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Original Article

Adverse Outcomes Associated with Frailty among Elderly Patients Undergoing Catheter Ablation for Atrial Fibrillation

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SUMMARY

Background: Frailty interferes both the management and the prognosis of atrial fibrillation (AF) in elderly patients. Catheter ablation (CA) is an important treatment for AF, but its safety for AF treatment among the elderly patients with frailty remains poorly studied. We thus aimed to investigate the prevalence of frailty among the elderly AF patients undergoing CA and to explore the association of frailty with adverse outcomes following CA.
Methods: A total of 1,134 elderly patients (aged ≥ 65 years) who underwent CA for AF in Guangdong Provincial People's Hospital from January 2015 to December 2019 were included. Subjects were divided into non-frail and frail groups according to the Canadian Study of Health and Aging Clinical Frailty Scale (CSHA-CFS) at admission. The in-hospital outcomes and their clinical data were analyzed.
Results: Frailty occurred in 19.3% of the included participants and the prevalence increased rapidly from 7.8% in 2015 to 34.0% in 2019. None of the patients had all-cause mortality in the hospital after CA. Compared with the non-frail group (n = 915), the frail group (n = 219) had significantly higher incidence of post-operative infection (5.5% vs. 1.9%, p = 0.002). Frailty was still significantly associated with an increased risk for post-operative infection in multivariate-adjusted regression analysis (OR = 2.72, 95% CI = 1.12–6.62, p = 0.027). There was no significantly statistical difference in other outcomes including procedure-related complications and length of stay.
Conclusions: Among the elderly patients with AF, frailty was associated with a higher rate of post-operative infection following CA treatment. However, frailty did not confer a higher mortality risk or more major complications.

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia in the elderly and is associated with increased mortality and disability, which seriously affect the quality of life among the elderly.[1] Frailty, as a common geriatric syndrome, is an age-related condition characterized by reduced physiological reserve, increased risk of disability, loss of resistance and greater vulnerability to adverse events, which thus is closely related to a variety of adverse clinical outcomes in the elderly.[2]

The relationship between AF and frailty is complicated. Their prevalence increases with age and they often occur simultaneously.[3] Frailty affects both the management and the prognosis of AF in the elderly. It can reflect more accurately the chronic health conditions and medical needs of the elderly than age, and can predict the prognosis of diseases or even death.[4] Frailty evaluation plays an important role in the diagnosis and treatment of diseases in elderly patients, which at present, is widely used in the preoperative evaluation of the elderly.[5,6] Catheter ablation (CA) is an important treatment for AF. However, the evidence of the impact of frailty on adverse outcomes following CA in elderly patients with AF is still scarce. The purpose of this study was thus to investigate the prevalence of frailty in elderly patients who underwent AF ablation, and to explore the association between frailty and adverse outcomes of AF ablation in elderly patients, so as to better guide the clinical treatment of AF for the elderly.

2. Materials and methods

2.1. Study design and subjects

The older patients (who aged 65 years and older) with AF catheter ablation performed between January 2015 and December 2019 were enrolled in this study. AF was diagnosed according to electrocardiogram or ambulatory electrocardiography. The exclusion criteria were as follows: 1) Moderate or severe mitral stenosis or mechanical valve; 2) CA for AF was not performed for the first time; 3) Surgical ablation; 4) Prior or current left atrial appendage occluder implantation; 5) Prior or preoperative pacemaker/ICD implantation; 6) Previous complex ablation due to congenital heart disease or ventricular tachycardia; or 7) Dementia. The study participants were divided into non-frail and frail groups. The in-hospital outcomes and

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clinical data of patients were analyzed. The study was approved by the Ethics Committee of Guangdong Provincial People's Hospital, with a waiver of informed consent due to retrospective study design.

2.2. Data collection and measurements

Clinical data including age, sex, medical history, laboratory and ancillary examination results were collected from electronic medical records by one researcher, and were randomly checked by another researcher. The estimated glomerular filtration rate (eGFR) was calculated using the equation pf Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).[7] Anemia was defined as hemoglobin concentration < 120 g/L for women, < 130 g/L for men, in accordance with the World Health Organization criteria for anemia.[8] The diagnosis of chronic heart failure (CHF) was based on 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, mainly based on the patient's clinical history, physical examination, electrocardiogram, N-terminal pro-B-type natriuretic peptide (NT-proBNP) and echocardiography.[9] Paroxysmal AF was defined as with spontaneous termination or with intervention within 7 days of onset, although episodes may recur with variable frequency. Persistent AF was defined as AF lasting > 7 days. Because of the sustained AF status of longstanding persistent AF and permanent AF defined in AF guidelines, the two patterns of AF were assigned to the persistent group in our study, using a simplified scheme from Levy et al.[10]

2.3. Frailty measurement

Frailty was evaluated at least 24 h before CA using the Canadian Study of Health and Aging Clinical Frailty Scale (CSHA-CFS).[11,12] The scale is simple and feasible, which is more suitable for clinical frailty screening. It is a seven-point scale with good predictive validity for mortality and prognostic power that relies on clinical judgment. Its predictive efficacy has been verified in previous studies.[11,12] Patients with values ≥ 5 were considered as frail group, while values ≤ 4 were regarded as non-frail group. All data were collected and evaluated by trained medical professionals based on the patient's previous hospitalization.

2.4. Ablation procedure

The preoperative preparation and postoperative management of CA were all carried out according to the guideline recommendations.[13] All procedures were performed under local anesthesia and modest sedation with fentanyl. Radiofrequency and cryoballoon ablation procedures were described detailly as previously described.[14,15] The endpoint of the ablation was bidirectional conduction block from the atrium to the pulmonary veins and vice versa. Super vena cava isolation, linear ablation of the left atrial roof or mitral isthmus, a cavotricuspid isthmus bidirectional block and complex segmented atrial electrogram were selected as additional ablation. Pharmacological (ibutilide or amiodarone) or electrical cardioversion were used to restore sinus rhythm if necessary.

2.5. In-hospital outcomes

The primary outcome was in-hospital death. Secondary outcomes included any complication related to the procedure itself or during the postprocedural hospitalization before discharge. Major complications[16] included at least one of the following: postprocedural hemorrhage requiring transfusion, cardiac drain or surgery, pulmonary embolism, stroke, transient ischemic attack (TIA), major cardiac events (acute myocardial infarction, cardiogenic shock, cardiac tamponade), acute kidney failure requiring dialysis, and sepsis. Minor complications included pericardial effusion that did not require pericardiocentesis or surgery, postoperative hemorrhage not requiring transfusion, acute kidney failure not requiring dialysis, postoperative infection without sepsis, etc.

2.6. Statistical analysis

Continuous variables were described using mean and standard deviation for normally distributed variables, and median with interquartile range for variables not normally distributed. Categorical variables were reported as counts and proportions. Independent Student's t-tests and Mann-Whitney U tests were used to compare continuous variables for normally and non-normally distributed data, respectively. The chi-square test was used to compare proportions between groups. Finally, multivariable logistic regression analysis was performed to analyze the relationship between frailty and surgical complications while controlling for the covariates that were significant in univariate analysis. All statistical analysis was performed using SPSS version 25.0. A value of $p < 0.05$ was considered significant.

3. Results

3.1. Baseline characteristics

A total of 1134 patients treated with AF ablation between 2015 and 2019 were included in this study, with an average age of 70.5 ± 4.5 years and 488 (43.0%) patients being female. In total, 219 (19.3%) patients were defined as frail with CSHA-CFS score ≥ 5, including 79 (7.0%) and 140 (12.3%) patients with CSHA-CFS scores of 5 and 6 (Figure 1). Table 1 shows baseline characteristics of patients according to frailty. Compared with non-frail group, frail group were significantly older [(72.1 ± 5.0) vs. (70.1 ± 4.3) years, $p < 0.05$], had significantly higher CHA_2DS_2-VASc score [(3.2 ± 1.4) vs. (2.7 ± 1.2) score, $p < 0.05$], HAS-BLED score [(1.9 ± 0.7) vs. (1.8 ± 0.7) score, $p < 0.05$] and plasma concentration of NT-proBNP [(916.3 ± 1792.2) vs. (468.3 ± 635.7) pg/mL, $p < 0.05$], and had lower serum potassium [(3.75 ± 0.32) vs. (3.80 ± 0.33) mmol/L, $p < 0.05$], hemoglobin concentration [(132.2 ± 15.5) vs. (135.4 ± 14.8) g/L, $p < 0.05$] and LVEF [(62.6 ± 7.2) vs. (64.6 ± 6.0)%, $p < 0.05$]. Moreover, frail patients had a higher

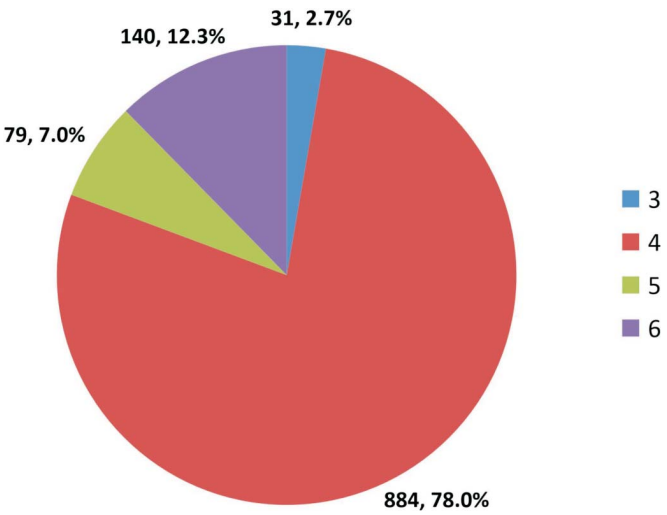

Figure 1. Distribution of the number of patients with CSHA-CFS.

prevalence of comorbidities such as anemia, coronary artery disease (CAD), chronic heart failure (CHF), valvular heart disease, stroke or transient ischemic attack (TIA). Paroxysmal AF was the main type of AF in both groups. Compared with the non-frail group, the frail group had lower proportion of paroxysmal AF (77.2% vs. 84.4%, $p < 0.05$) (Table 1).

3.2. Trend in prevalence of frailty

From 2015 to 2019, the number of elderly patients with frailty undergoing CA for AF for the first time increased rapidly (Figure 2). The incidence of frailty increased dramatically from 7.8% in 2015 to 34.0% in 2019 (Figure 3).

3.3. Adverse outcomes associated with frailty

Table 2 and Table 3 present the results for adverse outcomes according to frailty status among elderly AF patients undergoing CA. Results showed that in terms of the primary outcome, none of the patients died after the AF ablation during index admission (Table 3).

With regard to the secondary outcomes, there were no significant differences in overall, major and minor complications between frail and non-frail group (all $p > 0.05$) (Table 2). According to Table 3, taken each complication into consideration, we found that compared

Table 1
Baseline characteristics of patients according to frailty.

Characteristics	Frail group (N = 219)	Non-frail group (N = 915)	p-value
Age (years), mean ± SD	72.1 ± 5.0	70.1 ± 4.3	< 0.001
Gender, n (%)			0.971
Female	94 (42.9)	394 (43.1)	
Male	125 (57.1)	521 (56.9)	
BMI (kg/m^2), mean ± SD	24.0 ± 3.5	24.1 ± 3.0	0.904
eGFR (ml/min/1.73 m^2), mean ± SD	78.4 ± 21.1	79.4 ± 20.5	0.490
HbA_1c(%), mean ± SD	6.2 ± 0.8	6.1 ± 0.9	0.177
Serum potassium (mmol/L), mean ± SD	3.75 ± 0.32	3.80 ± 0.33	0.037
Hb (g/l), mean ± SD	132.2 ± 15.5	135.4 ± 14.8	0.005
Anemia, n (%)	63 (28.8)	177 (19.3)	0.002
Thrombocytopenia, n (%)	3 (1.4)	9 (1.0)	0.904
NT-proBNP (pg/ml), mean ± SD	916.3 ± 1792.2	468.3 ± 635.7	0.001
LVEF (%), mean ± SD	62.6 ± 7.2	64.6 ± 6.0	< 0.001
CHA_2DS_2-VASc score, mean ± SD	3.2 ± 1.4	2.7 ± 1.2	< 0.001
HAS-BLED score, mean ± SD	1.9 ± 0.7	1.8 ± 0.7	0.049
Hypertension, n (%)	127 (58.0)	522 (57.0)	0.800
Diabetes mellitus, n (%)	44 (20.1)	145 (15.8)	0.130
CAD, n (%)	46 (21.0)	125 (13.7)	0.006
CHF, n (%)	36 (16.4)	39 (4.3)	< 0.001
Valvular heart disease, n (%)	68 (31.1)	187 (20.4)	0.001
Stroke/TIA, n (%)	39 (17.8)	102 (11.1)	0.007
Peripheral vascular disease, n (%)	2 (0.9)	10 (1.1)	1.000
Hemorrhagic event, n (%)	8 (3.7)	18 (2.0)	0.134
Chronic lung disease, n (%)	13 (5.9)	32 (3.5)	0.097
Chronic kidney disease, n (%)	3 (1.4)	11 (1.2)	1.000
Type of AF, n (%)			0.011
Paroxysmal AF	169 (77.2)	772 (84.4)	
Persistent AF	50 (22.8)	143 (15.6)	
Type of produce, n(%)			0.779
Radiofrequency ablation	202 (92.2)	849 (92.8)	
Cryoballoon ablation	17 (7.8)	66 (7.2)	
Procedure time (min), mean ± SD	128.1 ± 44.5	130.9 ± 39.1	0.357

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; CHF, chronic heart failure; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HbA1c, glycated hemoglobin A1c; LVEF, left ventricular ejection fraction; TIA, transient ischemic attack; SD, standard deviation.

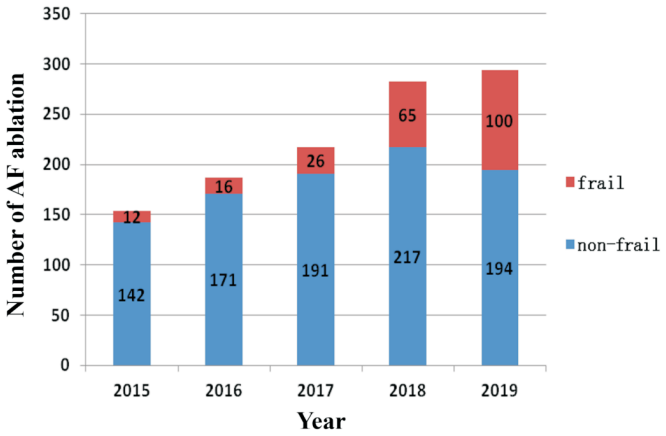

Figure 2. Distribution of frailty among patients undergoing CA for AF.

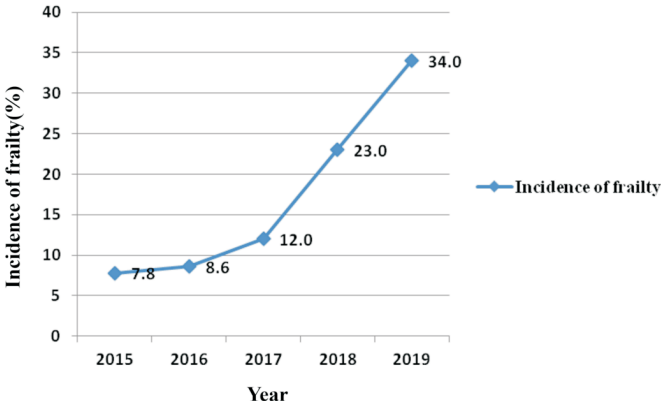

Figure 3. Incidence of frailty among patients undergoing CA for AF.

Table 2
In-hospital adverse outcomes for frail group versus non-frail group.

In-hospital outcomes	Frail group (N = 219)	Non-frail group (N = 915)	p-value
All complications	23 (10.5)	74 (8.1)	0.251
Minor complications	16 (7.3)	56 (6.1)	0.518
Major complications	7 (3.2)	18 (2.0)	0.288

Note: Data are expressed as absolute numbers (%).

with the non-frail group, the incidence of post-operative infection in the frail group was significantly higher (5.5% vs. 1.9%, $p < 0.05$). The main infection was the respiratory infection, accounting for 50% of all infections. There was no difference in other procedural complications and length of stay between two groups (all $p > 0.05$).

The results of multivariable logistic regression examining the association between frailty and post-operative infection are displayed in Table 4. Logistic regression analysis revealed that frailty was still associated with post-operative infection (adjusted OR = 2.72; 95% CI = 1.12–6.62; p = 0.027) after adjusting for covariates including age, serum potassium, CHA2DS2-VASC score, HAS-BLED score, NT-proBNP, LVEF, anemia, CAD, CHF, stroke or TIA, valvular heart disease, and type of AF. Besides, age, serum potassium, NT-proBNP, anemia and CHF were also related to post-operative infection (all $p < 0.05$).

4. Discussion

In recent years, with the advancement of CA technology, the number of elderly patients with AF undergoing CA has gradually increased.[16] Yet the safety of CA in the elderly is still controversial,[17,18] which may be related to the different populations and research methods in various studies. Previous studies mostly focused on the relationship between age and the safety of CA. However, due to the large heterogeneity of elderly individuals, the individual health status of patients with same age may vary greatly, and the same operation may have different clinical outcomes. Therefore, an indicator that can better reflect the health status of elderly is urgently needed. Frailty, as a common geriatric syndrome, can better reflect the actual biological age of patients, which is closely related to a variety of adverse health events and is increasingly used to predict the prognosis of patients with heart disease[19,20] and for the preoperative evaluation of the elderly. Therefore, research on the safety of CA in frail and elderly patients with AF has important clinical significance. For the first time, the study retrospectively analyzed the relationship between frailty and the safety of CA, as well as clarified the occurrence of frailty in the elderly undergoing CA for AF.

Our study found that the incidence of frailty was 19.3% in 1134 elderly patients. Compared with previous studies,[21,22] the incidence of frailty in our study is much lower, which may be due to following reasons: 1) The study population is different: Objects of our research are the elderly population who have undergone CA for AF for the first time, whose physical conditions may be better; 2) Different methods of frailty assessment are employed: in previous studies, the incidence of frailty in patients with AF is highly varied depending on the measurement scale used, ranging from 4.4% to 75.4%.[2,23] Moreover, our study found for the first time that, the number and proportion of elderly patients with frailty undergoing CA for AF increased rapidly from 2015 to 2019. This reminds us that there will be a large number of elderly patients with AF and frailty undergoing CA in the future. It is an urgent issue to clarify the relationship between frailty and safety of CA for AF.

There were few studies investigating the impact of frailty on CA in elderly patients with AF. Harun Kundi et al.[24] demonstrated that frailty was independently associated with end-point events such as survival rate, length of stay, and early post-operative mortality after CA for AF. Edward P et al.[17] found that surgical complications related to CA were closely related to the above-mentioned end-point events. Thus, frailty may be related to in-hospital mortality, post-operative complications and length of stay after CA. Our study found that the in-hospital mortality rate of elderly patients with AF after CA was zero, which was similar to the findings of Voskoboinik A et al.[25] and Abdur RK et al.[26] based upon single academic centers with rich experience. However, our finding concerning mortality was unlike the results of Hosseini SM et al.,[27] which found that the in-hospital mortality rate of 190,398 cases of AF after CA was 0.24% from 2000 to 2013. The difference may be due to the following factors: 1) The subjects of our study had better health status after rigorous screening. 2) All the operations were performed by highly professional and well-trained electrophysiologists and nursing teams from Cardiovascular Research Center of Guangdong Provincial People's Hospital. Approximately 378 elderly patients undergone CA for AF in this

Table 3
List of procedure-related complications for frail group versus non-frail group.

List of procedure-related complications	Frail group (N = 219)	Non-frail group (N = 915)	p-value
Pericardial effusion			0.710
Minor effusion[a]	1 (0.5)	5 (0.5)	
Serious effusion[b]	3 (1.4)	7 (0.8)	
Post-procedural infection	12 (5.5)	17 (1.9)	0.002
Post-procedural stroke/TIA	1 (0.5)	3 (0.3)	1.000
Vascular access-related complications			0.350
Hematoma	2 (0.9)	11 (1.2)	
Arteriovenous fistula	1 (0.5)	5 (0.6)	
Pseudoaneurysm	1 (0.5)	3 (0.3)	
Minor bleeding	6 (2.7)	12 (1.3)	0.223
Phrenic nerve injury	0 (0)	2 (0.2)	1.000
Need for pacemaker			0.960
Temporary pacemaker	1 (0.5)	3 (0.3)	
Permanent pacemaker	2 (0.9)	8 (0.9)	
In-hospital death	0 (0)	0 (0)	-
Length of stay	6.8 ± 3.5	6.3 ± 4.0	0.138

Note: Data are expressed as absolute numbers (%).
Abbreviations: TIA, transient ischemic attack.
[a] Minor effusion: pericardial effusion not requiring cardiac drain or surgery.
[b] Serious effusion: pericardial effusion requiring cardiac drain or surgery.

Table 4
Results of multivariable logistic regression examining the association between frailty and postoperative infection.

	Odds ratio (95% CI)	p-value
Frailty	2.72 (1.12–6.62)	0.027
Age	1.08 (1.04–1.13)	< 0.001
Serum potassium	0.50 (0.29–0.84)	0.009
CHA_2DS_2-VASc score	1.16 (0.93–1.44)	0.199
HAS-BLED score	0.76 (0.53–1.09)	0.134
NT-proBNP	1.00 (1.00–1.00)	0.026
LVEF%	0.99 (0.96–1.02)	0.624
Anemia	1.53 (1.02–2.29)	0.041
CAD	1.28 (0.82–2.00)	0.278
History of CHF	2.22 (1.07–4.62)	0.033
History of stroke/TIA	1.55 (0.83–2.89)	0.172
Valvular heart disease	1.23 (0.81–1.85)	0.332
Persistent AF	1.19 (0.74–1.91)	0.479

Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; CHF, chronic heart failure; LVEF, left ventricular ejection fraction; TIA, transient ischemic attack.

center per year. 3) The research subjects were all from the Guangdong Provincial People's Hospital, which was a high-level tertiary A general hospital in China, with world-class medical equipments and experienced medical experts in various fields. The multi-disciplinary collaborative diagnosis and treatment model can be quickly started to ensure the safety of patients to the greatest extent when patients have serious complications related to surgery.

Regarding the effect of frailty on complications of CA for AF in our study, the incidence of post-operative infections (mainly respiratory) was higher in frail group compared with non-frail group. There was no significant difference between two groups in other minor and serious complications related to surgery, which was similar to the results of Jorge Romero et al.[16] Their study found that compared with patients under the age of 80, patients over the age of 80 had a higher incidence of minor complications such as pneumonia, but no statistical difference was observed in major complications between two groups. Edward et al.[17] partially confirmed this research on the other hand, which found that sepsis was an important cause of death during readmission within 30 days after CA for AF, especially in patients with comorbidities, and the potential cause of sepsis might be lung infection and urinary tract infection. This implies that CA is safe for frail elderly patients with AF in a cardiovascular treatment center with rich experience. However, we need to be alert to the post-operative infection, especially respiratory infection. In addition, our study indicated that age, serum potassium, NT-proBNP, anemia and CHF were all related to post-operative infection. Therefore, it would be necessary to correct hypokalemia, anemia and improve heart function actively before CA to reduce the incidence of post-operative infection. However, this study has an important limitation. Since this study is a retrospective study and subjects are not followed up, there is a lack of analysis on the early and long-term prognosis after discharge. Further studies are needed to explore this area.

In conclusion, among elderly patients undergoing CA for AF, the number and proportion of frail patients are increasing rapidly. Although CA may be safe for elderly patients with frailty, it is necessary to notice that the occurrence of post-operative infection is one adverse outcome significantly associated with frailty. Frailty may be an important target for further reducing complications of CA for AF in elderly patients. How to incorporate frailty assessment into the risk prediction model for CA in elderly patients with AF warrants further research.

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Conflicts of interest

We declare that there are no conflicts of interest relevant to this study.

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