Association of N-terminal pro-brain natriuretic peptide with contrast-induced acute kidney injury and long-term mortality in patients with heart failure and mid-range ejection fraction

An observation study

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Abstract

The potential value of N-terminal pro-brain natriuretic peptide (NT-proBNP) for contrast-induced acute kidney injury (CI-AKI) in patients with heart failure and mid-range ejection fraction (HFmrEF) is unclear. We investigated whether NT-proBNP is associated with CI-AKI and long-term mortality following elective cardiac catheterization in patients with HFmrEF.

A total of 174 consecutive patients with HFmrEF undergoing elective coronary angiography or intervention were enrolled. The primary endpoint was the development of CI-AKI, defined as an absolute increase in ≥0.3 mg/dL or ≥50% from baseline serum creatinine with 48 hours after contrast medium exposure. Receiver-operating characteristic curve analysis was conducted, and Youden index was used to determine the best cutoff NT-proBNP value. Multivariable logistic regression and Cox proportional hazards regression analyses were performed to identify the independent risk factors for CI-AKI and long-term mortality, respectively.

The incidence of CI-AKI was 12.1%. Patients with CI-AKI had higher NT-proBNP values than those without [4373 (1561.9–7470.5) vs 1303 (2482.3–2482.3), P = 0.003]. Receiver-operating characteristic curve revealed that NT-proBNP was not significantly different from the Mehran risk score in predicting CI-AKI (area under the curve [AUC] = 0.723 vs 0.767, P = 0.516). The best cutoff NT-proBNP value for CI-AKI was 3299 pg/mL, with 70.6% sensitivity and 83.1% specificity. Multivariable analysis demonstrated that NT-proBNP ≥3299 pg/mL is significantly related to CI-AKI (odds ratio = 12.79; 95% confidence interval, 3.18–51.49; P < 0.001). Cox regression analysis showed that NT-proBNP ≥3299 pg/mL is associated with long-term mortality (adjusted hazard ratio = 11.91; 95% CI, 2.16–65.70; P = 0.004) during follow-up.

In patients with HFmrEF, NT-proBNP ≥3299 pg/mL is associated with CI-AKI and long-term mortality following elective coronary angiography or intervention.

Abbreviations: AUC = area under the curve, CI-AKI = contrast-induced acute kidney injury, CKD = chronic kidney disease, CM = contrast medium, eGFR = estimated glomerular filtration rate, HF = heart failure, HFmrEF = heart failure and mid-range ejection fraction, LVEF = left ventricular ejection fraction, NT-proBNP = N-terminal pro-brain natriuretic peptide, NYHA = New York Heart Association, PCI = percutaneous coronary intervention, SCR = serum creatinine.
1. Introduction

Contrast-induced acute kidney injury (CI-AKI) is a common and serious complication of coronary angiography and percutaneous coronary intervention (PCI), which significantly prolongs hospitalization and increases the risk of cardiovascular events and long-term mortality. However, as effective treatment for CI-AKI is lacking, risk identification is essential to ensuring that high-risk patients receive appropriate prophylactic measures.

The Mehran risk score is a classical risk assessment model for CI-AKI. However, of its 8 variables, those reflecting cardiac function (hypotension, use of intraaortic balloon pump, and New York Heart Association NYHA class III/IV heart failure [HF]) do not discriminate between more moderate degrees of cardiac dysfunction such as NYHA class II or relatively normal left ventricular ejection fraction (LVEF), both of which are common in clinical practice. The 2016 European Society of Cardiology guideline for HF highlighted that more attention should be paid to the patients with heart failure and mid-range ejection fraction (HFrEF; LVEF 40%–49%), whose cumulative prevalence ranges from 10% to 20% and in whom the incidence of acute kidney injury is higher than in HF with severely reduced ejection fraction. Serum creatinine (SCr) level has poor predictive accuracy and is a relatively late marker for renal injury; thus, identification of an early and simple biomarker for CI-AKI risk is essential, particularly for patients with HFrEF.

N-terminal pro-brain natriuretic peptide (NT-proBNP) is a biomarker of cardiac and renal function. Previous studies and our group’s analysis have demonstrated its predictive value for CI-AKI in patients with unselected cardiac function undergoing PCI. However, its potential value for CI-AKI and long-term mortality in patients with HFrEF remains unclear. Therefore, this analysis aimed to identify the association of NT-proBNP with CI-AKI and long-term mortality in patients with HFrEF undergoing elective coronary angiography or intervention.

2. Methods

2.1. Ethics statement

This study was performed according to the Declaration of Helsinki and the ethics committee of Guangdong General Hospital approved the study protocol. Written informed consent was obtained from the patients involved in the study.

2.2. Study population

This prospective observational analysis is a substudy of Predictive Value of Contrast Volume to Creatinine Clearance Ratio (PRECOMIN, ClinicalTrials.gov Identifier: NCT01400295) and a previous study, which was conducted at Guangdong General Hospital in April 2009 to December 2013. Based on the protocol, patients aged more than 18 years old with LVEF 40% to 49%, NYHA class II–IV, and undergoing elective coronary angiography or intervention were enrolled. Patients who were receiving peritoneal or hemodialysis treatment, with severe heart disease or malignancy, underwent cardiovascular surgery, and pregnant were excluded. Moreover, patients who received treatment for nephrotoxicity (eg, glucocorticoids, aminoglycosides) or nephroprotective drugs (eg, N-acetylcysteine) and were exposed to contrast medium (CM) within the perioperative period were excluded.

2.3. Laboratory data collection

NT-proBNP was measured using chemoluminescence immunoassay (Roche Diagnostics, Germany) before the procedure. The detection range was from 3 to 35,000 pg/mL. SCr levels were measured at admission, 24 and 48 hours after contrast administration. The estimated glomerular filtration rate (eGFR) was calculated according to the Modification of Diet in Renal Disease equation. Other biochemical indicators, such as hemoglobin (Hb) A1c, lipid profile, and Hb level, were measured in the morning prior to the procedure. In addition, LVEF was measured by echocardiography examination.

2.4. Cardiac catheterization

Cardiac catheterization was performed according to the standard clinical practice, employing the standard technique, by experienced interventional cardiologists. PCI was performed for patients with significant anatomic (≥50% left main or ≥75% nonleft main coronary artery disease) or physiological coronary artery stenosis (fractional flow reserve ≤0.80). The type of stents was selected according to the interventional cardiologists and the culprit vessels. Nonionic, low-osmolality CM was used for all patients. Patients were hydrated with normal saline 2 to 12 hours preoperatively and 6 to 12 hours postoperatively. Medical therapy for secondary prevention of coronary heart disease was administered according to the patients’ condition.

2.5. End points and follow-up

The primary end-point of this study was the development of CI-AKI, defined as an absolute increase of ≥0.3 mg/dL or ≥50% from baseline SCr level within 48 hours after CM exposure. Additional end-points included all-cause mortality, renal replacement therapy, nonfatal myocardial infarction, revascularization and stroke during in-hospital, and the all-cause mortality during the follow-up. The patients included in this study were followed up by telephone or office visits at 1, 6, 12, and 24 months after discharge. Adverse events were recorded on the case report form.

2.6. Statistical analysis

All statistical analyses were performed with SPSS software version 22.0 (SPSS Inc, Chicago, IL). Continuous variables were described as mean ± standard deviation or median (interquartile range), and analyzed using Student t test or Wilcoxon rank-sum test. Categorical variables were described as absolute values and percentages, and analyzed by the χ2 test or Fisher exact test. NT-proBNP values were transformed into logarithms since the distribution is skewed. Receiver-operating characteristic curve analysis was conducted, and Youden index was used to determine the best cutoff NT-proBNP value for predicting CI-AKI. The area under the curve (AUC) values between the NT-proBNP and Mehran score were compared by MedCalc statistical software (MedCalc Software, version 11.4, Mariakerke, Belgium). CI-AKI incidence in the higher and lower NT-proBNP values was compared with that in the best cutoff value.
Multivariable logistic regression and Cox proportional hazards regression analyses were performed to identify the independent risk factors for CI-AKI and long-term mortality, respectively. Kaplan–Meier method was used to describe the all-cause mortality by log-rank tests. A 2-tailed \( P < 0.05 \) was considered statistically significant.

### 3. Results

#### 3.1. Clinical characteristics and in-hospital events

A total of 174 patients with HfmrEF undergoing elective coronary angiography or intervention were included in the study (mean age 64.7±10.7 years, mean NT-proBNP 1448 [727.8, 3186.5] pg/mL, mean LVEF 44.2±3.0%, and mean eGFR 71.3±23.8 mL/min/1.73 m²), of which 21 patients (12.1%) developed CI-AKI.

The characteristics of patients are listed in Table 1. Compared with patients without CI-AKI, patients with CI-AKI had a lower baseline eGFR and LVEF, were more likely to have chronic kidney disease (CKD; eGFR < 60 mL/min/1.73 m²) and anemia, and had a higher HbA1c level. Furthermore, NT-proBNP and Mehran risk score were higher in patients with CI-AKI. However, demographics, medical history, feature of coronary artery, and perioperative medications were similar.

| Table 1: Baseline characteristic of patients with and without contrast-induced acute kidney injury. |
|----------------------------------|----------------------------------|----------------------------------|------------------|
| Variables                        | All (N=174)                      | CI-AKI (N=21)                    | Non-CI-AKI (N=153) |
| Demographics                     |                                 |                                 |                  |
| Age, years                       | 64.7±10.7                       | 67.6±9.9                        | 64.3±10.8        |
| Female, %                        | 32 (18.4%)                      | 4 (19.0%)                       | 28 (18.3%)       |
| Weight, kg                       | 64.5±10.8                       | 64.1±12.1                      | 64.5±10.7        |
| SBP, mmHg                        | 125.6±19.6                      | 131.0±16.8                     | 124.9±19.9       |
| DBP, mmHg                        | 74.9±13.3                       | 76.8±8.8                       | 74.7±13.8        |
| Medical history, n, %            |                                 |                                 |                  |
| Smoking                          | 75 (43.1%)                      | 10 (47.6%)                      | 65 (42.5%)       |
| Hypertension                     | 104 (59.8%)                     | 13 (61.9%)                      | 91 (59.5%)       |
| Diabetes                         | 43 (24.7%)                      | 5 (23.8%)                       | 38 (24.8%)       |
| Hyperlipidemia                   | 18 (10.3%)                      | 4 (19.0%)                       | 14 (9.2%)        |
| Laboratory index                 |                                 |                                 |                  |
| SCr µmol/L                       | 104.1±35.5                      | 127.6±51.2                     | 100.9±31.7       |
| eGFR mL/min/1.73 m²              | 71.3±23.8                       | 59.9±28.3                      | 72.8±22.8        |
| eGFR < 60 mL/min/1.73 m²         | 57 (62.6%)                      | 11 (91.7%)                      | 46 (58.2%)       |
| NT-proBNP, pg/mL                 | 1448.0 (727.8, 3186.5)          | 4373.0 (1561.9, 7470.5)        | 1303.0 (625.2, 2482.3) |
| lg-NT-proBNP, pg/mL              | 3.1±0.6                         | 3.5±0.6                         | 3.1±0.5          |
| LVEF, %                          | 44.2±3.0                        | 42.9±2.5                        | 44.4±3.1         |
| TG, mmol/L                       | 1.4±0.7                         | 1.4±0.8                         | 1.4±0.7          |
| CHO, mmol/L                      | 4.5±1.1                         | 5.0±1.3                         | 4.4±1.4          |
| HbA1c, %                         | 130.9±17.0                      | 123.0±16.5                      | 137.9±16.9       |
| Anemia, n, %                     | 74 (42.5%)                      | 15 (71.4%)                      | 59 (38.6%)       |
| Perioperative medications, n, %  |                                 |                                 |                  |
| ACEI/ARB                         | 152 (87.4%)                     | 18 (85.7%)                      | 134 (87.6%)      |
| β-blockers                       | 149 (85.6%)                     | 16 (76.2%)                      | 133 (86.9%)      |
| CCB                              | 25 (14.4%)                      | 4 (19.0%)                       | 21 (13.7%)       |
| Statins                          | 166 (95.4%)                     | 20 (95.2%)                      | 146 (95.4%)      |
| Diuretics                        | 67 (38.5%)                      | 12 (57.1%)                      | 55 (35.9%)       |
| Feature of coronary artery       |                                 |                                 |                  |
| Normal, %                        | 5 (2.9%)                        | 2 (0.5%)                        | 3 (2.0%)         |
| Single-vessel disease, %         | 33 (19.0%)                      | 3 (14.3%)                       | 30 (19.6%)       |
| Multivessel disease, %           | 136 (78.2%)                     | 16 (76.2%)                      | 120 (78.4%)      |
| Coronary lesion, n               | 2.5±1.1                         | 2.6±1.3                         | 2.5±1.0          |
| Number of stents, n              | 1.8±1.15                        | 1.8±1.33                        | 1.8±1.51         |
| Total length of stents, mm       | 44.7±40.6                       | 46.1±52.4                       | 44.5±30.0        |
| Procedural characteristics       |                                 |                                 |                  |
| CM volume, mL                    | 142.9±75.7                      | 125.0±89.6                      | 145.3±73.6       |
| Hydration volume, mL             | 871.6±467.6                     | 1083.0±506.1                   | 842.6±465.2      |
| Mehran risk score                | 7.9±5.1                         | 17.4±9.1                        | 13.6±8.5         |
| In-hospital complications, n, %  |                                 |                                 |                  |
| Mortality                        | 6 (3.5%)                        | 3 (14.3%)                       | 3 (2.0%)         |
| Intraaortic balloon pump         | 12 (6.9%)                       | 4 (19.0%)                       | 8 (5.2%)         |
| Renal replacement therapy        | 3 (1.7%)                        | 2 (0.5%)                        | 1 (0.7%)         |
| Stroke                           | 1 (0.6%)                        | 1 (4.8%)                        | 0 (0.0%)         |

ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, CCB = calcium channel blocker, CHO = cholest erol, CI-AKI = contrast-induced acute kidney injury, CM = contrast medium, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, HbA1c = hemoglobin A1c, HGB = hemoglobin, LVEF = left ventricular ejection fraction, NT-proBNP = N-terminal pro-brain natriuretic peptide, SBP = systolic blood pressure, SCr = serum creatinine, TG = triglyceride.
Moreover, patients with CI-AKI had a significantly higher rate of in-hospital mortality (14.3% vs 2.0%, \( P = 0.024 \)), requirement of intraaortic balloon pump (19.0% vs 5.2%, \( P = 0.041 \)), and renal replacement therapy (9.5% vs 0.7%, \( P = 0.039 \)) when compared with patients without CI-AKI (Table 1).

### 3.2. Association between NT-proBNP and CI-AKI

Receiver-operating characteristic analysis indicated that the AUC for CI-AKI was 0.723 (95% CI: 0.642–0.795). The Youden index indicated that the best cutoff value of NT-proBNP for CI-AKI was 3299 pg/mL (lg-NT-proBNP: 3.52 pg/mL), with 70.6% sensitivity and 83.1% specificity (Fig. 1). Furthermore, NT-proBNP was not significantly different from Mehran risk score (AUC = 0.723 vs 0.767, \( P = 0.516 \)).

Moreover, CI-AKI incidence was significantly higher in patients with NT-proBNP \( \geq 3299 \) pg/mL (36.4% vs 4.6%, \( P < 0.001 \)) (Fig. 2).

In a univariate logistic regression analysis, NT-proBNP \( \geq 3299 \) pg/mL was significantly associated with CI-AKI (odds ratio [OR] = 11.77, 95% CI, 3.75–36.95, \( P < 0.001 \)). Furthermore, LVEF and eGFR < 60 mL/min/1.73 m\(^2\) were found to be significant variables. Multivariate logistic regression results revealed that NT-proBNP \( \geq 3299 \) pg/mL was still related to CI-AKI (OR = 12.79, 95% CI, 3.18–51.49, \( P < 0.001 \)) after adjustment for potential confounding factors (Table 2).

### 3.3. NT-proBNP value for long-term mortality

During a mean follow-up of 21.4 months, 11 deaths were reported. Kaplan–Meier analysis indicated that higher NT-proBNP values were associated with higher mortality rate (cumulative all-cause mortality: 28.0% vs 4.3%, \( P < 0.001 \)) (Fig. 3). After adjusting for the confounders, including age > 75 years, diabetes, eGFR < 60 mL/min/1.73 m\(^2\), intraaortic balloon pump, anemia, LVEF, and multivessel diseases, multivariate Cox regression showed that NT-proBNP \( \geq 3299 \) pg/mL remains significantly associated with the long-term mortality (hazard ratio = 11.91, 95% CI, 2.16–65.70, \( P = 0.004 \)) (Table 3).

### 4. Discussion

To our knowledge, this is the 1st study to investigate the preoperative value of NT-proBNP, as a simple and useful biomarker, for CI-AKI and long-term mortality in patients with HFmrEF undergoing elective coronary angiography or intervention. Our data showed that in patients with HFmrEF, NT-proBNP \( \geq 3299 \) pg/mL was associated with the CI-AKI and long-term mortality following elective coronary angiography or intervention.

Heart failure with reduced ejection fraction (HFrEF; LVEF < 40%) is a known risk factor for CI-AKI[17]. In contrast, patients with HFmrEF may receive less attention than those with HFrEF, despite typically being older and thus more likely to have comorbid risk for CI-AKI, such as hypertension, diabetes,

![Figure 1. The ROC curve of NT-proBNP for CI-AKI. AUC = area under the curve, CI-AKI = contrast-induced acute kidney injury, NT-proBNP = N-terminal pro-brain natriuretic peptide, ROC = receiver operating characteristic.](image1)

![Figure 2. CI-AKI incidence based on the cutoff value of NT-proBNP. CI-AKI = contrast-induced acute kidney injury, NT-proBNP = N-terminal pro-brain natriuretic peptide.](image2)

**Table 2**

| Variable                        | Univariate | Multivariate |
|---------------------------------|------------|--------------|
|                                 | OR         | 95% CI       | \( P \)  | OR         | 95% CI       | \( P \)  |
| NT-proBNP \( \geq 3299 \) pg/mL | 11.77      | (3.75, 36.95) | <0.001 | 12.79      | (3.18, 51.49) | <0.001 |
| Age > 75 years                   | 1.46       | (0.49, 4.32) | 0.496  | 2.68       | (0.63, 11.36) | 0.180  |
| LVEF                             | 0.84       | (0.71, 0.99) | 0.043  | 0.67       | (0.50, 0.91)  | 0.011  |
| eGFR < 60 mL/min/1.73 m\(^2\)    | 2.56       | (1.02, 6.44) | 0.046  | 0.97       | (0.28, 3.69)  | 0.966  |
| Hypertension                     | 1.11       | (0.43, 2.83) | 0.832  | 1.01       | (0.28, 3.67)  | 0.967  |
| Diabetes mellitus                | 0.95       | (0.33, 2.76) | 0.919  | 3.14       | (0.72, 13.71) | 0.127  |
| CM dose > 100 mL                 | 0.43       | (0.17, 1.10) | 0.076  | 0.43       | (0.12, 1.48)  | 0.179  |

CI = confidence interval, CM = contrast medium, eGFR = estimated glomerular filtration rate, LVEF = left ventricular ejection fraction, NT-proBNP = N-terminal pro-brain natriuretic peptide, OR = odds ratio.

\( ^* \)lg-NT-proBNP \( \geq 3.52 \) pg/mL.
anemia, and renal insufficiency. Furthermore, recent studies indicate that the CI-AKI incidence in patients with LVEF ≥ 40% is 5.2% to 7.8%, ranging up to 12.0% in the subgroup with CKD. However, these studies included patients with unselected cardiac function and it is well established that the incidence of renal insufficiency and other adverse events is higher in patients with HF than in those without HF. In this study, the incidence of CI-AKI was 12.1% in all patients and 19.3% in patients with CKD, consistent with the higher risk associated with HFmrEF. Similar to previous studies, patients with CI-AKI had poor outcomes. Therefore, effective preprocedural identification of patients at high-risk of CI-AKI is vital.

NT-proBNP is a widely available and useful biomarker for triage and diagnosis of patients with dyspnea. This biomarker is associated not only with systolic and diastolic HF, but also with advanced age, CKD, anemia, and diabetes, all of which have been included in the Mehran risk score for CI-AKI. In this study, the NT-proBNP value and Mehran risk score were higher in patients with CI-AKI (P < 0.01). Furthermore, the predictive value of NT-proBNP was similar to that of Mehran risk score (P = 0.561). However, the Mehran risk score includes 8 variables; some of which are present only in a minority of critically unwell patients (use of IABP), or can only be determined postprocedure (CM volume). In contrast, NT-proBNP appears to be a promising simple and sensitive preoperative biomarker of CI-AKI risk in patients undergoing elective coronary angiography or interventions.

Our findings are consistent with previous work associating NT-proBNP with the development of CI-AKI. A substudy of HORIZONS-AMI including a total of 979 patients, found an independent predictive value of brain natriuretic peptide (BNP) for CI-AKI after PCI. Similarly, Moltrasio et al. and Akgul et al. also identified BNP level at admission as being associated with CI-AKI and its severity. Although BNP level correlates with NT-proBNP level, NT-proBNP levels are more stable and sensitive than BNP levels because of a longer half-life. A recent large prospective analysis by Goussot et al. further confirmed the value of NT-proBNP level for CI-AKI. However, all of these studies included patients with acute coronary syndrome, low LVEF, and non-HF. Therefore, the results cannot be extended to patients with HFmrEF undergoing elective procedures. In contrast, our present study is the 1st study to analyze the association between NT-proBNP and CI-AKI in this common patient group.

Few studies have examined the best NT-proBNP cutoff value for predicting CI-AKI. An observational study by Kurtul et al. including 436 patients with acute coronary syndrome demonstrated that preoperative NT-proBNP ≥ 2149 pg/mL was an independent predictor of CI-AKI after CM exposure. However, a total of 101(23.17%) patients with LVEF < 40% were included, and patients with NYHA class ≥ III were excluded in the analysis. Two more studies conducted by our group also indicated the best cutoff value of NT-proBNP for CI-AKI, however, the number of patients with HFmrEF was limited in these studies. Therefore, the present results are the useful supplements to this work.

The physiopathology of NT-proBNP and CI-AKI remains incompletely understood. Nevertheless, several mechanisms might be involved in the process. Pressure or volume overload and myocardial ischemia or infarction increase NT-proBNP level, which inhibits myocardial contractility, reduces cardiac output, and affects hemodynamics. Therefore, higher NT-proBNP level in HF patients may contribute to renal hypoperfusion and kidney injury. Renal hypoperfusion also triggers renin-angiotensin system and sympathetic nervous system activation, which plays a significant role in the development of CI-AKI. In contrast, NT-proBNP can oppose this neurohormonal activation through vasodilation, natriuresis, and diuresis. A high NT-proBNP level thus reflects adverse hemodynamic parameters, myocardial dysfunction, and activation of the neurohormonal system, all of which potentiate CI-AKI. It is likely that it is this position at the center of the cardiac-renal axis contributes to NT-proBNPs utility as a predictor of CI-AKI.

Finally, previous studies have indicated that the elevated NT-proBNP is strongly associated with poor long-term outcomes in patients with acute coronary syndrome and HF. Similarly,
our study demonstrated that NT-proBNP $\geq 3299$ pg/mL is associated with long-term mortality. Therefore, early identification of patients at high risk of CI-AKI and long-term mortality by NT-proBNP may assist in directing treatment and resource use where it will be of greatest benefit.

5. Limitations

We acknowledge several limitations of our study. First, this prospective observational study was conducted at a single center and included a relatively small number of patients with HHmREF. Second, the NT-proBNP level was measured in the clinical laboratory, with a detection range from 5 to 35,000 pg/mL. NT-proBNP level can also be measured by a point-of-care testing device, with a detection range from 60 to 9000 pg/mL. Therefore, the conclusions cannot be extended to point-of-care testing devices. Third, as the NT-proBNP level was not measured during the follow-up, we were unable to identify the association between temporal change in NT-proBNP and outcomes.

6. Conclusion

Our experience is consistent with other studies indicating that the elevated NT-proBNP, a simple and useful biomarker, is associated with the CI-AKI and long-term mortality in patients with HHmREF following elective coronary angiography or intervention. In this population, NT-proBNP $\geq 3299$ pg/mL was the best cut-off value, with 70.6% sensitivity and 83.1% specificity for CI-AKI, and was significantly associated with long-term mortality. The utility of NT-proBNP, both alone and in concert with CI-AKI risk models, warrants further evaluation in large-scale multicenter clinical trials.

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