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Effects of subarachnoid extension following intracerebral hemorrhage

A systematic review and meta-analysis

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Abstract

Background: The effects of subarachnoid extension (SAHE) following intracerebral hemorrhage (ICH) have not yet been fully understood. We conducted a systematic review and meta-analysis of published literature on this topic to better understand the effects of SAHE.

Methods: PubMed, Embase, and Cochrane databases were thoroughly searched from inception to October 16, 2022 to identify studies that evaluated the association between SAHE and mortality and worse functional outcomes in primary ICH. Crude odds ratios (cOR) and adjusted odds ratios (aOR) with 95% confidence interval (CI) were calculated to compare the endpoints.

Results: Three studies with 3368 participants were eventually included in the analysis. In the short-term follow-up of the primary endpoint, no association was observed between SAHE and mortality (cOR: 0.51, 95% CI: 0.01–28.19; aOR: 2.31, 95% CI: 0.72–7.45). In the long-term follow-up of the primary endpoint, SAHE was associated with a significantly increased mortality of patients with primary ICH (cOR: 3.00, 95% CI: 2.27–3.98); however, only 1 study provided the values of aOR and 95% CI and showed that SAHE was not associated with increased mortality (aOR: 1.14, 95% CI: 0.71–1.83). For the secondary endpoint, the data of only 1 study on major disability (modified Rankin Scale = 3–5) were available, and the results revealed that SAHE increased the probability of major disability, but not after adjusting for baseline hematoma volume.

Conclusion: There is insufficient evidence to demonstrate the correlation between SAHE and mortality and worse functional outcomes in primary ICH. The validation of this correlation requires further studies as the potential effect and mechanisms of SAHE remain unclear.

Abbreviations: aOR = adjusted odds ratios, aSAH = aneurysmal subarachnoid hemorrhage, CI = confidence interval, cOR = crude odds ratios, HE = hematoma expansion, ICH = intracerebral hemorrhage, mRS = modified Rankin Scale, NOS = Newcastle-Ottawa Scale, NR = not reported, OR = odds ratios, PRISMA = reporting items for systematic review and meta-analysis, SAH = subarachnoid hemorrhage, SAHE = subarachnoid extension.

Keywords: subarachnoid extension, intracerebral hemorrhage, mortality, functional outcomes, meta-analysis

1. Introduction

Intracerebral hemorrhage (ICH), with an incidence of approximately 20 per 100,000 person-years and a case fatality rate of up to 50%, is the second common and the most severe stroke subtype.[1,2] A larger baseline hematoma, a spot sign in computerized tomography angiography, hematoma expansion (HE), perihematomal edema, intraventricular hemorrhage, subarachnoid extension (SAHE), hydrocephalus, old age, prior use of anticoagulants, and leukoaraiosis are the factors that could increase the risk of neurological deterioration after ICH, which may further influence poor outcomes such as death and dependency.[3,4] SAHE is a characteristic sign of the extension of ICH into the subarachnoid space and might be caused by fragile vessels and active bleeding in the hematoma surrounding the vessels.[5,6] A previous study that focused on the association between SAHE and outcomes of primary ICH revealed that SAHE can cause cortical dysfunction, injury, and disability through pathways comparable to those observed in aneurysmal subarachnoid hemorrhage (aSAH).[7] The authors confirmed the association between SAHE and worse modified Rankin Scale (mRS) independent of traditional ICH severity measures.[7] They also inferred that blood is

TL, JM, and LP contributed equally to this work.

The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files]

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the proinflammatory substance present in the brain parenchyma after ICH; however, the dissemination of blood into the ventricular system or the subarachnoid space exposes more brain tissue to its deleterious inflammatory effects, thereby worsening the clinical status and functional outcome of the patient.[7] The biological effects and clinical outcomes, however, might differ because SAHE following ICH often results in less blood entering the subarachnoid space than that occurring in aSAH.[8]

Because the effects of SAHE on patients with primary ICH remain unclear, we conducted a meta-analysis to validate the hypothesis that SAHE worsens the outcomes of patients with ICH.

2. Methods

We conducted the present systematic review according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.[9] There is no need of ethical approval because this article is a systematic review and meta-analysis.

2.1. Search strategy

PubMed and Embase databases were thoroughly searched from inception to May 23, 2022 to extract studies that investigated the association between SAH and outcomes of ICH patients, with no restrictions on the language of the published study. For the literature search, the initial keywords were combined with MeSH or EMTREE terms such as "intracerebral hemorrhage," "subarachnoid," "extension," "diffuse," "permeate," "spread," and their variants. To identify further eligible papers, we also manually searched relevant literature, reviews, and meta-analysis. To ensure literature saturation, we repeated the literature search on October 16, 2022 by exploring the Cochrane library for relevant studies. The search session and literature screening process were performed independently by 2 researchers, who subsequently cross-checked their work. The detailed search strategy is shown in Supplemental Digital Content (Supporting Files 1, http://links.lww.com/MD/I91, 2, http://links.lww.com/MD/I92, and 3, http://links.lww.com/MD/I93). The third author assisted in reaching a consensus for any disagreements between the 2 researchers. Because all data and analyses were based on previously published studies, neither patient consent nor ethical approval was required for the present study.

2.2. Inclusion and exclusion criteria

Randomized controlled trials (RCTs) or observational studies that estimated the association between SAHE following ICH and mortality and worse functional outcomes were considered for detailed screening. Studies in which the patients were divided into 2 groups of SAHE present and SAHE absent after primary ICH and provided sufficient data related to deaths and worse functional outcomes for analysis were included. The exclusion criteria were as follows: studies that included patients with ICH attributed to trauma, hemorrhagic conversion of ischemic stroke, structural lesions, vascular malformations, and venous sinus thrombosis; studies that contained duplicate data on our outcomes of interest; studies that included animal experiments; studies presented as reviews, case reports, case series with <15 patients, comments, or letters; and studies that did not report outcomes of interest in the results.

2.3. Endpoints

Mortality was the main endpoint of interest. The secondary endpoint was a worse functional outcome, which was defined as a modified Rankin Scale (mRS)[10] score of 3 to 5. Each endpoint was classified as either a short-term endpoint (<1 month or on discharge) or a long-term endpoint (>1 month) according to the length of follow-up given in each study.

2.4. Data extraction

Two researchers independently reviewed the contents of the included studies and collected pertinent information, including the first author or study name, year of publication, country of origin, and the outcomes measured in each study. Data validation and disagreements were resolved by the third author.

2.5. Quality assessment

The quality of each included study was evaluated using the Newcastle–Ottawa Scale (NOS). A maximum of 9 stars can be assigned on this scale, with 4 stars assigned for the selection of participants and measurement of exposure, 2 stars for comparability, and 3 stars for the assessment of outcomes and adequacy of follow-up.[11] The study quality was assessed as low, moderate, and high according to the scores ranging from 0 to 3, 4 to 6, and 7 to 9, respectively.

2.6. Statistical analysis

To account for pooled results, crude odds ratio (cOR) and 95% confidence interval (CI) calculated from the meta-analysis of endpoint numbers in the study and control groups were used. If adjusted odds ratio (aOR) and 95% CI with adjusted potential confounding factors were mentioned in the included studies, we also assessed their pooled effect to confirm the robustness of the results. A P value of <.05 was considered statistically significant. The heterogeneity between the studies was quantitatively determined by the I^2 test. An I^2 value of > 50% indicates significant heterogeneity. Based on the obtained value of I^2, a fixed-effects model ($I^2 < 50\%$) or a random-effects model ($I^2 > 50\%$) was chosen based on the inherent differences between the included studies. Because only 3 studies were finally included in this meta-analysis, we did not perform publication bias analysis, sensitivity analysis, and meta-regression analysis. Stata software version 12.0 (StataCorp LLC, College Station, TX) with its METAN package was used to pool and analyze the results from the individual studies.

3. Results

3.1. Study selection and characteristics

The primary search for the initial review included 8474 studies (4624 in Embase 3326 in PubMed, and 5,24 in Chocrane library). We removed 2823 duplicate studies and further excluded 5635 unrelated studies by reading titles and abstracts. The 16 remaining studies were assessed by reading their full text, and of them, 13 studies were discarded because ten studies had no outcomes of interest and 3 papers were conference abstracts. Finally, 3 observational studies with 3368 patients were included in the meta-analysis (Fig. 1). The first study was a single-center study conducted in the United States.[7] The second study collected and analyzed unprocessed data from the INTERACT2 trial,[8] which was an international, multicenter, open, blinded endpoint RCT.[12] The third study was an Italian multicenter study.[13] Table 1 describes the fundamental characteristics of the individual trials.

3.2. Evaluation of literature quality

Based on the NOS quality assessment, the studies by Maas et al and Morotti et al received 7 stars each, and the study by Chen et al received 8 stars, which indicated that all 3 studies were high-quality studies (Table 2).

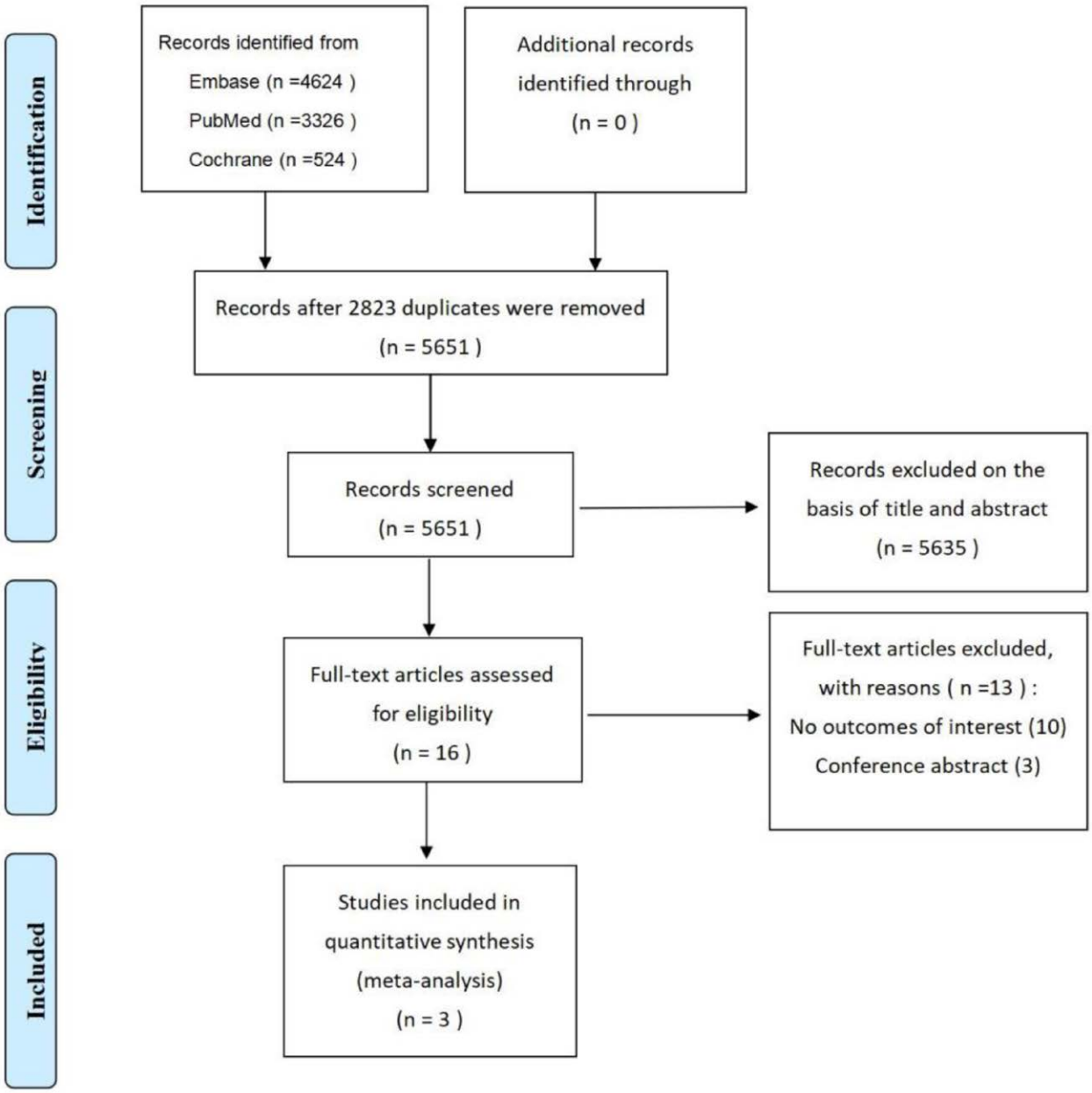

Figure 1. Flowchart of literature screening for the present systematic review and meta-analysis.

3.3. Main outcomes

Two studies provided information for the primary endpoint, including the number of deaths and survivals in the SAHE present group and the SAHE absent group as well as their aOR and 95% CI values in the short-term follow-up.[7,8] Pooled results showed that SAHE was not associated with mortality in patients with primary ICH (cOR: 0.51, 95% CI: 0.01–28.19). The I^2 test value was 99.0%, which demonstrated high heterogeneity (Fig. 2A). Similarly, no association was observed between SAHE and mortality after adjusting for potential confounding factors (aOR: 2.31, 95% CI: 0.72–7.45), with high heterogeneity (I^2 = 82.4%) (Fig. 2B). Two studies provided the number of deaths and survivals in each group,[8,13] and one of them also provided aOR and 95% CI values for long-term follow-up.[8] A pooled analysis revealed that SAHE was associated with a significantly increased mortality of patients with primary ICH (cOR: 3.00, 95% CI: 2.27–3.98) (Fig. 2C). Chen et al, however, demonstrated that SAHE was not associated with increased mortality after adjusting for potential confounding factors (aOR: 1.14, 95% CI: 0.71–1.83).[8]

For the secondary endpoint, 1 study did not assess the mRS score in the outcomes.[13] The study of Maas et al provided the mean value and its interquartile range of mRS, but not mRS of 3 to 5.[7] The study of Chen et al was the only study to provide information on major disability (mRS = 3–5), and this study suggested that SAHE following primary ICH was associated with an increased risk of major disability, but not after adjusting for baseline hematoma volume.

4. Discussion

4.1. Main findings

The findings of this meta-analysis indicate that there is currently no solid evidence that links SAHE with mortality. Our results

Table 1

Characteristics of the included studies.

			SAHE present			SAHE absent			Adjusted OR		
Study	Yr	Country	Total number	Short term death	Long term death	Total number	Short term death	Long term death	Short term	Long term	Adjustment for covariates
Maas et al	2013	United States	93	38	NR	141	13	NR	4.45 (1.88–10.53)	NR	ICH score
Chen et al	2014	Multinationals	192	51	54	2390	217	259	1.34 (0.83–2.17)	1.14 (0.71–1.83)	Age, region, lipid-lowering therapy, systolic blood pressure, glucose, hematoma location, intraventricular extension, randomized treatment and baseline hematoma volume
Morotti et al	2020	Italy	147	NR	36	405	NR	44	NR	NR	NR

ICH = intracerebral hemorrhage, NR = not reported, OR = odds ratio, SAHE = subarachnoid extension.

Table 2

Quality assessment of included studies by Newcastle-Ottawa scales.

	Selection					Outcome			
Study	Exposed cohort	Nonexposed cohort	Ascertainment of exposure	Outcome of interest	Comparability	Assessment of outcome	Length of follow-up	Adequacy of follow-up	Total score
Maas et al 2013	*	*	*	*	*	*	*	—	7
Chen et al 2014	*	*	*	*	**	*	*	—	8
Morotti et al 2020	*	*	*	*	*	*	*	—	7

Single asterisk indicates 1 score, double asterisk indicates 2 scores, and dash indicates 0 scores.

generally indicate that SAHE is not associated with mortality in patients with primary ICH, except for the pooled result of cOR in the long-term follow-up. There is also no evidence to show that SAHE affects functional outcomes in patients with primary ICH.

4.2. Possible mechanisms by which SAHE influences ICH

Both ICH and SAH are known for their high rate of mortality and disability.[1,2] If SAHE occurs after ICH, there is a possibility that SAHE might induce additional damage or worsen the clinical outcome of ICH patients through mechanisms similar to SAH.[7] Moreover, the damage caused by SAHE and ICH together may even exceed the outcomes of these 2 events occurring separately. Several potential pathways could account for the reason why SAHE affects ICH. First, SAHE of primary ICH is associated with fever and is an independent predictor of fever after ICH.[14] Fever can accelerate neuronal damage through increased metabolic demand and the resultant hyperemia, which can further aggravate excitotoxicity and inflammation and increase cerebral edema and intracranial pressure.[15–17] Second, SAHE is associated with early seizures in ICH patients on the basis of a biologically plausible hypothesis that subarachnoid blood is epileptogenic.[18] Seizures following ICH can lead to sudden blood pressure fluctuations, increased intracranial pressure, and neuronal injury due to increased metabolic demand and are independently associated with a worse outcome.[19–21] Third, SAHE, which could serve as a marker of vessel fragility and active bleeding in small vessels around the hemorrhage, is independently associated with HE, particularly in patients with a lobar hemorrhage.[13] HE is a common cause of clinical deterioration and correlates with a poor outcome.[3,4,22,23]

Therefore, it is conceivable that SAHE may affect the outcomes of patients with primary ICH through a similar damage process of SAH either directly or indirectly. Cerebral vasospasm is the leading contributor to delayed cerebral ischemia following SAH, which is regarded as the major preventable cause of a poor outcome.[24,25] Additionally, SAH-induced early brain injury may result in disruption of the blood-brain barrier, oxidative stress injury, cellular death, inflammatory response, microcirculation dysfunction, and mitochondrial disorder. These pathophysiological alterations may subsequently cause neurological injuries and a poor prognosis after SAH.[25] However, there is no evidence that SAHE causes vasospasm, and the precise pathophysiological mechanisms of SAHE are currently unclear. Additional studies are required to better understand the related biological pathways.

4.3. Other predictors of outcome after ICH

Several other predictors of the severity of neurological impairment after ICH deserve attention. The strongest outcome predictor is hematoma volume, which can increase intracranial pressure and cause a mass effect with distortion or shift of brain tissue (i.e., herniation) from 1 brain compartment into the surrounding compartment.[26] The location of the hemorrhage, such as infratentorial hemorrhage, thalamic hemorrhage, and lobar ICH, has also been demonstrated to be associated with an increased risk of mortality.[27] Intraventricular hemorrhage has also been consistently reported to be associated with a higher mortality rate, probably because of the risk of hydrocephalus and a severe increase in intracranial pressure.[27]

It is important to note that SAHE and other predictors after ICH may interact with each other or might be causally related. Other factors must be considered to confirm the precise association between SAHE and functional outcomes.

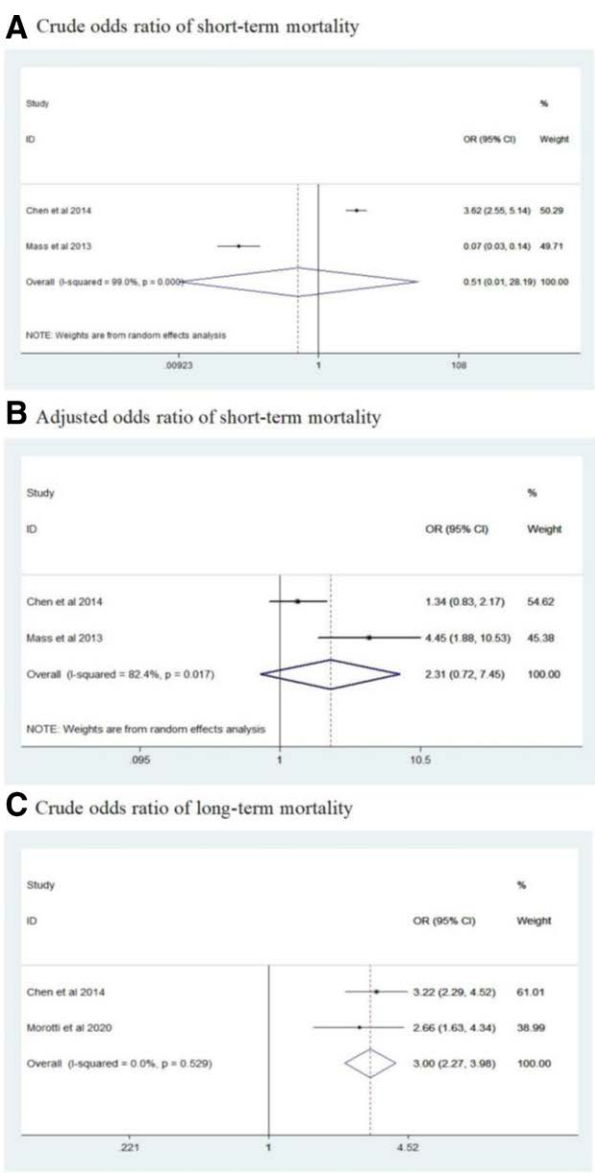

Figure 2. Forest plot of odds ratios for the association between SAHE following ICH and mortality. (A) Crude odds ratios of mortality in the short-term follow-up. (B) Adjusted odds ratios of mortality in the short-term follow-up. (C) Crude odds ratios of mortality in the long-term follow-up. ICH = intracerebral hemorrhage, SAHE = subarachnoid extension.

4.4. Implications and limitations

To the best of our knowledge, the present study is the first published meta-analysis that examined how SAHE and primary ICH are related to each other by analyzing cOR and aOR. Patients with SAHE should receive better medical care, including intensive monitoring and admission to a stroke unit or an intensive care unit, if they have a higher risk of mortality and worse functional outcomes. Future SAHE-targeting clinical studies and RCTs are required because of the small number of included studies and ambiguous results.

Our present study also has several limitations. First, because all the included studies were observational studies, there are several potential confounding variables such as the use of appropriate medical imaging equipment, the appropriate time to conduct imaging examination, the location of the hematoma of the ICH, and the use of antithrombotics. High heterogeneity in the pooled results may emerge from these variables. Additionally, the small number of included studies prevented us from conducting publication bias analysis, sensitivity analysis, and meta-regression analysis, which would have weakened the robustness of our findings. Last but not least, a cause-and-effect relationship between SAHE and poor outcomes was not established. SAHE may simply be an epiphenomenon of a large hematoma volume, which is possibly a determining factor of adverse outcomes. Therefore, further high-quality research studies are required to address the aforementioned limitations.

5. Conclusions

In summary, there is insufficient evidence to demonstrate the correlation between SAHE and mortality and worse functional outcomes in patients with primary ICH. Further studies are required to validate this correlation as the potential effect and mechanisms of SAHE are unclear.

Author contributions

Conceptualization: Tingzhi Liu, Jilin Mai, Peiying Qin.
Data curation: Tingzhi Liu, Jilin Mai, Weixiang Su, Kaichang Chen.
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Software: Ya Huang, Jing Han, Weixiang Su.
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Validation: Linlin Pang, Kaichang Chen, Peiying Qin.
Visualization: Linlin Pang, Kaichang Chen.
Writing – original draft: Tingzhi Liu.
Writing – review & editing: Linlin Pang.

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