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An Innovative Scoring System for Predicting Major Adverse Cardiac Events in Patients With Chest Pain Based on Machine Learning

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ABSTRACT Chest pain is a common complaint in the emergency department, but this may prevent a diagnosis of major adverse cardiac events, a composite of all-cause mortality associated with cardiovascular-related illnesses. To determine potential predictors of major adverse cardiac events in Taiwan, a pilot study was performed, involving the data from 268 patients with major adverse cardiac events, which was by an artificial neural network method. Nine biomarkers were selected for identifying non–ST-elevation myocardial infarction from common chest pain patients. By using a machine learning-based feature selection technique, five biomarkers were chosen from a set of 37 candidate variables. A full and a reduced risk stratification model were built. The full model was based on the characteristics of both invasive (i.e., creatinine and troponin I) and non-invasive (i.e., age, coronary artery disease risk factors, and corrected QT interval) variables, and the reduced model was based only on non-invasive variable characteristics. The full model showed a sensitivity of 0.948 and a specificity of 0.546 when the cutoff was set at 2 points, with a missed major adverse cardiac events rate of 1.32%, a positive predictive value of 0.228, and a negative predictive value of 0.987. High performance was also obtained with the five major biomarkers in the predictor built by the machine learning algorithm. The full model had the highest performance, but the reduced model can be applied as a quick and reasonably performing diagnostic tool.

INDEX TERMS Chest pain, emergency department, scoring system, major adverse cardiac events, ST-elevation myocardial infarction, non–ST-elevation myocardial infarction, risk stratification, machine learning.

I. INTRODUCTION

Major adverse cardiac events (MACE) is a composite of all-cause mortality associated with cardiovascular-related illnesses acute coronary syndrome (ACS), a type of MACE, is a syndrome that occurs after a sudden decrease in blood flow caused by an infarction or ischemia of a coronary artery or downstream cardiac tissues. Patients with ACS often have abrupt chest pain accompanied by shortness of breath, dizziness, nausea, or sweating [1]. As chest pain is a common complaint in the emergency department (ED), it may cloud the diagnosis of ACS or MACE. The characteristic electrocardiogram (ECG) is initially applied to quickly diagnose patients with chest pain in order to detect acute coronary obstruction. If an elevated ST signal is detected, ST-elevation myocardial infarction (STEMI) can be quickly detected and treated. However, numerous previous studies have identified patients with myocardial ischemia and subsequent

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cardiac injury without such an ST elevation [2]–[4]. In fact, approximately 70% of the 625,000 patients diagnosed with ACS annually have non–ST-elevation ACS, according to an American Heart Association report [5].

Based on its differential characteristics, ACS is divided into several subgroups: STEMI, non–ST-elevation myocardial infarction (NSTEMI), and unstable angina (UA). Despite the similarities between NSTEMI and UA, UA is characterized by coronary artery occlusion resulting in a reduction in blood flow not severe enough to produce cardiac injury [6]. Although ECG is a cost-effective and immediate test for the detection of STEMI [4], the existence of varying subgroups pose an unmet need for other approaches to accurately identify all ACS patients.

The first approach to distinguish ACS patients from all others with chest pain is to apply risk stratification for classification. Many elements including patient symptoms, physical exam results, findings of investigations, demographics, and risk factors can be applied to build a prediction model. Although some physicians do not use prediction models due to a lack of evidence of their superiority over pure clinical impression [7], prognostic and diagnostic prediction models can nonetheless better help EDs manage the resources. Several risk-scoring models have been developed to classify possible ACS. The three commonly used models for identifying potential ACS including NSTEMI are 1) thrombolysis in myocardial infarction (TIMI) [8]; 2) GRACE non-ST-elevation ACS [9]; and 3) HEART [10]–[14].

The variables considered in TIMI include medical history, demographics, ECG changes, and lab values. Seven factors were selected by using multivariate logistic regression [8]. In addition to the aforementioned variables, prior medical therapy is also included in the GRACE model by using the same regression method, for a total of eight variables [9]. The HEART score for predicting MACE was developed in 2008 based on clinical experience and the interpretation of medical literature [13]. In addition to ECG pattern, age, and risk factors for coronary artery disease (CAD), this model also incorporates patient history and troponin concentration, which were not included in the previous models. Troponin is a regulatory protein complex of troponin C, troponin I, and troponin T, found in skeletal and cardiac muscles. Troponin elevation has been suggested as a predictor of MACE [15], [16]. Troponins I and T have similar sensitivities, and both have been used as cardiac biomarkers [10], [14], [17]–[23].

The TIMI, GRACE, and HEART scoring systems have been validated for the prediction of MACE in an undifferentiated ED chest pain population [24]–[29]. Of the numerous studies comparing the performance of these models, many have suggested that the HEART scoring system has a higher sensitivity and greater negatives (negative predictive values) [10], [18], [21], [30]. However, these models all require lab values, such as creatinine or troponin, from invasive blood tests. It is still critically necessary to develop a faster, non-invasive diagnostic tool with high sensitivity that can predict and aid in preventing sudden ACS events in patients with chest pain in the ED. Machine learning (ML) is the study of algorithms that use statistical models to compute and predict outcomes without being restricted to explicit instructions. ML-derived algorithms are based on statistical analysis of input data, i.e., training data, to make predictions. Therefore, these algorithms can be dynamically exerted when new data are available.

Given the advances in ML, more and more studies have applied it to build risk stratification models in medicine to predict conditions including MACE, acute cardiac complications, and acute respiratory distress syndrome [31]–[35]. In a previous ML study for the perdition of MACE, an ensemble-based scoring system (ESS) was built based on physiologic heart rate variability (HRV), vital signs, and ECG changes in chest pain patients in the ED of Singapore General Hospital [34]. However, there has yet to be a machine-learning based scoring system for chest pain patients with potential MACE in Taiwan. Because of the dynamic characteristics in ML, there is a practical and critical need for a model to be specifically applied to individuals in Taiwan.

In this study, we developed a score as a predictor of MACE in patients presenting with chest pain in the ED through machine learning. A faster diagnostic model with fewer or only non-invasive variables is also being established.

II. METHODS

A. FEATURE SELECTION

The aim of feature extraction is to simplify the model and reduce training time overfitting. Feature or variable selection is method of data dimensionality reduction and is considered an important process in both statistical and ML modeling. To minimize the number of features in the model, we adopted ML-based feature selection techniques. Two estimated methods were used in this study, mutual information and recursive feature elimination. Mutual information measures the dependence between features and response variables (outcomes). More specifically, mutual information quantifies the amount of information obtained about one random variable through observations of the other random variable. We calculated the mutual information between MACE (outcome) and features one by one. The value of the mutual information ranges from 0 to 1. If the value is 0, the feature is independent of the response, while higher values mean higher dependency. Recursive elimination utilizes the importance scores based on the ML model and sorts the scores from largest to smallest. Then, the least important feature is pruned from the current set of features, and new scores are estimated again for the remaining features. This process is repeated until the number of remaining features is equal to the required number (set to 5 in this study).

B. PARTICIPANTS

The training data for the model were obtained from a cohort of 1175 patients with chest pain who presented to the ED

of Sanchong Hospital from December 2016 to June 2017, while the validation data were obtained from a cohort of 162 patients with chest pain who presented to the ED of Banqiao Hospital from March 2017 to June 2017. Sanchong Hospital and Banqiao Hospital are both regional hospitals of New Taipei City in Taiwan.

C. PATIENT INCLUSION AND ELIGIBILITY

All possible patients from the Internal Medicine departments of the above hospitals were considered for potential inclusion, and any patient with a primary diagnosis of STEMI, an age younger than 20 or incomplete data was excluded.

D. OUTCOME

The primary endpoint of this study was the occurrence of MACE, a composite outcome of death, acute myocardial infarction, unstable angina pectoris and revascularization, including coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI), within 90 days of presentation to the ED.

E. MACHINE LEARNING MODELS

In this study, the ML models included artificial neural network (ANN) [36]–[39], random forest (RF) and support vector machine (SVM), used to implement feature selection. Two regression models were also used for the feature selection: logistic regression (LR) and ridge regression (RR). The normal linear regression method can be used to train and predict response variables with continuous values. Unlike linear regression, LR transforms the response variable into a value >1, indicating a positive outcome, or ≤ 1, indicating a negative outcome, by logit transformation. While LR uses all the features to estimate the optimized weights of features that contribute to the responses, RR attempts to identify important features and sets the irrelevant features to zero. If the data set contains many irrelevant features, RR tends to have a higher performance than LR [40].

F. EXTRACTED FEATURES

Combining the 5 previously selected features and the top 5 features based on the ML models, we can identify 2 features, corrected QT interval (QTc) and Age, in common. Since CAD risk is an important factor, as described in the previous chapter, we finally included CAD risk in the later analysis to obtain a total of 3 features.

G. STATISTICAL ANALYSIS

All participants' characteristics and the between-individual comparisons of whether MACE occurred within 90 days of ED admission are presented as the means $\pm$ standard deviations or numbers (in percentage), and analyzed by t test and chi-squared test (or Fisher's exact test) for continuous and categorical variables, respectively. The composition of MACE was expressed as a percentage of the total study population. In order to identify potential risk factors for 90-day MACE, the derivation cohort was separated into two parts. First, we utilized the feature selection procedure to extract important features through the ML models. Second, univariate logistic regression was applied to assess whether the extracted features were risk factors for developing MACE within 90 days for the non-invasive variables, including basic characteristics, vital signs, and ECG variables. Among these, continuous variables, such as age, were categorized according to the definition generally recognized in epidemiology, and QTc was based on critical values commonly used in clinical settings as a cutoff. Significant variables ($p<0.01$) in univariate analysis were then entered into multivariate logistic regression to evaluate the risk of MACE. The final model had a score range between zero to two, based on the risk direction of each variable group. The same approach was used in the second part to confirm significant factors, though all variables in this study were submitted to univariate logistic regression. The final scores were determined by the standardized risk. All unstandardized coefficients of significant variables in the multivariate model were divided by the smallest coefficient and rounded to the nearest integer, which then became the points in the scoring model.

Model calibration for the two final models was assessed by Hosmer-Lemeshow goodness-of-fit test, and the performance of the model was assessed by using discriminatory values, such as the area under the receiver operating characteristic curve (AUROC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Validation was performed with the validation cohort according to the two risk score models obtained from the derivation model described above, and discriminatory values were used to evaluate model performance. All statistics were performed with SAS 9.4 software, and the feature selection procedure was implemented in WEKA ML Workbench. Unless specified otherwise, all P values < 0.05 were deemed statistically significant.

H. ETHICS APPROVAL

The study was approved by the Institutional Review Board in New Taipei City Hospital, with ERC NTPC No. 106001-E at trial sites in New Taipei City Hospitals.

III. RESULTS

After the exclusion of 237 patients with a primary diagnosis of STEMI and those younger than 20 years old, a final cohort of 938 patients were retained for further analysis. A total of 116 and 822 patients had chest pain with and without MACE, respectively (Table 1). The average age in this cohort was 52.2 years old, and the average age of the patients with MACE was 64.8 years old, approximately 14.3 years older than those without MACE (50.5 years old). Significantly more males were MACE patients (65.52% $>$ 34.48%, $p<0.0001$). This is consistent with a previous study on 763 patients in Singapore General Hospital [41]. More than half of the MACE patients had diabetes and hypertension, and merely half of the cohort had hyperlipidemia. Furthermore, the ECG variables PR, QRS, and QTc of the

TABLE 1. Baseline characteristics of chest pain patients in the study.

Characteristics	All patients (n=938)	No MACE (n=822)	MACE (n=116)	p value
Basic characteristics				
Age	52.2±19.4	50.5±19.5	64.8±13.5	<0.0001
Gender				
Male	419 (44.67)	350 (41.97)	76 (65.52)	
Female	518 (55.22)	484 (58.03)	40 (34.48)	
Diabetes	340 (36.25)	271 (32.97)	69(59.48)	<0.0001
Hypertension	455 (48.51)	379 (46.11)	76 (65.52)	<0.0001
Hyperlipidemia	225 (23.99)	171 (20.80)	54 (46.55)	<0.0001
Heart disease	236 (25.16)	186 (22.63)	50 (43.10)	<0.0001
Coronary artery disease risk factor				<0.0001
0	330 (35.18)	321 (39.05)	9 (7.76)	
1	221 (23.56)	198 (24.09)	23 (10.41)	
≥2	387 (41.26)	303 (36.86)	84 (72.41)	
ECG variables				
PR	157.8±25.3	157.0±24.8	163.3±28.1	0.0121
QRS	92.0±19.8	91.4±19.5	96.7±21.1	0.0066
QTc	438.5±43.0	434.0±42.0	470.2±36.9	<0.0001
Vital signs				
SBP	137.6±26.9	135.4±25.9	153.1±28.7	<0.0001
DBP	77.0±16.2	76.7±15.8	79.1±18.9	0.1923
HR	91.1±22.7	91.0±22.8	91.4±22.7	0.8553
RR	20.0±5.5	20.0±5.8	19.9±2.0	0.6651
Lab data				
Glucose	135.1±59.5	130.1±54.3	170.0±80.1	<0.0001
BUN	18.4±11.6	17.6±10.7	23.9±15.7	<0.0001
Creatinine	1.3±3.1	1.2±3.2	1.7±1.7	0.0088
eGFR	94.7±50.1	97.3±51.2	76.2±36.5	<0.0001
Na	138.1±10.5	138.0±11.2	138.2±3.5	0.6706
K	3.9±2.0	3.9±2.1	3.9±0.7	0.5992
GOP	30.0±33.5	28.8±32.2	38.0±40.9	0.0231
GPT	30.0±33.5	28.5±29.0	40.1±25.3	<0.0001
CPK	157.5±317.0	135.7±257.2	311.8±564.7	0.0012
CK-MB	3.7±10.6	2.3±6.4	14.1±22.4	<0.0001
Troponin I	2.8±81.7	0.03±0.12	22.5±233.1	0.3028
PT	11.2±4.8	11.1±3.9	11.9±9.1	0.3521
INR	1.0±0.7	1.0±0.7	1.1±0.9	0.5402
APTT	31.4±5.1	31.3±5.0	32.1±5.5	0.1165
WBC	8.8±3.7	8.8±3.8	8.8±3.3	0.9625
RBC	5.9±23.6	6.1±25.2	4.6±0.8	0.0918
Hb	14.0±9.5	14.1±10.1	13.4±2.3	0.1353
HcT	40.3±6.2	40.4±6.2	39.5±5.9	0.1635
MCV	86.2±7.9	86.1±8.0	86.6±7.5	0.5039
MCH	30.0±9.9	30.0±10.3	29.7±5.9	0.6542
MCHC	34.8±14.2	35.0±15.1	33.8±1.4	0.0373
Platelet count	252.5±74.0	253.4±73.1	246.3±80.1	0.3335
Segment	66.1±15.1	65.6±14.0	69.6±20.9	0.0510
Lymphocyte	26.0±13.4	26.2±13.5	24.5±12.6	0.2082
Monocyte	6.0±4.8	6.0±5.1	6.1±2.3	0.6970
Eosinophil	1.8±2.0	1.8±1.9	2.1±2.4	0.1468
Basophilic	0.4±0.4	0.4±0.4	0.5±0.4	0.2979

MACE patients were all higher than those of the non-MACE patients, $p < 0.05$.

Note that the most important features (set to 5 in this study) were those remaining after the feature selection procedure had been run, selected by the ML model. These were age, QTc, CAD risk factors, creatinine, and troponin I. A full and a reduced risk stratification model were built. The full model was built by multiple logistic regression based on the characteristics of both invasive (i.e., creatinine and troponin I) (Table 2) and non-invasive (i.e., age, number of CAD risk factors, and QTc) variables (Table 3). In this model, the unstandardized coefficients were normalized by dividing the total set by 0.6392, which was the smallest common multiplicative factor. The risk score of full model has a range of 0 to 10 points.

TABLE 2. Multivariate logistic regression and final corresponding score (ACE 2 and ACE 1 model).

Risk factor	ACE 2 Unstandardized β	ACE 2 Final score	Risk factor	ACE 1 Unstandardized β	ACE 1 Final score
Age (years)			Age (years)		
20-54	0	0	20-44	0	0
≥55	0.6392	1	45-64	0.9	1
			≥65	1.1333	2
CAD Risk Factors			CAD Risk Factors		
0	0	0	0	0	0
1-2	0.7701	1	1	0.8891	1
≥3	1.0153	2	≥2	1.3587	2
QTc (ms)			QTc (ms)		
<450	0	0	<450	0	0
≥450	1.3044	2			
Creatinine (mg/dL)					
≤1.5					
>1.5	0	0			
Troponin I (ng/mL)	1.1228	2			
<0.010					
≥0.010	0	0			

score 0-3: 1.68% probability of MACE over next 90 days → Low Risk
score 4-6: 18.27% probability of MACE over next 90 days → Medium Risk
score 7-10: 51.13% probability of MACE over next 90 days → High Risk

score 0-1: 1.22% probability of MACE over next 90 days → Low Risk
score 2-3: 9.36% probability of MACE over next 90 days → Medium Risk
score 4-6: 27.01% probability of MACE over next 90 days → High Risk

TABLE 3. Discriminatory values for the reduced model, full model and HEART scores (low-risk).

Score	Models		
	ACE 1 model	ACE 2 model	HEART scores
Cutoff	0-1	0-2	0-2
Sensitivity (%)	96.6 (93.2-99.9)	94.8 (90.8-98.9)	98.2 (93.9-99.8)
Specificity (%)	39.4 (36.1-42.8)	54.6 (51.2-58.0)	56.8 (53.4-60.2)
Positive predictive value (%)	18.4 (15.3-21.4)	22.8 (19.0-26.5)	24.3 (20.5-28.2)
Negative predictive value (%)	98.8 (96.9-99.7)	98.7 (97.6-99.7)	99.6 (98.5-99.9)
AUROC	0.8005 (0.7651-0.8360)	0.8795 (0.8511-0.9078)	0.8326 (0.8045 0-8607)
Hosmer-Lemeshow calibration test			
χ	3.4474	7.4936	6.5198
p value	0.3277	0.1864	0.1635

Reduced model: Age, CAD risk factors and QTc
Full model: Age, CAD risk factors, QTc, Creatinine and Troponin I

The second model, the reduced model, was developed by multivariate logistic regression based only on non-invasive characteristics (Table 3). Only age, CAD risk factors, and QTc were used as risk factors. Each risk factor was stratified to three levels (0, 1, and 2), an efficient application in a clinical setting. Therefore, the risk score of the reduced model has a range of 0 to 6.

For the low-risk setting, a sensitivity of 0.948 (95% CI 0.908-0.989) and a specificity of 0.546 (95% CI 0.512-0.580) were still seen with the full model for a score = 2 (Table 3). Although the specificity in the reduced model were lower than those in full model, a sensitivity of 0.966 (95% CI 0.932-0.999) could still be obtained. In addition, the full model has high performance for predicting MACE, with an

AUROC of 0.88 (95% CI, 0.851-0.908) (Table 3). Validation was performed using the external data from Banqiao Hospital; the AUROC was 0.853 (95% CI 0.7707-0.935) and 0.808 (95% CI 0.771-0.883) for the full (ACE 2) and reduced (ACE 1) model, respectively. The ROC curves for the full and reduced models are shown in Figure 1.

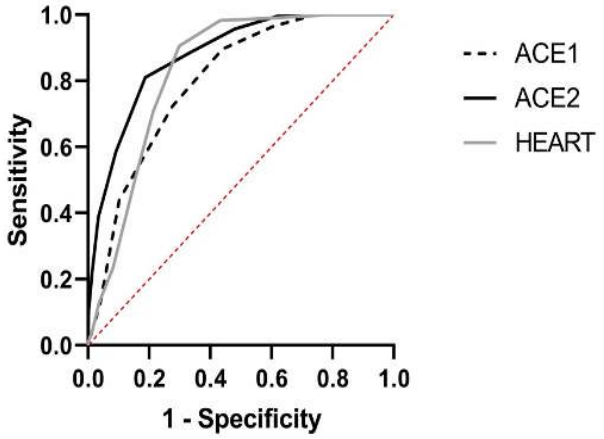

FIGURE 1. Receiver operating characteristic (ROC) curves of risk score for ACE 1 and ACE 2 model and HEART for the validation set from Sanchong Hospital.

IV. DISCUSSION

Two risk stratification models, one full and one reduced, were established by incorporating basic characteristics, vital sign, and lab data for the prediction of 90-day MACE in patients presenting to the ED with chest pain. In the derivation cohort, the AUROC of the full model was 0.880, better than the 0.801 of the reduced model. In the validation cohort, the AUROC of the full model was 0.830, also better than the 0.808 of the reduced model. This is reasonable because all five variables were used in the full model. It is surprising that the reduced model, which only took into consideration age, the number of CAD risk factors, and QTc, still demonstrated a high AUROC (above 0.8). The application of the reduced model is feasible, as only non-invasive characteristics were needed; these data are easy to collect, do not require additional lab work, and should therefore facilitate a simple and cost-effective workflow in a hospital setting.

Among these variables, age, CAD risk factors, and troponin are also used in the HEART scoring system. This was the first time, however, that QTc was included as a risk biomarker for MACE. Prolonged QTc intervals have been used as a risk marker for patients with acute coronary syndrome in many studies [42]–[44]. The cutoff for the QTc interval ranged between 440-450 ms. The best cutoff for QTc was determined to be 450 ms for predicting the risk of ACS with a moderately or severely abnormal subsequent stress test [45]. In an analysis of 45 individuals, a significant association was shown between myocardial infarction and a QTc interval of $\geq$440 ms [44]. Interestingly, although it has been known that the length of the QT interval in the population is associated with many factors, including age, sex, coexisting disease, medication usage, dietary habit, and genetic variants [46]–[48], a strong association between MACE and QTc still was identified in this study.

The risk score cutoff must be examined from three different perspectives. First, emergency medicine providers must ensure to some extent that no cases of MACE are missed. Time-to-decision is imperative within the context of the ED care setting. Any applicable approaches must integrate well into the workflows of the frontline emergency providers. Second, from society's perspective, minimal healthcare costs for maximal value should be deemed efficient and sustainable. Third, for patients, healthcare serves to maximize one's health [49].

The low-risk cutoff score for the full model was set to 2, although a cutoff score of 3 gave the highest sensitivity and specificity. Emergency doctors expect $<$1% missing MACE rate, which translates to a positive predictive value of $>$ 99%; the low-risk score was thus adjusted to 2 to obtain a missing MACE rate of 1.32% in the full model. As a result, the sensitivity increased from 0.914 to 0.948, while the specificity decreased from 0.714 to 0.546. This decreased specificity was consistent with a previous study: a pooled sensitivity of 99.4% was raised to what was considered an acceptable risk of missing MACE in the low-risk group in terms of the HEART score, while the specificity decreased to 22.0% [14].

V. CONCLUSION

Two risk stratification scoring systems specific to Taiwanese individuals were presented. **The full model** was shown to have **high performance** and a **low missed MACE rate**; **the reduced model** was found to be capable of providing **a quick and high-performing diagnosis**. Furthermore, we also identified **QTc prolongation as a potential predictor of MACE**. Future studies will be sure to shed light upon further associations between QTc prolongation and MACE.

DECLARATIONS

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

We confirm that all methods were performed in accordance with the relevant guidelines. This current study was approved by the Institutional Review Board of New Taipei City Hospital, with ERC NTPC No. 106001-E at the trial sites in New Taipei City Hospitals.

CONSENT FOR PUBLICATION

The author confirms patient consent to publication.

AVAILABILITY OF DATA AND MATERIAL

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

COMPETING INTERESTS

The authors declare that there are no competing interests with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript.

NON-FINANCIAL COMPETING INTERESTS

The authors declare that there are no non-financial competing interests in this study.

AUTHORS' CONTRIBUTIONS

CCW and YCL created the research idea, performed the analysis, wrote the results and discussion, and contributed to the literature review. WDH, YCW, WMK and JCL provided clinical suggestions and helped revise the manuscript. WDH, IST and CWH performed the laboratory analysis. CYH supported the analysis. IST supported the prepared protocol. CCW prepared the manuscript for submission. All authors read and approved the final manuscript.

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