest aOR value in multivariable analysis (aOR = 4.48, 95% CI = 1.83–10.98) (Table 3). Conversely, when accompanied by ATA, the ASL perfusion deficit lost its statistical significance with ERIL and showed an ERIL frequency similar to that in the [ASL deficit (−) ATA (−)] group (35.1% versus 31.9%, P = 0.756, Fig. 1). Thus, ATA appeared to negatively affect the occurrence of ERIL. Assessment of the effects of ATA according to the ERIL location showed, more ERIL-local in the [ASL deficit (+) ATA (−)] group than that in the [ASL deficit (+) ATA (+) ] group (44.0% versus 21.6%, P = 0.030). However, there was no significant difference in ERIL-distant between the two groups.

In contrast, the [ASL deficit (+) IAS (+)] group showed the highest frequency of ERIL (74.1%) and the highest aOR value (aOR = 7.97, 95% CI = 2.59–24.51, Table 3). There were no significant differences between the [ASL deficit (+) IAS (−)] and [ASL deficit (−) IAS (−)] groups (Fig. 1). These results indicated the positive effect of IAS on ERIL occurrence. Examination of the relationships between IAS and the ERIL location, showed more ERIL-local in the [ASL deficit (+) IAS (+)] group than in the [ASL deficit (+) IAS (−)] group (51.9% versus 26.7%, P = 0.022). However, no significant differences were observed for ERIL-distant.

We compared the characteristics of the four groups of stroke mechanisms included in this study (Table 4). Although not statistically significant, ERIL most commonly occurred in the EC-LAA group (P = 0.843), while ERIL-local was more frequently found in the IC-LAA and EC-LAA groups (P = 0.029) and ERIL-distant showed a statistical tendency of increased frequency in CE or cryptogenic groups (P = 0.092). ASL perfusion deficits and ATA/IAS did not differ depending on the stroke mechanisms; however, recanalization was clearly observed in the CE group (P = 0.012).

### Table 2. Multivariable logistic regression analysis of possible predictors for early recurrent ischemic lesion. NIHSS National Institutes of Health Stroke Scale, ASL arterial spin labeling.

|                | Crude OR (95% CI) | P-value | Adjusted OR (95% CI) | P-value |
|----------------|-------------------|---------|----------------------|---------|
| Age, years     | 1.02 [1.00–1.05]  | 0.107   | 1.03 [1.00–1.07]     | 0.039   |
| Sex, male      | 1.00 [0.50–2.03]  | 0.996   | 1.07 [0.50–2.27]     | 0.869   |
| Initial NIHSS score | 0.97 [0.92–1.03] | 0.348   | 0.95 [0.89–1.01]     | 0.108   |
| ASL perfusion deficit | 2.18 [1.04–4.59] | 0.040   | 2.82 [1.27–6.27]     | 0.011   |

### Table 3. Multivariable logistic regression analyses of possible predictors for ERIL, considering the interactive effects between ASL perfusion deficit and ATA/IAS. ERIL early recurrent ischemic lesion, ASL arterial spin labeling, ATA arterial transit artifact, IAS intraarterial high-intensity signal, NIHSS National Institutes of Health Stroke Scale.

|                | Crude OR (95% CI) | P-value | Adjusted OR (95% CI) | P-value |
|----------------|-------------------|---------|----------------------|---------|
| **Model 1**    |                   |         |                      |         |
| Age, years     | 1.02 [1.00–1.05]  | 0.107   | 1.03 [1.00–1.07]     | 0.043   |
| Sex, male      | 1.00 [0.50–2.03]  | 0.996   | 1.13 [0.52–2.42]     | 0.759   |
| Initial NIHSS score | 0.97 [0.92–1.03] | 0.348   | 0.94 [0.88–1.01]     | 0.105   |
| ASL deficit × ATA |                  |         |                      |         |
| ASL deficit (−) ATA (−) | Ref        | Ref     | Ref                  | Ref     |
| ASL deficit (+) ATA (−) | 3.48 [1.51–8.05] | 0.004   | 4.48 [1.83–10.98]    | 0.001   |
| ASL deficit (+) ATA (+) | 1.16 [0.46–2.88] | 0.756   | 1.47 [0.56–3.86]     | 0.436   |
| **Model 2**    |                   |         |                      |         |
| Age, years     | 1.02 [1.00–1.05]  | 0.107   | 1.03 [1.00–1.07]     | 0.043   |
| Sex, male      | 1.00 [0.50–2.03]  | 0.996   | 1.13 [0.52–2.42]     | 0.759   |
| Initial NIHSS score | 0.97 [0.92–1.03] | 0.348   | 0.94 [0.88–1.01]     | 0.105   |
| ASL deficit × IAS |                  |         |                      |         |
| ASL deficit (−) IAS (−) | Ref        | Ref     | Ref                  | Ref     |
| ASL deficit (+) IAS (−) | 1.42 [0.64–3.17] | 0.389   | 1.84 [0.78–4.31]     | 0.164   |
| ASL deficit (+) IAS (+) | 6.10 [2.12–17.54] | 0.001   | 7.97 [2.59–24.51]    | < 0.001 |
Discussion

The results of this study showed the significant association of perfusion deficits on multiphase ASL with ERIL in patients with AIS. The close association was attenuated by ATA and enhanced by IAS. Thus, ASL perfusion deficits and accompanying radiological parameters may be helpful in identifying high-risk groups for ERIL occurrence in AIS patients.

Similar to our previous study on transient ischemic attack, we again confirmed the clinical significance of ATA and IAS. Cortical ATA, which indicates rich leptomeningeal collateral flow, attenuates ischemic core progression and reduces the final infarct volume. In our results, ATA showed a protective effect on the occurrence of ERIL. This effect was related only to ERIL-local occurring within the region where the collateral flow was distributed, but not to ERIL-distant. Meanwhile, IAS refers to stagnant flow due to large vessel occlusion. Therefore, whether it is the actual recurrence due to embolism or in situ thrombosis, or a silent recurrence due to the breakup of the initial thrombi, it seems natural that IAS is positively correlated with ERIL.

ERIL occurred in different patterns according to the stroke mechanisms. Using the accompanying radiological parameters, we were able to speculate on the mechanism by which these differences occurred. Unsurprisingly, ERIL mainly appeared in the form of ERIL-local within the relevant vessel area in the IC-LAA and EC-LAA groups. There were three cases of exceptional ERIL-distant, in which there was no initial ASL perfusion deficit or when the embolism was transferred to the contralateral anterior cerebral artery territory along the circle of
and the breakup of initial thrombi)33. In the case of EC-LAA, all ERIL occurred only in relevant vessels that were IC-LAA group could be attributed to various mechanisms (e.g., artery-to-artery embolism, in situ thrombosis, and the breakup of initial thrombi)33. In the case of EC-LAA, all ERIL occurred only in relevant vessels that were advanced enough to accompany the ASL perfusion deficit (Supplementary Table 2). In addition, since there were no recanalization events in this group, all ERILs were thought to have occurred due to true recurrence events. Therefore, artery-to-artery embolism is likely the main mechanism of ERIL occurrence in EC-LAA as revealed in previous studies33. CE patients had a significantly higher recanalization rate (Table 4) and ERIL developed in 10 of these 16 patients with recanalization. In other words, there seemed to be a high rate of silent recurrence due to the breakup of the initial thrombi34. However, only four such cases in the present study occurred in the form of ERIL-local, while six were accompanied by ERIL-distant; therefore, the effect of additional embolic events cannot be ignored. Patients with cryptogenic stroke did not show distinct features, likely be due to the mixture of heterogeneous mechanisms (e.g., paradoxical embolism, paroxysmal atrial fibrillation, malignancy) in this patient group.

Despite the novel findings in this study, there are several limitations to consider when interpreting our results. First, this was a single-center, retrospective, cross-sectional study. Given the limitations of the cross-sectional analysis, our findings indicated associations rather than causal relationships. Second, ERIL used as an outcome variable did not consider the recurrence of clinical symptoms. Therefore, some of these instances may have been caused by the breakup of initial thrombi, regardless of actual recurrence events. However, in previous studies, ERIL greatly affected clinical recurrence and subsequent prognosis24. Third, in this study, ASL perfusion deficit, ATA, and IAS were measured manually by neuroradiologists. If these parameters were rated in an automatic way, the reproducibility would be higher. Fourth, we conducted this study using only qualitative ASL parameters. If we verify our study using quantitative parameters such as spatial coefficient of variation in future studies, higher reliability could be obtained34. Lastly, this study included only patients with ischemic stroke in the anterior circulation. With the advent of multiphase ASL technology, the resolution problem of ASL has significantly improved. However, due to the technical limitations of ASL images, their use in posterior circulation stroke remains limited.

The results of this study demonstrated that perfusion deficits on multiphase ASL was associated with ERIL in patients with AIS in the anterior circulation. In addition, using the accompanying ATA and IAS, we estimated the risk of ERIL and predicted the underlying pathophysiology of ERIL occurrence according to stroke mechanisms. These ASL parameters will help us to identify groups at high-risk for ERIL occurrence during the acute period and to perform early interventions according to the mechanisms. However, further prospective studies are required to confirm our findings.

Methods

Study population. We evaluated AIS patients who underwent multiphase ASL between April 2014 and May 2020. This study only included AIS of the anterior circulation (e.g., anterior/middle cerebral artery, internal carotid artery) (n = 331). This is considering the nature of the ASL image, in which the posterior circulation has relatively low resolution and it is difficult to measure ATA and IAS. Patients were then excluded according the following criteria: (1) visited 24 h after symptom onset (n = 7); (2) no follow-up MRI within 7 days (n = 81); and (3) administration of diagnostic or therapeutic intraarterial thrombolysis (n = 20)33. Similar to previous studies on ERIL, we also excluded patients with the following stroke mechanisms (n = 89): (1) small vessel occlusion, (2) other determined, and (3) more than two stroke mechanisms31. However, in recent years, the clinical importance of cryptogenic stroke has been highlighted; therefore, we included this group of patients, unlike previous studies.

Thus, the final analysis included 134 patients with AIS. This retrospective cross-sectional study was approved by the Institutional Review Board (IRB) of Seoul National University Hospital (IRB number: 1103-135-357), which waived the requirement for written informed consent due to the retrospective study design and the use of de-identified and anonymized patient information only. All experiments were conducted in accordance with the Declaration of Helsinki and all relevant guidelines and regulations. All data related to this study are included in the main text and supplemental materials.

Clinical assessment. In our center, all AIS patients were principally admitted by their physicians for a broad evaluation to identify the stroke etiology and prognosis. The demographic, clinical, and cardiovascular risk factors, assessed in this study were age, sex, hypertension, diabetes, dyslipidemia, atrial fibrillation, ischemic heart disease, current smoking, history of stroke, initial stroke severity, mechanisms of stroke, and use of intravenous thrombolysis32. Initial stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) score evaluated every day from admission to discharge by well-trained neurologists who were not involved in this study. The mechanism of stroke was determined according to the Trial of ORG 10172 in Acute Stroke Treatment classification35. Based on this, we classified our study population into four groups as follows: intracranial large artery atherosclerosis (IC-LAA), extracranial large artery atherosclerosis (EC-LAA), cardioembolism (CE), and cryptogenic35. IC-LAA was defined as symptomatic intracranial atherosclerosis (occlusion or ≥50% stenosis) without evidence of EC-LAA or CE35. EC-LAA was diagnosed when patients had symptomatic extracranial atherosclerosis without IC-LAA or CE35. Laboratory examinations were performed after a 12 h overnight fast, included glucose profiles, lipid profiles, white blood cell counts, and high-sensitivity C-reactive protein35.
Radiological assessment. All participants in this study underwent brain MRI and magnetic resonance angiography (MRA) within 24 h of admission and follow-up MRI within 7 days using a 3.0-T MR scanner (Discovery MR750w; GE healthcare, Milwaukee, WI, USA) with a 32-channel phased-array head coil. Basal MP-ASL perfusion-weighted MRI was obtained using three-dimensional (3D) spiral fast spin-echo sequences with a Hadamard-encoded pseudo-continuous ASL. The imaging parameters were as follows: repetition time, 5902.0 ms; echo time, 11.3 ms; slice thickness, 5 mm; number of averages, 1; number of slices, 28; readout, 4 spiral arms × 640 samples; field of view, 24 × 24 cm²; matrix, 128 × 128; and voxel resolution, 3.8 mm × 3.8 mm × 5.0 mm. The protocol encoded 7 different PLD times into a single acquisition. With the parameters tabulated above, images with PLD times of [1.00, 1.22, 1.48, 1.78, 2.15, 2.63, and 3.32] seconds and effective label durations of [0.22, 0.26, 0.30, 0.37, 0.48, 0.68, and 1.18] seconds were reconstructed. These PLD times are intended to probe the bolus arrival time. The ATT map (δ) and perfusion map (f) were calculated by fitting the seven-delay ASL difference signals as a function of the PLD (w) to the following equation:

\[
\Delta M = 2M_0^t \cdot \beta \cdot \alpha \cdot T1t \cdot f \cdot e^{\frac{\delta}{T1a}} \cdot \left( e^{-\frac{\text{max}(w-\delta, 0)/T1t}{T1t}} - e^{-\frac{\text{max}(\tau + w - \delta, 0)/T1t}{T1t}} \right) \beta^{23,37,37}
\]

where \( \Delta M \) is the ASL difference signal, \( f \) is the perfusion rate, \( T1a \) and \( T1t \) are the longitudinal relaxation times of blood and tissue, \( M_0^t \) is the fully relaxed equilibrium magnetization of brain tissue, \( \alpha \) is the efficiency of the labeling sequence, \( \beta \) is the tissue-to-blood partition coefficient of water, \( \delta \) is the transit delay, \( \tau \) is the labeling duration, and \( w \) is the PLD. Vascular signal suppression is assumed in this model. \( \beta \) has been added to the kinetic model to compensate for any static tissue signal loss caused by the vessel suppression pulse36,38–41. From this map, an ASL perfusion deficit was defined based on qualitative visual interpretation by two well-trained neuroradiologists (I.P.H. and C.-H.S.) who were blinded to the other clinical information (Fig. 2). Other radiological parameters related to ASL (ATA and IAS) were also measured as in our previous study (Fig. 2). ATA was defined as a focus or curvilinear hyperintensity located bordering the areas of ASL perfusion deficits25. IAS was a hyperintense signal appearing within the vascular lumen, directly proximal or distal to the relevant occluded vascular lesions15. Recanalization was rated based on the initial and follow-up MRA, including both partial and complete recanalization31.

As an outcome variable, ERIL was defined as a new diffusion-weighted imaging lesion outside the index symptomatic lesion area on initial MRI1. An enlargement of the index lesion was not considered an ERIL. We also classified ERIL into two groups—ERIL-local and ERIL-distant—according to the relationship between the locations of the ERIL and the initial ASL perfusion deficit (Supplementary Fig. 1). ERIL was classified as ERIL-local if new lesions occurred within the initial ASL perfusion deficit area and as ERIL-distant if they occurred outside the area1. ERILs occurring simultaneously in and out of the ASL perfusion deficit were classified as ERIL-distant, as previously described1. All radiological parameters were visually analyzed by well-trained neuroradiologists (I.P.H. and C.-H.S.), and disagreements were resolved by discussion with a third rater (C.K.K.).
**Statistical analysis.** All statistical analyses were performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA). Univariate analyses for evaluating the possible predictors for ERIL were performed using Student’s t or Mann–Whitney U-tests for continuous variables and chi-square or Fisher’s exact test for categorical variables. Variables with \( P < 0.10 \) in the univariate analyses, as well as age and sex, were included in the multivariable logistic regression analysis.

Based on their definitions, ATA and IAS are only found in patients with ASL perfusion deficits\(^{20}\). To interpret the individual or mutual meanings of these parameters, we classified the study population into three groups according to the presence of ASL perfusion deficit and ATA/IAS (e.g., [ASL deficit × ATA]) or [ASL deficit × IAS]). Using these multi-categorical variables, we performed an additional multivariable logistic regression analysis. We also analyzed the relationships between these variables and ERIL-local/ERIL-distant to understand the effect of these radiological parameters on the location of the ERIL occurrence.

This study included patients with four different stroke mechanisms. Thus, we also compared baseline characteristics, ASL parameters, and ERIL among patient groups according to stroke mechanism. In this study, all variables with \( P < 0.05 \) were considered statistically significant.

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**Competing interests**
The authors declare no competing interests.

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