BMJ Open Prognostic impact of albumin-bilirubin score on the prediction of in-hospital mortality in patients with heart failure: a retrospective cohort study

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ABSTRACT

Objectives Liver dysfunction is prevalent in patients with heart failure (HF) and can lead to poor prognosis. The albumin-bilirubin (ALBI) score is considered as an effective and convenient scoring system for assessing liver function. We analysed the correlation between ALBI and in-hospital mortality in patients with HF.

Design A retrospective cohort study.

Setting and participants A total of 9749 patients with HF (from January 2013 to December 2018) was enrolled and retrospectively analysed.

Main outcome measures The main outcome is in-hospital mortality.

Results ALBI score was calculated using the formula (log₁₀ bilirubin [umol/L] * 0.66) + (albumin [g/L] * −0.085), and analysed as a continuous variable as well as according to three categories. Following adjustment for multivariate analysis, patients which occurred in-hospital death was remarkably elevated in tertile 3 group (ALBI >2.27) (OR 1.671, 95% CI 1.228 to 2.274; p<0.001), relative to the other two groups (tertile 1: ≤2.59; tertile 2: −2.59 to −2.27). Considering ALBI score as a continuous variable, the in-hospital mortality among patients with HF increased by 8.2% for every 0.1-point increase in ALBI score (OR 1.082; 95% CI 1.052 to 1.114; p<0.001). The ALBI score for predicting in-hospital mortality under C-statistic was 0.650 (95% CI 0.641 to 0.660, p<0.001) and the cut-off value of ALBI score was −2.32 with a specificity of 0.630 and a sensitivity of 0.632. Moreover, ALBI score can enhance the predictive potential of NT-pro-BNP (NT-pro-BNP + ALBI vs NT-pro-BNP: C-statistic: z=−1.990, p=0.0467; net reclassification improvement=−0.4012, p<0.001; integrated discrimination improvement=0.0082, p<0.001).

Conclusions In patients with HF, the ALBI score was an independent prognosticator of in-hospital mortality. The predictive significance of NT-proBNP + ALBI score was superior to NT-proBNP, and ALBI score can enhance the predictive potential of NT-proBNP.

INTRODUCTION

Patients with heart failure (HF) usually have a poor quality of life and dismal prognosis.¹² It is increasingly becoming clear that HF is not a single-organ disease.³⁵ Liver dysfunction is prevalent in HF patients and it is mainly caused by liver hypoperfusion and hepatic congestion.³⁶⁻⁸ Several studies have confirmed that liver dysfunction in HF patients with HF can worsen prognosis due to impairments in liver reserve function, possibly influencing the energy supply to heart.³⁶⁻¹¹ Previous studies mostly measured the single parameter, such as bilirubin, albumin, alanine aminotransferase and γ-glutamyltransferase etc to predict the HF prognosis.⁶¹²⁻¹⁴ However, single parameter can only present liver single function like inflammation, metabolism or synthesis, which can not reflect the liver reserve function comprehensively.¹⁵ In addition to conventional measures, a new approach, the albumin-bilirubin (ALBI) score, has been considered as an important strategy to examine liver reserve function.¹⁵¹⁶ Previous studies have confirmed that the ALBI score is related to
adverse events in patients with HF following discharge, but there are no similar studies assessing the relationship between the ALBI score and in-hospital events.\(^7\)

In our study, we inspected whether the ALBI score is a significant clinical factor to estimate in-hospital mortality in patients with HF. Moreover, we verified whether the ALBI score could enhance the prognostic significance of n-terminal brain natriuretic peptide (NT-pro-BNP) for patients with HF.

**METHODS**

**Study design and setting**

Our retrospective study population comprised 11,556 consecutive patients aged >18 years with HF as the main diagnosis on admission from ShengJing Hospital of China Medical University located in the northeastern part of China (from January 2013 to December 2018). HF was defined based on the modified Framingham criteria.\(^17\)

We used a uniform questionnaire to collect the clinical and the procedural data of all the subjects. We employed the formula \((\log_{10} \text{bilirubin (umol/L)} \times 0.66) + (\text{albumin (g/L)} \times −0.085)\) to calculate the ALBI score according to the serum albumin and total bilirubin levels at baseline.\(^16\)

We collected samples of the venous blood from all the subjects on admission and kept them in standard tubes. Serum albumin and total bilirubin were assayed using completely automated enhanced immunonephelometric assay on a Beckman AU 5800 analyzer (Beckman Coulter, USA). The standard ranges for baseline albumin and total bilirubin are 35–53 g/L and 3.4–20.5 umol/L, respectively. The primary endpoint was all-cause in-hospital mortality.

Exclusion criteria were (1) acute myocardial infarction (492 cases); (2) chronic alcoholism (113 cases); (3) chronic kidney failure with dialysis and/or diagnosed liver disease on admission (483 cases); (4) prior history of cardiac transplantation (5 cases); (5) no albumin, no total bilirubin, or no NT-pro-BNP data (714 cases). We finally enrolled 9,749 HF subjects into the study. The mean hospitalisation period was 9.8±5.7 days. Figure 1 exhibits the flow chart of selecting the patients. We clustered the subjects into three study groups as per the tertile of ALBI score on hospital admission (tertile 1: \(\leq 2.59 \) (n=3250); tertile 2: \(-2.59 \) to \(-2.27 \) (n=3250); tertile 3: \(\geq 2.27 \) (n=3249)). This study accedes to the Declaration of Helsinki.

**Patient and public involvement**

No patients or public were involved in this study.

**Statistical analysis**

Normally distributed quantitative variables were presented as mean±SD and compared using the Kruskal-Wallis H-test, whereas non-normally distributed quantitative variables were presented as median (IQR) and employed the Mann-Whitney U-test to compare them. Categorical variables are presented as counts and proportions (%) and compared with \(\chi^2\) test. When the number of variables was lower than 5, Fisher’s exact test was used to detect the differences. We performed the logistic univariate assessments to examine the prognosticators of in-hospital mortality (online supplemental appendices S1), and then all the variables were entered into the multivariate logistic regression model to uncover the independent prognosticators of in-hospital mortality. ALBI score was tested in the form of continuous variable and categorical variable. The output results were presented by as ORs with corresponding 95% CIs.

The prognostic potential of ALBI, NT-pro-BNP and NT-pro-BNP +ALBI was inspected using the discrimination indices as below: (1) A receiver operating characteristic curve and the area under the curve in connection with the in-hospital mortality were determined by MedCalc statistical software (V.18.1.1),\(^18\) (2) We got individual risk of in-hospital mortality by entering each model into a logistic regression model.
Table 1  Baseline characteristics of the population by tertile of ALBI, median (IQR), or N (%), or means±SD

| Variable                                | Overall (n=9749) | Tertile 1 ALBI ≤2.59 (n=3250) | Tertile 2 ALBI –2.59 to –2.27 (n=3250) | Tertile 3 ALBI ≥2.27 (n=3249) | P value |
|-----------------------------------------|-----------------|-------------------------------|-----------------------------------------|-------------------------------|---------|
| Age (years)                             | 69.1±13.6       | 67.9±12.8                     | 70.2±13.1                               | 69.4±14.6                     | <0.001  |
| Male (n (%))                            | 5158 (52.9)     | 1650 (50.8)                   | 1731 (53.3)                             | 1777 (54.7)                   | 0.006   |
| NYHA grading (n (%))                    |                 |                               |                                         |                               | <0.001  |
|   II                                    | 1954 (20.0)     | 988 (30.4)                    | 637 (19.6)                              | 329 (10.1)                    |         |
|   III                                   | 4207 (43.2)     | 1434 (44.1)                   | 1428 (43.9)                             | 1345 (41.4)                   |         |
|   IV                                    | 3588 (36.8)     | 828 (25.5)                    | 1185 (36.5)                             | 1575 (48.5)                   |         |
| Heart rate on admission, bpm            | 87.7±22.3       | 85.0±21.0                     | 87.6±22.4                               | 90.5±23.2                     | <0.001  |
| SBP on admission, mm Hg                 | 135.2±22.7      | 136.1±21.0                    | 135.9±22.7                              | 133.5±24.1                    | <0.001  |
| SGPT, U/L                               | 25.5±11.9       | 25.5±11.0                     | 25.2±11.9                               | 26.0±12.7                     | 0.046   |
| SGOT, U/L                               | 31 (26,35)      | 34 (23,34)                    | 31 (24,35)                              | 33 (28,37)                    | <0.001  |
| Albumin, g/L                            | 37.1±4.5        | 41.3±2.5                      | 37.4±2.0                                | 32.6±3.5                      | <0.001  |
| TBIL, umol/L                            | 16.2±12.1       | 12.7±6.8                      | 15.2±8.7                                | 20.6±16.9                     | <0.001  |
| LDL, mmol/L                             | 2.52±0.91       | 2.70±0.94                     | 2.52±0.85                               | 2.36±0.92                     | <0.001  |
| Creatinine, mg/dL                       | 1.07±0.51       | 1.01±0.45                     | 1.06±0.50                               | 1.16±0.56                     | <0.001  |
| Haemoglobin, g/L                        | 127.6±21.9      | 132.0±19.6                    | 128.1±21.0                              | 122.8±24.1                    | <0.001  |
| Serum Na, mmol/L                        | 138.9±3.9       | 139.5±3.3                     | 139.2±3.6                               | 137.9±4.5                     | <0.001  |
| FBG, mmol/L                             | 6.5±1.6         | 6.6±1.7                       | 6.5±1.4                                 | 6.4±1.6                       | <0.001  |
| cTNI, ng/mL                             | 0.04 (0.01, 0.28)| 0.03 (0.01, 0.15)             | 0.04 (0.01, 0.31)                       | 0.06 (0.02, 0.35)             | <0.001  |
| NT-pro-BNP, pg/mL                       | 2538 (986, 5850)| 1376 (570, 3284)              | 2492 (1066, 5419)                       | 5186 (1987, 9085)             | <0.001  |
| LVEF, %                                 | 48.7±11.3       | 50.4±11.0                     | 48.9±11.3                               | 46.9±11.3                     | <0.001  |
| comorbidities, n (%)                    |                 |                               |                                         |                               |         |
| CHD                                     | 6282 (64.4)     | 2184 (67.2)                   | 2129 (65.5)                             | 1969 (60.6)                   | <0.001  |
| Hypertension                            | 5948 (61.0)     | 2149 (63.8)                   | 2129 (63.4)                             | 1860 (55.8)                   | <0.001  |
| AF                                      | 3086 (31.7)     | 1091 (33.6)                   | 1094 (33.7)                             | 901 (27.7)                    | <0.001  |
| DM                                      | 3118 (32.0)     | 1070 (32.9)                   | 1023 (31.5)                             | 1025 (31.5)                   | 0.371   |
| Smoking (n (%))                         | 2664 (27.3)     | 919 (28.3)                    | 855 (26.3)                              | 890 (27.4)                    | 0.203   |
| In-hospital mortality                   | 343 (3.5)       | 67 (2.1)                      | 78 (2.4)                                | 198 (6.1)                     | <0.001  |

AF, atrial fibrillation; ALBI, albumin-bilirubin; CHD, coronary heart disease; cTNI, cardiac troponin I; DM, diabetes mellitus; FBG, fasting blood glucose; LDL, Low Density Lipoprotein; LVEF, left ventricular ejection fraction; NT-proBNP, n-terminal brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; Serum Na, serum sodium; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamate-pyruvate transaminase; TBIL, total bilirubin.
The Nagelkerke-R2, as well as the Hosmer-Lemeshow (HL) test from the regression model were employed as indices of goodness-of-fit of each risk model and to examine their calibration potential. We additionally computed the Brier scores of ALBI score, NT-pro-BNP and NT-pro-BNP +ALBI score. Lower Brier scores exhibited improved precision and (3) The absolute integrated discrimination improvement (IDI), as well as the category-free net reclassification improvement (NRI) were used to examine enhancements in risk estimation quantification of ALBI score and NT-pro-BNP +ALBI. All the statistical tests were two sided, and the statistical significance was marked by p<0.05. We employed the Statistical Analysis Software (SAS Institute) V.9.4 to conduct all the statistical analysis.

## RESULTS

### General characteristics

The flow chart of patient selection was shown in figure 1. We finally enrolled a study cohort of 9749 HF patients. The general characteristics were indicated in table 1. The tertile 3 group had higher proportions of male patients and New York Heart Association (NYHA) grade IV than the other two groups. Moreover, patients in the tertile 3 group tended to have increasingly high heart rate, serum glutamate-pyruvate transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), cTNI, total bilirubin, creatinine and NT-pro-BNP levels on admission. Systolic blood pressure, albumin, low density lipoprotein (LDL), fasting blood glucose (FBG), left ventricular ejection fraction (LVEF) in the tertile 3 group had a distinct diminishing pattern compared with the other groups. The proportion percentage of coronary heart disease (CHD), hypertension, atrial fibrillation (AF) and diabetes mellitus (DM) were markedly lower in the group of tertile 3. Moreover, the tertile 3 group depicted the inclination of an elevated in-hospital mortality (6.1% vs 2.1% and 2.4%, p<0.001) (table 1).

### Ability of ALBI score in prognosis estimation

Numerous variables significantly influenced in-hospital mortality as observed on the univariate analysis supplemented online supplemental appendix S1: These variables were as follows: ALBI score, age, NYHA grading, heart rate on admission, systolic blood pressure on admission, SGPT, SGOT, creatinine, haemoglobin, serum Na, FBG, cTNI, LVEF, CHD, hypertension, AF, DM, smoking. AF; atrial fibrillation; ALBI, albumin-bilirubin; CHD, coronary heart disease; cTNI, cardiac troponin I; DM, diabetes mellitus; FBG, fasting blood glucose; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamate-pyruvate transaminase.

### Table 2 Effects of multiple variables on clinical outcomes in univariate and multivariate analysis

|                          | Univariate analysis |                      |                      |          |                      |                      |          |
|--------------------------|--------------------|----------------------|----------------------|----------|----------------------|----------------------|----------|
|                          | OR 95% CI          | P value              | OR 95% CI           | P value  |
| NT-pro-BNP per 100 pg/mL increase | 1.007 1.006 to 1.008 | <0.001              | 1.082 1.052 to 1.114 | <0.001  |
| ALBI as a continuous variable |                    |                      |                      |          |
| ALBI, per 0.1 score increase | 1.135 1.108 to 1.163 | <0.001              | 1.082 1.052 to 1.114 | <0.001  |
| ALBI as a categories variable |                    |                      |                      |          |
| Tertile 1 Reference      |                    |                      |                      |          |
| Tertile 2                | 1.167 0.839 to 1.624 | 0.358               | 0.863 0.612 to 1.212 | 0.398    |
| Tertile 3                | 3.082 2.326 to 4.084 | <0.001              | 1.671 1.228 to 2.274 | 0.001    |

*Adjusted for age, sex, NYHA grading, heart rate on admission, SBP on admission, SGPT, SGOT, LDL, creatinine, haemoglobin, serum Na, FBG, cTNI, LVEF, CHD, hypertension, AF, DM, smoking. AF; atrial fibrillation; ALBI, albumin-bilirubin; CHD, coronary heart disease; cTNI, cardiac troponin I; DM, diabetes mellitus; FBG, fasting blood glucose; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SBP, systolic blood pressure; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamate-pyruvate transaminase.
of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) study posited that the low baseline albumin and increased bilirubin, were associated with clinical outcome. Moreover, the PROTECT study demonstrated that increased aspartate aminotransferase and alanine transaminase levels on day 3 of admission and decreased albumin levels on day 4 of admission are independent predictors of 180-day outcomes in patients with HF. More and more studies have realised that the reserve of liver function is not only a single parameter, but also other factors with joint variables exist, so at present, the joint scoring system is mostly used to judge the liver function reserve of patients, including Child-Pugh classification (CP), MELD score and ALBI score. CP has some disadvantages in that some of its parameters are subjective (ascites and encephalopathy), and inter-related indices (serum albumin and ascites), and it was not statistically established. MELD score system is an independent prediction index of adverse outcomes in patients with HF. Nevertheless, few studies on the ALBI score have been conducted. To the best of our knowledge, no study has explored the prediction value of the ALBI score for the in-hospital mortality in patients with HF. In our study, we elucidated that the ALBI score was correlated with in-hospital mortality for patients with HF. Considering the ALBI score as a continuous variable, we established that the risk of in-hospital mortality increased by 8.2% for each 0.1-point increase in ALBI (OR 1.082, 95% CI 1.052 to 1.114, p<0.001). As illustrated in table 2, ALBI score was still associated with in-hospital mortality when considered as a categorical variable (OR 1.671, 95% CI 1.228 to 2.274, p=0.001). Previous reports have verified that NT-pro-BNP is linked to adverse events in HF patients, whether in hospital or discharged. NT-pro-BNP is excreted by the kidney, and its circulating concentrations must be interpreted based on renal clearance. The patients with HF usually suffer from a renal dysfunction, which abnormally increases the concentrations of NT-pro-BNP, limiting its clinical utility. The ALBI score has no such restrictions, and the predictive value of ALBI score is not less than that NT-pro-BNP (C-statistic: z=0.0938, p=0.9253). Furthermore, the ALBI score can enhance the predictive significance of NT-pro-BNP (C-statistic: z=1.990, p=0.0467; IDI=0.0082, p<0.001; NRI=0.4012, p<0.001) (table 4).

**DISCUSSION**

This study analysed the correlation between ALBI score and in-hospital mortality in patients with HF. We found that: (1) the ALBI score is an independent prognosticator of in-hospital death; (2) the predictive significance of NT-pro-BNP +ALBI score is superior to NT-pro-BNP, and ALBI score can enhance the estimation potential of the initial NT-pro-BNP model in patients with HF.

Various studies have assessed the prognostic clinical significance of distinct liver function test (LFT) indices in patients with HF. Post hoc evaluation of the Efficacy

| Table 3 | NT-pro-BNP, NT-pro-BNP +ALBI and ALBI performance for the prognosis prediction |
|-----------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| Discrimination | Calibration | Precision |
| C-statistic | SE | P value | 95% CI | HL P value | R² | Brier score |
| NT-pro-BNP | 0.652 | 0.0157 | <0.001 | 0.642 to 0.661 | 0.007 | 0.033 | 0.0336 |
| NT-pro-BNP +ALBI | 0.681 | 0.0157 | <0.001 | 0.672 to 0.690 | <0.001 | 0.039 | 0.0334 |
| ALBI | 0.650 | 0.0162 | <0.001 | 0.641 to 0.660 | 0.012 | 0.038 | 0.0335 |

ALBI, albumin-bilirubin; HL, Hosmer-Lemeshow; NT-proBNP, n-terminal brain natriuretic peptide.
Although the detailed pathophysiological association between liver dysfunction and HF requires further assessments, there may be numerous mechanisms underlying this association. Severe congestive HF is related to two different kinds of liver conditions: acute hepatocellular necrosis that is caused by compromised blood supply as well as jaundice, which is correlated with the passive congestion. Compromised blood supply due to diminished cardiac output has a connection with acute hepatocellular necrosis with distinct escalations in serum aminotransferases. The passive hepatic congestion is associated with the elevated central venous pressure, resulting in increments in the levels of liver enzymes, as well as indirect and direct circulating bilirubin. Kato et al have studied the liver metabolism of HF in a rat model and established that congestive HF is linked to atypical metabolism in tissues adjacent to the heart. In the congestive HF rats, hepatic protein blood concentrations, including albumin, transferrin, retinol-binding protein and transthyretin were reduced and correlated with elevated levels of circulatory proinflammatory cytokines (tumor necrosis factor-α and interleukin-1β). Because the heart has poor capacity of energy storage, and it needs a continuous energy supply, all the above studies support the possibility that liver dysfunction may lead to impaired cardiac energy supply, which may lead to a poor prognosis.

Although cardiogenic liver dysfunction was conventionally considered the result of cardiogenic shock, there is evidence that this is not the unique responsible incident. Our study comprised patients with acute exacerbation of chronic HF, and these patients may have a process of chronic congestion. Under such conditions, hepatocytes compensated impaired blood flow by increasing oxygen extraction. However, when patients occurred acute exacerbation of chronic HF with inadequate liver perfusion, this compensatory mechanism is exhausted, leading to hepatocellular hypoxia and necrosis. Thus, the patients having chronic congestion or portal hypertension, may exhibit acute cardiogenic liver injury even after mild circulatory disturbances. As shown in table 1 in our study, inadequate liver perfusion is manifested in two main aspects, one is lower SBP, and the other is a significantly reduced LVEF. Several studies have illustrated the complex relationship between lipid metabolism and liver dysfunction, and most of these studies described a decrease of total cholesterol, high density lipoprotein (HDL) and LDL cholesterol and triglycerides in patients with advanced liver disease. Furthermore, cholesterol homeostasis was markedly disturbed in liver cirrhosis and total systemic cholesterol was negatively correlated with the Model of End-Stage Liver Disease (MELD) score. Our study showed similar results in table 1. This was mainly because genes involved in cholesterol biosynthesis declined in liver dysfunction, and were more strongly repressed in cirrhosis and hepatocellular carcinoma (HCC).

The ALBI score was initially created from Japanese HCC patients to estimate the extent of liver dysfunction. However, it has also been widely used in patients without HCC. It is worthy to note that one study has demonstrated that the ALBI score is related to liver function using the indocyanine green injection test. These results support that the ALBI score can reflect residual liver function reserve, even in patients without HCC.

Our findings have some clinical significance. First, observing ALBI in patients with HF may be significant in establishing HF patients with elevated risk of in-hospital adverse events. Moreover, the predictive value of the ALBI score was revealed to be the same as that of NT-pro-BNP. If the patient with HF has kidney dysfunction, where NT-pro-BNP has limited clinical utility, ALBI score becomes useful. Finally, consideration of both the cardiac function and liver dysfunction of patients may help clinicians more accurately determine in-hospital adverse event risk.

The current study has several limitations. First, it constituted a retrospective and observational design; therefore, possible confounders and selection bias were not absolutely adjusted. Accordingly, a larger scale multicentre validation study is warranted to confirm the relationship between ALBI score and in-hospital mortality in patients with HF. Second, despite excluding diagnosed liver diseases, liver dysfunction might have been happened by pre-existing liver fibrosis due to non-HF aetiologies in some cases and we did not examine all the LFTs individually, as some biosignatures were missing in our dataset. For example, in the Finland risk (FINRISK) study, moderate to high levels of serum γ-glutamyltransferase were significantly correlated with HF.

### Table 4: Comparisons of the predictive performance of NT-pro-BNP, NT-pro-BNP + ALBI and ALBI for the prognosis prediction

|                      | Z for C-statistic | P for C-statistic | NRI | P for NRI | IDI | P for IDI |
|----------------------|-------------------|------------------|-----|-----------|-----|-----------|
| ALBI vs NT-pro-BNP   | 0.0938            | 0.9253           | 0.0518 | 0.3461 | 0.0018 | 0.4204    |
| ALBI+NT-pro-BNP vs NT-pro-BNP | 1.990 | 0.0467 | 0.4012 | <0.001 | 0.0082 | <0.001    |
| ALBI+NT-pro-BNP vs ALBI | 4.362 | <0.001 | 0.4054 | <0.001 | 0.0063 | 0.0001    |

ALBI, albumin-bilirubin; IDI, integrated discrimination improvement; NRI, net reclassification improvement; NT-pro-BNP, n-terminal brain natriuretic peptide.
incidence in a cohort of 38,076 people.45 In addition, higher alkaline phosphatase was linked to a dismal prognosis in patients with AHF.46 Finally, ALBI score was only calculated by baseline blood testing at admission, lacking of dynamic monitoring process. Accordingly, further studies on the relationship between changes in ALBI score at discharge and long-term clinical outcomes in patients with HF are warranted.

CONCLUSION
In patients with HF, ALBI score was an independent prognosticator of in-hospital death. The predictive significance of NT-pro-BNP +ALBI was superior to NT-pro-BNP, and ALBI score can enhance the predictive potential of NT-pro-BNP.

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