

ORIGINAL**A novel Doppler echocardiographic index integrating left and right ventricular function is superior to conventional indices for predicting adverse outcome of acute myocardial infarction**Yamato Fukuda¹⁾, Takeshi Soeki²⁾, and Masataka Sata²⁾

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Abstract : The ratio of peak diastolic early velocity (E) of left ventricular (LV) inflow to peak diastolic longitudinal velocity (e') of the mitral annulus (E/e') is thought to reflect LV filling pressure, and tricuspid annulus velocity at systole (s'-T) is thought to reflect right ventricular function. However, it has not been reported on significance of the combined use of E/e' and (s'-T) to predict outcome of acute myocardial infarction (AMI). Over 21 months, beginning in January 2007, we enrolled 65 AMI patients who were measured hemodynamic and echocardiographic parameters by Swan-Ganz (SG) catheterization just after reperfusion therapy and echocardiography immediately after reperfusion therapy. Cardiac index (CI) and pulmonary capillary wedge pressure (PCWP) via SG catheter were measured, and routine echocardiographic indices, including E, e', E/e', and (s'-T) were determined. In addition, we defined the functional integrated bi-myocardial tissue Doppler (FIT) index as (s'-T) ÷ E/e'. The relationships between CI, PCWP, and echocardiographic indices were investigated, including FIT index. Moreover, we investigated whether FIT index could predict adverse cardiac events. FIT index was significantly associated with not only CI but also PCWP. In the Cox proportional hazards model, FIT index < 1.0 was a significant predictor for adverse outcome of AMI after adjustment for age, Killip class, history of previous coronary revascularization, location of culprit lesion, and LV ejection fraction. The novel index defined as (s'-T) ÷ E/e' could be quite useful predictor of prognosis in AMI. *J. Med. Invest.* 60 : 97-105, February, 2013

Keywords : echocardiography, tissue Doppler imaging, acute myocardial infarction, left ventricular filling pressure, right ventricular function

INTRODUCTION

The ratio of peak early diastolic velocity (E) of

Received for publication December 11, 2012 ; accepted January 7, 2013.

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left ventricular (LV) inflow to peak early diastolic longitudinal velocity (e') of the mitral annulus, E/e', is thought to reflect LV filling pressure ; tricuspid annulus velocity at systole, (s'-T), measured by pulse and tissue Doppler imaging, is thought to reflect right ventricular (RV) function (1-5). Both LV filling pressure and RV function should be evaluated in cases of acute myocardial infarction (AMI) (6). We have reported that the value (s'-T) ÷ E/e',

termed the FIT index, is an independent predictor of peak VO_2 in patients with cardiovascular diseases (7). However, there are no reports of combined use of E/e' and RV function for predicting outcomes in patients with AMI. Therefore our present study is the first report to evaluate combined use of LV and RV function for outcomes in AMI. Although, we have shown the usefulness of echocardiographic features immediately after reperfusion therapy for predicting the prognosis of patients with AMI (8), there are a few reports evaluating the echocardiographic features immediately after the onset of AMI. In addition, that report showed the usefulness of the combination of echocardiographic features of only LV (8).

We investigated the substantial meaning of combined use of E/e' and $(s'-T)$ in patients with AMI. In addition, we evaluated the significance of combined use of E/e' and $(s'-T)$ for predicting prognosis after AMI. It should be emphasized that we obtained all these values immediately after reperfusion therapy, and not only the echocardiographic features of LV but also those of RV.

MATERIALS AND METHODS

Patients

Seventy two consecutive patients with AMI, who were compatible with the following inclusion and exclusion criteria, were enrolled in this study. AMI was defined based on the following criteria: first, chest pain ≥ 30 minutes in duration, second, electrocardiographic ST segment elevation ≥ 0.1 mV in two or more leads in the same perfusion area, and third, subsequent elevation of creatine phosphokinase (CK) to more than twice the normal range. All 72 patients who were examined over a period of 21 months, beginning in January 2007, to investigate the relationship between hemodynamic parameters and echocardiographic indices. All 72 patients (39 men; mean age: 67 ± 15 years; range, 26-90 years) had undergone Swan-Ganz (SG) catheterization and echocardiography immediately after reperfusion therapy (emergency percutaneous coronary intervention [PCI]). All 72 patients underwent emergency PCI within 24 hours after the onset of AMI. Patients with congenital heart disease, atrial fibrillation, implanted pacemaker, unsuccessful reperfusion, intra-aortic balloon pump, percutaneous cardiopulmonary support, history of open-heart surgery, congestive heart failure more than 24 hours

after admission, or unsatisfactory echocardiographic imaging were excluded. Finally, 65 of 72 patients were followed up for 217 ± 104 days. Endpoints included all-cause death, in-hospital development of congestive heart failure, and readmission for congestive heart failure. These 65 patients were divided into 2 groups based on the occurrence of cardiac events: cardiac events occurred in the E group ($n=19$) but not in the N group ($n=46$).

The study was approved by the in-hospital Ethical Review Board. Written informed consent to participate was obtained from each patient.

Blood samples

We obtained venous samples at the time of admission, before PCI, for measurement of plasma brain natriuretic peptide (BNP) concentration. Plasma BNP concentration was measured using a commercially available specific radioimmunoassay for human BNP (Shiono RIA BNP assay kit; Shionogi Co., Ltd., Tokyo, Japan). Venous samples were obtained every 4 hours for measurement of serum CK, until CK level peaked. Maximum CK was defined as the maximum CK concentration during hospitalization.

Hemodynamic parameters

We performed SG catheterization just after PCI. As hemodynamic parameters, we measured CI and pulmonary capillary wedge pressure (PCWP) by SG catheter.

Echocardiography

We measured left atrial diameter (LAD), LV end-diastolic volume index (LVEDVI), LV end-systolic volume index (LVESVI), LV ejection fraction (LVEF), peak early and late diastolic velocity (E and A) of LV inflow, and the ratio of E to A (E/A) immediately after PCI as routine echocardiographic parameters. LAD was measured as the maximum dimension along the parasternal long-axis view from 2-dimensionally guided M-mode tracings. LVEDVI and LVESVI were obtained using the modified biplane Simpson's method from the apical 4- and 2-chamber views, normalized by body surface area, and LVEF was calculated with the following formula: $(LVEDVI-LVESVI)/LVEDVI \times 100$ (9). The LV inflow velocity curve was obtained in the apical long-axis view with the pulsed Doppler sample volume positioned at the tips of the mitral leaflets during diastole (10). In the present study, we measured the peak systolic, early diastolic, and end-diastolic

longitudinal velocities of the mitral annulus using pulsed Doppler tissue imaging by placing a sample volume at the lateral and septal portions of the mitral annulus. And the average values of lateral and septal mitral annulus velocity were defined as the s' , e' , and a' velocities. Similarly, we measured the peak systolic longitudinal velocity of the tricuspid annulus ($s'-T$) using pulsed Doppler tissue imaging by placing a sample volume at the tricuspid annulus, in the apical 4 chamber. E/e' was defined the value of E divided by e' . We also calculated functional integrated bi-myocardial tissue Doppler index (FIT index), defined as $(s'-T) \div E/e'$, according to a previous study (7). Echocardiography was performed within 30 minutes after PCI with a SIEMENS SEQUOIA 512 ultrasound instrument equipped with a sector transducer (with a carrier frequency of 2.5 MHz).

Relationship between hemodynamic parameters and echocardiographic indices

Hemodynamic parameters (CI and PCWP) just after PCI were measured. Echocardiographic indices immediately after PCI were also obtained, and the relationship between them was investigated.

Prediction of prognosis with echocardiographic indices

We compared patient characteristics, plasma BNP and maximum CK levels (obtained during hospital visit), hemodynamic parameters, and echocardiographic indices between the 2 groups with and without subsequent cardiac events. We investigated whether the echocardiographic indices, including FIT index, measured immediately after PCI could predict prognosis after AMI.

Statistical analysis

We adopted linear regression analysis to evaluate the relationship between echocardiographic indices and hemodynamic parameters (PCWP and CI).

Differences between the 2 groups were evaluated with unpaired t -test for continuous variables and with the chi-squared test for categorical variables. In addition, a Cox proportional hazards analysis was performed to evaluate the associations between cardiac events and various features. Receiver operating characteristic (ROC) curve analysis was conducted to analyze various cutoff values of E/e' and FIT index for predicting cardiac events and to determine optimal sensitivity and specificity. We used

previously reported values of LVEF and Killip class (11), and we used median values of maximum CK, BNP, and LAD for Cox proportional hazard analysis.

All values were expressed as means and standard deviations. Values of p less than 0.05 were accepted as statistically significant. Statistical analysis was performed with standard statistical software (StatView 5.0 and SPSS 2.0).

RESULTS

Reproducibility of FIT index measurements

When FIT index of 20 subjects were recorded twice by the same observer, the measurements were strongly correlated ($r=0.94$), with a mean percentage error of 2.4%.

Relationship between hemodynamic parameters and echocardiographic variables (Table 1)

The association with CI was stronger for ($s'-T$) ($r=0.48$, $p<0.001$) than for s' ($r=0.38$, $p<0.01$). Moreover, of all the parameters with statistically significant associations with CI, FIT index had the strongest positive correlation ($r=0.52$, $p<0.001$).

PCWP showed significant positive correlations with E ($r=0.33$, $p<0.05$), E/e' ($r=0.34$, $p<0.05$), and FIT index ($r=-0.25$, $p<0.05$). There were no significant associations between PCWP and other echocardiographic variables, except for the indices just mentioned.

Baseline clinical characteristics and hemodynamic parameters (Table 2)

Four patients died due to sudden cardiac death, and congestive heart failure occurred in 15 patients, during the follow-up period (mean : 217 ± 104 days). Forty-nine patients' severity of AMI showed Killip class I, the other patients showed Killip class \geq II. Of 65 patients, the culprit lesion was left anterior descending artery in 30 patients, and left circumflex coronary artery in 7 patients, and right coronary artery in 28 patients. Killip class, BNP level, creatinine level, estimated glomerular filtration rate (eGFR) (12), and PCWP were significantly higher in the E group compared to the N group. Age of the E group was greater (not statistically significant) than that of the N group. Heart rate, blood pressure, hemoglobin A1c, or maximum CK had no significant differences between groups.

Table 1. Simple linear regression analysis of associations between echocardiographic parameters and hemodynamic parameters

	Simple linear regression analysis			
	PCWP		CI	
	Correlation coefficient (R)	p value	Correlation coefficient (R)	p value
LAD	0.17	N.S	-0.01	N.S
LVEDVI	-0.13	N.S	0.17	N.S
LVESVI	-0.10	N.S	0.12	N.S
LVEF	0.11	N.S	-0.01	N.S
E	0.33	< 0.05	-0.06	N.S
A	-0.04	N.S	0.07	N.S
E/A	0.17	N.S	0.02	N.S
s'	-0.17	N.S	0.38	< 0.01
e'	-0.10	N.S	0.37	< 0.01
a'	-0.17	N.S	0.41	< 0.01
E/e'	0.34	< 0.05	-0.29	< 0.05
s'-T	-0.15	N.S	0.47	< 0.001
FIT index	-0.25	< 0.05	0.53	< 0.001

PCWP, pulmonary capillary wedge pressure ; CI, cardiac output index ; LAD, left atrial dimension ; LVEDVI, left ventricular end-diastolic volume index ; LVESVI, left ventricular end-systolic volume index ; LVEF, left ventricular ejection fraction ; E, peak early diastolic velocity of the left ventricular inflow ; A, peak late diastolic velocity of the left ventricular inflow ; E/A, the ratio of E to A ; s', peak systolic longitudinal velocity of the mitral annulus ; e', peak early diastolic longitudinal velocity of the mitral annulus ; a', peak late diastolic longitudinal velocity of the mitral annulus ; E/e', the ratio of E to e' ; s'-T, peak systolic longitudinal velocity of the tricuspid annulus ; FIT index, the ratio of s'-T to E/ e'.

Table 2. Clinical characteristics and hemodynamic parameters at baseline

	E group (n=19)	N group (n=46)	p value
Age, y	71 ± 13	66 ± 14	N.S
Sex ratio, male/female	12/7	25/21	N.S
Systolic BP, mmHg	131 ± 23	133 ± 24	N.S
Diastolic BP, mmHg	72 ± 16	71 ± 13	N.S
HR, bpm	78 ± 14	75 ± 15	N.S
Max CK, mg/dL	2598 ± 2007	2799 ± 2323	N.S
BNP, pg/mL	288 ± 254	123 ± 153	< 0.05
Cre, mg/dL	1.1 ± 0.4	0.8 ± 0.3	< 0.05
eGFR, mL · min ⁻¹ · 1.73 m ⁻²	54 ± 28	75 ± 22	< 0.05
HbA1c, %	6.1 ± 1.1	6.2 ± 1.7	N.S
LDL-cho, mg/dL	121 ± 31	123 ± 32	N.S
CI, L · min ⁻¹ · m ⁻²	3.1 ± 0.6	3.1 ± 0.8	N.S
PCWP, mmHg	17 ± 9	13 ± 5	< 0.05

BP, blood pressure ; HR, heart rate ; CK, creatine kinase ; BNP, brain natriuretic peptide ; Cre, creatinine ; eGFR, estimated glomerular filtration rate ; HbA1c, hemoglobin A1c ; LDL-cho, low-density lipoprotein cholesterol ; CI, cardiac output index ; PCWP, pulmonary capillary wedge pressure.

Echocardiographic parameters (Table 3)

LVEF, s', e', a', (s'-T), and FIT index were significantly lower in the E group compared with the N group. LVEDVI, LVESVI, and E/e' showed significantly higher value in the E group compared with the N group. The groups did not differ significantly with respect to any other parameters.

Prognosis determined by univariate and multivariate Cox proportional hazards analyses (Tables 4, 5)

In univariate Cox proportional hazards analysis, we attempted to determine the relationships between cardiac events and basal characteristics, blood-related parameters (BNP and maximum CK level), and echocardiographic variables (Table 4).

Table 3. Echocardiographic parameters

	E group (n=19)	N group (n=46)	p value
LAD, mm	38 ± 9	35 ± 6	N.S
LVEDVI, mL/m ²	57 ± 15	47 ± 9	< 0.01
LVESVI, mL/m ²	29 ± 11	21 ± 6	< 0.01
LVEF, %	50 ± 9	55 ± 7	< 0.01
E, cm/s	68 ± 18	59 ± 15	N.S
A, cm/s	79 ± 24	72 ± 22	N.S
E/A	0.9 ± 0.3	0.9 ± 0.4	N.S
s', cm/s	6.8 ± 1.7	8.0 ± 1.9	< 0.05
e', cm/s	5.5 ± 1.3	7.0 ± 2.1	< 0.01
a', cm/s	8.8 ± 2.4	10.3 ± 2.6	< 0.05
E/e'	12.8 ± 4.0	9.0 ± 2.8	< 0.001
s'-T	11.8 ± 4.3	14.7 ± 5.0	< 0.05
FIT index	1.0 ± 0.4	1.8 ± 0.9	< 0.001

LAD, left atrial dimension ; LVEDVI, left ventricular end-diastolic volume index ; LVESVI, left ventricular end-systolic volume index ; LVEF, left ventricular ejection fraction ; E, peak early diastolic velocity of the left ventricular inflow ; A, peak late diastolic velocity of the left ventricular inflow ; E/A, the ratio of E to A ; s', peak systolic longitudinal velocity of the mitral annulus ; e', peak early diastolic longitudinal velocity of the mitral annulus ; a', peak late diastolic longitudinal velocity of the mitral annulus ; E/e', the ratio of E to e' ; s'-T, peak systolic longitudinal velocity of the tricuspid annulus ; FIT index, the ratio of s'-T to E/ e'.

Table 4. Univariate Cox proportional hazards analysis for adverse events

Variables	Hazard Ratio	95% Confidence Interval	p value
Age, per-year increase	1.031	0.993-1.071	N.S
Killip class ≥ 2	16.813	6.196-45.621	< 0.01
Previous PCI	2.051	0.737-5.710	N.S
Left anterior descending artery (culprit lesion)	1.568	0.630-3.906	N.S
Right coronary artery (culprit lesion)	0.629	0.238-1.663	N.S
Max CK ≥ 2477 mg/dL	0.907	0.530-1.551	N.S
BNP ≥ 98 pg/mL	1.466	0.867-5.629	N.S
eGFR < 60 mL · min ⁻¹ · 1.73 m ²	6.506	2.531-16.725	< 0.01
LVEF < 40%	2.707	1.025-7.144	< 0.05
LAD ≥ 36 mm	1.081	0.650-1.796	N.S
E/e' ≥ 11.5	4.805	1.909-12.094	< 0.01
FIT index < 1.0	6.623	2.640-16.616	< 0.01

max CK, maximum creatine kinase ; BNP, brain natriuretic peptide ; eGFR, estimated glomerular filtration rate ; LVEF, left ventricular ejection fraction ; LAD, left atrial dimension ; E/e', the ratio of peak early diastolic longitudinal velocity of the left ventricular inflow to peak early diastolic longitudinal velocity of the mitral annulus ; FIT index, the ratio of peak systolic longitudinal velocity of the tricuspid annulus to E/e'.

Table 5. Multivariate Cox proportional hazards analysis for adverse events

Variables	Hazard Ratio	95% Confidence Interval	p value
Age, per-year increase	1.081	0.967-1.070	N.S
Killip class ≥ 2	14.674	4.701-45.802	< 0.01
Previous PCI	1.338	0.389-4.589	N.S
Left anterior descending artery (culprit lesion)	1.081	0.178-6.556	N.S
Right coronary artery (culprit lesion)	0.258	0.038-1.714	N.S
LVEF < 40%	3.743	0.964-14.527	0.06
LAD ≥ 36 mm	1.368	0.479-3.908	N.S
FIT index < 1.0	7.020	1.652-31.753	< 0.01

PCI, percutaneous coronary intervention ; LVEF, left ventricular ejection fraction ; LAD, left atrial dimension ; FIT index, the ratio of peak systolic longitudinal velocity of the tricuspid annulus to E/e'.

FIT index less than 1.0 proved to be a significant risk factor (hazard ratio : 6.623 ; 95% confidence interval : 2.64 to 16.62 ; $p < 0.05$). Furthermore, we could predict adverse outcomes significantly with Killip class, eGFR, LVEF, and E/e' .

Even when adjusted for age, Killip class, history of previous PCI, culprit vessels of AMI, LAD and LVEF, multivariate Cox proportional hazards analysis indicated that FIT index was an independent predictor of adverse outcomes (Table 5).

ROC curve analysis of FIT index

In ROC curve analysis (see figure), it was indicated that the optimal cutoff values for FIT index (1.0) and E/e' (11.5) had 90% and 71% sensitivity and 68% and 64% specificity for predicting cardiac events (area under the ROC curve [AUC]=0.753, 0.738, $p < 0.01$), respectively. The AUC and sensitivity of FIT index were greater than that of E/e' .

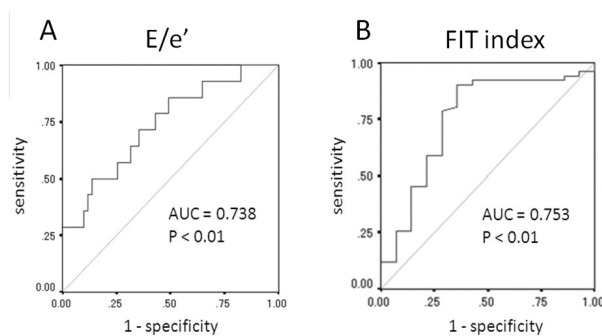


Figure 2 Receiver operating characteristic (ROC) curves for E/e' (panel A) and FIT index (panel B). The area under the ROC curve of E/e' and FIT index was 0.738 and 0.753, respectively. FIT index = $(s'-T) \div E/e'$

Abbreviations : E, peak early diastolic velocity of mitral inflow ; e' , peak early diastolic longitudinal velocity of the mitral annulus ; FIT index, functional integrated bi-myocardial tissue Doppler index

DISCUSSION

We found that FIT index, a novel echocardiographic index defined as $(s'-T) \div E/e'$, was superior to conventional indices, especially E/e' , for predicting cardiac events in AMI patients (13-15). Moreover, this study is particularly valuable because it addresses how to predict of AMI patients with echocardiographic data obtained immediately after emergency PCI.

FIT index could be thought of as a modification of E/e' by $(s'-T)$. A high E/e' value indicates high

LV filling pressure and LV disorder. On the other hand, a low indicates RV dysfunction, a rise in chronic LA pressure, and involvement of acute RVMI (5). Therefore, the FIT index could be a measure of not only general cardiac function that integrates LV diastolic hemodynamics and RV contractility, but also RV residual function against LV filling pressure (16). In the present study, FIT index had a significant association with both CI and PCWP. We reported elsewhere that FIT index had a significant association with peak VO_2 , which is a strong predictor in patients with cardiovascular diseases (7, 17). Moreover, Dokainish *et al* reported that patients with a low $(s'-T)$ value are likely to have worse prognosis, even if the E/e' value of those patients is low in the patients with heart failure (18). These may be because FIT index is a better index than the other echocardiographic features.

In clinical settings, early prediction of adverse outcomes after onset of AMI is quite important, because the patient's condition or hemodynamic parameters may change minute by minute, especially during the super-acute phase. Previous studies have shown that E/e' and other echocardiographic features are significant predictors of AMI (15, 19, 20). However, the echocardiographic data used in those studies were obtained within approximately 12 to 48 hours after admission, or at unknown time during hospitalization (15, 19, 20). However, our results revealed that LVEF, E/e' , and FIT index measured immediately after PCI predicted adverse outcomes. Consequently, the present findings will be very useful in clinical settings.

Hemmelgarn *et al* have found that renal function was an important predictor of adverse outcomes in various cardiac diseases (21, 22). Our present research showed renal dysfunction could predict adverse outcomes in AMI patients. This result is compatible with those previous reports.

Arakawa *et al* have reported that BNP level is a significant predictor of adverse outcomes in AMI patients (23, 24) ; however, the result in our present study was not compatible with those previous studies. The cause of discrepancy may be that the mechanism underlying the rise in BNP after AMI is complicated (25). Because we determined BNP levels at the time of admission, before PCI, these levels might therefore be lower than those reported in previous studies. FIT index might be superior to BNP in predicting adverse outcome at an earlier stage of AMI.

We have reported that a value subtracted scored

s' from scored E/e' could predict prognosis in AMI patients (8). However, in the present study, we evaluated FIT index in the different patients group from the previous study, i.e., we did not exclude the patients with congestive heart failure (Killip class II or more). Moreover, we adopted (s'-T), indicating RV contractility, in present study. In that previous study, RV function has not been evaluated, while it has evaluated s', indicating LV contractility. In present study, (s'-T) had a better correlation with CI than s' (Table 1). From the viewpoints of the different subjects and including RV function, FIT index could be better predictor than the value subtracted scored s' from scored E/e', that we have reported (8).

It is important that we can simply divide the sample into only 2 groups for the purpose of predicting prognosis when we detect the need for more active therapy. When the value of E/e' is in the "gray area" of 9-14, it can be difficult to estimate LV filling pressure or predict adverse outcomes in patients with cardiac diseases. However, FIT index may have greater sensitivity than E/e' for predicting adverse outcomes. The present study suggests that if FIT index just after AMI is < 1.0, closely monitoring the patient and administration of more active, preventive therapies should be needed.

Limitations

This study had several limitations. First, the influence of drugs, in especially β -blockers, hANP (26), or statins (27), was not evaluated. We administered nicorandil, renin-angiotensin system inhibitors, and statins to all patients enrolled. We also administered a β -blocker to patients who required it based on existing guidelines. However, in the future, the influence of these drugs on the relationship with FIT index should be clarified. The second limitation is the influence of the culprit lesion on the velocity of the tricuspid annulus. In the case of involvement of RVMI, values of both (s'-T) and E/e' could tend to be low, without marked LV disorder and increased LV filling pressure. As a result, FIT index reflects the relationship between LV filling pressure and RV function, regardless whether RVMI is involved or not. Moreover, we investigated FIT index adjusted to location of culprit lesion with the multivariate analysis to avoid that influence. Finally, there are few subjects in present study compared to the previous studies (13-16, 18, 19). In the future, large-size study between FIT index and the prognosis of AMI patients is needed.

CONCLUSIONS

The novel echocardiographic index, FIT index, defined as (s'-T) \div E/e' could be measured very simply and easily, even though the patient with AMI is in an intensive care unit immediately after reperfusion therapy. FIT index could be highly useful for predicting of outcomes in AMI patients.

CONFLICT OF INTEREST

There are no conflicts of interest related to this study.

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