# Aspartate Aminotransferase to Alanine Aminotransferase Ratio is Associated with Frailty and Mortality in Older Patients with Heart Failure

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## Abstract

Frailty is a common comorbidity associated with adverse events in patients with heart failure, and early recognition is key to improving its management. We hypothesized that the AST to ALT ratio (AAR) could be a marker of frailty in patients with heart failure. Data from FRAGILE-HF study were analyzed. A total of 1,327 patients aged ≥ 65 years with hospitalized heart failure were divided into three groups based on their AAR at discharge: low AAR (AAR < 1.16, n = 434); middle AAR (1.16 ≤ AAR < 1.70, n = 487); high AAR (AAR ≥ 1.70, n = 406). The primary endpoint was one-year mortality. The association between AAR and physical function were also assessed. High AAR was associated with lower short physical performance battery and shorter 6-minute walk distance, and these associations were independent of age and sex. Logistic regression analysis revealed that high AAR was an independent marker of physical frailty after adjustment for age and sex. During follow-up, all-cause death occurred in 161 patients. After adjusting for confounding factors, high AAR was associated with all-cause death (low AAR vs. high AAR, hazard ratio: 1.57, 95% confidence interval, 1.02–2.42; P = 0.040). In conclusion, AAR is a marker for frailty and prognostic of all-cause mortality in older patients with heart failure.

## Introduction

Frailty is a geriatric syndrome characterized by a declined functional reserve and increased vulnerability to stressors [1]. Frailty is common and is associated with worse clinical outcomes in patients with acute [2] and chronic heart failure [3 4]. Since frailty is reversible and patients can possibly return to a healthy state, early identification is essential. However, simple and readily available markers for frailty are yet to be found.

We previously demonstrated a significant association between high aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio (AAR) and low body mass index, malnutrition, and worse outcomes in patients with acute heart failure [5], which suggests high AAR as a marker of frail status in patients with heart failure. However, the direct association between AAR and physical frailty or exercise capacity has not been evaluated in older patients with heart failure. Therefore, we aimed to evaluate the association between AAR and physical frailty, exercise capacity, and prognosis in older patients with heart failure.

## Results

During our study period, 1,332 hospitalized heart failure patients aged ≥65 years were registered in the FRAGILE-HF study. Patients lacking AST or ALT values (n=5) were excluded; thus, a total of 1,327 patients (age: 80.2±7.8 years, 43% females) were enrolled in the analysis. Patients were divided into three groups according to the cut-off values of AAR: low AAR, AAR<1.16 (n=434); middle AAR, 1.16≤AAR<1.70 (n=487); and high AAR, AAR≥1.70 (n=406) (Fig. 1). The baseline characteristics are described in Table 1. Higher AAR was associated with older age, New York Heart Association class III/IV, prior history of heart failure, use of loop diuretics, female sex, lower body mass index, and higher left ventricular ejection

fraction. Laboratory data showed that patients with high AAR had higher brain natriuretic peptide (BNP) and lower albumin, AST, ALT, estimated glomerular filtration rate, and hemoglobin levels.

Regarding frailty and nutritional status, univariable and multivariable logistic analysis revealed that hand grip strength, 6-minute walk distance, the short physical performance battery (SPPB), and the geriatric nutritional risk index (GNRI) were significantly lower in patients with AAR≥1.70 compared to those with AAR<1.16 after adjustment for age and sex (Table 2). Univariate and multivariable logistic regression showed that AAR≥1.70 was significantly associated with physical frailty even after adjustment for age and sex (Table 3). We also checked the association between all these factors and AAR as a continuous variable on univariate/multivariable linear regression analysis, and found that these findings were not significantly changed (hand grip strength, t value −4.69, P<0.001; 6-minute walk distance, t value −2.04, P=0.041; SPPB, t value −1.70, P=0.089; GNRI, t value −4.36, P<0.001).

The data regarding 1-year mortality were collected for 97.5% of the 1,327 study patients, and all-cause death occurred in 161 (12.4%) patients. Kaplan-Meier curves showed that event-free rates were lower among patients with high AAR than those in the other two groups (Fig. 2, log-rank P<0.001). On the Cox proportional hazards analysis, patients with high AAR had significant higher risk for 1-year mortality than those with low AAR even after adjustment for the Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) risk score and log-transformed BNP (Table 4).

To test if this association was mainly driven by AST alone or ALT alone, we performed the same analysis by dividing the entire cohort into three groups stratified by the tertile of AST and ALT. With respect to ALT, a higher tertile group was associated with lower hand grip strength and higher GNRI, but not with SPPB and 6-minute walk distance after adjustment for age and sex (Supplementary Table 1). Likewise, higher tertile groups of AST were not associated with hand grip strength, 6-minute walk distance, SPPB, and GNRI (Supplementary Table 2). We compared the prognostic predictability of AST, ALT, and AAR using the area under the receiver operating characteristic curve (AUC) (AAR: AUC 0.60, 95% confidence interval [CI] 0.56–0.65; AST: AUC 0.51, 95% CI 0.46–0.56; ALT: AUC 0.56, 95% CI 0.51–0.61), and found that AAR exceeded AST and ALT in AUC (AAR vs. AST, P=0.014; AAR vs. ALT, P=0.017). Moreover, neither AST nor ALT was associated with 1-year mortality after adjustment for the MAGGIC risk score and log-transformed BNP (Supplementary Table 3).

# Discussion

In the current study evaluating patients hospitalized for heart failure, we demonstrated that: 1) high AAR was associated with physical frailty, malnutrition, and lower exercise capacity independent of age and sex, 2) high AAR was independently associated with greater 1-year mortality. Our study results imply that AAR can be a potential surrogate marker of frailty in patients with heart failure.

Physical frailty is known as a clinical syndrome composed of five physical conditions including weakness, slow gait speed, exhaustion, weight loss, and low physical activities [6], and progresses through

a vicious circle of decrease in muscle strength, metabolic rate, energy expenditure, and worsening nutritional status [7]. Thus, decreased physical activity and malnutrition are the important components of physical frailty. In the current study, we showed that high AAR was associated with low SPPB, short 6-minute walk distance, poor hand grip strength, and worse nutritional status. Although we demonstrated the association between high AAR and poor prognosis, the mechanism behind the association of AAR and physical function has not been well demonstrated. However, several possible mechanisms have been proposed for the association between high AAR and frailty. For instance, ALT plays an essential role in gluconeogenesis that breaks down muscle protein into amino acids, converting alanine to α-ketoglutarate to produce energy [8]. Moreover, a previous study on a diabetes mellitus cohort reported that low ALT was correlated with low hand grip strength [9]. Given these study results, it could be that ALT is the main driver of the association between higher AAR and frailty; however, as we clearly showed in our study results, AAR was more strongly associated with frailty, exercise capacity, and 1-year mortality independently of other covariates, than ALT alone. This may because the proportion of AST and ALT offsets the impact of liver dysfunction and makes AAR more specific to muscle capacity, which cannot be evaluated otherwise. AAR is thus a potential prognostic predictor independent of other covariates in patients with heart failure.

We also reconfirmed the association between AAR and malnutrition, which we have previously described in patients with acute heart failure [5]. Malnutrition often leads to the deficiency of pyridoxal-5'-phosphatase [10], which is the biologically active form of vitamin B6. ALT is more vulnerable to the deprivation of pyridoxal-5'-phosphatase than AST [11], which may explain the association between malnutrition and higher AAR. Indeed, in healthy populations aged ≥ 65 years, lower ALT was associated with lower vitamin B6 levels and physical frailty [12]. Reconfirmation of this association in the FRAGILE-HF cohort with predominantly older patients strengthens our hypothesis; however, it should be further investigated in future studies as GNRI is not a gold standard of nutritional status in patients with heart failure, and pyridoxal-5-phosphatase was not directly evaluated in this study.

In summary, our study results suggest that high AAR may reflect poor physical function and malnutrition, which are important components of the frailty cycle. This implies the possibility of AAR to serve as a marker for screening/monitoring of frailty and subsequent poor prognostic outcomes in older patients with heart failure. As both AST and ALT are readily available and are easily measurable biomarkers in daily clinical practice, early identification of those at a high-risk of frailty among older patients with heart failure may lead to early intervention, including nutritional intervention or exercise rehabilitation, and subsequently, a better prognosis. Muscle training and nutritional supplements may be effective for frail patients with heart failure. Aerobic endurance training and resistance training were associated with an improvement in exercise capacity and quality of life in patients with heart failure [13,14]. However, this hypothesis should be evaluated in large-scale randomized controlled trials in the future.

There are several limitations in the current study. First, we could not exclude those with a history of liver disease or heavy consumption of alcohol that can impact liver function tests and subsequently AAR and its association with the prognosis. Second, because laboratory data were obtained only at discharge,

serial changes in AAR were not available, and we could not analyze their clinical characteristics and prognostic implications. Third, as our current study did not include patients under hemodialysis and those aged < 65 years, whether our study results can be applicable to such patients should be tested in future studies. Last, our study included only Japanese patients, and our cohort (mean BMI, 21.4 ± 3.8 $kg/m^2$) was much smaller physically than a general Western cohort. Therefore, whether the results of our study can apply to Western population is fully unknown.

In conclusion, AAR, which is readily and inexpensively available, is strongly associated with frailty and poor prognosis in older patients with hospitalized heart failure.

## Methods

# Study design and patient population

This is a post-hoc analysis of the FRAGILE-HF cohort study, in which 1,332 hospitalized patients aged ≥65 years with decompensation of heart failure, who could ambulate at discharge, were included. The study design and main results have already been published elsewhere [15]. Briefly, the main objective of FRAGILE-HF was to evaluate the prevalence and prognostic impact of multi-frailty domains in older patients with heart failure who require hospitalization. The exclusion criteria were: (1) previous heart transplantation or left ventricular assist device implantation, (2) chronic peritoneal dialysis or hemodialysis, and (3) acute myocarditis. Patients with missing BNP or N-terminal-proBNP data, and patients with a BNP level <100 pg/mL or N-terminal-proBNP level <300 pg/mL at admission were also excluded as the diagnosis could be unclear in these cases. We enrolled patients with both heart failure with reduced and preserved ejection fraction. Fifteen hospitals in Japan enrolled patients from September 2016 to March 2018. Physical examination, echocardiography, blood samples, and drug history were obtained when patients were stable, prior to discharge. From the AST and ALT values obtained before discharge, patients were divided into three groups based on predetermined cut-off values of AAR as follows: low AAR, AAR<1.16; middle AAR, 1.16≤AAR<1.70; and high AAR, AAR≥1.70 [5].

All participants were notified regarding their participation in the present study and it was explained that they were free to opt out of participation at any time. Written, informed consent was obtained from each patient prior to enrolment. Our study complies with the Declaration of Helsinki and Japanese Ethical Guideline for Medical and Health Research involving Human Subjects. The study protocol was approved by the Sakakibara Heart Institution of Okayama Research Ethics Committee. Study information including objectives, inclusion and exclusion criteria, primary outcome, and the names of participating hospitals were published in the publicly available University Hospital Information Network (UMIN-CTR, unique identifier: UMIN000023929) before the first patient was enrolled.

# Assessment of physical frailty and physical function

Physical frailty was defined by the Fried phenotype model, which is the most widely applied model, and generally considered as the standard model for physical frailty [6]. According to Fried's model, the frailty phenotype consists of the following five elements: slowness (gait speed), weakness (hand grip strength), weight loss, exhaustion, and low physical activity [16].

We also evaluated SPPB and 6-minute walk distance, performed by experienced physical therapists and/or heart failure specialists. The SPPB consists of 3 physical performance tests to assess each frailty domain, including balance (static standing balance), gait speed test (4-meter walk time), and weakness (time to complete 5 repeated chair stands) [17]. Each test is scored from 0–4, for a total score of 0–12. For balance, the participants were asked to maintain their feet in side-by-side, semi-tandem, and tandem positions for 10 seconds each. For the gait speed assessment test, the participants' usual speed was timed during a 4-meter walk. For the chair stand test, participants were asked to stand up and sit down five times as quickly as possible. The 6-minute walk distance was assessed in an unobstructed hallway according to the guideline as follows [18]: patients were instructed to walk as fast as possible between two points positioned 30-meter apart and the distance walked in 6 min was recorded. Patients were allowed to use an assist device if needed.

# Assessment of nutritional status

GNRI[19] was used to evaluate the nutritional status of patients. The index was calculated as follows: 14.89 × serum albumin concentration (g/L) + 41.7 × (weight [kg]/ideal weight [kg]). Ideal weight was defined as: 22 × height ($m^2$).

# Outcomes

Prognosis of registered patients within 1 year of discharge was prospectively collected up to March 2019. Our primary outcome was all-cause death. After discharge, most patients were followed up in outpatient clinics at least every 3 months, and additionally on need-basis. For those without in-person follow-up scheduled in clinics, prognostic data were obtained from telephone interviews and medical records of other medical departments that cared for the patient or from the family.

# Statistical analysis

Normally distributed data are expressed as mean and standard deviation, and non-normally distributed data are reported as median with interquartile range. Categorical data are shown as numbers and percentages. Data were compared between groups using Student's t-tests or Mann-Whitney U tests for continuous variables and chi-squared or Fisher exact tests for categorical variables as appropriate. The associations between AAR and physical function and nutritional status were investigated using linear regression analysis. Association between physical frailty and AAR was evaluated with logistic regression

analysis. In both multivariable analyses, age and gender were used as adjustment variables. Regarding time-dependent survival analysis, event-free survival curves were constructed using the Kaplan-Meier survival method and compared with log-rank statistics. The AUC for 1-year mortality was used to evaluate the predictive value of AAR for 1-year mortality. As for the prognostic outcome of all-cause death, the MAGGIC risk score was calculated for each patient as previously described [20]. The discrimination and calibration of this risk score have been well validated in Japanese patients with heart failure [21]. As adding BNP level at discharge has been shown to be associated with improvement of discrimination with adequate calibration [21], we used the MAGGIC risk score and log-transformed BNP as an adjustment variable in a multivariable prognostic model for the outcome of all-cause death.

A two-tailed P value <0.05 was considered statistically significant. Statistical analyses were performed using R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria; ISBN 3-900051-07-0, URL http://www.R-project.org).

# Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request

## Declarations

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None.

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# Author contributions:

DM and YM contributed to the conception or design of the work. DM, NK, KJ, KS, KK, HS, YO, EM, MK, TK, KI, HW, MH, TD, TS, TK, HN, TO, KI, SY, NA, RY, KO, SM and YM contributed to the acquisition, analysis, or interpretation of data for the work. DM and YM drafted the manuscript. KJ and MK critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

# Competing interests:

Dr. Yuya Matsue and Takatoshi Kasai are affiliated with a department endowed by Philips Respironics, ResMed, Teijin Home Healthcare, and Fukuda Denshi, and Dr. Yuya Matsue received an honorarium from Otsuka Pharmaceutical Co., Ltd., and Novartis Japan. Dr. Kagiyama reports grants from Philips, Asahi KASEI Corporation, Toho Holdings Co., Ltd, and Inter Reha Co., Ltd. outside the submitted work. Dr. Kamiya has received research funding from Eiken Chemical Co. Ltd. Other authors have nothing to declare.

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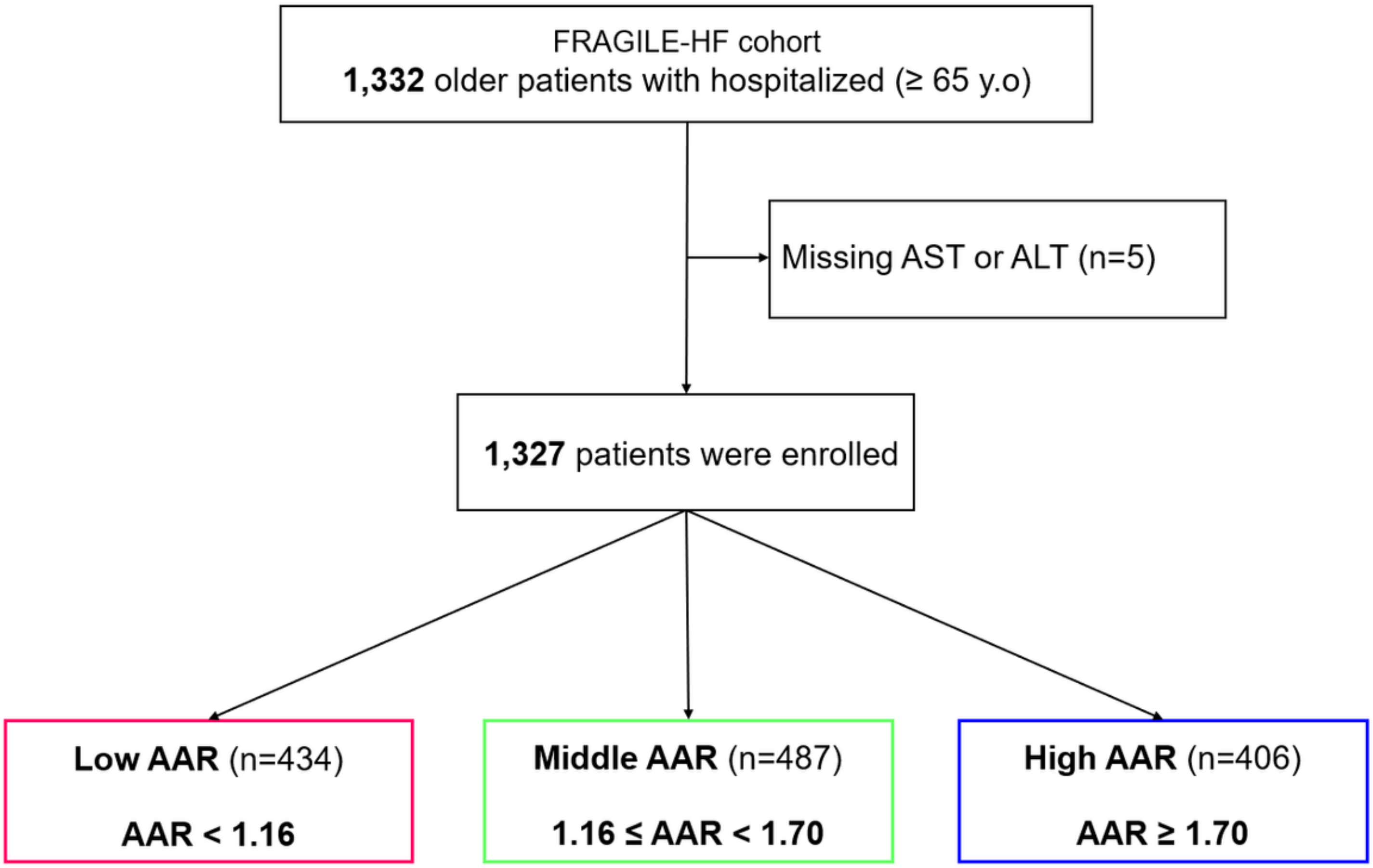
# Tables

Due to technical limitations, tables are only available as a download in the Supplemental Files section.

# Figures




## Figure 1

Study flowchart: Participants were divided into three groups based on their aspartate aminotransferase to alanine aminotransferase ratio. AAR, aspartate aminotransferase to alanine aminotransferase ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HF, heart failure

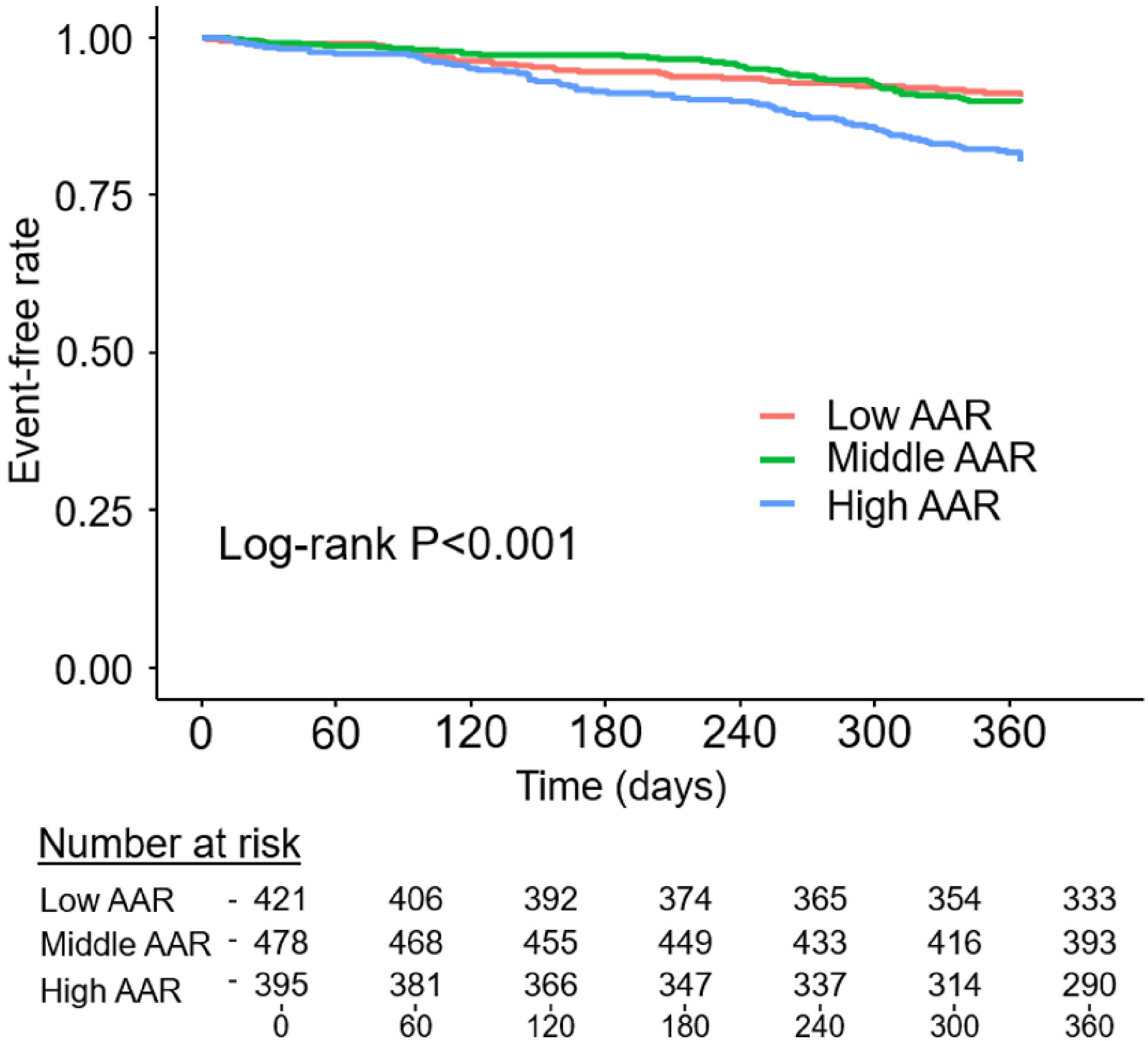



**Figure 2**

Kaplan–Meier curves of all-cause death stratified by aspartate aminotransferase to alanine aminotransferase ratio. AAR, aspartate aminotransferase to alanine aminotransferase ratio

## Supplementary Files

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